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**Derivados Xantónicos Prenilados: Optimização de
Métodos de Obtenção, Caracterização Estrutural e
Avaliação de Bioactividades**



Faculdade de Farmácia da Universidade do Porto

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Derivados Xantónicos Prenilados: Optimização de Métodos de Obtenção, Caracterização Estrutural e Avaliação de Bioactividades

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7. Cravo, S., **Castanheiro, R.**, Vrbata, P., Pinto, M., Silva, A., Campos, N., Nascimento, M.S.J., "Microwave-Assisted Synthesis of Hydroxyxanthenes", *Rev. Port. Farm.*, **2008**, *LII (nº2) Suplemento*: "1º Encontro Nacional de Química Terapêutica", P-103, 151.
6. **Castanheiro, R.**, Pinto, M., Cravo, S., Nazareth, N., Nascimento, M. S. J., "Cyclic Xanthonic Derivatives: A Key Approach to Optimize Antitumor Activity", *Drugs Fut.*, **2008**, *33 (Suppl. A)*: "XXth International Symposium on Medicinal Chemistry", P-197, 123.
5. Cravo, S., **Castanheiro, R.**, Pinto, M., Nazareth, N., Nascimento, M. S. J., "Optimization of Synthetic Methodologies of Biological Active Prenylated Xanthenes", *Drugs Fut.*, **2008**, *33 (Suppl. A)*: "XXth International Symposium on Medicinal Chemistry", P-220, 133.
4. Pinto, M., Sousa, M. E., **Castanheiro, R.**, Saraiva, L., Pereira, G., Gonçalves, J., "Inhibition of α , β I, δ , η and ζ Protein Kinase C Isoforms by Xanthenes: Improvements Towards Selectivity", *Drugs Fut.*, **2006**, *31 (Suppl. A)*: "XIXth International Symposium on Medicinal Chemistry", P-232, 154.
3. Pinto, M., **Castanheiro, R.**, Cravo, S., Pinto, D., Silva, A., "Xanthone derivatives: prenylation and cyclization under microwaves and heterogeneous catalysis", *J. Mex. Chem. Soc.*, **2006**, *50 (special issue 1)*: "16th International Conference on Organic Synthesis", P-133, 165.
2. **Castanheiro, R.**, Pinto, M., Silva, A., Cravo, S., Pedro, M., Wilairat, R., Nazareth, N., Nascimento, M. S. J., "Prenylated Xanthonic Derivatives: Synthesis, Structure Elucidation and Inhibition of Growth of Human Tumor Cell Lines", *Sci. Pharm.*, **2005**, *73(2), Suppl.1*: Abstracts of the Contributions of the Joint Meeting on Medicinal Chemistry, P-161, S219.
1. **Castanheiro, R.**, Pinto, M., Silva, A., Cravo, S., "Prenylated Xanthenes: Synthesis and Structure Elucidation", *Rev. Port. Farm.*, **2005**, *LII (nº2) Suplemento*: 2nd Congress of the Portuguese Society of Pharmaceutical Sciences and 6th Congress of the Portuguese-Spanish Chapter of the Controlled Release Society (Trends and Challenges in Pharmaceutics), P-19, 84-85.

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Comunicações em Painel:

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19. Cravo, S.*, **Castanheiro, R.**, Vrbata, P., Pinto, M., Silva, A., Campos, N., Nascimento, M.S.J., "Microwave-Assisted Synthesis of Hydroxyxanthones", comunicação em painel apresentada no "1^o Encontro Nacional de Química Terapêutica", Porto, Portugal, 13-15 Novembro, **2008** (P-103).
18. **Castanheiro, R.***, Cravo, S., Pinto, M., Nazareth, N., Nascimento, M.S.J., "Cyclic Xanthonic Derivatives: A Key Approach to Optimize Antitumor Activity", comunicação em painel apresentada no "XXth International Symposium on Medicinal Chemistry – EFMC-ISMC 2008", Viena, Áustria, 31 Agosto a 4 Setembro, **2008** (P197).
17. Cravo, S.*, **Castanheiro, R.**, Pinto, M., Nazareth, N., Nascimento, M.S.J., "Optimization of Synthetic Methodologies of Biological Active Prenylated Xanthones", comunicação em painel apresentada no "XXth International Symposium on Medicinal Chemistry – EFMC-ISMC 2008", Viena, Áustria, 31 Agosto a 4 Setembro, **2008** (P220).
16. Vrbata, P.*, Pinto, M., **Castanheiro, R.**, Cravo, S., "Synthesis of Xanthone Derivatives by Microwave-Assisted Methods", comunicação em painel apresentada no "IJUP 2008: First Meeting of Young Researchers of University of Porto", Porto, Portugal, 20-22 Fevereiro, **2008** (P-138).
15. Pinto, M.*, **Castanheiro, R.**, Cravo, S., Cidade, H., Neves, M., "Prenylation on Xanthonic and Flavonic Scaffolds: A Key Approach for Antitumor Activity", comunicação em painel

apresentada no “1st International Conference on Drug Design and Discovery”, Dubai, UAE, 4-7 Fevereiro, **2008** (Ref-125).

14. Cravo, S.*, **Castanheiro, R.**, Pinto, M., Pinto, D., Silva, A., “Dihydropyran Xanthone Derivatives: Optimization of Synthetic Methodologies”, comunicação em painel apresentada no “41st IUPAC World Chemistry Congress”, Turim, Itália, 5-11 Agosto, **2007** (P35).
13. **Castanheiro, R.***, Cravo, S., Pinto, M., Azevedo, C. G., Afonso, C. M. M., Reis, S. H., “Microwave Assisted Synthesis of Xanthenes: 1-Hydroxanthone, 1-Methoxyxanthone and one Dihydropyranoxanthone”, comunicação em painel apresentada no “7th National Meeting of Organic Chemistry”, Lisboa, Portugal, 16-18 Julho, **2007** (PC24).
12. Fernandes, I.*, **Castanheiro, R.**, Pinto, M., Nascimento, M. S. J., “Assaying *in vitro* the Estrogenic/Antiestrogenic Activities of Two New Synthetic Prenylated Xanthenes on Human Breast Cancer Cell lines”, comunicação em painel apresentada no “XVth National Congress of Biochemistry”, Aveiro, Portugal, 8-10 Dezembro, **2006** (P-38).
11. Pinto, M.*, Sousa, M. E., **Castanheiro, R.**, Saraiva, L., Pereira, G., Gonçalves, J., “Inhibition of α , β I, δ , η and ζ Protein Kinase C Isoforms by Xanthenes: Improvements towards Selectivity” comunicação em painel apresentada no “XIXth International Symposium on Medicinal Chemistry (ISMC 2006)”, Istambul, Turquia, 29 de Agosto a 2 de Setembro de **2006** (P-232).
10. **Castanheiro, R.***, Cravo, S., Pinto, M., Silva, A., Pedro, M., Nazareth, N., Nascimento, M. S. J., “Molecular Modification of Prenylated Xanthenes: Heterogeneous Catalysis” comunicação em painel apresentada no “1st European Chemistry Congress”, Budapeste, Hungria, 27-31 Agosto de **2006** (N-PO-29).
9. Cravo, S.*, **Castanheiro, R.**, Pinto, M., Pinto, D., Silva, A., Pedro, M., Nazareth, N., Nascimento, M. S. J., “Optimization of the Synthesis of Prenylated Xanthenes by Using Microwaves” comunicação em painel apresentada no “1st European Chemistry Congress”, Budapeste, Hungria, 27-31 Agosto de **2006** (N-PO-40).
8. **Castanheiro, R.***, Pinto, M., Silva, A., “Synthesis of Prenylated Xanthenes: An Update”, comunicação em painel apresentada no “4th Transmediterranean Colloquium on Heterocyclic Chemistry (TRAMECH 4)”, Aveiro, Portugal, 23-27 Junho de **2006** (PO-57).

7. Pinto, M.*, **Castanheiro, R.**, Cravo, S., Pinto, D., Silva, A., "Xanthone derivatives: prenylation and cyclization under microwaves and heterogeneous catalysis", comunicação em painel apresentada no "16th International Conference on Organic Synthesis", Mérida, México, 11-15 Junho de **2006** (PO-133).
6. **Castanheiro, R.***, Pinto, M., Silva, A., "Montmorillonite Clays em Síntese Orgânica: Obtenção de Di-hidropiranoxantonas", comunicação em painel apresentada no "6^o Encontro Nacional de Química Orgânica", Braga, Portugal, 20-22 Julho de **2005** (PO-114).
5. **Castanheiro, R.**, Cravo, S.*, Pinto, M., Pinto, D., Silva, A., "Derivados Xantónicos Prenilados: Síntese Assistida por Microondas", comunicação em painel apresentada no "6^o Encontro Nacional de Química Orgânica", Braga, Portugal, 20-22 Julho de **2005** (PO-59).
4. **Castanheiro, R.**, Pinto, M.*, Silva, A., Cravo, S., Pedro, M., Wilairat, R., Nazareth, N., Nascimento, M. S. J., "Prenylated Xanthonic Derivatives: Synthesis, Structure Elucidation and Inhibition of Growth of Human Tumor Cell Lines", comunicação em painel apresentada no "Joint Meeting on Medicinal Chemistry", Viena, Áustria, 20-23 Junho de **2005** (PO-161).
3. Pinto, M.*, Afonso, C., Nascimento, M., González, M., Cidade, H., Tiritan, E., Vieira, L., Sousa, E., Teixeira, M., Portela, C., Pedro, M., Cerqueira, F., **Castanheiro, R.**, Cravo, S., Campos, N., Silva, M., Fernandes, C., "Substâncias Bioactivas de Origem Natural e de Síntese: Obtenção, Caracterização Estrutural, Actividades Biológicas e Elucidação de Mecanismos de Acção", comunicação em painel apresentada no Simpósio "Os Farmacêuticos no Sistema de Saúde", Lisboa, Portugal, 19 e 20 de Maio de **2005** (P- 105).
2. **Castanheiro, R.***, Pinto, M., Silva, A., Cravo, S., "Prenylated Xanthonenes: Synthesis and Structure Elucidation", comunicação em painel apresentada no "2nd Congress of the Portuguese Society of Pharmaceutical Sciences and 6th Congress of the Portuguese-Spanish Chapter of the Controlled Release Society (Trends and Challenges in Pharmaceutics) ", Coimbra, Portugal, 31 de Março a 2 de Abril de **2005** (P-19).
1. **Castanheiro, R.***, Pinto, M., Silva, A., Cravo, S., Pedro, M., Wilairat, R., Nazareth, N., Nascimento, M. S. J., "Prenylated Xanthonenes as Inhibitors of Growth of Human Tumour Cell Lines: Synthesis and Biological Assay", comunicação em painel apresentada no "3rd Transmediterranean Colloquium on Heterocyclic Chemistry (TRAMECH 2004)", Marrakech, Marrocos, 23-27 Novembro de **2004** (P-28).

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RESUMO

As xantonas são compostos que, devido a um largo espectro de actividades biológicas e farmacológicas, têm vindo a apresentar um interesse crescente em Química Medicinal, especialmente no que se refere a derivados prenilados.

No sentido de obter maior diversidade estrutural e quantidades para ensaios de actividade, são necessários processos de síntese adequados e eficientes, sendo esse um dos objectivos deste trabalho.

Assim, foram obtidos derivados prenilados por modificação molecular de xantonas hidroxiladas simples, através da aplicação de metodologias sintéticas clássicas e “não clássicas”.

A aplicação de metodologias clássicas de síntese levou à obtenção de xantonas preniladas simples, di-hidropiranoxantonas e piranoxantonas, através de métodos clássicos de prenilação, ciclização de precursores prenilados e desidrogenação, respectivamente. A prenilação foi realizada a partir de hidroxixantonas por uma reacção de substituição nucleofílica; as di-hidropiranoxantonas foram obtidas a partir da ciclização de xantonas mono-oxipreniladas, enquanto as piranoxantonas foram obtidas por desidrogenação das di-hidropiranoxantonas.

No sentido de otimizar os processos de obtenção de xantonas preniladas foram aplicadas duas metodologias “não clássicas”, nomeadamente síntese assistida por microondas e por catálise heterogénea. Foi ainda aplicada a metodologia combinada de catálise heterogénea assistida por microondas.

A metodologia de microondas foi aplicada pela primeira vez na síntese destes derivados, tendo sido obtidas onze xantonas preniladas, com melhores rendimentos, menores tempos reaccionais e maior selectividade na obtenção de alguns derivados prenilados, quando comparada com a síntese convencional.

A metodologia de catálise heterogénea foi utilizada também pela primeira vez, na obtenção de di-hidropiranoxantonas. Através deste método, foram obtidas di-hidropiranoxantonas, num só passo directamente a partir das hidroxixantonas, na presença de *montmorillonite K10 clay* como catalisador sólido. O acoplamento das metodologias de catálise heterogénea com microondas, apresentou vantagens em relação ao método clássico, nomeadamente maior rapidez na reacção, melhores rendimentos, maior selectividade na obtenção de xantonas com um anel di-hidropirano extra.

Esta tese inclui, assim, a síntese e a elucidação estrutural de vinte e três xantonas preniladas bem como a avaliação das respectivas actividades biológicas, nomeadamente antitumoral, moduladora da cínase C de proteínas e estrogénica/antiestrogénica. De entre os derivados xantónicos prenilados obtidos, três são mono-O-prenilados, quatro mono-C-prenilados, quatro C, O-

diprenilados e doze com um anel extra, sendo catorze xantonas preniladas descritas pela primeira vez.

As estruturas dos compostos obtidos foram estabelecidas através da aplicação conjunta de diversas técnicas espectroscópicas nomeadamente, IV, UV, RMN (^1H , ^{13}C , HSQC e HMBC), EM de impacto electrónico e de alta resolução e, adicionalmente, por cristalografia de RX para quatro xantonas preniladas.

Neste trabalho foi avaliado o efeito de dezanove xantonas preniladas no crescimento *in vitro* de linhas celulares tumorais humanas: MCF-7 (adenocarcinoma da mama), NCI-H460 (cancro das células não pequenas do pulmão), SF-268 (cancro do sistema nervoso central) e UACC-62 (melanoma). Foi também investigado o efeito de duas xantonas preniladas na modulação das isoformas α , βI , δ , η e ζ da cínase C de proteínas. A actividade estrogénica / antiestrogénica de outras duas xantonas preniladas foi também estudada.

ABSTRACT

Xanthenes are compounds that, due to a broad spectrum of biological and pharmacological activities are of great interest in Medicinal Chemistry, especially the prenylated derivatives.

In order to obtain more structural diversity and quantities for biological assays, suitable and efficient synthetic processes are necessary.

Therefore, in this work prenylated derivatives were obtained by molecular modification of simple hydroxylated xanthenes, through the application of classical and “non-classical” synthetic methodologies.

The application of classical synthetic methodologies led to the attainment of simple prenylated xanthenes, dihydropyranoxanthenes and pyranoxanthenes, through classical methods of prenylation, cyclization of prenylated precursors and dehydrogenation, respectively. Prenylation was carried out from hydroxyxanthenes by a nucleophilic substitution reaction; dihydropyranoxanthenes were obtained by cyclization of mono-oxyprenylated xanthenes, while pyranoxanthenes were achieved by dehydrogenation of dihydropyranoxanthenes.

In order to optimize the synthetic approach to obtain prenylated xanthenes, two “non-classical” methodologies were used namely microwave-assisted organic synthesis and heterogeneous catalysis. It was also applied the combined method of heterogeneous catalysis with microwave irradiation.

Microwave methodology was applied for the first time to the synthesis of these derivatives, having been obtained eleven prenylated xanthenes, with better yields, less time-consuming and selectivity for some prenylated derivatives, when compared to conventional synthesis.

Heterogeneous catalysis methodology was also used for the first time, in the synthesis of dihydropyranoxanthenes. By this method, dihydropyranoxanthenes were obtained from hydroxyxanthenes, through a one-pot synthesis, in the presence of montmorillonite K10 clay as solid catalyst. The coupling of heterogeneous catalysis with microwave irradiation provided a chemical process with several advantages when compared to classical method, such as enhanced reaction rates, better yields and selectivity to obtain xanthenes with an extra dihydropyran ring.

Thus, this thesis reports the synthesis and structure elucidation of twenty-three prenylated xanthenes as well as the evaluation of their biological activities, namely antitumor, modulation of protein kinase C and estrogenic/anti-estrogenic. Among the prenylated xanthenic derivatives, three are mono-O-prenylated, four mono-C-prenylated, four C,O-diprenylated and twelve with an extra ring, being fourteen prenylated xanthenes described for the first time.

The structures of the obtained compounds were established by a whole of several spectroscopic methods, including IR, UV, NMR (^1H , ^{13}C , HSQC and HMBC), electronic impact and high resolution mass spectrometry and additionally by X-ray crystallography to four prenylated xanthenes.

The effect of nineteen prenylated xanthenes on the *in vitro* growth of human tumor cell lines: MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), SF-268 (central nervous system cancer) and UACC-62 (melanoma) was evaluated. The effect of two prenylated xanthenes on the modulation of α , βI , δ , η and ζ isoforms of protein kinase C was also investigated. The estrogenic / anti-estrogenic activity of other two prenylated xanthenes was also studied.

ABREVIATURAS E SÍMBOLOS

^{13}C RMN	Ressonância Magnética Nuclear de Carbono
^1H RMN	Ressonância Magnética Nuclear de Protão
ADN	Ácido desoxirribonucleico
CEQOFFUP	Centro de Estudos de Química Orgânica Fitoquímica e Farmacologia da Universidade do Porto
CEQUIMED-UP	Centro de Química Medicinal da Universidade do Porto
DDQ	2,3-Dicloro-5,6-diciano-1,4-benzoquinona
DMF	<i>N,N</i> -Dimetilformamida
DMXAA	Ácido 2-(5,6-dimetil-9-oxo-9 <i>H</i> -xanten-4-il)acético
E ₂	17- β -Estradiol
EC ₅₀	Concentração de composto que origina 50% de reversão da inibição de crescimento causada pelo inibidor
EM	Espectrometria de massa
ER	Receptor de Estrogénios
ER-	Linha celular sem receptores de estrogénios
ER+	Linha celular com receptores de estrogénios
Et	Grupo etilo (-CH ₂ -CH ₃)
GI ₅₀	Concentração de composto que causa 50% de inibição do crescimento celular
GSS	<i>Grover, Shah and Shah</i>
HMBC	<i>Heteronuclear Multiple Bond Correlation</i>
HSQC	<i>Heteronuclear Single Quantum Correlation</i>
IUPAC	<i>International Union of Pure and Applied Chemistry</i>
IV	Infravermelho
MAOS	Síntese Orgânica Assistida por Microondas (<i>Microwave Assisted Organic Synthesis</i>)
MCF-7	Linha celular de adenocarcinoma da mama com receptores de estrogénios
Me	Grupo metilo (-CH ₃)
MW	Microondas (<i>Microwaves</i>)
<i>N,N</i> -DEA	<i>N,N</i> -dietilanilina
NCI-H460	Linha celular de cancro das células não pequenas do pulmão
NMP	<i>N</i> -metil-2-pirrolidona
PKC	Cínase C de proteínas (<i>Protein Kinase C</i>)
RMN	Ressonância Magnética Nuclear

SF-268	Linha celular de cancro do sistema nervoso central
t.a.	Temperatura ambiente
TAM	Tamoxifeno
UACC-62	Linha celular de melanoma
UV	Ultravioleta
X	Xantona
XP	Xantona Prenilada

Para algumas abreviaturas foi mantida a notação anglo-saxónica dado o seu carácter universal ou para facilitar o seu reconhecimento. Nesses casos a notação anglo-saxónica é apresentada em itálico.

ORGANIZAÇÃO DA TESE

A presente tese está organizada em três capítulos principais:

CAPÍTULO I – Introdução

Este capítulo encontra-se dividido em quatro subcapítulos:

- ***Introdução Geral***

É feito o enquadramento do trabalho dando especial ênfase a xantonas e xantonas prenilhadas, à importância destes compostos e ao trabalho realizado no grupo de investigação onde este projecto se insere. É incluído um trabalho de revisão (**Anexo I**) sobre xantonas prenilhadas de origem natural, no que toca à sua ocorrência, biossíntese, elucidação estrutural, actividades biológicas e relação estrutura actividade e que faz parte integrante desta tese. É ainda incluída uma tabela (**Anexo II**) na qual é feita uma actualização das xantonas prenilhadas isoladas de produtos naturais, no período compreendido entre a finalização do referido trabalho de revisão e da presente tese, bem como as actividades biológicas demonstradas.

- ***Objectivos***

São indicados os principais objectivos da presente tese.

- ***Metodologias de Síntese***

É feita uma breve introdução aos processos utilizados na síntese de derivados xantónicos, com a descrição das metodologias utilizadas, nomeadamente síntese clássica, síntese assistida por microondas (MW), síntese por catálise heterogénea e síntese por catálise heterogénea assistida por MW, os respectivos fundamentos teóricos e a justificação da sua aplicação no presente trabalho. É integrado neste subcapítulo um trabalho de revisão (**Anexo III**) sobre a síntese de xantonas prenilhadas e que faz parte integrante desta tese.

- ***Procedimento Geral de Síntese***

É discutida a aplicação das metodologias de síntese descritas no subcapítulo anterior, na obtenção das xantonas a utilizar como blocos construtores para modificação molecular bem como das xantonas prenilhadas.

É ainda feita uma breve referência às técnicas utilizadas para a elucidação estrutural das xantonas prenilhadas sintetizadas, nomeadamente IV, UV, RMN, EM e cristalografia de raios X. Os resultados relativos à caracterização estrutural dos derivados prenilhados sintetizados são apresentados e discutidos nos artigos científicos integrados nos **Anexos IV-VII**. Os espectros de

RMN, bem como os espectros de massa foram obtidos no Departamento de Química da Universidade de Aveiro, respectivamente pelo grupo do Professor Doutor Artur Silva e pela Dr.^a Cristina Barros. Os espectros de massa de alta resolução foram obtidos pelo Doutor Graham Eaton da Universidade de Leicester e no CACTI na Universidade de Vigo. Os dados de cristalografia de raios X foram obtidos pelo grupo da Professora Doutora Ana Margarida Damas do Instituto de Biologia Molecular e Celular / Instituto de Ciências Biomédicas Abel Salazar.

CAPÍTULO II – Obtenção de Derivados Xantónicos Prenilados

Este capítulo encontra-se dividido em três subcapítulos:

- ***Parte Experimental***

É feita a descrição dos métodos utilizados na obtenção dos derivados prenilados, através da aplicação de metodologias clássicas e “não clássicas” de síntese, apresentando-se sumariados os procedimentos gerais adoptados.

- ***Discussão dos Resultados***

São apresentados e discutidos os resultados obtidos na síntese dos derivados xantónicos prenilados. A maior parte dos resultados está apresentada em artigos científicos, já publicados ou em fase de publicação e que fazem parte integrante desta tese (**Anexos IV-VI**). Nos referidos artigos encontram-se compilados os métodos de síntese utilizados, resultados obtidos e, também, as conclusões dos trabalhos incluídos na presente tese.

- ***Ensaio Biológicos***

É feita referência às actividades biológicas avaliadas para algumas xantonas preniladas sintetizadas, nomeadamente actividade antitumoral, moduladora da PKC e estrogénica /antiestrogénica dos derivados prenilados que se revelaram mais promissores em ensaios de *screening*. Os ensaios biológicos foram efectuados nos grupos de Microbiologia da Faculdade de Farmácia da Universidade do Porto (FFUP) sob orientação da Professora Doutora Maria de São José Nascimento e da Professora Doutora Lucília Saraiva.

CAPÍTULO III – Conclusões

São salientadas as conclusões gerais da presente tese, tendo em conta os objectivos propostos.

Para maior facilidade de consulta, as estruturas dos compostos sintetizados no presente trabalho encontram-se num Anexo desdobrável (**Anexo X**) no final da tese. Nesse Anexo é também

apresentada a correspondência entre as siglas de cada XP, referenciadas ao longo da tese, com a respectiva numeração nas diferentes publicações.

ANEXOS

Os **anexos I e III – IX** compreendem oito publicações (ao abrigo do artigo 8º, do decreto-lei nº.388/70):

- Anexo I** *Pinto, M.; Castanheiro, R.; Natural Prenylated Xanthenes: Chemistry and Biological Activities. Em Natural Products: Chemistry, Biochemistry and Pharmacology. Ed. Brahmachari, G., Narosa Publishing House PVT. LTD., Nova Deli, Índia, ISBN: 978-81-7319-886-1, 2009, Cap. 17, pp.520-676.*
- Anexo II** **Tabela 8:** *Xantonas Preniladas isoladas de fontes naturais no período de 2007-2009.*
- Anexo III** *Pinto, M. M. M. & Castanheiro, R. A. P. Synthesis of Prenylated Xanthenes: An Overview. Curr. Org. Chem. 2009, submetido (Abstract aceite).*
- Anexo IV** *Castanheiro, R. A. P., Pinto, M. M. M., Silva, A. M. S., Cravo, S. M. M., Gales, L., Damas, A. M., Nazareth, N., Nascimento, M. S. J., Eaton, G. Dihydroxyxanthenes Prenylated Derivatives: Synthesis, Structure Elucidation and Growth Inhibitory Activity on Human Tumor Cell Lines with Improvement of Selectivity for MCF-7; Bioorg. Med. Chem. 2007, 15, 6080-6088.*
- Anexo V** *Castanheiro, R. A. P.; Pinto, M. M. M.; Silva, A. M. S., Campos, N. A. N.; Nascimento, M. S. J. Antitumor Xanthone Derivatives: Prenylation as a Key Approach to Improve Activity. Chem. & Biodiv. 2009, submetido.*
- Anexo VI** *Castanheiro, R. A. P.; Pinto, M. M. M.; Cravo, S. M. M.; Pinto, D. C. G. A.; Silva, A. M. S.; Kijjoo, A. Improved Methodologies for Synthesis of Prenylated Xanthenes by Microwave Irradiation and Combination of Heterogeneous Catalysis (K10 clay) with Microwave Irradiation. Tetrahedron 2009, 65, 3848-3857.*
- Anexo VII** *Gales, L.; Castanheiro, R. A. P.; Pinto, M. M. M.; Damas, A. M. 1-Hydroxy-3-(3-methylbut-2-enyloxy)xanthone. Acta Cryst. E. 2009, submetido.*
- Anexo VIII** *Cravo, S.; Castanheiro, R.; Pinto, M.; Nazareth, N.; Nascimento, M. S. J.; Optimization of Synthetic Methodologies of Biological Active Prenylated Xanthenes. Drugs Fut. 2008, 33 (Suppl. A), P-220, 133.*
- Anexo IX** *Pinto, M.; Sousa, M. E.; Castanheiro, R.; Saraiva, L.; Pereira, G.; Gonçalves, J.; Inhibition of α , β , δ , η and ζ Protein Kinase C Isoforms by Xanthenes: Improvements Towards Selectivity. Drugs Fut. 2006, 31 (Suppl. A), P-232, 154.*
- Anexo X** *Anexo de Estruturas*

CAPÍTULO I

INTRODUÇÃO

1. INTRODUÇÃO GERAL

A Química Orgânica, especialmente na vertente sintética, exerce um papel fundamental na obtenção de novas substâncias que, após avaliação das suas actividades biológicas e farmacológicas, poderão servir como base no desenvolvimento de novos agentes terapêuticos, constituindo assim um pilar essencial para o progresso da Química Medicinal.

Os produtos naturais, especialmente originários de plantas, eram utilizados na medicina tradicional no tratamento de diversas patologias, tendo sido quase exclusivamente o único recurso terapêutico disponível durante um longo período. Actualmente, uma das principais fontes na descoberta de novos fármacos continua a ser baseada na medicina tradicional, correspondendo uma grande parte a produtos naturais, ou a produtos sintéticos derivados e/ou baseados em modelos de produtos naturais (Hostettmann *et al.*, 1998; Montanari & Bolzani, 2001; Haefner, 2003; Butler, 2004, 2008; Jimeno *et al.*, 2004; Kijjoa & Sawangwong, 2004; Newman & Cragg, 2004, 2007; Chin *et al.*, 2006; Füllbeck *et al.*, 2006; Viegas Jr *et al.*, 2006; Baker *et al.*, 2007; Lam, 2007; Saleem *et al.*, 2007; Ganesan, 2008; Saklani & Kutty, 2008; Harvey, 2008; Dholwani *et al.*, 2008; Quinn *et al.*, 2008; Nicolaou *et al.*, 2009).

Algumas plantas contendo xantonas têm vindo a ser utilizadas desde há muitos anos pela medicina tradicional, devido ao número alargado de actividades biológicas exibidas por estes compostos (Pinto *et al.*, 2005b). São exemplos os extractos de *Hypericum perforatum*, *Mangifera indica* e *Garcinia mangostana*, empregues especialmente devido às suas propriedades antidepressivas (Rodríguez-Landa & Contreras, 2003; Mennini & Gobbi, 2004; Bach-Rojecky *et al.*, 2004; www.esalq.usp.br/siesalq/pm/hipericao.pdf; http://pt.wikipedia.org/wiki/Hypericum_perforatum) e antioxidantes (Pinto *et al.*, 2005b; Correia *et al.*, 2006; Garrido *et al.*, 2008), respectivamente.

O estudo de compostos do tipo xantónico tem sido um dos principais alvos de interesse por parte do CEQOFFUP/CEQUIMED-UP. Desse interesse, resultaram vários estudos relativos à investigação das acções biológicas quer de compostos de origem natural (Pinto *et al.*, 1997; Gonzalez *et al.*, 1999; Saraiva *et al.*, 2002a; Pedro *et al.*, 2002; Maia *et al.*, 2005; Teixeira *et al.*, 2005; Wilairat *et al.*, 2005; Kijjoa *et al.*, 2008) quer de derivados obtidos por síntese (Fernandes *et al.*, 1995; Fernandes, 1996; Pinto & Nascimento, 1997; Pedro *et al.*, 2002; Saraiva *et al.*, 2002b, 2003; Sousa, 2003; Teixeira *et al.*, 2005; Portela, 2006; Pedro de Oliveira, 2006; Fernandes, 2006; Castanheiro *et al.*, 2007a; Oliveira *et al.*, 2007; Portela *et al.*, 2007; Teixeira, 2008).

1.1. XANTONAS

As xantonas ou xanten-9-onas, com o núcleo dibenzo- γ -pirona (**Figura 1**), constituem uma classe importante de heterociclos oxigenados. São metabolitos secundários de elevado valor

taxonômico e de ocorrência em alguns fungos, líquenes e plantas superiores, sendo, nestas últimas, restrita essencialmente a duas famílias, *Guttiferae* (*Clusiaceae*) e *Gentianaceae* (Sultanbawa, 1980; Bennett & Lee, 1989; Peres & Nagem, 1997a, b; Peres *et al.*, 2000; Vieira & Kijjoa, 2005; Pinto & Castanheiro, 2009a).

A biossíntese de xantonas em plantas superiores está bem determinada seguindo a via acetato-xiquimato (Rezende & Gottlieb, 1973; Afzal & Al-Hassan, 1980; Fernandes, 1996; Sousa, 2003; Cidade *et al.*, 2008; Pinto & Castanheiro, 2009a). Em determinado tipo de organismos, nomeadamente fungos e líquenes, o padrão de oxigenação das xantonas é diferente do das plantas superiores o que levou a propor para a sua génese a via poliacetato (Sultanbawa, 1980; Afzal & Al-Hassan, 1980; Fernandes, 1996; Sousa, 2003; Pinto & Castanheiro, 2009a e referências).

Em função da natureza dos substituintes presentes na estrutura dibenzo- γ -pirona, as xantonas de origem natural podem ser divididas em: xantonas simples oxigenadas, xantonas glicosiladas, xantonas preniladas e seus derivados, dímeros xantónicos, xantonas em “jaula” (*caged*), xantolignóides e xantonas mistas. Estes grupos podem ainda ser subdivididos de acordo com o grau de oxigenação em substâncias mono-, di-, tri-, tetra-, penta- e hexa-oxigenadas (Vieira & Kijjoa, 2005; Pinto *et al.*, 2005b; Feng *et al.*, 2007; Reutrakul *et al.*, 2007; Shadid *et al.*, 2007; Masullo *et al.*, 2008; Wang *et al.*, 2008b; Xu *et al.*, 2008; Pouli & Marakos, 2009; Tao *et al.*, 2009; Pinto & Castanheiro, 2009a).

No caso das xantonas simples oxigenadas, provenientes de plantas superiores, os átomos de carbono são normalmente numerados de acordo com uma convenção biossintética. Assim, o anel A, numerado de 1-4, refere-se à porção derivada da via acetato, enquanto o anel B, numerado de 5-8, corresponde à porção derivada da via xiquimato. No caso de apenas o anel B ser oxigenado é utilizada a regra da IUPAC que atribui os números mais baixos aos grupos substituintes, excepto no caso de análises de carácter biossintético (Bennett & Lee, 1989; Fotie & Bohle, 2006; Pinto & Castanheiro, 2009a).

Uma vez que a numeração do núcleo xantónico não é uniforme ao longo da literatura, a adoptada neste trabalho é a recomendada pela IUPAC, a título provisório, em 2004 (*).

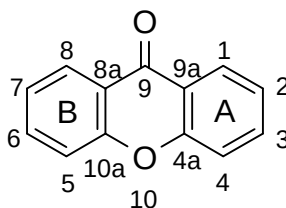


Figura 1. Esqueleto xantónico e respectiva numeração.

* <http://old.iupac.org/reports/provisional/abstract04/BB-prs310305/Chapter2-Sec25.pdf>

As xantonas de origem sintética podem apresentar grupos químicos simples como hidroxilo, metoxilo, metilo, carboxilo, bem como substituintes mais complexos tais como epóxido, azole, metilideno-butirolactona, aminoálcool, sulfamoilo, ácido metiltio-carboxílico e di-hidropiridina em diferentes posições da estrutura dibenzo- γ -pirona (Pinto *et al.*, 2005b).

Podem ser encontradas na literatura algumas revisões interessantes sobre a ocorrência (Vieira & Kijjoa, 2005), a biossíntese (Rezende & Gottlieb, 1973; Bennett & Lee, 1989; Peres & Nagem, 1997a), a síntese (Sousa & Pinto, 2005) e a determinação estrutural de xantonas (Fernandes *et al.*, 1996; Silva & Pinto, 2005; Gales & Damas, 2005).

O elevado valor taxonómico das xantonas bem como as interessantes propriedades biológicas reveladas, quer por produtos naturais quer por derivados obtidos por síntese, tem vindo a despertar um interesse crescente por esta classe de compostos (Pinto *et al.*, 2005b; Pinto & Castanheiro, 2009a; Pouli & Marakos, 2009; Filho *et al.*, 2009). De facto, diversos estudos realizados revelaram actividades das quais se destacam anti-hepatotóxica (Fernandes, 1995, 1996), inibidora da monoaminoxidase (Gnerre *et al.*, 2001), moduladora da cínase C de proteínas (Saraiva *et al.*, 2002a, b, 2003; Pinto *et al.*, 2005b), imunomoduladora (Pinto & Nascimento, 1997; Pinto *et al.*, 1997; Gonzalez *et al.*, 1999), antimalárica (Riscoe *et al.*, 2005; Fotie & Bohle, 2006; Portela, 2006; Portela *et al.*, 2007; Zelefsack *et al.*, 2009), antioxidante (Pinto *et al.*, 2005b; Yu *et al.*, 2007; Zhong *et al.*, 2008b; Zhong *et al.*, 2009) e antitumoral (Pedro *et al.*, 2002; Sousa, 2003; Pinto *et al.*, 2005b; Wilairat *et al.*, 2005; Pedro de Oliveira, 2006; Oliveira *et al.*, 2007; Cao *et al.*, 2007; Feng *et al.*, 2007; Han *et al.*, 2007; Reutrakul *et al.*, 2007; Shadid *et al.*, 2007; Yang *et al.*, 2007; Elya *et al.*, 2008; Han *et al.*, 2008a; Kijjoa *et al.*, 2008; Leet *et al.*, 2008; Wang *et al.*, 2008b; Wen *et al.*, 2008; Xiao *et al.*, 2008; Xu *et al.*, 2008; Huang *et al.*, 2009; Pouli & Marakos, 2009; Tao *et al.*, 2009; Hung *et al.*, 2009; Zelefsack *et al.*, 2009; Filho *et al.*, 2009).

Das muitas actividades descritas para as xantonas, sobressai a capacidade de inibição do crescimento *in vitro* de uma grande variedade de linhas celulares tumorais, representativas de diferentes tipos de cancro, nomeadamente leucemia, melanoma, cólon, mama, próstata, pulmão, fígado entre outros (Pinto *et al.*, 2005b e referências; Pedro de Oliveira, 2006; Fernandes, 2006; Oliveira *et al.*, 2007; Cao *et al.*, 2007; Feng *et al.*, 2007; Han *et al.*, 2007; Reutrakul *et al.*, 2007; Shadid *et al.*, 2007; Yang *et al.*, 2007; Elya *et al.*, 2008; Han *et al.*, 2008a; Kijjoa *et al.*, 2008; Leet *et al.*, 2008; Wang *et al.*, 2008b; Wen *et al.*, 2008; Xiao *et al.*, 2008; Xu *et al.*, 2008; Huang *et al.*, 2009; Pouli & Marakos, 2009; Tao *et al.*, 2009; Hung *et al.*, 2009; Zelefsack *et al.*, 2009; Filho *et al.*, 2009).

Actualmente existem alguns derivados xantônicos promissores no campo de desenvolvimento de fármacos antineoplásicos, nomeadamente a psorospermina (1) e o ácido 2-(5,6-dimetil-9-oxo-9H-xanten-4-il)acético (DMXAA) (2) (Figura 2).

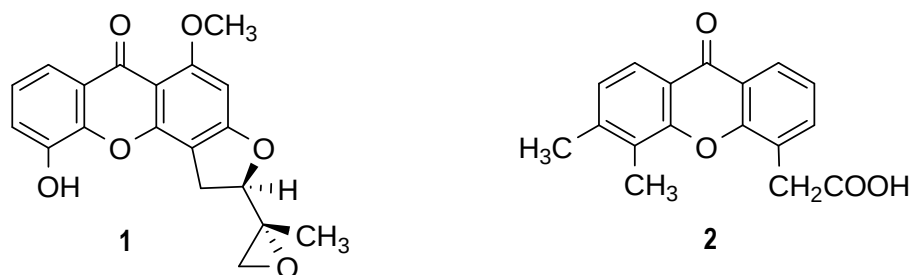


Figura 2. Estruturas da Psorospermina (1) e do DMXAA (2).

A psorospermina é uma di-hidrofuranoxantona natural isolada a partir da raiz e casca da planta tropical africana *Psorospermum febrifugum* (Kupchan *et al.*, 1980; Pachuta *et al.*, 1986), mas foi recentemente sintetizada (Schwaebe *et al.*, 2005; Hurley *et al.*, 2007). Esta xantona, presentemente em estudos pré-clínicos, mostrou inibir o crescimento de várias linhas celulares tumorais (Kupchan *et al.*, 1980; Permana *et al.*, 1994), tendo sido já descrito o seu mecanismo de acção (Permana *et al.*, 1994; Hansen *et al.*, 1995, 1996; Kwok & Hurley, 1998; Kwok *et al.*, 1998; Hurley *et al.*, 2007).

Por outro lado, o DMXAA, uma xantona carboxilada sintética (Rewcastle *et al.*, 1991; Atwell *et al.*, 2002), tem sido considerado uma molécula promissora no campo de desenvolvimento de novos fármacos antitumorais, nomeadamente na classe dos agentes antivasculares. Estudos recentes sugeriram que a inibição do fluxo sanguíneo é consequência da indução da apoptose das células endoteliais vasculares tumorais (Baguley, 2003; Chaplin *et al.*, 2006; Roberts *et al.*, 2007). Esta xantona encontra-se, actualmente, em ensaios clínicos de fase III para tratamento do cancro de células não pequenas do pulmão (Wang *et al.*, 2008a; Rehman & Rustin, 2008).

Num estudo realizado no CEQOFFUP/CEQUIMED-UP foi avaliado o efeito de 27 xantonas oxigenadas, naturais e sintéticas estruturalmente relacionadas, no crescimento de 3 linhas celulares tumorais humanas: MCF-7 (adenocarcinoma da mama), TK-10 (carcinoma renal) e UACC-62 (melanoma), tendo sido demonstrado que as diferenças de potência observadas na actividade destas xantonas estavam relacionadas com a natureza, posição e número de substituintes no núcleo xantónico (Pedro *et al.*, 2002). Entre os compostos estudados, a 1,3-di-hidroxi-2-metilxantona (X1) foi a que apresentou o efeito inibidor mais potente do crescimento das 3 linhas tumorais ensaiadas, considerando-se assim como um composto “hit” para a série testada (Pedro *et al.*, 2002).

Tendo como base os resultados promissores da avaliação da actividade antitumoral do molecular do CEQOFFUP/CEQUIMED-UP, foram seleccionados alguns compostos “hit” para se

proceder a diversas modificações moleculares, no sentido de potenciar a sua actividade, especialmente a actividade antitumoral.

1.2. XANTONAS PRENILADAS

As xantonas preniladas são o grupo mais abundante de xantonas naturais sendo consideradas como marcadores taxonómicos para algumas famílias de plantas superiores, especialmente *Guttiferae* (*Clusiaceae*) e *Gentianaceae* (Vieira & Kijjoa, 2005; Pinto & Castanheiro, 2009a e referências).

As xantonas preniladas são caracterizadas por apresentarem um grupo substituinte prenilo no esqueleto xantónico. Os principais substituintes prenilo encontrados (**Figura 3**) incluem o grupo 3-metilbut-2-enilo, também designado por 3,3-dimetilalilo (**A**) (mais vulgarmente encontrado) e os menos frequentes 3-hidroxi-3-metilbutilo (**B**) e 1,1-dimetilprop-2-enilo ou 1,1-dimetilalilo (**C**). Além destes substituintes são também encontrados grupos resultantes da ciclização dos substituintes **A** e/ou **C** com o grupo hidroxilo *orto* do anel benzénico, como sejam os grupos 2,2-dimetilpirano (**D**) e 2,3,3-trimetil-di-hidrofurano (**E**) e ainda o raro 2-isopropenil-di-hidrofurano (**F**). Menos frequentes são os substituintes com maior número de unidades C₅ como é o caso do grupo geranilo (C₁₀) (**G**) e o farnesilo (C₁₅) (**H**), sendo este último raramente encontrado. Podem também surgir modificações destas cadeias laterais por hidroxilação, hidrogenação, epoxidação e lactonização. Um subgrupo que se tem vindo a tornar bastante importante, devido às propriedades antitumorais demonstradas, são as xantonas preniladas complexas, designadas de “caged” ou xantonas em “jaula” (Pinto & Castanheiro, 2009a; Feng *et al.*, 2007; Reutrakul *et al.*, 2007; Shadid *et al.*, 2007; Masullo *et al.*, 2008; Wang *et al.*, 2008b; Xu *et al.*, 2008; Pouli & Marakos, 2009; Tao *et al.*, 2009).

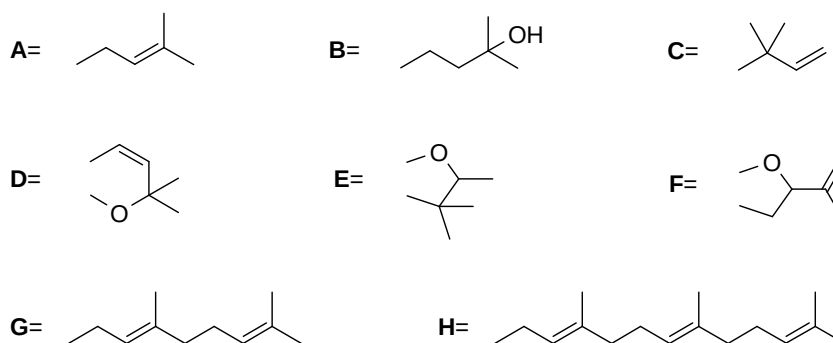


Figura 3. Principais substituintes C₅ encontrados nas xantonas preniladas.

Embora os derivados C-prenilados sejam predominantes na Natureza, os compostos oxiprenilados também podem ser encontrados e de entre estes, apenas um pequeno número corresponde a compostos simultaneamente C- e O-prenilados. Os substituintes prenilo podem ocorrer em qualquer posição do núcleo xantónico mas existem posições preferenciais. Por exemplo,

os substituintes **A** e **C** surgem normalmente em C-2, C-4 e também em C-8, enquanto os substituintes cíclicos, como os grupos **D** e **E**, se localizam frequentemente em C-2–C-3, C-3–C-4, C-5–C-6 e C-7–C-8 e em C-2–C-3 ou C-3–C-4, respectivamente (Pinto & Castanheiro, 2009a).

Como já referido anteriormente, os derivados xantónicos apresentam uma diversidade de actividades biológicas apreciável, dependendo da natureza e localização dos grupos substituintes nos anéis aromáticos (Pinto *et al.*, 2005b; Pinto & Castanheiro, 2009a). Muitos dos compostos xantónicos com actividades interessantes, como seja a moduladora da PKC, imunomoduladora, anti-inflamatória, antibacteriana, antifúngica, antitumoral, mostraram existir uma relação entre a presença de actividade biológica e a existência de grupos prenilo em posições-chave no esqueleto xantónico. Deste modo, a presença dos grupos prenilo torna-se um factor estrutural importante para a interacção de xantonas com certos alvos, o que poderá permitir um aumento da potência e da selectividade. A influência destes grupos pode ser considerada *dual*, tendo em consideração a sua influência nas propriedades físico-químicas, nomeadamente lipofilia, e nas propriedades tridimensionais fomentando efeitos estéricos na interacção com alvos biológicos, assim como uma porção molecular adicional para interacções hidrofóbicas (Barreiro & Fraga, 2001; Avendaño, 2001; Patrick, 2005; Pinto & Castanheiro, 2009a).

Na revisão feita na literatura num período compreendido entre Janeiro de 1963 e Março de 2009 (finalização da presente tese) foram encontrados um total de 630 xantonas preniladas isoladas de fontes naturais (**Anexos I e II**) e 93 obtidas por síntese (**Anexo III**).

O **Anexo I** descreve a ocorrência, biossíntese, elucidação estrutural de xantonas preniladas naturais isoladas nos últimos quarenta anos (entre Janeiro de 1963 e Dezembro de 2006), bem como as actividades biológicas exibidas por estes compostos. É ainda discutida a relação estrutura-actividade com especial ênfase para a actividade antitumoral. O **Anexo II** compreende uma tabela que complementa as *tabelas 1 e 2* presentes no **Anexo I**, na qual é feita uma actualização das xantonas preniladas isoladas de fontes naturais nos últimos dois anos (Janeiro de 2007 e Março de 2009), bem como as principais actividades biológicas reveladas. De acordo com a informação presente em ambos os anexos, foi possível verificar que as xantonas preniladas constituem uma importante classe de compostos devido à ampla variedade de actividades biológicas interessantes e promissoras reveladas. Embora tenham sido descritas diversas actividades para as xantonas preniladas, o seu potencial quimioterapêutico parece estar associado predominantemente a propriedades citotóxicas, antitumorais, antimicrobianas, antifúngicas e antivirais. Apesar de a grande maioria dos compostos “hit” para as actividades descritas serem derivados C- e O-prenilados simples, também as furano- e piranoxantonas naturais demonstraram ser particularmente

interessantes em termos de potência citotóxica e de novos mecanismos de acção, podendo servir como modelo para o desenvolvimento de agentes antitumorais clinicamente eficazes (Cao *et al.*, 2007; Feng *et al.*, 2007; Han *et al.*, 2007; Reutrakul *et al.*, 2007; Shadid *et al.*, 2007; Yang *et al.*, 2007; Akao *et al.*, 2008; Ee *et al.*, 2008; Elya *et al.*, 2008; Han *et al.*, 2008a; Kijjoa *et al.*, 2008; Leet *et al.*, 2008; Pedraza-Chaverri *et al.*, 2008; Wang *et al.*, 2008b, c; Wen *et al.*, 2008; Xiao *et al.*, 2008; Xu *et al.*, 2008; Huang *et al.*, 2009; Pouli & Marakos, 2009; Tao *et al.*, 2009; Hung *et al.*, 2009; Zelefsack *et al.*, 2009; Filho *et al.*, 2009; Pinto & Castanheiro, 2009a).

Também no trabalho de revisão incluído no **Anexo I** foi possível demonstrar que, além das potenciais propriedades biológicas associadas às xantonas prenildas, o respectivo esqueleto pode funcionar como palanque estrutural para a realização de modificações moleculares de modo a melhorar as suas propriedades físico-químicas e biológicas.

A avaliação da relação estrutura-actividade permitiu verificar que a posição no núcleo xantónico, quer de grupos hidroxilo quer de grupos prenilo, pode ser um factor decisivo para a especificidade das actividades biológicas. Deste modo, as xantonas prenildas podem constituir um excelente material de partida para o desenvolvimento de novos fármacos mais eficazes, tendo servido como modelo para a síntese dos compostos descritos na presente tese.

2. OBJECTIVOS

A presente tese teve como principais objectivos:

- Obtenção de derivados prenilados de xantonas hidroxiladas simples por modificação molecular, tendo como propósito não só a optimização de processos clássicos, como também a aplicação de novos métodos à síntese de derivados xantónicos, nomeadamente:
 - a) Obtenção de xantonas preniladas simples e de xantonas com anéis extra, através de metodologias clássicas de síntese,
 - b) Optimização dos processos de obtenção das xantonas referidas em a), através da aplicação de duas metodologias sintéticas “não clássicas”, nomeadamente síntese assistida por MW e por catálise heterogénea,
 - c) Comparação dos resultados obtidos pela aplicação das metodologias clássicas (a) e “não clássicas” (b);
- Elucidação estrutural das xantonas obtidas, através da aplicação conjunta de diversas técnicas espectroscópicas nomeadamente, IV, UV, RMN (^1H , ^{13}C , HSQC e HMBC), EM de impacto electrónico e de alta resolução e por cristalografia de RX;
- Avaliação de actividades biológicas dos compostos sintetizados, nomeadamente:
 - a) Efeito dos derivados xantónicos no crescimento *in vitro* de linhas celulares tumorais humanas: MCF-7, NCI-H460, SF-268 e UACC-62,
 - b) Modulação das isoformas α , βI , δ , η e ζ da PKC,
 - c) Actividade estrogénica/antiestrogénica dos derivados prenilados que se revelarem mais promissores em ensaios de *screening*.

3. METODOLOGIAS DE SÍNTESE

Nos últimos anos tem-se vindo a verificar uma diversificação das diferentes metodologias de síntese aplicáveis à obtenção de derivados xantónicos simples oxigenados (Dean, 1973; Sousa & Pinto, 2005). Tradicionalmente, consideram-se três métodos como clássicos: a síntese via reacção de Grover, Shah e Shah (GSS) (Grover *et al.*, 1955), a síntese via intermediário benzofenona (Quillinan & Scheinmann, 1973) e a síntese via intermediário éter diarílico (Moroz & Shvartsberg, 1974).

A reacção de GSS (Grover *et al.*, 1955) corresponde a um método simples e conveniente para preparar hidroxixantonas e desfruta ainda de grande popularidade devido à possibilidade de se utilizarem reagentes de fácil aquisição. A reacção, cujo exemplo se encontra descrito na **Figura 4**, consiste na condensação de um derivado do ácido salicílico (**3**) com um fenol apropriado (**4**), sendo estes compostos submetidos a aquecimento na presença de cloreto de zinco, em oxicloreto de fósforo. O método de GSS pode originar directamente o esqueleto xantónico (**6**) apenas se no intermediário benzofenona (**5**) existir uma posição alternativa para a ciclização (*) (Grover *et al.*, 1955; Dean, 1973; Sousa & Pinto, 2005) (**Figura 4**).

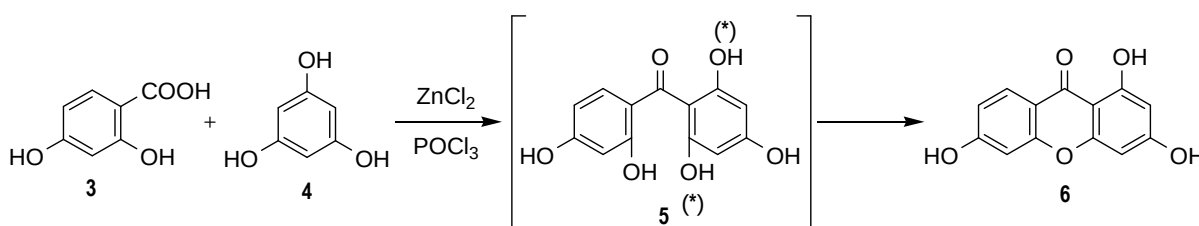


Figura 4. Síntese de xantonas via reacção de GSS (Sousa & Pinto, 2005).

Devido ao número de limitações deste processo sintético, outras metodologias têm sido utilizadas na síntese de xantonas simples oxigenadas (Dean, 1973; Sousa & Pinto, 2005). Estas incluem a via benzofenona a) $\rightarrow$ b) e a via éter diarílico c) $\rightarrow$ d) (**Figura 5**). A síntese de xantonas pela formação de uma benzofenona intermediária (**I**) inicia-se por uma acilação de Friedel-Crafts do cloreto de benzoílo substituído, com um derivado fenólico adequado (a), na presença de cloreto de alumínio e éter etílico anidro como solvente, seguida da etapa de ciclização intramolecular (b) (Ruske, 1964; Quillinan & Scheinmann, 1973; Dean, 1973) (**Figura 5**).

A síntese de xantonas pela formação de um éter diarílico intermediário (**II**) é uma aplicação da reacção de Ullmann (Moroz & Shvartsberg, 1974; Sousa & Pinto, 2005), consistindo a primeira etapa na condensação de um fenóxido de sódio apropriado com um ácido benzóico *orto* halogenado

(c). A segunda etapa consiste na formação do anel por uma cicloadição electrofílica de ácidos 2-ariloxibenzóicos (d) (Hassal & Lewis, 1961; Moroz & Shvartsberg, 1974) (**Figura 5**).

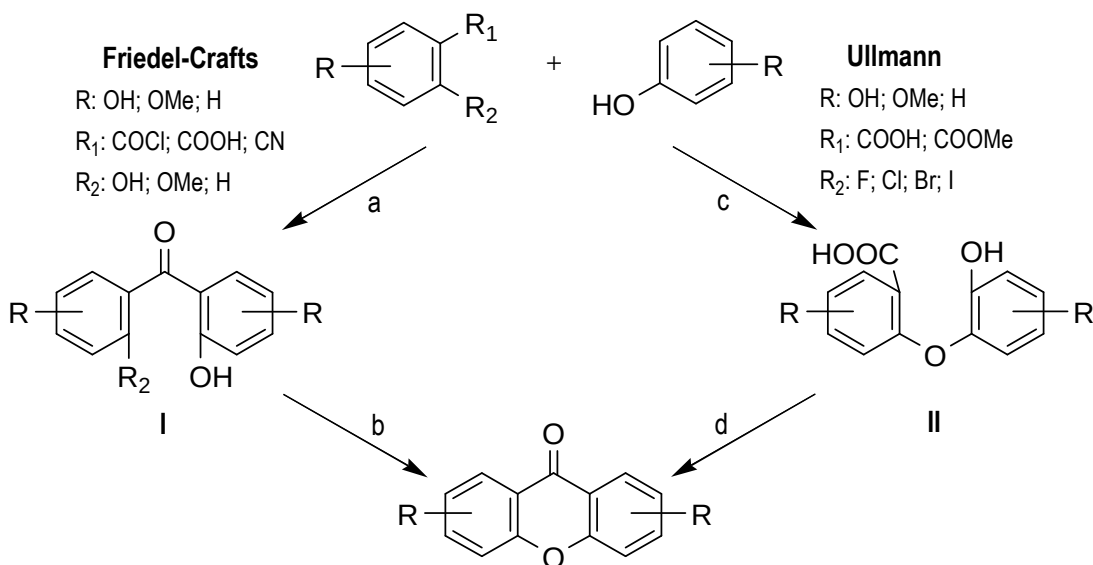


Figura 5. Síntese de xantonas via benzofenona e via éter diarílico (Sousa & Pinto, 2005).

Recentemente, foram introduzidas algumas modificações experimentais aos métodos clássicos anteriormente descritos, nomeadamente à reacção de GSS. Alguns estudos revelaram que é desnecessário fundir o cloreto de zinco antes da condensação, sendo que este procedimento poderá reduzir o rendimento devido à insolubilidade do cloreto de zinco fundido. Deste modo, o cloreto de zinco é aquecido directamente em oxicloreto de fósforo anteriormente à adição do ácido *o*-hidroxibenzóico e o aquecimento mantido antes da adição do polifenol (Schwaebe *et al.*, 2005). Este método passará a ser designado, nesta tese, como GSS modificado.

O método utilizado no presente trabalho para a obtenção de derivados xantónicos a utilizar como blocos construtores para modificação molecular foi a reacção de GSS, visto se adequar mais à síntese dos compostos pretendidos.

Num trabalho recente de revisão (Sousa & Pinto, 2005) podem ser encontradas diversas adaptações aos métodos clássicos, bem como novas abordagens na obtenção de derivados xantónicos.

3.1. Modificação Molecular Por Prenilação

As metodologias de síntese para obter xantonas preniladas, bem como os respectivos derivados cíclicos, são baseadas em diferentes estratégias de modificação molecular, tais como extensão molecular, através da prenilação de blocos construtores adequados, e rigidificação

molecular através de rearranjo de Claisen e / ou ciclização de precursores prenilados (Barreiro & Fraga, 2001; Avendaño, 2001; Patrick, 2005) e encontram-se descritas num trabalho de revisão no **Anexo III**.

No presente trabalho, estas modificações moleculares foram efectuadas pela aplicação de diversas metodologias clássicas (**Anexos IV e V**) e “não clássicas”, as quais envolveram síntese assistida por MW e síntese por catálise heterogénea (**Anexo VI**).

3.1.1. Metodologias Clássicas

A prenilação de xantonas hidroxiladas ocorre através de uma reacção de substituição nucleofílica, na presença de uma base (normalmente carbonato de potássio), entre o brometo de prenilo e a xantona. Normalmente este método origina preniloxixantonas mas, em alguns casos, podem ser obtidos derivados diprenilados com um grupo prenilo num carbono adjacente ao grupo hidroxilo (Tchamo *et al.*, 2000; Subba Rao & Raghavan, 2001; Castanheiro *et al.*, 2007a).

Como descrito anteriormente, existem outros grupos prenilo encontrados na Natureza como é o caso do 1,1-dimetilalilo. Os derivados prenilados com este grupo são obtidos por rearranjo de *o*-Claisen de preniloxixantonas apropriadas, com migração do grupo prenilo para a posição *orto* adjacente. O rearranjo de Claisen ocorre normalmente por refluxo da xantona prenilada numa amina, geralmente *N,N*-dietilanilina, *N,N*-dimetilanilina ou *N*-metil-2-pirrolidona (Patel & Trivedi, 1988; Tchamo *et al.*, 2000; Subba Rao & Raghavan, 2001; Castanheiro *et al.*, 2009a). Pode acontecer que, em vez de derivados 1,1-dimetilalilados, se obtenham di-hidrofuranoxantonas. A formação destes derivados cíclicos pode ser explicado pela ocorrência de rearranjo de Claisen do grupo 3,3-dimetilalilo para as posições *orto* disponíveis, obtendo-se a 1,1-dimetilalilxantona, seguida de uma ciclização espontânea envolvendo o grupo hidroxilo (Patel & Trivedi, 1988; Tchamo *et al.*, 2000; Subba Rao & Raghavan, 2001; Castanheiro *et al.*, 2009a).

A modificação molecular de xantonas ou de xantonas preniladas pode ser realizada através da formação de um anel extra, por exemplo di-hidropirano ou pirano. As di-hidropiranoxantonas são obtidas a partir de xantonas monopreniladas, por refluxo em *o*-xileno anidro, na presença de um ácido de Lewis, como o cloreto de zinco, ou, se esta for *C*-prenilada, por refluxo da xantona em meio ácido (Mahabusarakam *et al.*, 1998; Tchamo *et al.*, 2000; Subba Rao & Raghavan, 2001; Castanheiro *et al.*, 2007a). As piranoxantonas são vulgarmente obtidas a partir das di-hidropiranoxantonas por uma reacção de desidrogenação com 2,3-dicloro-5,6-diciano-1,4-benzoquinona (DDQ) em dioxano anidro (Ho *et al.*, 2001; Castanheiro *et al.*, 2009b).

3.1.2. Metodologias “Não Clássicas”

Os processos clássicos de síntese possuem alguns inconvenientes como baixos rendimentos, tempos reaccionais longos, baixa selectividade e, muitas vezes, condições reaccionais drásticas, com a utilização de reagentes agressivos para o ambiente. Por isso, urge a procura e aplicação de metodologias sintéticas que visem ultrapassar ou pelo menos minimizar estes inconvenientes.

O conceito de Química Verde surgiu por volta dos anos 90 e com ele uma definição: *A química verde utiliza eficientemente matérias-primas de preferência renováveis, elimina desperdícios e evita o uso de reagentes e solventes tóxicos e / ou perigosos, na produção e aplicação de produtos químicos* (Sheldon *et al.*, 2007).

No sentido de tornar os processos de síntese para a obtenção de derivados xantónicos mais próximos do conceito referido, foram aplicadas, no presente trabalho, duas metodologias sintéticas “não clássicas”, nomeadamente síntese orgânica assistida por microondas (MAOS) e síntese por catálise heterogénea, a seguir indicadas.

3.1.2.1. Síntese Orgânica Assistida por Microondas (MAOS)

O aquecimento assistido por MW sob condições controladas constitui uma tecnologia de grande valor em Química Orgânica em geral e em Química Medicinal e, particularmente, em processos de obtenção de novos fármacos, uma vez que poderá reduzir os tempos reaccionais, de dias ou horas para minutos ou mesmo segundos (Kappe & Stadler, 2005; Kappe, 2008). Como resultado, a indústria farmacêutica tem vindo a incorporar metodologias de MW em processos de obtenção e descoberta de pequenas moléculas farmacologicamente activas (Kappe & Dallinger, 2006). Muitos parâmetros reaccionais, tais como a temperatura e o tempo de reacção, solventes, aditivos e catalisadores, podem ser avaliados de modo a otimizar a química desejada. Deste modo, a MAOS é uma metodologia em desenvolvimento, a qual não só acelera muitas reacções orgânicas, de uma forma limpa, eficiente e conveniente, mas também poderá contribuir para aumentar o rendimento e a selectividade (Loupy, 2002; Kappe, 2004). Assim, não é de estranhar que cada vez mais grupos de investigação estejam a utilizar a MAOS como tecnologia de ponta para a rápida optimização das reacções, na síntese de novas entidades químicas e para descobrir e explorar novos caminhos sintéticos.

Os primeiros relatos de MAOS surgiram em 1986 em publicações de dois grupos de investigação de Gedye *et al.* e de Guigere *et al.* Estas reacções foram efectuadas em fornos microondas domésticos parcialmente modificados, tendo sido observada uma diminuição considerável nos tempos de reacção. Nessa altura, as experiências eram realizadas em vasos fechados de teflon ou de vidro, sem qualquer controlo de pressão e temperatura, o que acarretava

riscos no manuseamento. O resultado era a ocorrência de explosões violentas devido ao rápido e descontrolado aquecimento dos solventes orgânicos nos vasos fechados. Desde então, os equipamentos têm vindo a ser melhorados e actualizados, tendo surgido microondas mais modernos e específicos para reacções orgânicas, com a possibilidade de controlo de pressão e temperatura, com detector de fugas e também com a capacidade de libertarem impulsos constantes de energia (Lidström *et al.*, 2001; Sanseverino, 2002; Rosini *et al.*, 2004; Kappe, 2004; Kappe & Stadler, 2005; Kappe, 2008).

Actualmente, todos os reactores de microondas comercialmente disponíveis para síntese se encontram adaptados com um sistema de agitação magnética, controlo directo de temperatura da mistura reaccional através de sensores internos de fibra óptica e externos de infra-vermelho e software que permite o controlo da pressão e temperatura regulando a potência aplicada (Kappe & Stadler, 2005).

A radiação MW é uma radiação electromagnética situada na faixa de frequências de 0.3 a 300GHz, o que corresponde a comprimentos de onda de 1mm a 1m. No entanto, quer os MW domésticos, quer os industriais para síntese química operam a uma frequência de 2.45GHz (que corresponde a um comprimento de onda de 12.2cm), para evitar interferências com as frequências das telecomunicações e de telefones celulares (**Figura 6**) (Lidström *et al.*, 2001; Sanseverino, 2002; Rosini *et al.*, 2004; Kappe, 2004; Kappe & Stadler, 2005).

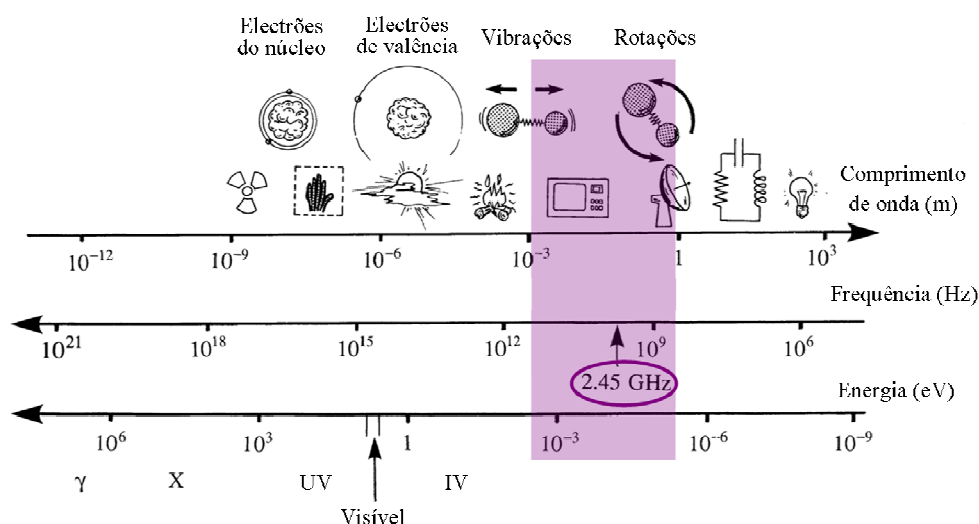


Figura 6. Espectro electromagnético (Loupy, 2002, adaptado).

O aquecimento por MW, também denominado aquecimento dieléctrico, é dependente da capacidade de um material específico (solvente ou reagente) para absorver energia MW e convertê-la em calor. A irradiação MW desencadeia aquecimento por dois mecanismos principais:

polarização dipolar e condução iónica. No entanto, a capacidade de um material ou solvente específico para converter energia MW em calor, a uma dada frequência e temperatura, é determinada pelo factor de dissipação ou delta tangente ($\tan\delta$), e em geral, um meio reaccional com uma $\tan\delta$ elevada, à frequência de 2.45GHz, é um requisito importante para uma boa absorção e consequentemente para um aquecimento eficiente (Kappe & Stadler, 2005; Kappe, 2008). Embora não seja o único factor determinante na conversão de energia MW absorvida em calor, a polaridade do solvente torna-se uma ferramenta importante para verificar se um solvente irá aquecer quando exposto à radiação MW. Geralmente, solventes polares absorvem bem a radiação MW (por exemplo água, etanol, acetonitrilo), enquanto que os menos polares (hidrocarbonetos alifáticos ou aromáticos) ou com momento dipolar nulo (como o tetracloreto de carbono) absorvem pouco ou são praticamente transparentes à radiação MW (Lidström *et al.*, 2001; Sanseverino, 2002; Rosini *et al.*, 2004; Kappe, 2004; Kappe & Stadler, 2005; Kappe, 2008).

Tradicionalmente, o aquecimento em síntese orgânica ocorre por condução de calor através de uma fonte externa de aquecimento, normalmente um banho de silicone ou uma manta / placa de aquecimento, no qual a energia é transferida lentamente do recipiente da reacção para a mistura reaccional. Este método é comparativamente lento e ineficiente de transferir energia para o sistema, uma vez que depende da condutividade térmica dos diversos materiais utilizados, resultando na temperatura mais elevada do vaso do que a da mistura reaccional. Consequentemente, esta forma de aquecimento pode gerar um gradiente de temperatura na mistura reaccional e um sobreaquecimento do vaso reaccional o que pode levar à decomposição dos reagentes e produtos (Figura 7) (Kappe, 2004; Kappe & Stadler, 2005; Kappe & Dallinger, 2006).

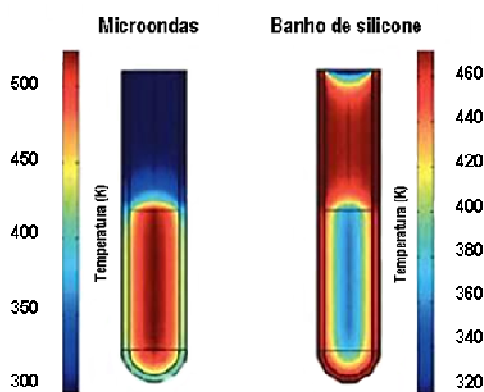


Figura 7. Gradientes de temperatura invertidos no aquecimento MW vs banho de silicone (Kappe, 2004; Kappe & Dallinger, 2006, adaptado).

Em contraste, a radiação MW produz um aquecimento interno eficiente por interacção directa da energia MW com as moléculas (solventes, reagentes, catalisadores) presentes na mistura

reaccional. Uma vez que os vasos reaccionais utilizados são geralmente de materiais transparentes às radiações MW, como por exemplo vidro borossilicato, quartzo ou teflon, ocorre um gradiente de temperatura invertido quando comparado com o aquecimento tradicional (**Figura 7**) (Kappe, 2004; Kappe & Stadler, 2005; Kappe & Dallinger, 2006).

Como indicado anteriormente, a energia MW é absorvida directamente pelas moléculas presentes no meio reaccional, proporcionando um aquecimento mais rápido e uniforme, o que poderá levar a uma diminuição de formação de produtos secundários e / ou produtos de decomposição. Como o aumento de temperatura é muito rápido, consegue-se obter um perfil de aquecimento que não é possível pelos métodos tradicionais, o que pode contribuir para a diminuição significativa dos tempos de reacção (**Figura 8**) (Kappe, 2004; Kappe & Stadler, 2005; Kappe & Dallinger, 2006).

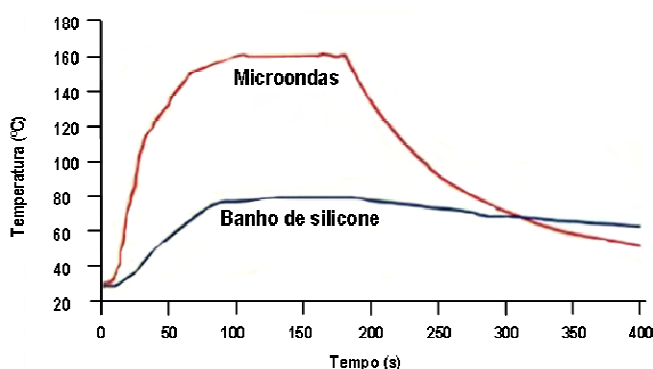


Figura 8. Comparação do perfil de aquecimento por MW vs banho de silicone (Kappe & Dallinger, 2006, adaptado).

Assim, a utilização de radiação MW pode apresentar claras vantagens quando comparada com os métodos tradicionais, como seja diminuição dos tempos reaccionais, obtenção de melhores rendimentos, maior selectividade, menos produtos secundários, possibilidade de realização de reacções sem solvente e reacções em pequena ou em grande escala (Kappe, 2004; Kappe & Stadler, 2005; Kappe & Dallinger, 2006; Kappe, 2008).

Foram utilizados dois equipamentos para a realização das experiências descritas no presente trabalho. Um encontra-se no Laboratório de Química Orgânica da Universidade de Aveiro e outro no CEQOFFUP/CEQUIMED-UP, ambos com características semelhantes apenas diferindo no modelo. Tratam-se de equipamentos *MicroSYNTH* com design multi-modo o qual permite que a radiação MW seja distribuída uniformemente por toda a cavidade por meio de um sistema de agitação, proporcionando deste modo um aquecimento eficiente e homogêneo o que promove a obtenção de resultados reprodutíveis (Kappe & Stadler, 2005; <http://www.uni-graz.at/~kappeco/index.htm>; <http://www.milestonesci.com/synth-micro.php>).

Os acessórios e a variedade de vasos reaccionais disponíveis e adaptáveis ao *MicroSYNTH* permitem que este equipamento possa ser utilizado em diferentes áreas da síntese orgânica, em pequena ou em grande escala, nomeadamente em química combinatória, medicinal, paralela ou à escala industrial. Estão disponíveis diferentes vasos reaccionais que se adaptam ao tipo de síntese pretendida, nomeadamente vasos abertos que permitem a realização de reacções à pressão normal e vasos fechados que podem ser utilizados em reacções de média (vasos de vidro e quartzo) ou alta pressão (vasos de teflon) (Kappe & Stadler, 2005; <http://www.milestonesci.com/synth-micro.php>; <http://www.uni-graz.at/~kappeco/index.htm>).

O controlo da temperatura no meio reaccional no interior do vaso é monitorizada através de um sensor de fibra óptica e a temperatura externa do vaso dentro da cavidade é medida através de um sensor de IV. No caso de reacções realizadas em vaso fechado, existe um sensor de pressão que permite o acompanhamento da pressão no interior do vaso (<http://www.milestonesci.com/synth-micro.php>; Kappe & Stadler, 2005).

Quando o tipo de reacção requer o uso de solventes não polares (transparentes às radiações MW), existem elementos de aquecimento passivos tais como barras magnéticas de *weflon™* (fluoropolímero grafitado quimicamente inerte), que absorvem directamente as MW e transferem o calor para a mistura reaccional (<http://www.milestonesci.com/synth-micro.php>).

Existem várias revisões na literatura que descrevem extensivamente a teoria associada à radiação MW, características dos equipamentos e diversas aplicações desta metodologia (Lidström *et al.*, 2001; Sanseverino, 2002; Loupy, 2002; Rosini *et al.*, 2004; Kappe, 2004; Kappe & Stadler, 2005; Kappe, 2008). Nesse sentido, têm surgido diversos trabalhos nos quais se demonstra a utilização de MW nos mais variados tipos de reacções orgânicas (Lidström *et al.*, 2001; Kappe, 2004; Silva *et al.*, 2004; Jacob & Moody, 2005; Pinto *et al.*, 2005a; Brito *et al.*, 2006; Zhang & Zhang, 2006; Evangelista *et al.*, 2006; Patonay *et al.*, 2006; Dallinger & Kappe, 2007; Benakki *et al.*, 2008; Kappe, 2008; Oliveira-Campos *et al.*, 2008; Marjani *et al.*, 2009; Li *et al.*, 2009; Mekheimer & Sadek, 2009; Wei *et al.*, 2009; Chan *et al.*, 2009; Huang *et al.*, 2009).

Esta metodologia foi utilizada pela primeira vez, no presente trabalho, quer para a síntese de blocos construtores xantónicos, quer para a obtenção de derivados prenitados, fundamentalmente com dois objectivos:

- Melhorar os processos de síntese dos compostos pretendidos,
- Adaptar os métodos clássicos à utilização de MW.

3.1.2.2. Catálise Heterogénea

Como já foi dito, um dos desafios de muitos laboratórios tem sido o desenvolvimento de métodos sintéticos menos prejudiciais para o ambiente, ou seja, o planeamento de transformações “limpas” ou “verdes”.

O uso de catalisadores sólidos em síntese orgânica proporciona um método com vantagens acrescidas quando comparado com a síntese convencional, tais como a facilidade de manuseamento experimental, maior segurança, procedimentos de separação e purificação facilitados e ainda a regenerabilidade e reciclabilidade do catalisador (Nagendrappa, 2002; Sheldon *et al.*, 2007).

Recentemente tem sido dada muita atenção ao uso de argilas ou *clays* (como vão ser designadas ao longo desta tese) como catalisadores inorgânicos em diversas reacções orgânicas. As *clays* são minerais de ocorrência natural no solo, constituídas por partículas cristalinas hidratadas de aluminosilicatos, com diâmetro inferior a 2 mm, podendo funcionar como catalisadores sólidos ácidos para uma variedade de reacções orgânicas (Nagendrappa, 2002). As *clays* podem ser divididas em quatro grupos principais, de acordo com a sua composição química e estrutura cristalina, tais como os grupos da *illite*, *smectite*, *vermiculite* e *kaolinite*. Entre estes, aquele que é considerado como sendo o catalisador mais útil em síntese orgânica é um subgrupo das “*smectite clays*”, chamado *montmorillonite* (**Figura 9**) (<http://en.wikipedia.org/wiki/Montmorillonite>; Nagendrappa, 2002).



Figura 9. Aspecto cristalino e comercial da *montmorillonite K10 clay* (<http://www.saint-hilaire.ca/>; <http://www.fromnaturewithlove.com/>).

A estrutura da *montmorillonite* é do tipo *TOT* (**Figura 10**) o que corresponde a uma folha de unidades de hidróxido de alumínio ou *gibbsite* $[\text{Al}(\text{OH})_3]$ (**Figura 10**) coordenadas octaedricamente, encaixada entre duas folhas de unidades de silicatos $[\text{SiO}_4]^{4-}$ coordenadas tetraedricamente (**Figura 10**). Esta camada de três folhas repete-se entre si e no espaço inter-camadas encontram-se catiões e moléculas de água que permitem a troca iónica, neutralizam as cargas e conferem as propriedades químicas e físicas desta *clay* (**Figura 10**) (Nagendrappa, 2002;

http://foundationstabilization.com/html/the_theory.html; <http://en.wikipedia.org/wiki/Montmorillonite>;
<http://pubs.usgs.gov/of/2001/of01-041/html/docs/clays/smc.htm>).

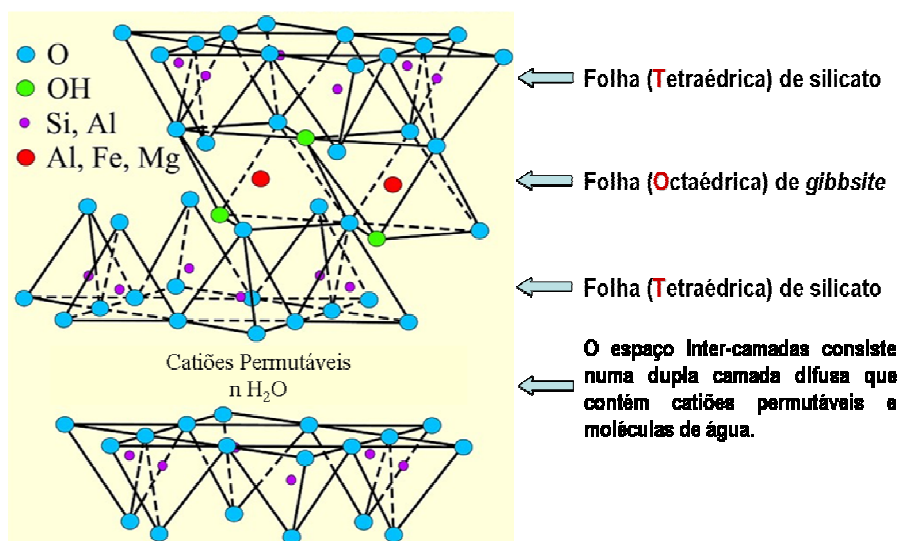


Figura 10. Representação esquemática da estrutura da *montmorillonite* (<http://pubs.usgs.gov/of/2001/of01-041/html/docs/clays/smc.htm>, adaptado).

Uma variedade de reacções orgânicas tradicionalmente catalisadas por ácidos de Brönsted (H_2SO_4 , HCl , HNO_3 , AcOH ...) ou ácidos de Lewis (AlCl_3 , ZnCl_2 , FeCl_3 ...) têm revelado ocorrer na presença de *clays*, especialmente *montmorillonite*, de um modo mais eficiente. Estas reacções ocorrem não só em condições mais suaves, mas também com elevada selectividade, melhor rendimento e em menores tempos reaccionais. O catalisador é facilmente separado da mistura reaccional, podendo ser regenerado, o que facilita os processos de purificação (Nagendrappa, 2002).

As *clays* são, deste modo, perfeitamente ajustáveis ao avanço e modernização da síntese química: são baratos, não tóxicos, quimicamente diversos e recicláveis (Nagendrappa, 2002).

Podem ser encontrados diversos trabalhos na literatura que descrevem a utilização de *clays* como catalisadores nos mais variados tipos de reacções orgânicas, como por exemplo, adições, eliminações, substituições, rearranjos, reacções de diels-alder, oxidações-reduções entre outras (Vaccari, 1998, 1999; Varma, 2002; Dintzner *et al.*, 2007; Kantevari *et al.*, 2007; Coelho *et al.*, 2007; Huang *et al.*, 2008; An *et al.*, 2008; Dhakshinamoorthy & Pitchumani, 2009; Vijayakumar *et al.*, 2009; Liu *et al.*, 2009; Garade *et al.*, 2009; Daqing *et al.*, 2009). Existem ainda algumas experiências bem sucedidas de reacções de prenilação de derivados fenólicos utilizando *montmorillonite* como catalisador (Dintzner *et al.*, 2004a, b, 2005, 2006).

No sentido de otimizar as metodologias clássicas de síntese na obtenção de derivados xantônicos prenilados, foi utilizado o método de catálise heterogénea. Neste trabalho será descrita a aplicação do método de catálise heterogénea com *montmorillonite K10 clay* como catalisador, para a obtenção de derivados xantônicos prenilados, nomeadamente na síntese de dihidropiranoxantonas, num só passo, a partir de hidroxixantonas (Castanheiro *et al.*, 2009a). Esta metodologia de síntese foi aplicada pela primeira vez no CEQOFFUP/CEQUIMED-UP para a obtenção de derivados xantônicos, mais especificamente, derivados prenilados.

3.1.2.3. Catálise Heterogénea Assistida por MW

Uma técnica frequentemente empregue em MAOS ou em catálise heterogénea com o auxílio de MW, envolve reacções sem solvente (a “seco”), na qual os reagentes podem ser pré-adsorvidos na superfície de suportes inorgânicos fortemente absorventes (grafite) ou fracamente absorventes (sílica, alumina ou *clay*) de radiação MW.

Em geral, esta metodologia combinada utiliza suportes inorgânicos de origem mineral como catalisadores sólidos, tais como sílica, aluminas ou *clays*, na superfície dos quais os reagentes/substratos são pré-adsorvidos, sendo posteriormente expostos à radiação MW.

O acoplamento das técnicas de MW com o uso de suportes inorgânicos sólidos como catalisadores origina um processo químico com diversas vantagens. Estas compreendem tempos reacionais melhorados, aumento dos rendimentos, facilidade de manipulação experimental, maior selectividade, possibilidade de trabalhar em vasos abertos e de realizar reacções em grande escala. Muitos têm sido os trabalhos que surgiram na literatura nos últimos anos, nos quais se descrevem vários tipos de reacções realizadas com catálise em fase sólida e com o auxílio de radiação MW (Varma, *et al.*, 1998; Varma, 1999, 2001, 2002; Olsson *et al.*, 2000; Usyatinsky & Khmel'nitsky, 2000; Kidwai, 2001; Loghmani-Khouzani *et al.*, 2001; Mortoni *et al.*, 2004; Kotha *et al.*, 2004; Dintzner *et al.*, 2005, 2006; Singh *et al.*, 2006; Zare *et al.*, 2009; Lenardão, *et al.*, 2009; Kulkarni *et al.*, 2009; Cooke *et al.*, 2009).

Nesse sentido, foi também aplicada pela primeira vez no CEQOFFUP/CEQUIMED-UP, a metodologia combinada de catálise heterogénea (utilizando *montmorillonite K10 clay* como catalisador sólido) com a síntese assistida por MW, quer com quer sem solvente, à síntese de dihidropiranoxantonas (Castanheiro *et al.*, 2009a).

4. PROCEDIMENTO GERAL DE SÍNTESE

4.1. Obtenção de Xantonas a utilizar como Blocos Construtores para Modificação Molecular

O **Anexo IV** reporta a síntese dos blocos construtores xantônicos, 1,3-di-hidroxi-2-metilxantona (**X1**) e 1,3-di-hidroxixantona (**X38**), a utilizar posteriormente para modificação molecular por prenilação. A síntese destes compostos já havia sido descrita (Grover *et al.*, 1955; Pinto & Polónia, 1974), mas no presente trabalho o método de obtenção e de purificação foi melhorado, através da realização de uma cromatografia em coluna “flash”.

Assim, pela reacção de GSS foram obtidas as xantonas hidroxiladas: 1,3-di-hidroxi-2-metilxantona (**X1**), 1,3-di-hidroxi-4-metilxantona (**X2MP**) e 1,3-di-hidroxixantona (**X38**). Na **Figura 11** exemplifica-se para as 1,3-di-hidroxi-2-metilxantona (**X1**) e 1,3-di-hidroxi-4-metilxantona (**X2MP**), a estratégia geral seguida para a síntese de xantonas com este padrão de hidroxilação.

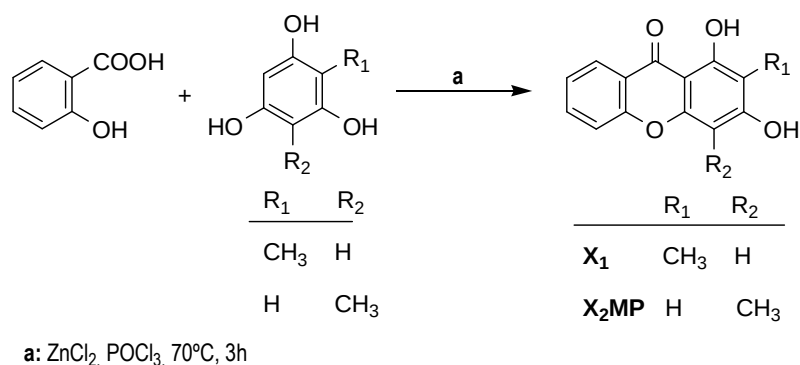


Figura 11. Síntese das 1,3-di-hidroxi-2-metilxantona e 1,3-di-hidroxi-4-metilxantona pela reacção de GSS.

Esta metodologia de síntese foi posteriormente otimizada em termos de rendimentos e tempos reaccionais, através da realização da síntese assistida por MW (**Figura 12**).

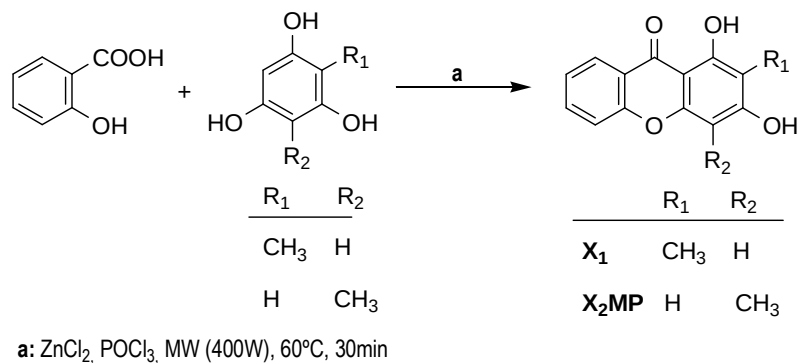


Figura 12. Síntese das 1,3-di-hidroxi-2-metilxantona e 1,3-di-hidroxi-4-metilxantona pela reacção de GSS em MW.

Com base em dados presentes na literatura (Schwaebe *et al.*, 2005; Sousa & Pinto, 2005), foram introduzidas algumas modificações experimentais à reacção de GSS (GSS modificada)

nomeadamente a adição faseada dos reagentes (**Figura 13**) e também a realização desta reacção de GSS modificada assistida por MW (**Figura 14**).

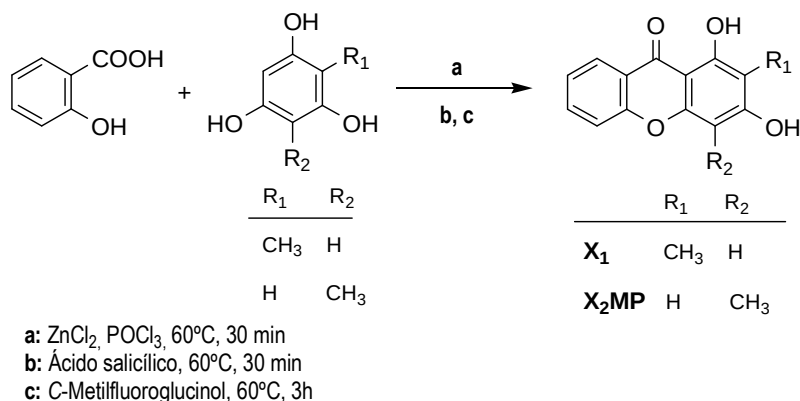


Figura 13. Síntese das 1,3-di-hidroxi-2-metilxantona e 1,3-di-hidroxi-4-metilxantona pela reacção de GSS modificada.

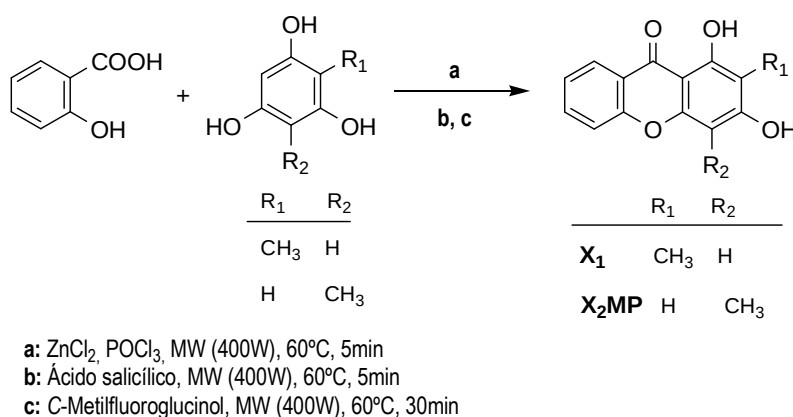


Figura 14. Síntese das 1,3-di-hidroxi-2-metilxantona e 1,3-di-hidroxi-4-metilxantona pela reacção de GSS modificada em MW.

Foram ainda obtidas as 1-hidroxixantona (**X2**) e 3-hidroxixantona (**X20**) (Fernandes, 1996; Sousa, 2003; Azevedo, 2007) também a utilizar posteriormente como blocos construtores para prenilação.

Pela reacção de Nencki (Pankajamani & Seshadri, 1954), da qual derivou o método de GSS (Grover *et al.*, 1955), obteve-se a 1-hidroxixantona (**X2**). No entanto, o processo de síntese foi otimizado em termos de tempo reaccional pela introdução de radiação MW (Castanheiro *et al.*, 2007b; Azevedo, 2007). O caminho sintético e as condições reaccionais são apresentados na **Figura 15**.

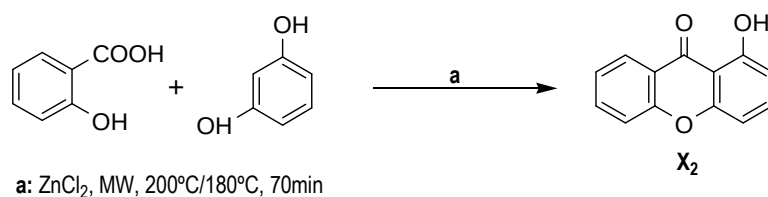


Figura 15. Síntese da 1-hidroxixantona pela reacção de Nencki em MW.

A formação de benzofenonas como intermediários ciclizáveis foi o método utilizado para a obtenção do bloco construtor 3-hidroxixantona (**X20**) (**Figura 16**) (Fernandes, 1996; Azevedo, 2007).

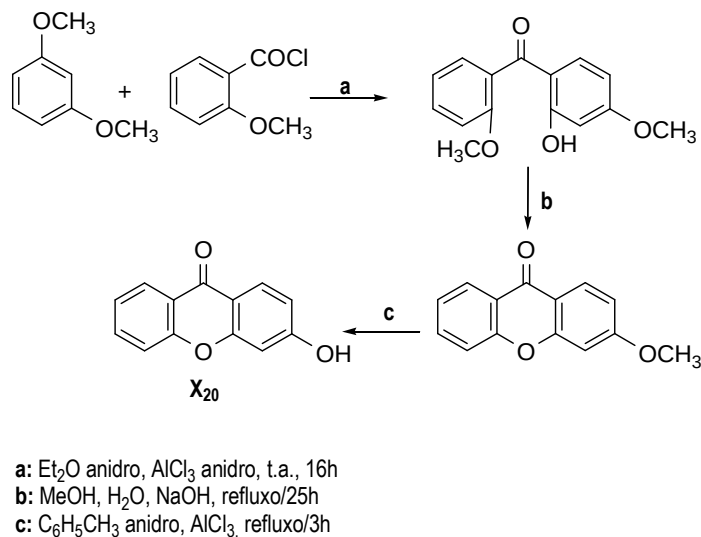


Figura 16. Síntese da 3-hidroxixantona pela via intermediário benzofenona.

4.2. Obtenção de Derivados Prenilados por Modificação Molecular de Xantonas

4.2.1. Modificação Molecular por Prenilação

No **Anexo IV** encontra-se descrita a síntese das xantonas preniladas **XP1**, **XP2**, **XP3**, **XP4**, **XP5** e **XP7**, pela aplicação do método clássico. A reacção de prenilação foi efectuada através de uma substituição nucleofílica, na presença de base, entre a xantona hidroxilada e brometo de prenilo tal como exemplificado na **Figura 17**, para a síntese das **XP1** e **XP2**. A **XP6** foi também obtida pelo mesmo método, mas por prenilação da 3-hidroxixantona (**X20**) (Castanheiro *et al.*, 2006).

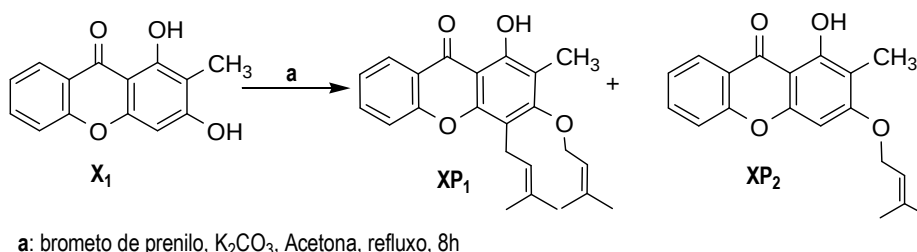
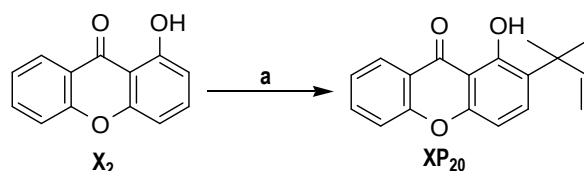


Figura 17. Reacção de prenilação da **X1**.

Posteriormente, o processo de síntese para obtenção destas xantonas foi otimizado, utilizando radiação MW, tendo-se observado um melhoramento substancial, nomeadamente nos rendimentos e nos tempos reaccionais, como descrito no **Anexo VI**. Neste artigo também é descrita a obtenção

das xantonas preniladas **XP21** e **XP22**, mas por rearranjo de Claisen, com auxílio de MW, da xantona monoprenilada **XP3**, derivadas da 1,3-di-hidroxixantona (**X38**).

A prenilação da 1-hidroxixantona (**X2**) foi efectuada através de uma reacção de substituição nucleofílica, na presença de base, entre a xantona e brometo de prenilo, em condições ligeiramente diferentes das anteriores (**Figura 18**). No entanto, ao contrário do sucedido nas reacções de prenilação efectuadas (**Figura 17**), foi obtida a 1-hidroxi-2-(1,1-dimetilalil)xantona (**XP20**) em vez da 1-preniloxixantona. Como as condições reaccionais clássicas utilizadas para a prenilação envolveram um aquecimento a temperaturas mais elevadas, provavelmente ocorreu a prenilação no grupo OH na posição 1, seguida de rearranjo de Claisen, o que levou à alquilação em C-2 e não à obtenção do derivado O-prenilado em C-1.

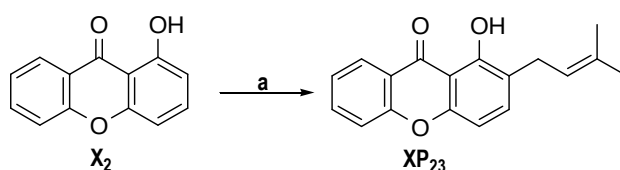


a: Brometo de prenilo, K_2CO_3 anidro, DMF anidra, 85°C; 150°C, 24h

Figura 18. Reacção de prenilação da **X2**.

Por reacção da 1-hidroxixantona com isopreno, em xileno, na presença de ácido fosfórico obteve-se a **XP23** (**Figura 19**).

A obtenção das xantonas **XP20** e **XP23** encontra-se descrita no **Anexo V**.



a: Isopreno, H_3PO_4 85%, xileno, 30h

Figura 19. Reacção de prenilação da **X2**, com isopreno.

4.2.2. Obtenção de Xantonas com Anéis Extra

4.2.2.1. De di-hidropirano

A obtenção das di-hidropiranoxantonas **XP8**, **XP11** e **XP12**, pelo método clássico encontram-se descritas no **Anexo IV**. Estes derivados, bem como as **XP16** e **XP17** (Castanheiro *et al.*, 2006),

foram obtidas a partir das xantonas monopreniladas, por refluxo em *o*-xileno anidro, na presença de cloreto de zinco anidro, tal como se exemplifica na **Figura 20**, para a obtenção da **XP8**.

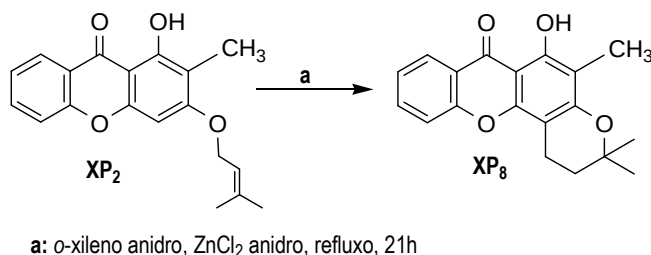


Figura 20. Obtenção da di-hidropiranoxantonona **XP8** pelo método clássico.

No sentido de melhorar o processo de obtenção de di-hidropiranoxantonas, pela aplicação de um método eficaz, selectivo, rápido e mais limpo, foi utilizada a metodologia de catálise heterogénea. No **Anexo VI**, é descrita a síntese das di-hidropiranoxantonas **XP8**, **XP11**, **XP12**, **XP16**, **XP17** e **XP24**, através da condensação das hidroxixantonas, 3-hidroxixantonona (**X20**), 1,3-di-hidroxi-2-metilxantonona (**X1**) e 1,3-di-hidroxixantonona (**X38**) com brometo de prenilo, utilizando *montmorillonite K10 clay* como catalisador. As reacções foram realizadas quer à temperatura ambiente, quer com aquecimento convencional. Ainda no sentido de otimizar as metodologias de obtenção de di-hidropiranoxantonas, foi utilizado o método combinado de catálise heterogénea com MW, como se exemplifica para a **XP8** (**Figura 21**).

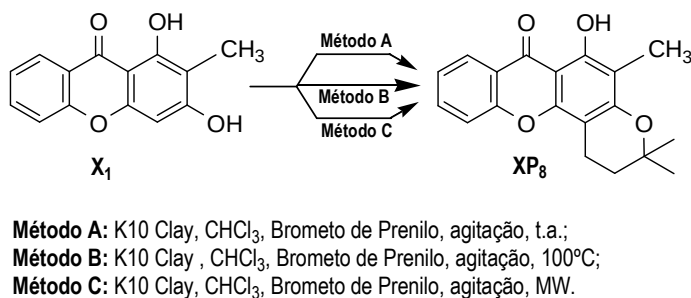


Figura 21. Obtenção da di-hidropiranoxantonona **XP8** por métodos “não clássicos”.

4.2.2.2. De pirano

No **Anexo V**, encontra-se descrita a síntese das piranoxantonas **XP19**, **XP25** e **XP26**. Na Natureza, encontram-se mais frequentemente derivados xantónicos com um anel pirano como substituinte derivado de prenilo, do que um anel di-hidropirano, exibindo as piranoxantonas uma maior diversidade de actividades biológicas (Pinto & Castanheiro, 2009a). Deste modo, numa tentativa de obter compostos biologicamente mais interessantes, procedeu-se à síntese das piranoxantonas **XP19**, **XP25** e **XP26** derivadas das di-hidropiranoxantonas **XP8**, **XP11** e **XP12**,

respectivamente, por desidrogenação com DDQ (2,3-dicloro-5,6-diciano-*p*-benzoquinona) em dioxano anidro, como se exemplifica para a **XP19** (Figura 22).

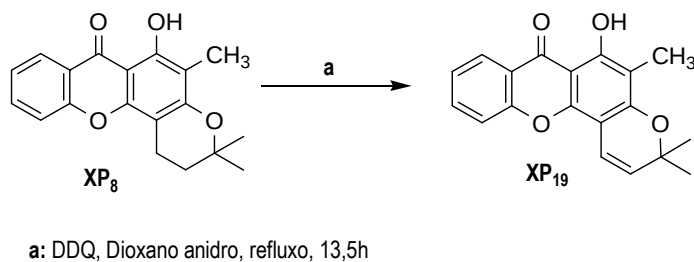


Figura 22. Obtenção da piranoxantona **XP19** por desidrogenação da di-hidropiranoxantona **XP8**.

4.2.2.3. De di-hidrofurano

No **Anexo VI**, encontra-se descrita a síntese das di-hidrofuranoxantonas **XP9**, **XP10** e **XP18**, por rearranjo de Claisen das xantonas monopreniladas **XP3** e **XP2**, respectivamente, via MW, utilizando vários solventes, tais como *N*-metil-2-pirrolidona e *N,N*-dietilanilina, tal como exemplificado na **Figura 23**, para a síntese da **XP18**.

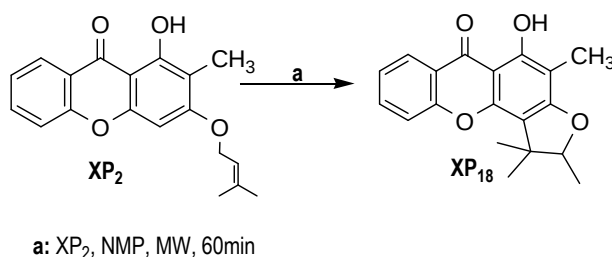


Figura 23. Obtenção da di-hidrofuranoxantona **XP18** por rearranjo de Claisen da xantona monoprenilada **XP2**.

A formação das di-hidrofuranoxantonas resulta da ocorrência de rearranjo de Claisen do grupo 3,3-dimetilalilo para as posições *orto* disponíveis, seguida de uma ciclização espontânea envolvendo o grupo hidroxilo.

4.3. Elucidação Estrutural

A determinação estrutural das xantonas preniladas, através da aplicação conjunta de diversas técnicas de espectroscopia, possibilitou de forma inequívoca a elucidação estrutural dos compostos sintetizados.

As estruturas das xantonas preniladas sintetizadas foram estabelecidas através de técnicas de IV, UV, técnicas de RMN, nomeadamente de ¹H e ¹³C e de correlação espectroscópica heteronuclear (HSQC e HMBC), EM de impacto electrónico e de alta resolução e adicionalmente por cristalografia de raios X para os compostos **XP2**, **XP3**, **XP4** e **XP11**.

Os derivados xantônicos utilizados como blocos construtores, **X1**, **X2**, **X20** e **X38**, foram identificados por comparação com amostras autênticas por cromatografia em camada fina (Pinto & Polónia, 1974; Fernandes, 1996; Sousa, 2003) e por análise e comparação de dados espectrais (Grover *et al.*, 1955; Fernandes *et al.*, 1998; Fernandes, 1996; Gnerre *et al.*, 2001; Sousa, 2003).

Os dados relativos à elucidação estrutural das xantonas preniladas sintetizadas encontram-se descritos nos **Anexos IV, V, VI e VII**.

Uma perspectiva da estrutura cristalina da xantona **XP3** (**Anexo VII**), obtida utilizando ORTEP (Farrugia, 1997) e mostrando a numeração dos átomos, está presente na **Figura 24**.

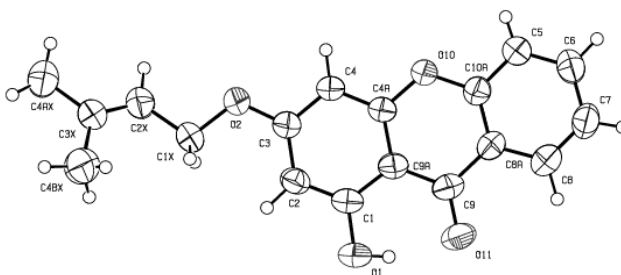


Figura 24. Perspectiva da estrutura cristalina da xantona **XP3**.

CAPÍTULO II

OBTENÇÃO DE DERIVADOS XANTÓNICOS

PRENILADOS

1. PARTE EXPERIMENTAL

Nos artigos em anexo, encontram-se descritos os métodos, reagentes e procedimentos, utilizados na obtenção das xantonas prenilhadas, através da aplicação de metodologias clássicas (**Anexo IV e V**) e “não clássicas” de síntese (**Anexo VI**).

1.1. Métodos Gerais

- As reacções foram monitorizadas por cromatografia em camada fina usando placas (suporte de alumínio) de gel de sílica 60 (com indicador de fluorescência UV₂₅₄) da *Merck* ou *Macherey-Nagel*;
- As reacções em MW foram efectuadas utilizando vasos de vidro abertos (reacções à pressão atmosférica) ou vasos de vidro ou quartzo fechados (reacções de média pressão) em um MW – *Ethos MicroSYNTH 1600 Microwave Labstation* – da Milestone. A temperatura interna da reacção foi medida através de um sensor de fibra óptica;
- A purificação dos compostos foi realizada por cromatografia em coluna “flash” utilizando gel de sílica 60 (0.040-0.063mm) da *Merck* ou *Macherey-Nagel* e por cromatografia preparativa em camada fina usando placas (suporte de vidro) de gel de sílica 60 com espessura de 300 µm (com indicador de fluorescência UV₂₅₄) da *Merck* ou *Macherey-Nagel*;
- Os pontos de fusão, não corrigidos, foram obtidos num microscópio *Kofler*;
- Os espectros de IV foram obtidos num espectrofotómetro FTIR – *ATI Mattson Genesis series* – em discos de KBr;
- Os espectros de UV, em etanol, foram obtidos num espectrofotómetro *Varian CARY 100*;
- Os espectros de ¹H e ¹³C RMN (incluindo HSQC e HMBC) das XP foram adquiridos em CDCl₃ à temperatura ambiente num espectrómetro *Bruker Avance 300 ou 500*;
- Os espectros de massa foram obtidos por impacto electrónico num espectrómetro *VG Autospec Q*;
- Os espectros de massa de alta resolução foram obtidos por impacto electrónico em espectrómetros *VG Autospec M* e *Kratos Concept III*;
- Os reagentes utilizados foram de qualidade p.a. ou “para-análise” e adquiridos à empresa *Sigma-Aldrich*.
- Para utilização da *K10 clay* seca, esta é previamente colocada na estufa a 110°C durante aproximadamente 2h, após o qual é transferida para um excicador, para arrefecimento, antes de ser utilizada.

De seguida encontram-se sumariados os procedimentos gerais para a síntese das xantonas preniladas descritas nesta tese.

1.2. Metodologias Clássicas

1.2.1. Prenilação das Xantonas **X1**, **X20** e **X38**

Uma mistura de xantona **X1**, **X20** ou **X38** (1mmol), brometo de prenilo (2mmol) e K_2CO_3 anidro (2mmol) em Me_2CO (90ml) foi mantida com refluxo durante 8h. Após arrefecimento e filtração para remoção do sólido, este foi lavado e o solvente evaporado a pressão reduzida, tendo-se obtido um produto bruto. Este foi purificado por cromatografia em coluna “flash” e por cromatografia preparativa.

1.2.2. Prenilação da Xantona **X2** – Obtenção da **XP20**

Uma mistura de xantona **X2** (1mmol), brometo de prenilo (2mmol,) e K_2CO_3 anidro (3mmol) em DMF anidra (7ml) foi mantida com refluxo durante 24h. Após arrefecimento e filtração para remoção do sólido, este foi lavado e o solvente evaporado a pressão reduzida, tendo-se obtido um produto bruto viscoso. Este foi purificado por cromatografia em coluna “flash” e por cromatografia preparativa, tendo-se obtido a **XP20**.

1.2.3. Prenilação da Xantona **X2** – Obtenção da **XP23**

Uma mistura de xantona **X2** (1mmol), H_3PO_4 85% (1ml) em *o*-xileno (4ml) foi mantida a 30°C com agitação constante. A esta mistura foi adicionada uma solução de isopreno (2mmol) em *o*-xileno (1ml), e mantida a agitação, à mesma temperatura, durante cerca de 2h, tendo-se posteriormente prolongado a agitação por mais 28h, à temperatura ambiente. Após o final da reacção, foi adicionado 1ml de solução de hidrogenocarbonato de sódio 5% e a solução mantida em agitação durante aproximadamente 5 min; procedeu-se seguidamente a uma extracção com Et_2O (3×20ml). As fases etéreas reunidas foram lavadas com água, secas com Na_2SO_4 anidro e o solvente evaporado a pressão reduzida. O produto bruto obtido foi purificado por cromatografia em coluna “flash” e por cromatografia preparativa, tendo-se obtido a **XP23**.

1.2.4. Obtenção de Xantonas com Anéis Extra

1.2.4.1. Di-hidropiranoxantonas

A uma solução de xantona **XP2**, **XP3** ou **XP6** mono-oxiprenilada (1mmol) em *o*-xileno anidro (1ml), foi adicionado $ZnCl_2$ anidro (0.06mmol) e a mistura mantida com refluxo durante 21 horas.

Após arrefecimento, a mistura reaccional foi purificada por cromatografia em coluna “flash” e por cromatografia preparativa.

1.2.4.2. Piranoxantonas

A uma solução de di-hidropiranoxantona **XP8**, **XP11** ou **XP12** (1mmol) em dioxano anidro (10ml), foi adicionada DDQ (2mmol) e a mistura mantida com refluxo durante 9-18h. Após arrefecimento, o sólido foi removido por filtração, lavado e o solvente evaporado a pressão reduzida. O produto bruto obtido foi purificado por cromatografia em coluna “flash” e por cromatografia preparativa.

1.3. Metodologias “Não Clássicas”

1.3.1. Síntese Orgânica Assistida por Microondas (MAOS)

1.3.1.1. Prenilação das Xantonas **X1** e **X38**

Uma mistura de xantona **X1** ou **X38** (1mmol), brometo de prenilo (2mmol) e K_2CO_3 anidro (2mmol) em Me_2CO (90ml) foi transferida para um sistema reaccional de MW em vaso aberto. A mistura foi irradiada 3×20min de acordo com o seguinte programa de MW: Potência aplicada: 200W; temperatura programada: 62°C; tempo em rampa: 5min; tempo em patamar: 15min; temperatura final atingida: 59°C.

Após arrefecimento e filtração, o sólido foi lavado e o solvente evaporado a pressão reduzida, tendo-se obtido um produto bruto. Este foi purificado por cromatografia em coluna “flash” e por cromatografia preparativa.

1.3.1.2. Obtenção de Xantonas com Anéis Extra

1.3.1.2.1. Di-hidrofuranoxantonas

Uma solução de xantona **XP3** mono-oxiprenilada (0.34mmol) em *N,N*-DEA (4ml), foi irradiada 3×15min a uma potência de 750W, para uma temperatura de 225°C. A mistura reaccional foi vertida sobre gelo, acidificada com HCl 5N (até pH=1) e extraída sucessivamente com éter de petróleo (3×20ml), Et_2O (3×20ml) e CH_2Cl_2 (3×20ml). Cada uma destas fracções foi lavada com H_2O , seca com Na_2SO_4 anidro e o solvente evaporado a pressão reduzida. O produto bruto obtido foi purificado por cromatografia em coluna “flash” e por cromatografia preparativa.

Uma solução de xantona **XP2** ou **XP3** mono-oxiprenilada (0.35mmol) em NMP (15ml) foi irradiada 2×30min de acordo com o seguinte programa de MW: **Passo 1**: Potência aplicada: 800W;

temperatura programada: 202°C; tempo em rampa: 5min; **Passo 2:** Potência aplicada: 300W; temperatura programada: 202°C; tempo em patamar: 25min; temperatura final atingida: 202°C.

Após reacção a mistura foi vertida sobre gelo, acidificada com HCl 5N (até pH=1) e extraída sucessivamente com éter de petróleo (3×50ml), Et₂O (3×50ml) e CH₂Cl₂ (2×50ml). Cada uma destas fracções foi lavada com H₂O, seca com Na₂SO₄ anidro e o solvente evaporado a pressão reduzida. Os produtos brutos obtidos foram purificados por cromatografia preparativa.

1.3.2. Catálise Heterogénea

1.3.2.1. Obtenção de Di-hidropiranoxantonas

A uma suspensão de *K10 clay* (20 equiv por massa) em CHCl₃, foi adicionada xantona **X1**, **X20** ou **X38** (0.50mmol), seguida da adição de brometo de prenilo (1mmol). A mistura foi mantida sob agitação à temperatura ambiente durante 5 dias. A mistura reaccional foi filtrada a pressão reduzida para remoção da *K10 clay*, e esta lavada com CH₂Cl₂, Me₂CO e por fim com MeOH até já não se observar coloração no filtrado. O produto bruto obtido, após evaporação do solvente a pressão reduzida, foi purificado por cromatografia em coluna “flash” e por cromatografia preparativa.

A uma suspensão de *K10 clay* (20 equiv por massa) em CHCl₃, foi adicionada xantona **X1** ou **X38** (0.50mmol), seguida da adição de brometo de prenilo (1mmol). A mistura foi mantida em agitação a 100°C em tubo fechado durante 60min. A mistura reaccional foi filtrada a pressão reduzida para remoção da *K10 clay*, e esta lavada com CH₂Cl₂, Me₂CO e por fim com MeOH até já não se observar coloração no filtrado. O produto bruto obtido, após evaporação do solvente a pressão reduzida, foi purificado por cromatografia em coluna “flash” e por cromatografia preparativa.

1.3.3. Catálise Heterogénea Assistida por MW

1.3.3.1. Obtenção de Di-hidropiranoxantonas

Em um vaso reaccional de MW fechado e de média pressão, efectuou-se uma suspensão de *K10 clay* (20 equiv por massa) em CHCl₃, à qual foi adicionada xantona **X1**, **X20** ou **X38** (0.50mmol), seguida da adição de brometo de prenilo (1mmol). A mistura reaccional, sob agitação, foi irradiada a uma potência de 150W durante 20min, tendo-se atingido temperaturas na ordem dos 105-115°C.

A mistura reaccional foi filtrada a pressão reduzida para remoção da *K10 clay*, e esta lavada com CH₂Cl₂, Me₂CO e por fim com MeOH até já não se observar coloração no filtrado. O produto bruto obtido, após evaporação do solvente a pressão reduzida, foi purificado por cromatografia em coluna “flash” e por cromatografia preparativa.

Na reacção realizada na ausência de solvente, a xantona **X1**, **X20** ou **X38** foi previamente misturada e incorporada com a *K₁₀ clay* num almofariz, transferida para um vaso de MW, fechado e de média pressão, adicionado o brometo de prenilo, e seguido o procedimento idêntico ao realizado na presença de solvente.

2. DISCUSSÃO DOS RESULTADOS

São referidos e discutidos de seguida os resultados obtidos para a síntese das xantonas prenilhadas. A maior parte dos resultados encontra-se apresentada na forma de artigo científico nos **Anexos IV, V e VI**.

O efeito de vários derivados xantónicos hidroxi- e metoxilados no crescimento *in vitro* de linhas celulares tumorais humanas tem sido investigado ao longo destes últimos anos no CEQOFFUP/CEQUIMED-UP. Entre vinte e sete xantonas testadas, algumas di-hidroxixantonas exibiram uma actividade interessante nas linhas MCF-7, TK-10 e UACC-62, das quais se destacou a 1,3-di-hidroxi-2-metilxantona (**X1**) que apresentou valores de GI_{50} na ordem dos $20\mu M$ (Pedro *et al.*, 2002), tendo sido seleccionada, como material de partida, para a realização de modificações moleculares, no sentido de potenciar a sua actividade antitumoral. Tendo em conta a semelhança estrutural de porções moleculares, foram seleccionados mais três blocos construtores xantónicos para serem submetidos a prenilação: 1,3-di-hidroxixantona (**X38**), 1-hidroxixantona (**X2**) e 3-hidroxixantona (**X20**) (**Figura 25**).

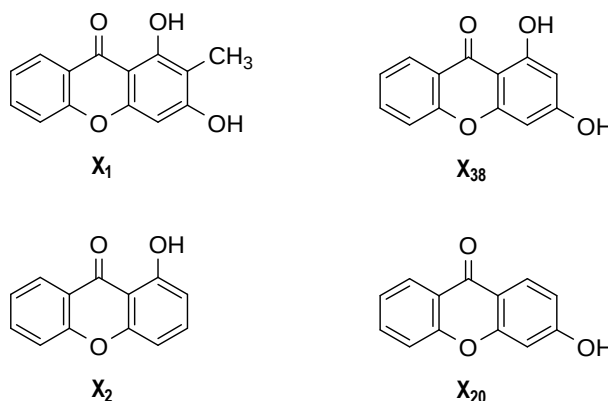


Figura 25. Blocos construtores xantónicos para modificação molecular.

O critério para selecção destes três compostos obdeceu à estratégia de simplificação molecular.

Estas xantonas foram também testadas quanto ao seu efeito no crescimento *in vitro* de algumas linhas celulares tumorais humanas, tendo demonstrado a xantona **X38** uma actividade moderada (**Anexo IV**), a xantona **X2** não se mostrou activa (Pedro *et al.*, 2002) e a xantona **X20** exibiu apenas fraca actividade (Pedro *et al.*, 2002).

A modificação molecular dos quatro substractos reaccionais referidos permitirá obter um seriado de xantonas estruturalmente semelhantes que, após avaliação da actividade antitumoral, permitirá estudar a relação estrutura-actividade.

Uma vez que as XP naturais, quer simples (C- e O-preniladas) quer com anéis extra (pirano- e furanoxantonas), têm demonstrado potentes e variadas actividades biológicas (Cao *et al.*, 2007; Feng *et al.*, 2007; Han *et al.*, 2007; Kuete *et al.*, 2007; Reutrakul *et al.*, 2007; Shadid *et al.*, 2007; Tala *et al.*, 2007; Yang *et al.*, 2007; Yu *et al.*, 2007; Akao *et al.*, 2008; Azebaze *et al.*, 2008; Chin *et al.*, 2008; Ee *et al.*, 2008; Elya *et al.*, 2008; Figueroa *et al.*, 2009; Han *et al.*, 2008a; Kijjoa *et al.*, 2008; Leet *et al.*, 2008; Louh *et al.*, 2008; Masullo *et al.*, 2008; Pedraza-Chaverri *et al.*, 2008; Wang *et al.*, 2008b, c; Wen *et al.*, 2008; Xiao *et al.*, 2008; Xu *et al.*, 2008; Zhong *et al.*, 2008b; Huang *et al.*, 2009; Pouli & Marakos, 2009; Tao *et al.*, 2009; Hung, *et al.*, 2009; Zelefsky, *et al.*, 2009; Filho, *et al.*, 2009; Zhong, *et al.*, 2009; Boonnak, *et al.*, 2009; Ryu *et al.*, 2009; Pinto & Castanheiro, 2009a), destacando-se a antitumoral, recorreu-se assim à estratégia de prenilação de xantonas simples hidroxiladas.

Procedeu-se à síntese de derivados prenilados (lineares e di-hidropiranoxantonas, piranoxantonas e di-hidrofuranoxantonas) das xantonas di-hidroxiladas **X1** e **X38** (**Anexos IV, V e VI**), bem como das xantonas mono-hidroxiladas **X2** (**Anexo V**) e **X20** (**Anexo VI**; Castanheiro *et al.*, 2006) com o intuito, não só de potenciar a actividade antitumoral mas também de avaliar e comparar a reactividade das xantonas mono-hidroxiladas e di-hidroxiladas face à prenilação.

2.1. Metodologias Clássicas

Os resultados obtidos para as reacções de prenilação das **X1** e **X38**, através de metodologias clássicas de síntese, encontram-se descritos no **Anexo IV**.

A prenilação de xantonas hidroxiladas **X1**, **X20** e **X38** foi realizada através de uma reacção de substituição nucleofílica, na presença de carbonato de potássio, entre o brometo de prenilo e a respectiva xantona, tendo-se verificado que:

- A xantona **X1** originou dois derivados prenilados, um diprenilado (**XP1**) e um monoprenilado (**XP2**); a xantona **X20** originou um único produto monoprenilado (**XP6**), enquanto que a prenilação da xantona **X38** resultou em quatro derivados prenilados, três diprenilados (**XP4**, **XP5** e **XP7**) e um monoprenilado (**XP3**);
- Os rendimentos obtidos para os derivados monoprenilados (**XP2**, **XP3** e **XP6**) foram significativamente superiores aos obtidos para os derivados diprenilados (**XP1**, **XP4**, **XP5** e **XP7**).

Os derivados com anéis adicionais, no caso as di-hidropiranoxantonas, foram obtidas a partir do refluxo das xantonas mono-oxipreniladas **XP2**, **XP3** ou **XP6** em *o*-xileno anidro, na presença de um ácido de Lewis (ZnCl_2). Verificou-se que:

- A xantona **XP2** originou a di-hidropiranoxantona angular **XP8**; a xantona **XP3** originou duas di-hidropiranoxantonas, uma linear (**XP11**) e outra angular (**XP12**); o mesmo aconteceu com a xantona **XP6** que deu origem às di-hidropiranoxantonas linear (**XP16**) e angular (**XP17**);

Na **Tabela 1** encontram-se sumariados as condições reaccionais e os resultados obtidos para a síntese das **XP1-8**, **XP11-12** e **XP16-17**:

Tabela 1: Condições reaccionais e resultados obtidos para a síntese das xantonas preniladas **XP 1-8**, **XP11-12** e **XP16-17** pelo método clássico.

Substrato	Solvente	Produto	Tempo (h)	Rendimento (%)
X1	Acetona	XP1	8	3
X1		XP2		48
X38	Acetona	XP3	8	25
X38		XP4		5
X38		XP5		2
X38		XP7		3
X20	Acetona	XP6	8	70
XP2	o-xileno	XP8	21	22
XP3	o-xileno	XP11	20	3
XP3		XP12		4
XP6	o-xileno	XP16	22	2
XP6		XP17		5

- O rendimento obtido para a xantona **XP8** foi superior aos obtidos para as restantes di-hidropiranoxantonas, uma vez que na xantona **XP2** só existe a posição C4 *orto* livre e nas **XP3** e **XP6** existem ambas as posições C2 e C4 *orto* livres, o que poderia ter implicado uma disputa reaccional pelas duas posições, diminuindo assim o seu rendimento;
- Foram obtidas maiores quantidades de di-hidropiranoxantonas angulares (**XP8**, **XP12** e **XP17**) do que lineares (**XP11** e **XP16**), uma vez que a posição C4 está mais activada devido aos efeitos mesomérico e indutivo conjuntos;
- Das doze xantonas preniladas obtidas nestes trabalhos, através de um método clássico de prenilação e de ciclização de precursores prenilados, cinco xantonas preniladas simples (**XP1**, **XP2**, **XP4**, **XP5** e **XP7**) e três cíclicas (**XP8**, **XP16** e **XP17**) foram descritas pela primeira vez;
- As estruturas das xantonas preniladas foram estabelecidas através de técnicas de IV, UV, RMN, EM e adicionalmente por cristalografia de RX para as **XP2**, **XP3**, **XP4** e **XP11**.

Os resultados obtidos, quer para as reacções de prenilação da xantona **X2**, quer para as reacções de formação das piranoxantonas **XP19**, **XP25** e **XP26**, encontram-se descritos no **Anexo V**.

O método de prenilação da xantona **X2** sofreu modificações em relação ao utilizado para a síntese das restantes xantonas preniladas. As condições reaccionais utilizadas para a prenilação envolveram um aquecimento a temperaturas mais elevadas na tentativa de prenilar no grupo hidroxilo da posição 1, que se encontra em ligação de hidrogénio com o carbonilo adjacente. Utilizou-se DMF como solvente, o que permitiu a execução da reacção a temperaturas mais elevadas. Verificou-se que:

- Foi obtido um único derivado monoprenilado (**XP20**), com um grupo substituinte 1,1-dimetilalilo na posição C2, *orto* relativamente ao grupo hidroxilo;
- A obtenção deste derivado pode ser explicada pela ocorrência de prenilação no grupo hidroxilo, seguida de rearranjo de Claisen do grupo prenilo para a posição C2 *orto* do esqueleto xantónico.

Na tentativa de obter a di-hidropiranoxantona derivada da 1-hidroxixantona (**X2**), utilizou-se um método descrito na literatura (Ahluwalia *et al.*, 1983), no qual a reacção de prenilação foi efectuada por condensação da xantona **X2** com isopreno na presença de ácido fosfórico. No entanto, não foi obtido este derivado cíclico, mas o derivado monoprenilado **XP23**.

Com o objectivo de aumentar a potência e a selectividade das di-hidropiranoxantonas obtidas anteriormente, em relação à linha celular MCF-7, foram obtidas as piranoxantonas **XP19**, **XP25** e **XP26**, aplicando a estratégia de rigidificação molecular com a introdução de uma insaturação nas di-hidropiranoxantonas **XP8**, **XP11** e **XP12**, respectivamente, através de uma reacção de desidrogenação.

Na **Tabela 2** encontram-se sumariados as condições reaccionais e os resultados obtidos para a síntese das **XP19-20**, **XP23** e **XP25-26**:

Tabela 2: Condições reaccionais e resultados obtidos para a síntese das xantonas preniladas **XP 19-20**, **XP23** e **XP25-26**.

Substrato	Solvente	Produto	Tempo (h)	Rendimento (%)
XP8	Dioxano	XP19	9	67
XP11		XP25	18	25
XP12		XP26	10	41
X2	DMF	XP20	24	6
X2	Xileno	XP23	30	4

- Foram obtidos rendimentos baixos para as reacções de prenilação da **X2**, provavelmente devido ao grupo hidroxilo da posição 1, se encontrar em ligação de hidrogénio com o carbonilo adjacente;

- O rendimento obtido para a piranoxantona **XP19** foi superior aos obtidos para as restantes piranoxantonas;
- Foram obtidas maiores quantidades de piranoxantonas angulares (**XP19** e **XP26**) do que linear (**XP25**);
- Das cinco xantonas preniladas obtidas nestes trabalhos, através de um método clássico de prenilação e de desidrogenação, duas xantonas preniladas simples (**XP20** e **XP23**) e uma cíclica (**XP19**) foram descritas pela primeira vez;
- As estruturas das xantonas preniladas foram estabelecidas através de técnicas de IV, UV, RMN e EM;

2.2. Metodologias “Não Clássicas”

Os processos clássicos de síntese possuem, muitas vezes, alguns inconvenientes como baixos rendimentos, tempos reaccionais longos, baixa selectividade e condições reaccionais drásticas.

A optimização dos métodos de obtenção de derivados xantónicos prenilados constituiu outro dos objectivos da presente tese. Deste modo, foram aplicadas as metodologias quer de MAOS, quer de catálise heterogénea e catálise heterogénea assistida por MW, na obtenção de xantonas preniladas, descritas no **Anexo VI**.

2.2.1. Síntese Orgânica Assistida por Microondas (MAOS)

Esta metodologia foi utilizada, pela primeira vez no presente trabalho, na obtenção de derivados prenilados, tendo em conta que:

- Constitui uma técnica em desenvolvimento, uma vez que leva a uma diminuição dos tempos reaccionais, obtenção de melhores rendimentos, maior selectividade, formação de menos produtos secundários, possibilidade de reacções com ou sem solvente, em vasos abertos ou fechados, com ou sem o auxílio de catalisadores sólidos, reacções em pequena ou grande escala;
- Existem vários trabalhos na literatura que demonstram as referidas vantagens;
- Experiência de outros grupos de investigação, nomeadamente da Universidade de Aveiro, com o qual existe algum trabalho de cooperação e onde se iniciou o trabalho envolvendo esta técnica.

Na **Tabela 3** encontram-se sumariados as condições reaccionais e os resultados obtidos para a síntese das **XP 1-5** e **XP7**, em MW:

Tabela 3: Condições reaccionais e resultados obtidos para a síntese das xantonas prenildas **XP 1-5** e **XP7** em MW.

Substrato	Solvente	Produto	Tempo (min)	Rendimento (%)
X1	Acetona	XP1	60	5
X1		XP2		83
X38	Acetona	XP3	60	53
X38		XP4		1
X38		XP5		1
X38		XP7		2

Comparando os resultados obtidos para o método de prenilação utilizando radiação MW com os obtidos com aquecimento convencional, verificou-se que:

- Foram obtidas as mesmas xantonas prenildas simples, **XP 1-5** e **XP7**;
- Os rendimentos obtidos para as **XP1** e **XP2**, derivadas da xantona **X1**, aumentaram aproximadamente para o dobro para ambos os produtos;
- No caso dos derivados prenildos obtidos a partir da **X38**, apenas o rendimento da **XP3** monoprenilada melhorou (cerca do dobro), tendo diminuído ligeiramente para as **XP4**, **XP5** e **XP7** diprenildas;
- O tempo de reacção diminuiu drasticamente, de 8 horas para 60 minutos;
- Conseguiram-se reproduzir as mesmas condições experimentais da síntese clássica, apenas com a substituição da fonte de aquecimento (MW vs banho de silicone).

No que diz respeito ao rearranjo de Claisen, foram obtidas di-hidrofuranoxantonas em vez de derivados 1,1-dimetilalilados, uma vez que o grupo prenilo, após rearranjo para as posições *orto* disponíveis, sofreu ciclização espontânea com o grupo hidroxilo.

O rearranjo de Claisen de xantonas mono-oxiprenildas, através da aplicação de metodologias clássicas de síntese, já tinha sido descrito na literatura (Pinto & Castanheiro, 2009b). Estas envolveram aquecimento dos derivados mono-oxiprenildos em vácuo ou, em alternativa, refluxo da xantona em meio básico, como a *N,N*-DEA, *N,N*-DMA ou quinolina, funcionando esta última como solvente (Pinto & Castanheiro, 2009b). Em um dos trabalhos presentes na literatura, encontra-se descrita a reacção de rearranjo de Claisen da xantona **XP3**, por dois métodos diferentes, na qual foram obtidas as di-hidrofuranoxantonas **XP9** e **XP10** (Jain & Anand, 1974, **Tabela 4**). Como os rendimentos obtidos foram muito baixos e os tempos de reacção relativamente longos, procedeu-se, ao rearranjo da **XP3** com o auxílio de radiação MW, mas por refluxo da xantona em *N,N*-DEA (**Tabela 4**).

Na **Tabela 4** encontram-se sumariados as condições reaccionais e os resultados obtidos para a síntese das **XP9-10**, **XP18** e **XP21-22**:

Tabela 4: Condições reaccionais e resultados obtidos para a síntese das xantonas prenildas **XP9-10**, **XP18** e **XP21-22** por métodos clássicos e por MW.

Metodologia	Substrato	Solvente	Produto	Tempo (min)	Rendimento (%)
Clássica	XP3	Sem solvente (em vácuo)	XP9	120	18
	XP3		XP10		9
	XP3	Quinolina	XP9	600	9
	XP3		XP10		4
MW	XP3	N,N-DEA	XP9	45	6
	XP3		XP10		7
	XP3		XP21		5
	XP3		XP22		5
	XP3	NMP	XP9	60	20
	XP2	NMP	XP18	60	72

Comparando os resultados obtidos com radiação MW e com os obtidos com aquecimento convencional, verificou-se que:

- Foram obtidas as mesmas di-hidrofuranoxantonas linear (**XP9**) e angular (**XP10**), juntamente com dois derivados rearranjados isoméricos, **XP21** e **XP22**, obtidos a partir de um rearranjo anormal do grupo prenilo;
- Foram obtidos rendimentos ligeiramente menores do que os da síntese clássica;
- O tempo reaccional diminuiu consideravelmente, de 10 ou 2 horas para 45 minutos.

Face aos resultados obtidos por refluxo em *N,N*-DEA, e com base em descrições na literatura (Kappe & Stadler, 2005; Chan *et al.*, 2009), foi utilizada outra base como solvente, a NMP, para efectuar a reacção de rearranjo de Claisen. Por comparação dos resultados obtidos para as reacções de rearranjo com as duas bases por MW, verificou-se que:

- Utilizando a NMP apenas foi obtida a di-hidrofuranoxantona linear **XP9**;
- Esta foi obtida com melhor rendimento (20% vs 7%), na presença de NMP;
- Os tempos reaccionais foram ligeiramente diferentes, mas não significativamente;
- Método aparentemente selectivo para a obtenção da di-hidrofuranoxantona linear (com NMP);
- Como os rendimentos obtidos foram melhores utilizando a NMP, utilizou-se esta base para realizar o rearranjo de Claisen da **XP2**, tendo-se obtido a di-hidrofuranoxantona **XP18**, com bom rendimento e tempo reduzido.

Concluindo,

- Foi a primeira vez que se descreveu a utilização de radiação MW na síntese de xantonas prenildas;

- Foram obtidos melhores rendimentos para a síntese de algumas xantonas prenildas;
- Os tempos reaccionais diminuíram significativamente;
- A reacção de prenildação foi mais selectiva, obtendo-se quase exclusivamente xantonas monoprenildas;
- Nas reacções de rearranjo de Claisen, apenas foram observadas melhorias nos rendimentos quando se utilizou a NMP como solvente;
- Das onze xantonas prenildas obtidas neste trabalho, através da síntese assistida por MW, duas xantonas prenildas (**XP21** e **XP22**) e uma cíclica (**XP18**) foram descritas pela primeira vez;
- As estruturas das xantonas prenildas foram estabelecidas através de técnicas de IV, UV, RMN, EM.

2.2.2. Catálise Heterogénea e Catálise Heterogénea Assistida por MW

Esta metodologia foi utilizada pela primeira vez na obtenção de di-hidropiranoxantonas, no presente trabalho, tendo em conta que:

- A síntese por catálise heterogénea, especialmente na presença de *montmorillonite K10 clay* como catalisador sólido, se processa em condições reaccionais mais suaves, elevada selectividade, menores tempos reaccionais quando comparada com os processos clássicos de síntese; além disso, os processos de purificação são mais simples uma vez que o catalisador é facilmente separado da mistura reaccional, podendo ser regenerado;
- O acoplamento das técnicas de MW com o uso de suportes inorgânicos sólidos como catalisadores, tais como *montmorillonite K10 clay*, quer com solvente quer na ausência deste, resulta num processo químico com diversas vantagens, como sejam tempos reaccionais melhorados, aumento dos rendimentos, facilidade de manipulação experimental, maior selectividade, possibilidade de trabalhar em vasos abertos e de realizar reacções em grande escala;
- Existem trabalhos na literatura (Dintzner *et al.*, 2004a, b) que descrevem a obtenção de derivados com anéis di-hidropirano, directamente a partir da reacção de fenóis com brometo de prenilo na presença de *montmorillonite K10 clay*.

Com o objectivo de:

- Desenvolver uma metodologia de síntese “verde” (*Green chemistry*), utilizando reagentes e condições experimentais menos drásticas e,
- Optimizar a metodologia de síntese de di-hidropiranoxantonas, nomeadamente em termos de rendimentos, tempos reaccionais e selectividade para estes compostos,

procedeu-se à síntese de di-hidropiranoxantonas, num só passo, a partir das hidroxixantonas **X1**, **X20** ou **X38**, na presença de *montmorillonite K10 clay* como catalisador sólido. Foram ainda estudadas, algumas variantes às condições experimentais, nomeadamente a realização da reacção:

- À temperatura ambiente,
- A 100°C em tubo fechado, com aquecimento convencional,
- Com radiação MW.

Na **Tabela 5** encontram-se sumariados as condições reaccionais e os resultados obtidos para a síntese das di-hidropiranoxantonas **XP8**, **XP11-12**, **XP16-17** e **XP24**, por catálise heterogénea e catálise heterogénea assistida com MW:

Tabela 5: Condições reaccionais e resultados obtidos com os diferentes métodos para síntese das di-hidropiranoxantonas **XP8**, **XP11-12**, **XP16-17** e **XP24**.

Substrato	Método	K10 clay	Produto	Tempo	Temperatura final (°C)	Rendimento (%)	
						Com K10 clay	Com aquecimento convencional*
X1 X38 X38 X38 X20 X20	A: <i>K10 clay</i>	Comercial	XP8 XP11 XP12 XP24 XP16 XP17	5 dias	t.a.	51 9 3 † † †	10.5 0.5 1 - 1.4 3.6
X1 X38 X38 X38	B: <i>K10 clay</i> com aquecimento convencional	Comercial	XP8 XP11 XP12 XP24	60min	100	63 12 7 6	10.5 0.5 1 -
X1 X38 X38 X38	B: <i>K10 clay</i> com aquecimento convencional	Seca	XP8 XP11 XP12 XP24	60min	100	63 18 8 7	10.5 0.5 1 -
X1 X38 X38 X38 X20 X20	C: MW + <i>K10 clay</i> (sem solvente)	Comercial	XP8 XP11 XP12 XP24 XP16 XP17	20min	110 150 150 150 132 132	53 † † † 3 9	10.5 0.5 1 - 1.4 3.6
X1 X38 X38 X38 X20 X20	C: MW + <i>K10 clay</i> (com solvente)	Comercial	XP8 XP11 XP12 XP24 XP16 XP17	20min	105 113 113 113 115 115	86 14 10 4 9 25	10.5 0.5 1 - 1.4 3.6
X38 X38 X38	C: MW + <i>K10 clay</i> (com solvente)	Seca	XP11 XP12 XP24	20min	110	20 10 5	0.5 1 -

* Rendimentos dos produtos relativamente aos precursores **X1**, **X38** e **X20**.

† Quantidades residuais.

Comparando os resultados obtidos com os métodos A-C de catálise heterogénea com a metodologia clássica de síntese, para a obtenção das di-hidropiranoxantonas **XP8**, **XP11-12**, **XP16-17** e **XP24**, verificou-se o que:

Derivados da X1

- Foi obtida a mesma di-hidropiranoxantona **XP8**, mas num só passo a partir do bloco construtor **X1**, evitando dois passos intermédios de prenilação da **X1** e ciclização da **XP2**;
- Foi obtido melhor rendimento (cerca de 5 vezes maior) para a síntese da **XP8** a partir da **X1** (51% vs 10.5%), num só passo e na presença de *montmorillonite K10 clay* como catalisador, à temperatura ambiente, no entanto num tempo reaccional longo;
- Quando se efectuou a reacção em tubo fechado com aquecimento convencional a 100°C, foi obtida a **XP8** com melhor rendimento e num tempo reaccional significativamente menor (5 dias vs 60min);
- O uso de *K10 clay* comercial ou previamente seca na estufa não influenciou o curso da reacção, nem em termos de rendimento nem de tempo reaccional;
- Quando se utilizou o método combinado de catálise heterogénea com radiação MW, na ausência de solvente, foi obtida a **XP8** com menor rendimento do que o obtido com aquecimento convencional (53% vs 63%), mas em menor tempo (20min vs 60min); na presença de solvente a **XP8** foi obtida com o rendimento consideravelmente mais elevado (53% vs 86%).

Derivados da X38

- Foram obtidas as mesmas di-hidropiranoxantonas **XP11** e **XP12**, num só passo a partir do bloco construtor **X38**;
- A utilização de *montmorillonite K10 clay* à temperatura ambiente levou a uma ligeira melhoria dos rendimentos de obtenção das di-hidropiranoxantonas **XP11** e **XP12**; além disso foi obtido um composto diprenilado adicional (**XP24**), que aparentemente só se forma na presença de *K10 clay*;
- Quando a reacção foi efectuada em tubo fechado com aquecimento convencional a 100°C, houve um ligeiro aumento dos rendimentos e uma diminuição significativa do tempo de reacção (5 dias vs 60min); neste caso, o uso de *K10 clay* previamente seca na estufa, fomentou um ligeiro aumento nos rendimentos, especialmente para a **XP11** (12% vs 18%);
- O acoplamento do método de catálise heterogénea com radiação MW, na ausência de solvente, originou rendimentos mais baixos para as **XP11**, **XP12** e **XP24**, mas num menor

período de tempo (20min vs 60min); a presença de solvente levou a uma melhoria significativa nos rendimentos para todas as XP;

- A utilização de *K10 clay* previamente seca promoveu um aumento dos rendimentos apenas para as di-hidropiranoxantonas **XP11** e **XP24** e não para a **XP12**;
- O melhor rendimento para a di-hidropiranoxantona **XP24** foi obtido quando se utilizou aquecimento convencional em vez de radiação MW.

Derivados da X20

- Foram obtidas as mesmas di-hidropiranoxantonas **XP16** e **XP17**, num só passo a partir do bloco construtor **X20**;
- A utilização de *montmorillonite K10 clay* à temperatura ambiente levou a uma diminuição nos rendimentos de obtenção das di-hidropiranoxantonas **XP16** e **XP17**, quando comparados com os obtidos através da síntese convencional;
- Quando se utilizou o método combinado de catálise heterogénea com radiação MW, na ausência de solvente, foram obtidas as **XP16** e **XP17** com melhores rendimentos e em muito menor tempo (20min vs 5 dias); na presença de solvente os rendimentos triplicaram para ambas as **XP16** e **XP17**;
- A di-hidropiranoxantona angular foi obtida em quantidade três vezes maior do que o isómero linear, quando se utilizou o método combinado de catálise heterogénea com radiação MW na presença de solvente.

Concluindo,

- A utilização de *montmorillonite K10 clay* como catalisador, facilmente separável da mistura reaccional após reacção e regenerado para utilização posterior, evitou o uso de reagentes tais como ZnCl_2 , permitindo a realização de uma síntese mais “verde”;
- O acoplamento do método de catálise heterogénea utilizando *K10 clay* como catalisador com radiação MW, apresentou vantagens em relação à síntese clássica, nomeadamente reacções mais rápidas, melhores rendimentos, maior selectividade na obtenção de xantonas com um anel extra de di-hidropirano, num só passo, a partir de hidroxixantonas;
- A utilização de *K10 clay* previamente seca, resultou na obtenção de melhores rendimentos para as di-hidropiranoxantonas derivadas da **X38**;
- A di-hidropiranoxantona **XP24** foi obtida em maior quantidade quando se utilizou *montmorillonite K10 clay* com aquecimento convencional em vez de radiação MW, ao contrário das restantes di-hidropiranoxantonas;

- A utilização ou não utilização de solvente não alterou os tempos reacionais, no entanto na presença de solvente foram obtidos melhores rendimentos;
- Face às vantagens descritas, esta metodologia de catálise heterogénea assistida por MW poderá tornar-se num método atractivo e alternativo às vias sintéticas clássicas.

2.2.3. Comparação das metodologias clássicas e “não clássicas” na síntese das xantonas prenildas obtidas

Como se pode constatar ao longo da presente tese, foram utilizadas para a síntese de xantonas prenildas, quer metodologias clássicas, quer metodologias “não clássicas” de síntese, conforme o tipo de xantonas prenildas pretendidas: simples ou com anéis adicionais.

Na **Tabela 6** são comparadas as metodologias utilizadas nas diversas sínteses realizadas no presente trabalho, relativamente às suas vantagens e desvantagens.

Tabela 6: Comparação das metodologias clássicas e “não clássicas” de síntese.

Metodologia Utilizada	Vantagens	Desvantagens
<i>Clássica</i>	• Método já estabelecido e descrito na literatura • Reacções fáceis de controlar	• Tempos de reacção longos • Por vezes condições reacionais drásticas • Baixos rendimentos e selectividade
<i>MW</i>	• Menores tempos reacionais • Melhores rendimentos • Maior selectividade para algumas XP • Possibilidade de reacções com ou sem solvente • Possibilidade de reacções com auxílio de catalisadores sólidos • Possibilidade de reacções em vaso aberto ou fechado	• Equipamento e acessórios caros • Nem sempre são obtidos melhores rendimentos • Nem sempre se conseguem reproduzir os procedimentos clássicos; • Difícil ajustar programa às condições pretendidas.
<i>Catálise Heterogénea</i>	• Menor “time consuming” • Melhores rendimentos • Maior selectividade para di-hidropiranoxantonas • Obtidos derivados diprenildados adicionais	• Por vezes tempos reacionais longos, especialmente para reacções à t. a.
<i>Catálise Heterogénea + MW</i>	• Reacções mais rápidas • Melhores rendimentos • Maior selectividade • Possibilidade de reacções com ou sem solvente	• Difícil ajustar programa às condições pretendidas • Difícil de controlar as reacções em vaso fechado

Face aos resultados apresentados na **Tabela 6**, pode concluir-se que as técnicas de MW e catálise heterogénea especialmente acoplada com MW, possuem vantagens acrescidas

relativamente às metodologias clássicas, embora contenham igualmente alguns inconvenientes, mas pouco significativos quando comparados com os benefícios.

No futuro, após ajuste das condições experimentais ao tipo de reacção pretendida, poderão tornar-se em metodologias de eleição para a síntese de derivados xantónicos, quer prenilados quer com outro tipo de substituintes.

3. ENSAIOS BIOLÓGICOS

Como já referido anteriormente, no capítulo da Introdução Geral, os derivados xantónicos apresentam uma diversidade de actividades biológicas apreciável, dependendo da natureza e localização dos grupos substituintes nos anéis aromáticos (Pinto *et al.*, 2005b). Quando os substituintes são grupos prenilo, podem ser observadas actividades biológicas interessantes, como a moduladora da PKC, imunomoduladora, anti-inflamatória, antibacteriana, antifúngica, antitumoral, sendo evidente uma relação entre a presença de actividade biológica e a existência de grupos prenilo em posições-chave no esqueleto xantónico (Pinto & Castanheiro, 2009a).

Os **Anexos I e II** descrevem as actividades biológicas exibidas pelos derivados xantónicos prenilados, bem como a relação estrutura-actividade com especial ênfase para a actividade antitumoral (**Anexo I**).

A obtenção de novos agentes antitumorais é uma necessidade permanente, tanto no sentido de minimizar efeitos secundários, como de diminuir os fenómenos de resistência aos fármacos convencionais (Atkins & Gershell, 2002; Broxterman & Georgopapadakou, 2005; Bryan, 2005; Wu *et al.*, 2008; Harrison, 2008).

Neste enquadramento, foi avaliada a actividade antitumoral das **XP1-12**, **XP18-20**, **XP23-26**, (**Anexos IV, V e VIII**), a actividade moduladora da PKC para as **XP1** e **XP6** (**Anexo IX**) e a actividade estrogénica/antiestrogénica das **XP4** e **XP5** (Fernandes, 2006). A selecção das actividades biológicas foi baseada na experiência do grupo e no enquadramento em projectos em curso no CEQOFFUP/CEQUIMED-UP e, também, em dados encontrados na literatura para esta classe de compostos (Pinto & Castanheiro, 2009a).

3.1. Inibição do Crescimento de Linhas Celulares Tumorais Humanas

Das diversas actividades biológicas demonstradas pelas xantonas preniladas, destaca-se a actividade antitumoral, uma vez que estes compostos exercem o seu efeito numa ampla variedade de linhas celulares tumorais humanas (Pinto & Castanheiro, 2009a).

Com base neste conhecimento e em estudos já efectuados, nomeadamente com diversas xantonas simples oxigenadas obtidas no CEQOFFUP/CEQUIMED-UP (Pedro *et al.*, 2002), foi avaliado o efeito das xantonas preniladas no crescimento de linhas celulares tumorais humanas: MCF-7 (adenocarcinoma da mama), NCI-H460 (cancro das células não pequenas do pulmão), SF-268 (cancro do sistema nervoso central) e UACC-62 (melanoma).

Os resultados referentes à actividade de algumas xantonas preniladas sintetizadas no crescimento de linhas celulares tumorais humanas e à relação estrutura-actividade encontram-se descritos nos **Anexos IV** (**XP1-5**, **XP7-8** e **XP11-12**) e **V** (**XP19-20**, **XP23** e **XP25-26**). Na **Tabela 7**

encontram-se compilados os resultados de actividade relativos às xantonas preniladas, **XP1-12**, **XP18-20**, **XP23-26**, bem como aos respectivos precursores xantónicos de síntese, **X1**, **X2**, **X20** e **X38**.

Tabela 7: Efeito dos derivados xantónicos no crescimento de linhas celulares tumorais humanas.

Xantonas	GI ₅₀ (μM)			
	MCF-7	NCI-H460	SF-268	UACC-62
X₁	21.9 ± 0.4	20.6 ± 0.9	33.4 ± 0.2	20.0 ± 0.5
X₂	>200	ND	ND	142.9 ± 20.1
X₂₀	125.5 ± 23.8	ND	ND	117.9 ± 9.4
X₃₈	50.8 ± 2.2	37.9 ± 2.9	61.4 ± 5.2	38.0 ± 1.6
XP₁	>130	>130	>130	>130
XP₂	>150	>150	>150	>150
XP₃	>150	>150	>150	>150
XP₄	6.0 ± 0.7	>130	>130	>130
XP₅	9.1 ± 1.5	>130	>130	>130
XP₆	>150	124.9 ± 16.1	>130	ND
XP₇	112.5 ± 10.1	>130	>130	>130
XP₈	18.4 ± 1.9^a	>150 ^a	>150 ^a	ND
XP₉	>150	>150 ^b	ND	ND
XP₁₀	74^a	>150 ^b	ND	ND
XP₁₁	88.6 ± 12.9	>150	>150	ND
XP₁₂	>150	>150	>150	ND
XP₁₆	ND ^c	ND ^c	ND ^c	ND ^c
XP₁₇	ND ^c	ND ^c	ND ^c	ND ^c
XP₁₈	>150 ^b	>150 ^b	>150	ND
XP₁₉	>150 ^b	>150 ^b	>150	ND
XP₂₀	55^a	>150 ^b	ND	ND
XP₂₁	ND ^c	ND ^c	ND ^c	ND ^c
XP₂₂	ND ^c	ND ^c	ND ^c	ND ^c
XP₂₃	88^b	ND	ND	ND
XP₂₄	>150 ^a	>150 ^b	ND	ND
XP₂₅	>150 ^a	>150 ^b	ND	ND
XP₂₆	>150	>150 ^b	ND	ND

O efeito dos derivados xantónicos no crescimento de linhas celulares tumorais humanas é expresso em GI₅₀, ou seja, concentração de composto que causa 50% de inibição no crescimento celular. Doxorubicina foi usada como controlo positivo: GI₅₀ MCF-7=42.8±8.2 nM; GI₅₀ NCI-H460=94.0±8.7 nM; GI₅₀ SF-268=93.0±7.0 nM; GI₅₀ UACC-62=94.0±9.4 nM; Resultados correspondem à média ± SEM de 3-8 experiências independentes realizadas em duplicado; ^aResultados de 2 experiências independentes realizadas em duplicado; ^bResultados de uma experiência realizada em duplicado; ^cND = não determinado por insuficiente quantidade de composto; ND = não determinado.

Comparando a actividade dos quatro blocos construtores xantónicos no crescimento das linhas celulares tumorais testadas, verificou-se que as xantonas mono-hidroxiladas **X2** e **X20** mostraram uma actividade mais baixa (GI₅₀ > 100μM) do que a exibida pelas xantonas di-hidroxiladas **X1** e **X38** (GI₅₀ < 60μM), facto que indica que a di-hidroxilação de xantonas poderá favorecer esta actividade

antitumoral. No entanto, quando comparadas as duas xantonas di-hidroxiladas **X1** e **X38** constatou-se que a presença do grupo CH₃ na posição C2 do núcleo da xantona **X1** parece estar associada a uma actividade antitumoral mais potente exibida por esta xantona.

No que respeita às xantonas prenidadas, apenas as **XP4**, **XP5**, **XP8**, **XP10**, **XP11**, **XP20** e **XP23** mostraram actividade, mas esta limitou-se apenas à linha de adenocarcinoma da mama MCF-7, o que parece ser indicativo de uma selectividade destas xantonas para esta linha celular. Há que realçar, no entanto, a actividade potente das **XP4**, **XP5** e **XP8** ao inverso da actividade apenas moderada das **XP10**, **XP11**, **XP20** e **XP23**.

Uma análise dos resultados por famílias de xantonas prenidadas e a sua comparação com os respectivos precursores xantónicos, permitiu verificar que, relativamente ao efeito inibidor no crescimento de linhas celulares tumorais humanas:

Derivados prenidados da X1:

- Os derivados prenidados **XP1** e **XP2**, obtidos a partir da xantona **X1**, não revelaram actividade relativamente ao precursor de síntese (**Anexo IV**);
- A presença de um anel extra ao palanque estrutural da **X1**, no caso de formação da di-hidropiranoxantona **XP8**, levou à perda de actividade nas linhas celulares NCI-H460, SF-268 e UACC-62, tendo-se mantido para a linha MCF-7, o que poderá sugerir uma selectividade para esta linha celular;
- A rigidificação molecular da xantona monoprenitada **XP2**, no caso de formação da di-hidropiranoxantona **XP8** (**Anexo IV**), foi responsável pelo aparecimento de uma actividade potente e selectiva para a linha MCF-7; no entanto, a rigidificação da xantona **XP2** levando à formação da di-hidrofuranoxantona **XP18** não teve tal efeito (**Anexo VIII**);
- A rigidificação da **XP8** através da introdução de uma insaturação no anel di-hidropirano, que levou à formação da piranoxantona **XP19**, conduziu à perda de actividade na linha MCF-7 (**Anexo V**).

Derivados prenidados da X38:

- A prenidação da xantona **X38** deu origem a quatro derivados prenidados, dos quais as **XP4** e **XP5** exibiram uma actividade potente e selectiva para a linha celular MCF-7, enquanto os compostos **XP3** e **XP7** se mostraram inactivos (**Anexo IV**);
- A rigidificação molecular da **XP3**, por formação das di-hidropiranoxantonas **XP11** e **XP12**, levou ao aparecimento de actividade para a linha MCF-7 na **XP11**, mas não para o derivado **XP12** (**Anexo IV**);

- Comparando as actividades das di-hidropiranoxantonas **XP11**, **XP12** e **XP24** desta vez com o precursor de síntese **X38**, observou-se para as **XP12** e **XP24** uma perda de actividade para todas as linhas celulares tumorais testadas, enquanto que para a **XP11** esta actividade, embora ligeiramente menos potente, foi apenas mantida para a linha MCF-7 o que poderá ser indicativo de uma selectividade para esta linha celular;
- A rigidificação molecular da **XP3**, por formação das di-hidrofuranoxantonas **XP9** e **XP10**, levou ao aparecimento de actividade para a linha MCF-7 na **XP10**, mas não para o derivado **XP9** (*Anexo VIII*);
- A rigidificação molecular da di-hidropiranoxantona **XP11**, com uma actividade moderada para a linha celular MCF-7, formou a piranoxantona **XP25** inactiva; por seu lado a rigidificação da di-hidropiranoxantona **XP12**, xantona não activa, formou a piranoxantona **XP26** activa (*Anexo V*).

Derivados prenilados da X20:

- A prenilação da xantona **X20**, por formação da **XP6**, não levou a uma melhoria na actividade para a linha celular MCF-7.

Derivados prenilados da X2:

- A prenilação da xantona **X2** formou as xantonas **XP20** ou **XP23**, com actividade na linha MCF-7 (*Anexo V*).

Resumindo:

- No que diz respeito à actividade inibidora das xantonas preniladas no crescimento de linhas celulares tumorais humanas, verificou-se que os compostos **XP4**, **XP5** e **XP8** mostraram, relativamente aos seus precursores de síntese, uma actividade mais potente e selectiva para a linha celular de adenocarcinoma da mama MCF-7, o que permitiu concluir que a modificação molecular por prenilação das **X1** e **X38**, levou a uma melhoria na actividade para as **XP4**, **XP5** e **XP8**.
- Embora apenas tenham sido realizadas duas e uma experiência relativamente ao efeito das **XP20** e **XP23**, respectivamente, no crescimento da linha celular MCF-7, foi possível observar o aparecimento de um efeito moderado na actividade destes compostos, quando comparados com o precursor de síntese **X2** inactivo;
- A actividade antitumoral não foi melhorada para as piranoxantonas **XP19**, **XP25** e **XP26** derivadas das di-hidropiranoxantonas **XP8**, **XP11** e **XP12**.

- Embora apenas tenham sido realizadas duas e uma experiência relativamente ao efeito das **XP10** e **XP18**, respectivamente, no crescimento da linha celular MCF-7, foi possível observar um efeito moderado na actividade da **XP10**, quando comparada com o precursor inactivo de síntese **XP3**.

Comparação da actividade das xantonas prenilladas e relação estrutura-actividade putativa:

É feita de seguida uma comparação relativamente às xantonas prenilladas que se mostraram activas na linha celular MCF-7 e uma aproximação da relação estrutura-actividade. Assim:

- A prenillação dos blocos construtores xantónicos pareceu conferir aos compostos obtidos, uma selectividade para a linha celular tumoral MCF-7, uma vez que todas as xantonas prenilladas activas só o foram na linha MCF-7;
- Considerando as xantonas prenilladas activas **XP4**, **XP5**, **XP8**, **XP10**, **XP11**, **XP20** e **XP23**, verificou-se que a existência de um grupo alquilo, especialmente o grupo prenilo, na posição C2 do núcleo xantónico parece ser um factor importante para a actividade;
- Considerando as xantonas **XP4**, **XP5**, **XP20** e **XP23**, todas elas com um grupo prenilo na posição C2 do esqueleto xantónico, verificou-se que as **XP4** e **XP5** foram significativamente mais activas do que as **XP20** e **XP23**, o que poderá indicar que a existência de um grupo prenilo em C3 nas xantonas **XP4** e **XP5**, possa ser importante para a actividade;
- Considerando as xantonas **XP8**, **XP10** e **XP11**, verificou-se que a existência de um anel dihidropirano em posição angular parece ser favorável à actividade;
- As **XP4**, **XP5**, **XP8** (**Figura 26**) demonstraram ser as XP mais potentes para a linha celular tumoral MCF-7 e poderão constituir compostos “hit” para posterior desenvolvimento de possíveis agentes antitumorais.

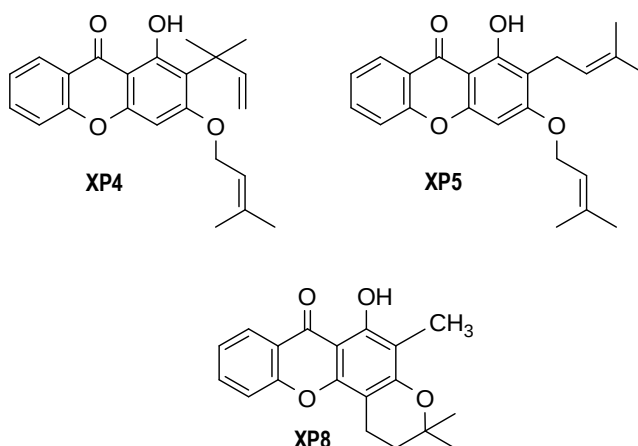


Figura 26. Estruturas das xantonas, **XP4**, **XP5**, **XP8**, mais potentes para a linha celular MCF-7.

3.2. Modulação da Cínase C de Proteínas (PKC, *Protein Kinase C*)

A PKC constitui uma família de cínases que fosforila resíduos de serina e treonina em proteínas alvo e, além disso, funciona como catalisador em numerosas reacções bioquímicas cruciais à função de muitos constituintes celulares (Webb *et al.*, 2000).

A família da PKC é constituída por várias isoformas que podem ser agrupadas, com base no seu modo de activação, em pelo menos três subgrupos: o subgrupo das PKCs clássicas, que inclui as isoformas α , β I, β II, e γ ; o subgrupo das PKCs *novel*, que inclui as isoformas δ , ϵ , η e θ e o subgrupo das PKCs atípicas, que inclui as isoformas ζ e ι / λ (Spitaler & Cantrell, 2004). As isoenzimas da PKC encontram-se distribuídas por várias células e tecidos de mamíferos (Webb *et al.*, 2000) e estão relacionadas com acções biológicas muito importantes, como seja a tumorigénese. Para compreender melhor a função celular e fisiológica de cada isoforma da PKC é necessário o desenvolvimento de novos agentes que exibam selectividade para cada isoforma individualmente.

No que diz respeito à classe de xantonas, já vários derivados foram avaliadas na modulação da PKC (Saraiva *et al.*, 2002a, b, 2003), demonstrando, particularmente as XP, terem um comportamento consentâneo com a inibição da PKC (Pinto & Castanheiro, 2009a).

Pelo exposto, e com o intuito de procurar novos agentes quimioterápicos baseados na modulação da PKC, foi avaliado o efeito das **XP1** e **XP6** (**Anexo IX; Figura 27**) na modulação *in vivo* nas isoformas α , β I, δ , η e ζ da PKC.

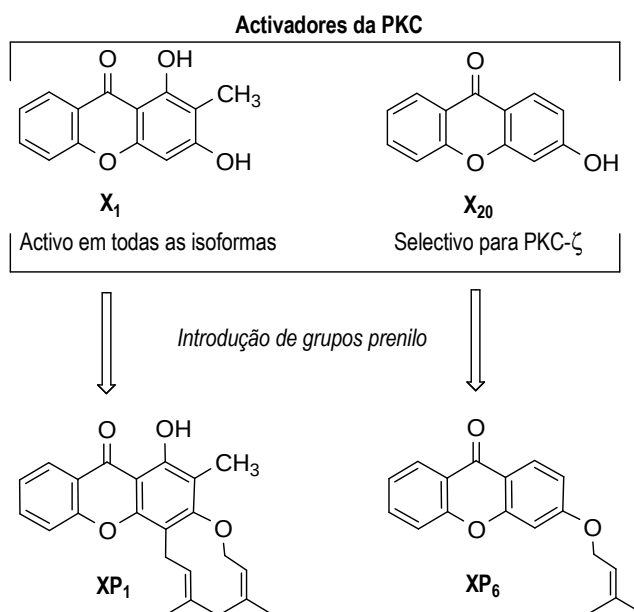


Figura 27. Estratégia para aumentar a potência/selectividade na modulação da PKC.

Relativamente aos seus precursores xantónicos, **X1** e **X20**, respectivamente (**Figura 27**), foi verificado que:

- A xantona **X1**, activador da PKC não selectivo (Saraiva *et al.*, 2002b), deu origem a um novo inibidor selectivo (**XP1**) para a isoforma η da PKC;
- A xantona **X20**, activador da PKC selectivo para a isoforma ζ (Saraiva *et al.*, 2002b), deu origem a um composto inactivo (**XP6**) para as isoformas da PKC testadas;
- A **XP1** revelou um efeito compatível com a inibição da PKC e também selectividade para a isoforma η da PKC.

Devido aos resultados promissores encontrados, estão a decorrer diversos estudos baseados na modulação da PKC, com vários derivados prenilados.

3.3. Actividade Estrogénica/Antiestrogénica (†)

No decurso da pesquisa de novas classes de compostos sintéticos com actividade antitumoral, foram obtidos no presente trabalho, derivados xantónicos prenilados que apresentaram uma actividade inibidora potente e selectiva no crescimento da linha celular MCF-7 de adenocarcinoma mamário com receptores de estrogénios (ER+) (Castanheiro *et al.*, 2007a). A sua elevada selectividade para esta linha celular de cancro da mama conduziu à pesquisa de uma possível actividade estrogénica/antiestrogénica *in vitro* nestes compostos.

Nesse sentido, as xantonas **XP4** e **XP5** foram objecto de estudo por forma a: (i) avaliar a sua capacidade em estimular o crescimento da linha celular MCF-7 (ER+) a baixas concentrações e comparar com o efeito apresentado na linha celular de cancro da mama MDA-MB-231 (ER-); (ii) avaliar se o efeito inibidor do crescimento (antiproliferativo), anteriormente demonstrado, se estendia à linha celular MDA-MB-231 (ER-); (iii) investigar o seu efeito na presença do estrogénio natural humano 17- β -estradiol; (iv) examinar o seu efeito na presença de 4-OH-tamoxifeno (antiestrogénio) e (v) avaliar o seu efeito na expressão do receptor de estrogénios (ER).

A baixas concentrações, ambas as xantonas **XP4** e **XP5** estimularam o crescimento da linha celular MCF-7 (ER+), no entanto não foi observada qualquer estimulação na linha celular MDA-MB-231 (ER-), o que é consistente com um efeito estrogénico e sugere um envolvimento do ER na indução do efeito estimulador destes compostos. O tratamento simultâneo da linha celular MCF-7 (ER+), com as duas xantonas preniladas e com o 17- β -estradiol não foi acompanhado por um

† Ensaio efectuados pela Licenciada Iva Fernandes (Relatório de estágio da Licenciatura em Bioquímica, 2006) realizado sob orientação da Professora Doutora Maria de São José Nascimento.

aumento no efeito proliferativo, contudo o tratamento destas células com 4-OH-tamoxifeno aboliu a estimulação da linha celular MCF-7 induzida por estas xantonas. O tratamento das células MCF-7 com baixas concentrações das xantonas mostraram um aumento da expressão do ER, o que pode explicar o efeito proliferativo observado.

A altas concentrações, a xantona **XP5** inibiu de forma dependente da concentração o crescimento das linhas celulares MCF-7 (ER+) e MDA-MB-231 (ER-), apesar do efeito antiproliferativo ser menos intenso na linha celular (ER-). Este efeito antiproliferativo esteve associado, nas células MCF-7, a uma morte celular por apoptose. Curiosamente, a **XP5** foi capaz de provocar, quando em concentrações elevadas, um aumento do efeito inibidor do crescimento (efeito antiestrogénico) do 4-OH-tamoxifeno na linha celular MCF-7 (ER+).

Deste modo, estes resultados constituem a primeira evidência da actividade estrogénica *in vitro* pelas **XP4** e **XP5**, mostrando que estes compostos poderão vir a constituir uma fonte promissora na terapia de substituição estrogénica.

Simultaneamente este trabalho demonstrou um efeito aditivo relevante por parte destas xantonas preniladas quando na presença de 4-OH-tamoxifeno, conferindo também a esta família de compostos novas perspectivas como candidatos na terapia combinada para o cancro da mama hormono dependente (Fernandes, 2006).

CAPÍTULO III

CONCLUSÕES

CONCLUSÕES

Os derivados xantónicos apresentam uma diversidade de actividades biológicas considerável, dependendo da natureza e localização dos grupos substituintes nos anéis aromáticos, em especial grupos prenilo, tendo vindo a revelar-se como um material de investigação extremamente relevante em Química Medicinal.

Tendo em conta os objectivos anteriormente indicados,

- a) Obtenção quer de xantonas preniladas simples quer de xantonas com anéis extra, através de metodologias clássicas de síntese,
- b) Optimização dos processos de obtenção dessas xantonas, através da aplicação de duas metodologias sintéticas não clássicas, nomeadamente síntese assistida por MW e por catálise heterogénea,
- c) Comparação dos resultados obtidos pela aplicação das metodologias clássicas (a) e “não clássicas” (b),
- d) Elucidação estrutural das xantonas preniladas obtidas por síntese,
- e) Avaliação de actividades biológicas dos compostos sintetizados, nomeadamente, antitumoral, moduladora da PKC e estrogénica/antiestrogénica,

apresentam-se de seguida as principais conclusões que resultaram destes estudos:

- Foram obtidos vinte e três derivados xantónicos prenilados através da aplicação de diferentes estratégias de modificação molecular ao núcleo xantónico, nomeadamente extensão e rigidificação moleculares e introdução de anéis extra; destes, três são mono-O-prenilados, quatro mono-C-prenilados, quatro C, O-diprenilados e doze com um anel extra, dos quais catorze correspondem a compostos novos (**XP1-2**, **XP4-5**, **XP7-8** e **XP16-23**);
- Pelo método clássico foram obtidas dezassete xantonas preniladas através de métodos clássicos;
- Pela síntese em MW foram obtidas onze xantonas preniladas;
- Foram obtidas seis di-hidropiranoxantonas, pela aplicação das metodologias de catálise heterogénea e / ou catálise heterogénea assistida por MW, directamente a partir das hidroxixantonas num só passo e na presença de *montmorillonite K10 clay* como catalisador;
- As metodologias de MW e catálise heterogénea foram aplicadas pela primeira vez à síntese de derivados xantónicos prenilados;
- A metodologia de MW foi aplicada com sucesso à síntese de xantonas preniladas simples e di-hidrofuranoxantonas, com a obtenção de melhores rendimentos, menores tempos reaccionais e maior selectividade;

- A metodologia de catálise heterogénea foi aplicada com sucesso à síntese de di-hidropiranoxantonas. O acoplamento dos métodos de catálise heterogénea com MW, apresentou vantagens em relação ao método clássico, nomeadamente reacções mais rápidas, melhores rendimentos, maior selectividade na obtenção de xantonas com um anel di-hidropirano extra num só passo a partir de hidroxixantonas;
- As metodologias de catálise heterogénea e MW permitiram a aplicação da “química verde” à obtenção de derivados xantónicos;
- No geral, foi conseguida a melhoria dos processos de obtenção de xantonas prenilhadas;
- As xantonas prenilhadas sintetizadas foram caracterizadas através das técnicas de IV, UV, RMN, EM e adicionalmente por cristalografia de raios X para os compostos **XP2**, **XP3**, **XP4** e **XP11**.

Tendo em conta que outro dos objectivos do presente trabalho foi dirigido para a obtenção de derivados prenilhados de xantonas hidroxiladas por modificação molecular de compostos “hit”, de modo a melhorar a sua actividade biológica, especialmente antitumoral, apresentam-se de seguida as principais conclusões:

- Os resultados da avaliação da actividade inibidora das xantonas prenilhadas no crescimento de linhas celulares tumorais humanas permitiram concluir que a prenilhação de alguns derivados xantónicos levou à obtenção de compostos mais potentes e selectivos para a linha celular de adenocarcinoma da mama, MCF-7;
- As **XP4**, **XP5**, **XP8**, **XP10**, **XP11**, **XP20** e **XP23** exibiram actividade inibidora do crescimento da linha celular MCF-7, mostrando-se as restantes xantonas prenilhadas inactivas. Destas, as **XP4**, **XP5** e **XP8** exibiram uma actividade potente, enquanto que as restantes exibiram apenas uma actividade moderada;
- A xantona **XP1** revelou um efeito compatível com a inibição da PKC e além disso selectividade para a isoforma η ;
- As **XP4** e **XP5** exibiram actividade estrogénica *in vitro*.

O esqueleto xantónico prenilado revelou-se promissor para o desenvolvimento de novos compostos com potencial acção antitumoral, podendo considerar-se privilegiado para o desenvolvimento de derivados biologicamente activos.

No futuro torna-se importante otimizar algumas condições experimentais, quer para a realização da síntese assistida por MW, quer por catálise heterogénea, e estas poderão constituir as

metodologias de eleição para a obtenção de derivados xantónicos, quer prenilados, quer com outro tipo de substituintes.

O trabalho desenvolvido mostra que a evolução da Química de Síntese, nomeadamente através da aplicação de novas metodologias à obtenção de compostos da família química das xantonas, pode constituir uma valiosa ferramenta, não só na optimização de processos mas também na criação de diversidade estrutural. A variedade e novidade das estruturas obtidas poderão levar, no futuro, ao planeamento de novos compostos, nomeadamente com actividade antitumoral melhorada, sendo este um dos campos com grande interesse na área de Química Medicinal.

BIBLIOGRAFIA

BIBLIOGRAFIA

- Os motores de busca utilizados para a pesquisa bibliográfica foram os a seguir indicados, com a data do último acesso em Abril de 2009:

<http://atoz.ebsco.com/titles.asp?id=556&sid=219581517&TabID=2>

<http://isiwebofknowledge.com/>

<http://pubs.acs.org/about.html>

<http://www.cas.org/>

<http://www.google.pt/>

<http://www.ncbi.nlm.nih.gov/pubmed/>

<http://www.rsc.org/Publishing/index.asp>

<http://www.sciencedirect.com/>

<http://www.scirus.com/srsapp/>

<http://www.scopus.com/scopus/home.url>

<http://www3.interscience.wiley.com/cgi-bin/home>

- A indexação das referências bibliográficas segue as disposições gerais do *American Chemical Society Style Guide*, 3rd ed., **2006**:

Afzal, M.; Al-Hassan, J. M. Synthesis and Biosynthesis of Phytotoxanthones. *Heterocycles* **1980**, 14 (8), 1173-1205.

Ahluwalia, V. K.; Jolly, R. S.; Tehim, A. K. A Convenient Synthesis of Dihydropyranoanthones. *J. Chem. Soc. Perkin Trans. I* **1983**, 1229-1233.

Akao, Y.; Nakagawa, Y.; Iinuma, M.; Nozawa, Y. Anti-Cancer Effects of Xanthones from Pericarps of Mangosteen. *Int. J. Mol. Sci.* **2008**, 9, 355-370.

Alarcón, A. B.; Cuesta-Rubio, O.; Pérez, J. C.; Piccinelli, A. L.; Rastrelli, L. Constituents of the Cuban Endemic Species *Calophyllum pinetorum*. *J. Nat. Prod.* **2008**, 71, 1283-1286.

An, L.-T.; Ding, F.-Q.; Zou, J.-P.; Lu, X.-H. Montmorillonite K10: An Efficient Catalyst for Solvent-Free Synthesis of 1,5-Benzodiazepine Derivatives. *Synth. Commun.* **2008**, 38, 1259-1267.

Atkins, J. H.; Gershell, L. J. Selective anticancer drugs. *Nature Rev. Drug Discov.* **2002**, 1, 491-492.

Atwell, G. J.; Yang, S.; Denny, W. A. An improved synthesis of 5,6-dimethylxanthenone-4-acetic acid (DMXAA). *Eur. J. Med. Chem.* **2002**, 37(10), 825-828.

Avendaño, M. C. Em Introducción a la Química Farmacêutica; McGraw-Hill – Interamericana de España; **2001**.

- Azebaze, A. G. B.; Ouahouo, B. M. W.; Vardamides, J. C.; Valentin, A.; Kuete, V.; Acebeys, L.; Beng, V. P.; Nkengfack, A. E.; Meyer, M. Antimicrobial and Antileishmanial xanthenes from the stem bark of *Allanblackia gabonensis* (Guttiferae). *Nat. Prod. Res.* **2008**, 22(4), 333-341.
- Azevedo, C. M. B. P. G. Síntese e Determinação de Parâmetros Físico-Químicos de Xantonas. *Tese de mestrado, Faculdade de Farmácia da Universidade do Porto, Porto*, **2007**.
- Bach-Rojecky, L.; Kalodera, Z.; Samaržija, I. The antidepressant activity of *Hypericum perforatum* L. measured by two experimental methods on mice, *Acta Pharm.* **2004**, 54, 157–162.
- Baguley, B. C. Antivascular Therapy of Cancer: DMXAA. *Lancet Oncol.* **2003**, 4(3), 141-148.
- Baker, D. D.; Chu, M.; Oza, U.; Rajgarhia, V. The value of natural products to future pharmaceutical discovery. *Nat. Prod. Rep.* **2007**, 24, 1225–1244.
- Barreiro, E. J.; Fraga, C. A. M. Em Química Medicinal: As Bases Moleculares da Ação dos Fármacos; Artemed Editora, Porto Alegre, **2001**.
- Benakki, H.; Colacino, E.; André, C.; Guenoun, F.; Martinez, J.; Lamaty, F. Microwave-assisted multi-step synthesis of novel pyrrolo-[3,2-c]quinoline derivatives. *Tetrahedron* **2008**, 64, 5949-5955.
- Bennett, G.J.; Lee, H.-H. Xanthenes from Guttiferae. *Phytochemistry* **1989**, 28(4), 967-998.
- Boonnak, N.; Chantrapromma, S.; Fun, H.-K.; Karalai, C. 4,8-Dihydroxy-2,3-dimethoxy-1-(3-methylbut-2-enyl)-9H-xanthen-9-one. *Acta Cryst.* **2007**, E63, o4903–o4904.
- Boonnak, N.; Karalai, C.; Chantrapromma, S.; Ponglimanont, C.; Fun, H.-K.; Kanjana-Opas, A.; Chantrapromma, K.; Kato, S. Anti-*Pseudomonas aeruginosa* xanthenes from the resin and green fruits of *Cratogeomys cochinchinense*. *Tetrahedron* **2009**, 65, 3003-3013.
- Brito, C. M.; Pinto, D. C. G. A.; Silva, A. M. S.; Silva, A. M. G.; Tomé, A. C.; Cavaleiro, J. A. S. Diels–Alder Reactions of 2-Hydroxychalcones with ortho-Benzoquinodimethane: A New Synthesis of 3-Aryl-2-naphthyl 2-Hydroxyphenyl Ketones. *Eur. J. Org. Chem.* **2006**, 2558-2569.
- Broxterman, H. J.; Georgopapadakou, N. H. Anticancer therapeutics: “Addictive” targets, multi-targeted drugs, new drug combinations. *Drug Resist. Updates* **2005**, 8, 183-197.
- Bryan, J. How new drug technologies might overcome toxicity from chemotherapy. *The Pharma. J.* **2005**, 274, 397.
- Butler, M. S. The Role of Natural Product Chemistry in Drug Discovery. *J. Nat. Prod.* **2004**, 67, 2141-2153.
- Butler, M.S. Natural products to drugs: natural product-derived compounds in clinical trials. *Nat. Prod. Rep.* **2008**, 25, 475–516.

- Cao, S.; Brodie, P. J.; Miller, J. S.; Randrianaivo, R.; Ratovoson, F.; Birkinshaw, C.; Andriantsiferana, R.; Rasamison, V. E.; Kingston, D. G. I. Antiproliferative Xanthoness of *Terminalia calcicola* from the Madagascar Rain Forest. *J. Nat. Prod.* **2007**, *70*, 679-681.
- Castanheiro, R. A. P.; Pinto, M. M. M.; Silva, A. M. S.; Cravo, S. M. M.; Gales, L.; Damas, A. M.; Nazareth, N.; Nascimento, M. S. J.; Eaton, G. Dihydroxyxanthoness Prenylated Derivatives: Synthesis, Structure Elucidation and Growth Inhibitory Activity on Human Tumor Cell Lines with Improvement of Selectivity for MCF-7; *Bioorg. Med. Chem.* **2007a**, *15*, 6080-6088.
- Castanheiro, R. A. P.; Pinto, M. M. M.; Cravo, S. M. M.; Pinto, D. C. G. A.; Silva, A. M. S.; Kijjoa, A. Improved Methodologies for Synthesis of Prenylated Xanthoness by Microwave Irradiation and Combination of Heterogeneous Catalysis (K10 clay) with Microwave Irradiation. *Tetrahedron* **2009a**, *65*, 3848-3857.
- Castanheiro, R. A. P.; Pinto, M. M. M.; Silva, A. M. S.; Campos, N. A. N.; Nascimento, M. S. J. Antitumor Xanthone Derivatives: Prenylation as a Key Approach to Improve Activity. *Chem. & Biodiv.* **2009b**, *submetido*.
- Castanheiro, R.; Cravo, S.; Pinto, M.; Azevedo, C. G.; Afonso, C. M. M.; Reis, S. H. Microwave Assisted Synthesis of Xanthoness: 1-Hydroxyxanthone, 1-Methoxyxanthone and one Dihydropyranoxyxanthone. *Abstracts Book from the "7th National Meeting of Organic Chemistry"*, Lisboa, Portugal, 16-18 Julho, **2007b**, PC24.
- Castanheiro, R.; Pinto, M.; Silva, A. Synthesis of Prenylated Xanthoness: An Update". *Abstracts Book from the "4th Transmediterranean Colloquium on Heterocyclic Chemistry (TRAMECH 4)"*, Aveiro, Portugal, 23-27 Junho, **2006**, 93.
- Chan, S.-C.; Jang, J.-P.; Cherng, Y.-J. Microwave-assisted synthesis of substituted phenanthreness, anthraceness, acenaphtheness, and fluoreness. *Tetrahedron* **2009**, *65*, 1977-1981.
- Chaplin, D. J.; Horsman, M. R.; Siemann, D. W. Current development status of small-molecule vascular disrupting agents. *Curr. Opin. Investig. Drugs.* **2006**, *7*(6), 522-528.
- Chen, G.-Y.; Zhu, G.-Y.; Han, C.-R.; Zhao, J.; Song, X.-P.; Fong, W.-F. A new pyranoxyxanthone from the stems of *Calophyllum membranaceum*. *Arkivoc* **2008a**, *xiii*, 249-254.
- Chen, Y.; Zhong, F.; He, H.; Hu, Y.; Zhu, D.; Yang, G. Structure elucidation and NMR spectral assignment of five new xanthoness from the bark of *Garcinia xanthochymus*. *Magn. Reson. Chem.* **2008b**, *46*, 1180-1184.
- Chin, Y.-W.; Balunas, M. J.; Chai, H. B.; Kinghorn, A. D. Drug Discovery from Natural Sources. *AAPS J.* **2006**, *8*, E239-E253.

- Chin, Y.-W.; Jung, H.-A.; Chai, H.; Keller, W. J.; Kinghorn, A. D. Xanthonenes with quinone reductase-inducing activity from the fruits of *Garcinia mangostana* (Mangosteen). *Phytochemistry* **2008**, *69*, 754-758.
- Cidade, H.; Neves, M.; Kijjoa, A. Natural Prenylated Flavones: Chemistry and Biological Activities – An Overview. Em *Natural Products: Chemistry, Biochemistry and Pharmacology*. Ed. Brahmachari, G., Narosa Publishing House PVT. LTD., Nova Deli, Índia, **2008**, Cap. 16, pp. 463-519.
- Coelho, A. C. V.; Santos, P. S.; Santos, H. S. Argilas Especiais: Argilas Quimicamente Modificadas – Uma Revisão. *Quim. Nova* **2007**, *30*(5), 1282-1294.
- Cooke, M.; Clark, J.; Breeden, S. Lewis acid catalysed microwave-assisted synthesis of diaryl sulfones and comparison of associated carbon dioxide emissions. *J. Mol. Catal. A: Chem.* **2009**.
- Corrêa, B.; Silva L. G. F.; Gottlieb, O. R.; Gonçalves, S. J. Quinone and Xanthone Constituents of *Kielmeyera rupestris*. *Phytochemistry* **1970**, *9*, 447-451.
- Correia, S. J.; David, J. P.; David, J. M. Metabólitos Secundários de Espécies de *Anacardiaceae*. *Quim. Nova* **2006**, *29* (6), 1287-1300.
- Costa, C. T.; Dalluge, J. J.; Welch, M. J.; Coxon, B.; Margolis, S. A.; Horton, D. Characterization of prenylated xanthonenes and flavanones by liquid chromatography/atmospheric pressure chemical ionization mass spectrometry. *J. Mass Spectrom.* **2000**, *35*(4), 540-549.
- Cravo, S., Castanheiro, R., Pinto, M., Nazareth, N., Nascimento, M. S. J. "Optimization of Synthetic Methodologies of Biological Active Prenylated Xanthonenes", *Drugs of the Future*, **2008**, *33*, Suppl. A, Abstracts from the "XXth International Symposium on Medicinal Chemistry (EFMC-ISMC 2008)", 133.
- Dallinger, D.; Kappe, C. O. Microwave-Assisted Synthesis in Water as Solvent. *Chem. Rev.* **2007**, *107*, 2563-2591.
- Deachathai, S.; Phongpaichit, S.; Mahabusarakam, W. Phenolic compounds from the seeds of *Garcinia dulcis*. *Nat. Prod. Res.* **2008**, *22*(15), 1327-1332.
- Dean, F. M. Xanthonenes. Em *The Total Synthesis of Natural Products*. Ed. Apsimon, J., **1973**, *1*, 534-562.
- Dhakshinamoorthy, A.; Pitchumani, K. Clay-supported ceric ammonium nitrate as an effective, viable catalyst in the oxidation of olefins, chalcones and sulfides by molecular oxygen. *Catal. Commun.* **2009**, *10*, 872-878.
- Dholwani, K. K.; Saluja, A. K.; Gupta, A. R.; Shah, D. R. A review on plant-derived natural products and their analogs with anti-tumor activity. *Indian J. Pharmacol.* **2008**, *40*(2), 49-58.

- Dintzner, M. R.; Little, A. J.; Pacilli, M.; Pileggi, D. J.; Osner, Z. R.; Lyons, T. W. Montmorillonite Clay-Catalyzed Hetero-Diels-Alder Reaction of 2,3-Dimethyl-1,3-Butadiene with Benzaldehydes. *Tetrahedron Lett.* **2007**, 48, 1577-1579.
- Dintzner, M. R.; Lyons, T. W.; Akroush, M. H.; Wucka, P.; Rzepka, A. T. A Quick, Clean and Green Synthesis of Methylenedioxyprococene and other Chromenes over Basic Montmorillonite K10 Clay. *Synlett* **2005**, 5, 785-788.
- Dintzner, M. R.; McClelland, K. M.; Morse, K. M.; Akroush, M. H. Montmorillonite Clays in Organic Synthesis: A One-Pot Conversion of Phenols to 2,2-Dimethylbenzopyrans. *Synlett* **2004a**, 11, 2028-2030.
- Dintzner, M. R.; Morse, K. M.; McClelland, K. M.; Coligado, D. M. Investigation of the Montmorillonite Clay-Catalyzed [1,3] Shift reaction of 3-methyl-2-butenyl phenyl ether. *Tet. Lett.* **2004b**, 45, 79-81.
- Dintzner, M. R.; Wucka, P. R.; Lyons, T.W. Microwave-Assisted Synthesis of a Natural Insecticide on Basic Montmorillonite K10 Clay. *J. Chem. Edu.* **2006**, 83(2), 270-272.
- Ee, G. C. L.; Daud, S.; Izzaddin, S. A.; Rahmani, M. *Garcinia mangostana*: a source of potential anti-cancer lead compounds against CEM-SS cell line. *J. Asian Nat. Prod. Res.* **2008**, 10(5), 481-485.
- Elya, B.; He, H. P.; Kosela, S.; Hanafi, M.; Hao, X. J. A new cytotoxic xanthone from *Garcinia rigida*. *Fitoterapia* **2008**, 79, 182-184.
- Evangelista, E. A.; Couri, M. R. C.; Alves, R. B.; Raslan, D. S.; Gil, R. P. F. Microwave-Assisted Xanthone Synthesis. *Synth. Commun.* **2006**, 36, 2275-2280.
- Farrugia, L. J. ORTEP-3 for Windows – a version of ORTEP-III with a Graphical User Interface (GUI). *J. Appl. Cryst.* **1997**, 30, 565.
- Feng, F.; Liu, W.-Y.; Chen, Y.-S.; Guo, Q.-L.; You, Q.-D. Five novel prenylated xanthenes from *Resina Garciniae*. *J. Asian Nat. Prod. Res.* **2007**, 9(8), 735-741.
- Fernandes, E. G. R. Síntese e Elucidação Estrutural de Xantonas, Xantolignóides e Determinação da Actividade Biológica. *Tese de doutoramento, Faculdade de Farmácia da Universidade do Porto*, Porto, **1996**.
- Fernandes, E. G. R.; Silva, A. M. S.; Cavaleiro, J. A. S.; Silva, F. M.; Borges, M. F. M.; Pinto, M. M. ¹H and ¹³C NMR Spectroscopy of Mono-, Di-, Tri-, and Tetrasubstituted Xanthenes. *Magn. Reson. Chem.* **1998**, 36, 305-309.
- Fernandes, E. R.; Carvalho, F. D.; Remião, F. G.; Bastos, M. L.; Pinto, M. M.; Gottlieb, O. R. Hepatoprotective Activity of Xanthenes and Xanthonolignoids Against tert-

- Butylhydroperoxide-Induced Toxicity in Isolated Rat Hepatocytes- Comparison with Silybin. *Pharm. Res.* **1995**, *12*(11), 1756-1760.
- Fernandes, I. L. R. Avaliação da Actividade Estrogénica/Antiestrogénica de Xantonas Preniladas com Potente Efeito Antiproliferativo, *In Vitro*, na Linha Celular de Adenocarcinoma da Mama. *Relatório de Estágio, Faculdade de Ciências e Instituto de Ciências Biomédicas Abel Salazar*, Porto, **2006**.
- Figueroa, M.; González, M. C.; Rodríguez-Sotres, R.; Sosa-Peinado, A.; González-Andrade, M.; Cerda-García-Rojas, C. M.; Mata, R. Calmodulin inhibitors from the fungus *Emericella* sp. *Bioorg. Med. Chem.* **2009**, *17*, 2167-2174.
- Filho, V. C.; Meyre-Silva, C.; Niero, R. Chemical and Pharmacological Aspects of the Genus *Calophyllum*. *Chem. Biodiv.* **2009**, *6*, 313-327.
- Fotie, J.; Bohle, D. S. Pharmacological and Biological Activities of Xanthones. *Anti Infect. Agents Med. Chem.* **2006**, *5*, 15-31.
- Füllbeck, M.; Michalsky, E.; Dunkel, M.; Preissner, R. Natural products: sources and databases. *Nat. Prod. Rep.*, **2006**, *23*, 347–356.
- Gales, L.; Castanheiro, R. A. P.; Pinto, M. M. M.; Damas, A. M. 1-Hydroxy-3-(3-methylbut-2-enyloxy)xanthone. *Acta Cryst. E.* **2009**, *submetido*.
- Gales, L.; Damas, A. M. Xanthones – A Structural Perspective. *Curr. Med. Chem.* **2005**, *12*, 2499-2515.
- Gales, L.; Sousa, M. E.; Pinto, M. M. M.; Kijjoa, A.; Damas, A. M. Naturally occurring 1,2,8-trimethoxyxanthone and biphenyl ether intermediates leading to 1,2-dimethoxyxanthone. *Acta crystallogr. C: Cryst. struct. commun.* **2001**, *57*, 1319-1323.
- Ganesan, A. The impact of natural products upon modern drug discovery. *Curr. Opin. Chem. Biol.* **2008**, *12*, 306–317.
- Garade, A. C.; Mate, V. R.; Rode, C. V. Montmorillonite for selective hydroxyalkylation of π -cresol. *Appl. Clay Sci.* **2009**, *43*, 113–117.
- Garrido, G.; González, D.; Romay, C.; Núñez-Sellés, A. J.; Delgado, R. Scavenger effect of a mango (*Mangifera indica* L.) food supplement's active ingredient on free radicals produced by human polymorphonuclear cells and hypoxanthine–xanthine oxidase chemiluminescence systems. *Food Chem.* **2008**, *107*, 1008-1014.
- Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. The use of microwave ovens for rapid organic synthesis. *Tetrahedron Lett.* **1986**, *27*(3), 279-282.
- Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. Application of commercial microwave ovens to organic synthesis. *Tetrahedron Lett.* **1986**, *27*(41), 4945-4948.

- Gnerre, C.; Thull, U.; Gaillar, P.; Carrupt, P.A.; Testa, B.; Fernandes, E.; Silva, F.; Pinto, M.; Pinto, M.M.; Wolfender, J.L.; Hostettman, K.; Cruciani, G. Natural and Synthetic Xanthenes as Monoamine Oxidase Inhibitors: Biological Assay and 3D-QSAR. *Helv. Chim. Acta* **2001**, *84*, 552-570.
- Gonzalez, M. J.; Nascimento, M. S. J.; Cidade, H. M.; Pinto, M. M. M.; Kijjoa, A.; Anantachoke, C.; Silva, A. M. S.; Herz, W. Immunomodulatory Activity of Xanthenes from *Calophyllum tesmanni* var. *inophylloide*. *Planta Med.* **1999**, *65*, 368-371.
- Grover, P. K.; Shah, G. D.; Shah, R. C. Xanthenes. Part IV. A New Synthesis of Hydroxyxanthenes and Hydroxybenzophenones. *J. Chem. Soc.* **1955**, 3982-3985.
- Haefner, B. Drugs from the deep: marine natural products as drug candidates. *Drug Discov. Today* **2003**, *8*(12), 536-544.
- Han, Q. B.; Yang, N. Y.; Tian, H. L.; Qiao, C. F.; Song, J. Z.; Chang, D. C.; Chen, S. L.; Luo, K. Q.; Xu, H. X. Xanthenes with growth inhibition against HeLa cells from *Garcinia xipshuanbannaensis*. *Phytochemistry* **2008a**, *69*, 2187-2192.
- Han, Q.-B.; Qiao, C.-F.; Song, J.-Z.; Yang, N.-Y.; Cao, X.-W.; Peng, Y.; Yang, D.-J.; Chen, S.-L.; Xu, H.-X. Cytotoxic Prenylated Phenolic Compounds from the Twig Bark of *Garcinia xanthochymus*. *Chem. Biodiv.* **2007**, *4*, 940-946.
- Han, Q.-B.; Tian, H.-L.; Yang, N.-Y.; Qiao, C.-F.; Song, J.-Z.; Chang, D. C.; Luo, K. Q.; Xu, H.-X. Polyprenylated Xanthenes from *Garcinia lancilimba* Showing Apoptotic Effects against HeLa-C3 Cells. *Chem. Biodiv.* **2008b**, *5*, 2710-2717.
- Hansen, M.; Seung-Joo, L.; Cassady, J. M.; Hurley, L. Molecular Details of the Structure of a Psorospermin-DNA Covalent/Intercalation Complex and Associated DNA Sequence Selectivity. *J. Am. Chem. Soc.* **1996**, *118*, 5553-5561.
- Hansen, M.; Yun, S.; Hurley, L. Hedamycin intercalates the DNA helix and, through carbohydrate-mediated recognition in the minor groove, directs N7-alkylation of guanine in the major groove in a sequence-specific manner. *Chem. Biol.* **1995**, *2*, 229-240.
- Harrison, C. Anticancer Drugs: Partnering to promote apoptosis. *Nature Rev. Drug Discov.* **2008**, *7*, 805.
- Hartati, S.; Kadono, L. B. S.; Kosela, S.; Harrison, L. J. A New Pyrano Xanthone from the Stem Barks of *Garcinia tetrandra* Pierre. *J. Biol. Sci.* **2008**, *8*(1), 137-142.
- Harvey, A. L. Natural products in drug discovery. *Drug Discov. Today* **2008**, *13*(19/20), 894-901.
- Hashida, W.; Tanaka, N.; Takaishi, Y. Prenylated xanthenes from *Hypericum ascyron*. *J. Nat. Med.* **2007**, *61*(4), 371-374.

- Hassal, C. H.; Lewis, J. R. The Biosynthesis of Phenols. Part III. Oxidative Coupling Leading to Geodoxin and Related Compounds. *J. Chem. Soc.* **1961**, 2, 2312-2315.
- Hay, A.-E.; Merza, J.; Landreau, A.; Litaudon, M.; Pagniez, F.; Pape, P. L.; Richomme, P. Antileishmanial polyphenols from *Garcinia vieillardii*. *Fitoterapia* **2008**, 79, 42–46.
- Ho, L.-K.; Yu, H.-J.; Ho, C.-T.; Don, M.-J. Synthesis of Naturally Occurring Rubilactone, Mollugin, and Dihydromollugin of *Rubia cordifolia*. *J. Chin. Chem. Soc.* **2001**, 48, 77-79.
- Hostettmann, K.; Potterat, O.; Wolfender, J.-L. The Potencial of Higher Plants as a Source of New Drugs. *Chimia* **1998**, 52, 10-17.
- <http://en.wikipedia.org/wiki/Montmorillonite> (acedido em Novembro de 2008)
- http://foundationstabilization.com/html/the_theory.html (acedido em Novembro de 2008)
- <http://old.iupac.org/reports/provisional/abstract04/BB-prs310305/Chapter2-Sec25.pdf> (acedido em Outubro de 2008)
- http://pt.wikipedia.org/wiki/Hypericum_perforatum (acedido em Outubro de 2008).
- <http://pubs.usgs.gov/of/2001/of01-041/html/docs/clays/smc.htm> (acedido em Março de 2009)
- <http://www.esalq.usp.br/siesalq/pm/hipericao.pdf> (acedido em Outubro de 2008)
- <http://www.fromnaturewithlove.com/> (acedido em Março de 2009)
- <http://www.microwavesynthesis.net/> (acedido em Março de 2009)
- <http://www.milestonesci.com/synth-micro.php> (acedido em Abril de 2009)
- <http://www.saint-hilaire.ca/> (acedido em Março de 2009)
- <http://www.uni-graz.at/~kappeco/index.htm> (acedido em Março de 2009)
- Huang, P.-J. J.; Cameron, T. S.; Jha, A. Novel synthesis of 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans. *Tetrahedron Lett.* **2009**, 50, 51–54.
- Huang, S.-X.; Feng, C.; Zhou, Y.; Xu, G.; Han, Q.-B.; Qiao, C.-F.; Chang, D. C.; Luo, K. Q.; Xu, H.-X. Bioassay-Guided Isolation of Xanthenes and Polycyclic Prenylated Acylphloroglucinols from *Garcinia oblongifolia*. *J. Nat. Prod.* **2009**, 72, 130-135.
- Huang, T.-K.; Wang, R.; Shi, L.; Lu, X.-X. Montmorillonite K-10: An efficient and reusable catalyst for the synthesis of quinoxaline derivatives in water. *Catal. Commun.* **2008**, 9, 1143–1147.
- Hung, S.-H.; Shen, K.-H.; Wu, C.-H.; Liu, C.-L.; Shih, Y.-W. α -Mangostin Suppresses PC-3 Human Prostate Carcinoma Cell Metastasis by Inhibiting Matrix Metalloproteinase-2/9 and Urokinase-Plasminogen Expression through the JNK Signaling Pathway. *J. Agric. Food Chem.* **2009**, 57, 1291–1298.
- Hurley, L.; Fellows, I.; Schwaebe, M. K.; Whitten, J. P. Methods for preparation and use of psorospermin analogs. United States Patent 7244760, **2007**.

- Hwang, J. H.; Hong, S. S.; Han, X. H.; Hwang, J. S.; Lee, D.; Lee, H.; Yun, Y. P.; Kim, Y.; Ro, J. S.; Hwang, B. Y. Prenylated Xanthenes from the Root Bark of *Cudrania tricuspidata*. *J. Nat. Prod.* **2007**, *70*, 1207-1209.
- Jacob, A. M.; Moody, C. J. Microwave-assisted combined Mitsunobu reaction–Claisen rearrangement and microwave-assisted phenol oxidation: rapid synthesis of 2,6-disubstituted-1,4-benzoquinone natural products. *Tetrahedron Lett.* **2005**, *46*, 8823-8825.
- Jain, A. C.; Anand, S. M. Claisen Rearrangement of 1-Hydroxy-3-(3-methylbut-2-enyloxy)xanthenes. *J. Chem. Soc. Perkin Trans. 1*, **1974**, 329-333.
- Jimeno, J.; Faircloth, G.; Sousa-Faro, J.M. F.; Scheuer, P.; Rinehart, K. New Marine Derived Anticancer Therapeutics — A Journey from the Sea to Clinical Trials. *Mar. Drugs* **2004**, *2*, 14-29.
- Kantevari, S.; Vuppapapati, S. V. N.; Nagarapu, L. Montmorillonite K10 catalyzed efficient synthesis of amidoalkyl naphthols under solvent free conditions. *Catal. Commun.* **2007**, *8*, 1857–1862.
- Kappe, C. O. Controlled Microwave Heating in Modern Organic Synthesis. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250-6284.
- Kappe, C. O. Microwave Dielectric Heating in Synthetic Organic Chemistry. *Chem. Soc. Rev.* **2008**, *37*, 1127-1139.
- Kappe, C. O. Microwave dielectric heating in synthetic organic chemistry. *Chem. Soc. Rev.*, **2008**, *37*, 1127–1139.
- Kappe, C. O.; Dallinger, D. The Impact of Microwave Synthesis on Drug Discovery. *Nature Rev. Drug Disc.* **2006**, *5*, 51-63.
- Kappe, C. O.; Stadler, A. *Em Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2005**, Vol. 25.
- Kidwai, M. Dry media reactions. *Pure Appl. Chem.* **2001**, *73(1)*, 147–151.
- Kijjoa, A.; Gonzalez, M. J.; Pinto, M. M.; Nascimento, M. S. J.; Campos, N.; Mondranondra, I.-O.; Silva, A. M. S.; Eaton, G.; Herz, W. Cytotoxicity of Prenylated Xanthenes and Other Constituents from the Wood of *Garcinia merguensis*. *Planta Med.* **2008**, *74*, 864-866.
- Kijjoa, A.; Sawangwong, P. Drugs and Cosmetics from the Sea. *Mar. Drugs* **2004**, *2*, 73-82.
- Kim, T.-J.; Han, H.-J.; Hong, S.-S.; Hwang, J.-H.; Hwang, B.-Y.; Yoo, H.-S.; Jin, Y.-R.; Lee, J.-J.; Yu, J.-Y.; Lee, K.-H.; Kang, B.-W.; Yun, Y.-P. Cudraticusxanthone A isolated from the root bark of *Cudrania tricuspidata* inhibits the proliferation of vascular smooth muscle cells through the suppression of PDGF-Receptor beta tyrosine kinase. *Biol. Pharm. Bull.* **2007**, *30(4)*, 805-809.

- Kotha, S.; Mandal, K.; Deb, A. C.; Banerjee, S. Microwave-assisted Claisen rearrangement on a silica gel support. *Tetrahedron Lett.* **2004**, 45, 9603–9605.
- Kuete, V.; Nguemaving, J. R.; Beng, V. P.; Azebaze, A. G. B.; Etoa, F.-X.; Meyer, M.; Bodo, B.; Nkengfack, A. E. Antimicrobial activity of the methanolic extracts and compounds from *Vismia laurentii* De Wild (Guttiferae). *J. Ethnopharmacol.* **2007**, 109, 372-379.
- Kulkarni, A.; Abid, M.; Török, B.; Huang, X. A direct synthesis of β -carbolines via a three-step one-pot domino approach with a bifunctional Pd/C/K-10 catalyst. *Tetrahedron Lett.* **2009**, 50, 1791–1794.
- Kupchan, S. M.; Streelman, D. R.; Sneden, A. T. Psorospermin, a new antileukemic xanthone from *Psorospermum febrifugum*. *J. Nat. Prod.* **1980**, 43(2), 296-301.
- Kwok, Y.; Hurley, L. H. Topoisomerase II Site-Directed Alkylation of DNA by Psorospermin and its Effect on Topoisomerase II-Mediated DNA Cleavage. *J. Biol. Chem.* **1998**, 273(49), 33020-33026.
- Kwok, Y.; Zeng, Q.; Hurley, L. H. Topoisomerase II-mediated Site-Directed Alkylation of DNA by Psorospermin and Its Use in Mapping Other Topoisomerase II Poison Binding Sites. *Proc. Natl. Acad. Sci.* **1998**, 95(23), 13531-13536.
- Lam, K.S. New aspects of natural products in drug discovery. *Trends Microbiol.* **2007**, 15(6), 279–289.
- Laphookhieo, S.; Maneerat, W.; Buatip, T.; Syers, J. K. New Xanthenes from *Cratoxylum cochinchinense*. *Can. J. Chem.* **2008**, 86, 757-760.
- Leet, J. E.; Liu, X.; Drexler, D. M.; Cantone, J. L.; Huang, S.; Mamber, S. W.; Fairchild, C. R.; Hussain, R.; Newman, D. J.; Kingston, D. G. I. Cytotoxic Xanthenes from *Psorospermum molluscum* from the Madagascar Rain Forest. *J. Nat. Prod.* **2008**, 71, 460–463.
- Lenardão, E. J.; Trecha, D. O.; Ferreira, P. C.; Jacob, R. G.; Perin, G. Green Michael Addition of Thiols to Electron Deficient Alkenes using KF/Alumina and Recyclable Solvent or Solvent-free Conditions. *J. Braz. Chem. Soc.* **2009**, 20(1), 93-99.
- Li, J.; Liu, Q.; Xing, R. G.; Shen, X. X.; Liu, Z. G.; Zhou, B. Microwave-assisted one-pot synthesis of 3-substituted-3,4-dihydrocoumarins via tandem Knoevenagel and Hantzsch reactions. *Chinese Chem. Lett.* **2009**, 20, 25–28.
- Liang, B.; Li, H.-R.; Xu, L.-Z.; Yang, S.-L. Xanthenes from the roots of *Cudrania fruticosa* Wight. *J. Asian Nat. Prod. Res.* **2007**, 9(4), 393-397.
- Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. Microwave Assisted Organic Synthesis – A Review. *Tetrahedron* **2001**, 57, 9225-9283.

- Liu, Y.-H.; Liu, Q.-S.; Zhang, Z.-H. An efficient Friedel–Crafts alkylation of nitrogen heterocycles catalyzed by antimony trichloride/montmorillonite K-10. *Tetrahedron Lett.* **2009**, *50*, 916–921.
- Loghmani-Khouzani, H.; Sadeghi, M. M.; Safari, J.; Minaeifar, A. A novel method for the synthesis of 2-ketomethylquinolines under solvent-free conditions using microwave irradiation. *Tetrahedron Lett.* **2001**, *42*, 4363–4364
- Louh, G. N.; Lannang, A. M.; Mbazoa, C. D.; Tangmouo, J. G.; Komguem, J.; Castilho, P.; Ngninzeko, F. N.; Qamar, N.; Lontsi, D.; Choudhary, M. I.; Sondengam, B. L. Polyanxanthone A, B and C, three xanthenes from the wood trunk of *Garcinia polyantha* Oliv. *Phytochemistry* **2008**, *69*, 1013–1017.
- Loupy, A. Ed. *Em Microwaves in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2002**.
- Mahabusarakam, W.; Pakawatchai, C.; Wiriyachitra, P.; Taylor, W. C.; Skelton, B. W.; White, A. H. Bicyclomangostin: a New Acid-Catalysed Cyclisation Product from Mangostin. *Aust. J. Chem.* **1998**, *51*, 249–254.
- Mahabusarakam, W.; Rattanaburi, S.; Phongpaichit, S.; Kanjana-Opas, A. Antibacterial and cytotoxic xanthenes from *Cratoxylum cochinchinense*. *Phytochemistry Lett.* **2008**, *1*, 211–214.
- Maia, F.; Almeida, M. R.; Gales, L.; Kijjoa, A.; Pinto, M. M. M.; Saraiva, M. J.; Damas, A. M. The binding of xanthone derivatives to transthyretin. *Biochem. Pharmacol.* **2005**, *70*, 1861–1869.
- Marjani, K.; Asgari, M.; Ashouri, A.; Mahdavinia, G. H.; Ahangar, H. A. Microwave-assisted aldol condensation of benzil with ketones. *Chinese Chem. Lett.* **2009**, *20*, 401–403.
- Masullo, M.; Bassarello, C.; Suzuki, H.; Pizza, C.; Piacente, S. Polyisoprenylated Benzophenones and an Unusual Polyisoprenylated Tetracyclic Xanthone from the Fruits of *Garcinia Cambogia*. *J. Agric. Food Chem.* **2008**, *56*, 5205–5210.
- McKeown, S. R.; Cowen, R. L.; Williams, K. J. Bioreductive Drugs: from Concept to Clinic. *Clinical Oncol.* **2007**, *19*, 427–442.
- Mekheimer, R. A.; Sadek, K. U. Microwave-assisted reactions: Three-component process for the synthesis of 2-amino-2-chromenes under microwave heating. *Chinese Chem. Lett.* **2009**, *20*, 271–274.
- Mennini, T.; Gobbi, M. The antidepressant mechanism of *Hypericum perforatum*. *Life Sciences* **2004**, *75*, 1021–1027.
- Mesquita, A. A. L.; Corrêa, D. B.; Gottlieb, O. R.; Magalhães, M. T. Methods for the Structural Investigation of Xanthenes. Part II. Location of the Hydroxyl Groups by Ultra-Violet and Visible Spectroscopy. *Anal. Chim. Acta* **1968**, *42*, 331–323.

- Montanari, C. A.; Bolzani, V. S. Planejamento Racional de Fármacos Baseado em Produtos Naturais. *Quim. Nova* **2001**, 24(1), 105-111.
- Moreau, S.; Varache-Lembège, M.; Larroure, S.; Fall, D.; Neveu, A.; Deffieux, G.; Vercauteren, J.; Nuhric, A. (2-Arylhyaazonomethyl)-substituted xanthonas as antimycotics: synthesis and fungistatic activity against *Candida species*. *Eur. J. Med. Chem.* **2002**, 37, 237-253.
- Moroz, A. A.; Shvartsberg, M. S. The Ullmann Ether Condensation. *Russ. Chem. Rev.* **1974**, 43(8), 679-689.
- Mortoni, A.; Martinelli, M.; Piarulli, U.; Regalia, N.; Gagliardi, S. Microwave-Assisted Solvent-Free Synthesis of a Quinoline-3,4-Dicarboximide Library on Inorganic Solid Supports. *Tetrahedron Lett.* **2004**, 45, 6623-6627.
- Nagendrappa, G. Organic Synthesis Using Clay Catalysts – Clays for Green Chemistry. *Resonance* **2002**, 64-77.
- Newman, D. J.; Cragg, G. M. Marine Natural Products and Related Compounds in Clinical and Advanced Preclinical Trials. *J. Nat. Prod.* **2004**, 67, 1216-1238.
- Newman, D. J.; Cragg, G. M.; Natural products as sources of new drugs over the last 25 years. *J. Nat. Prod.* **2007**, 70, 461-477.
- Nicolaou, K. C.; Chen, J. S.; Dalby, S. M. From nature to the laboratory and into the clinic. *Bioorg. Med. Chem.* **2009**, 17, 2290-2303.
- Oliveira, A. M. A. G.; Oliveira-Campos, A. M. F.; Rodrigues, L. M.; Raposo, M. M. M.; Machado, A. E. H.; Nascimento, M. S. J.; Nazareth, N.; Pinto, M. Synthesis and Antitumor Evaluation of Benzopsoralen Analogues. *Chem. Biodiv.* **2007**, 4, 980-990.
- Oliveira-Campos, A. M. F.; Sivasubramanian, A.; Rodrigues, L. M.; Seijas, J. A.; Vázquez-Tato, M. P.; Peixoto, F.; Abreu, C. G.; Cidade, H.; Oliveira, A. E.; Pinto, M. Substituted Pyrazolo[3,4-d]pyrimidines: Microwave-Assisted, Solvent-Free Synthesis and Biological Evaluation. *Helv. Chim. Acta* **2008**, 91, 1336-1345.
- Olsson, R.; Hansen, H. C.; Andersson, C. M. Microwave-assisted solvent-free parallel synthesis of Thioamides. *Tetrahedron Lett.* **2000**, 41, 7947-7950.
- Pachuta, R. R.; Cooks, R. G.; Cassady, J. M.; Cong, P.; McCloud, T. G.; Chang, C. J. Antineoplastic Agents from Higher Plants: Application of Tandem Mass Spectrometry to Xanthonas from *Psorospermum febrifugum*. *J. Nat. Prod.* **1986**, 49(3), 412-423.
- Pankajamani, K. S.; Seshadri, T. R. Synthetic Experiments in the Benzopyrone Series: Part XLVI- Application on the Nencki Reaction in the Synthesis of Xanthonas. *J. Sci. Industr. Res.* **1954**, 13B, 396-400.

- Patel, G. N.; Trivedi, K. N. Abnormal Claisen Rearrangement of 3-prenyloxyxanthone and 3-prenyloxy-4-methylxanthone. *J. Indian Chem. Soc.* **1988**, *65*, 192-193.
- Patonay, T.; Kiss-Szikszai, A.; Silva, V. M. L.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Jekó, J. Microwave-Induced Synthesis and Regio- and Stereoselective Epoxidation of 3-Styrylchromones. *Eur. J. Org. Chem.* **2008**, 1937-1946.
- Patrick, G. L. Em An Introduction to Medicinal Chemistry; Oxford University Press Inc., New York, **2005**.
- Pavia, D. L.; Lampman, G. M.; Kriz, G. S. Em Introduction to Spectroscopy. Harcourt College Publishers, Philadelphia, 3rd ed., **2001**.
- Pedraza-Chaverri, J.; Cárdenas-Rodríguez, N.; Orozco-Ibarra, M.; Pérez-Rojas, J. M. Medicinal properties of mangosteen (*Garcinia mangostana*). *Food Chem. Toxicol.* **2008**, *46*, 3227-3239.
- Pedro de Oliveira, M. M. M. Pesquisa de Actividade Antitumoral em Compostos de Origem Natural e Sintética. Avaliação dos mecanismos celulares afectados pela acção de flavonas preniladas, estililcromonas e diterpenos abietânicos. *Tese de doutoramento, Faculdade de Farmácia da Universidade do Porto, Porto*, **2006**.
- Pedro, M. M.; Cerqueira, F.; Sousa, M. E.; Nascimento, M. S. J.; Pinto, M. M. M. Xanthonas as Inhibitors of Growth of Human Cancer Cell Lines and Their Effects on the Proliferation of Human Lymphocytes *In Vitro*. *Bioorg. Med. Chem.* **2002**, *10*, 3725-3730.
- Peres, V.; Nagem, T. J. Naturally Occurring Penta-oxygenated, Hexa-oxygenated and Dimeric Xanthonas. *Quimica Nova* **1997b**, *20*(4), 388-397.
- Peres, V.; Nagem, T. J. Tri-oxygenated Naturally Occurring Xanthonas. *Phytochemistry* **1997a**, *44*(2), 191-214.
- Peres, V.; Nagem, T. J.; Oliveira, F. F. Tetra-oxygenated Naturally Occurring Xanthonas. *Phytochemistry* **2000**, *55*, 683-710.
- Permana, P. A.; Ho, D. K.; Cassady, J. M.; Snapka, R. M. Mechanism of Action of the Antileukemic Xanthone Psorospermin: DNA Strand Breaks, Abasic Sites, and Protein-DNA Cross-Links. *Cancer Res.* **1994**, *54*(12), 3191-3195.
- Pillai, R. K. M.; Naiksatam, P.; Johnson, F.; Rajagopalan, R.; Watts, P. C.; Cricchio, R.; Borrás, S. Thermorubin II: 1,3-Dihydroxy-9*H*-xanthonas and 1,3-Dihydroxy-9*H*-xanthenes. New Methods of Synthesis. *J. Org. Chem.* **1986**, *51*(5), 717-723.
- Pinto, D. C. G. A.; Silva, A. M. S.; Brito, C. M.; Sandulache, A.; Carrillo, J. R.; Prieto, P.; Díaz-Ortiz, A.; Hoz, A.; Cavaleiro, J. A. S. Reactivity of 3-Styrylchromones as Dienes in Diels–Alder

- Reactions under Microwave Irradiation: A New Synthesis of Xanthenes. *Eur. J. Org. Chem.* **2005a**, 2973-2986.
- Pinto, M. & Castanheiro, R.; Natural Prenylated Xanthenes: Chemistry and Biological Activities. Em *Natural Products: Chemistry, Biochemistry and Pharmacology*. Ed. Brahmachari, G., Narosa Publishing House PVT. LTD., Nova Deli, Índia, ISBN: 978-81-7319-886-1, **2009a**, Cap. 17, pp. 520-676.
- Pinto, M. M. M. & Castanheiro, R. A. P. Synthesis of Prenylated Xanthenes: An Overview. *Curr. Org. Chem.* **2009b**, submetido.
- Pinto, M. M. M.; Polónia, J. Synthesis of New Xanthenes, I. *Helv. Chim. Acta* **1974**, 57(8), 2613-2618.
- Pinto, M. M. M.; Sousa, M. E.; Nascimento, M. S. J. Xanthone Derivatives: New Insights in Biological Activities. *Curr. Med. Chem.* **2005b**, 12, 2517-2538.
- Pinto, M., Sousa, M. E., Castanheiro, R., Saraiva, L., Pereira, G., Gonçalves, J., "Inhibition of α , β I, δ , η and ζ Protein Kinase C Isoforms by Xanthenes: Improvements Towards Selectivity", *Drugs of the Future*, **2006**, 31, Suppl. A, Abstracts from the "XIXth International Symposium on Medicinal Chemistry (ISMC 2006)", 154.
- Pinto, M.; Nascimento, M. S. J. Anticomplementary Activity of Hydroxy and Methoxyxanthenes. *Pharm. Pharmacol. Lett.* **1997**, 7 (2/3), 125-127.
- Pinto, M.; Nascimento, M. S. J.; Gonzalez, M.J.; Mondranondra, I. O. Anticomplementary Activity and Constituents of *Cratogeomys maynardi* DYER. *Pharm. Pharmacol. Lett.* **1997**, 7 (2/3), 128-130.
- Portela, C. A. S. Obtenção e Estudo de Derivados Xantônicos, Candidatos a Novos Agentes Antimaláricos. *Tese de doutoramento, Faculdade de Farmácia da Universidade do Porto*, Porto, **2006**.
- Portela, C.; Afonso, C. M. M.; Pinto, M. M. M.; Lopes, D.; Nogueira, F.; Rosário, V. Synthesis and Antimalarial Properties of New Chloro-9H-xanthenes with an Aminoalkyl Side Chain. *Chem Biodiv.* **2007**, 4, 1508-1519.
- Pouli, N.; Marakos, P. Fused Xanthone Derivatives as Antiproliferative Agents. *Anti Canc Agents in Med. Chem.* **2009**, 9(1), 71-98.
- Qiang, L.; Yang, Y.; You, Q.-D.; Ma, Y.-J.; Yang, L.; Nie, F.-F.; Gu, H.-Y.; Zhao, L.; Lu, N.; Qi, Q.; Liu, W.; Wang, X.-T.; Guo, Q.-L. Inhibition of glioblastoma growth and angiogenesis by gambogic acid: An *in vitro* and *in vivo* study. *Biochem. Pharmacol.* **2008**, 75, 1083-1092.

- Quillinan, A. J.; Scheinmann, F. Studies in the Xanthone Series. Part XII. A General Synthesis of Polyoxygenated Xanthenes from Benzophenone Precursors. *J. Chem. Soc. Perkin Trans. 1* **1973**, 2, 1329-1337.
- Quinn, R. J.; Carroll, A. R.; Pham, N. B.; Baron, P.; Palframan, M. E.; Suraweera, L.; Pierens, G. K.; Muresan, S. Developing a Drug-like Natural Product Library. *J. Nat. Prod.* **2008**, 71, 464-468.
- Rehman, F.; Rustin, G. ASA404: Update on drug development. *Expert Opin. Investig. Drugs* **2008**, 17(10), 1547-1551.
- Reutrakul, V.; Anantachoke, N.; Pohmakotr, M.; Jaipetch, T.; Sophasan, S.; Yoosook, C.; Kasisit, J.; Napaswat, C.; Santisuk, T.; Tuchinda, P. Cytotoxic and Anti-HIV Caged Xanthenes, from the Resin and Fruits of *Garcinia hanburyi*. *Planta Med.* **2007**, 73, 33-40.
- Rewcastle, G. W.; Atwell, G. J.; Li, Z. A.; Baguley, B. C.; Denny, W. A. Potential Antitumor Agents. 61. Structure-Activity Relationships for *In Vivo* Colon 38 Activity among Disubstituted 9-Oxo-9H-xanthene-4-acetic Acids. *J. Med. Chem.* **1991**, 34(1), 217-222.
- Rezende, C. M. A. M.; Gottlieb, O. R. Xanthenes as Systematic Markers. *Biochemical Systematics* **1973**, 1, 111-118.
- Riscoe, M.; Kelly, J. X.; Winter, R. Xanthenes as Antimalarial Agents: Discovery, Mode of Action and Optimization. *Curr. Med. Chem.* **2005**, 12, 2539-2549.
- Roberts, Z. J.; Goutagny, N.; Perera, P.-Y.; Kato, H.; Kumar, H.; Kawai, T.; Akira, S.; Savan, R.; Echo, D. V.; Fitzgerald, K. A.; Young, H. A.; Ching, L.-M.; Vogel, S. N. The Chemotherapeutic Agent DMXAA Potently and Specifically Activates the TBK1-IRF-3 Signaling Axis. *J. Exp. Med.* **2007**, 204(7), 1559-1569.
- Rodríguez-Landa, J. F.; Contreras, C. M. A review of clinical and experimental observations about antidepressant actions and side effects produced by *Hypericum perforatum* extracts. *Phytomedicine* **2003**, 10, 688-699.
- Rosini, F.; Nascentes, C. C.; Nóbrega, J. A. Experimentos Didáticos Envolvendo Radiação Microondas. *Quim. Nova* **2004**, 27(6), 1012-1015.
- Ruske, W., Friedel-Crafts and related reactions, Olah, G.A. Ed.; Interscience Publishers, John Wiley & Sons: New York, **1964**, 383-497.
- Ryu, Y. B.; Curtis-Long, M. J.; Lee, J. W.; Kim, J. H.; Kim, J. Y.; Kang, K. Y.; Lee, W. S.; Park, K. H. Characteristic of neuraminidase inhibitory xanthenes from *Cudrania tricuspidata*. *Bioorg. Med. Chem.* **2009**, 17, 2744-2750.
- Saklani, A.; Kutty, S. K. Plant-derived compounds in clinical trials. *Drug Discov. Today* **2008**, 13(3/4), 161-171.

- Saleem, M.; Ali, M. S.; Hussain, S.; Jabbar, A.; Ashraf, M.; Lee, Y. S. Marine natural products of fungal origin. *Nat. Prod. Rep.*, **2007**, 24, 1142–1152.
- Sanseverino, A. M. Microondas e Síntese Orgânica. *Quim. Nova* **2002**, 25(4), 660-667.
- Saraiva, L.; Fresco, P.; Kijjoa, A.; Gonzalez, M. J.; Gonçalves, J. Differential Activation of Protein Kinase C Isoforms by Euxanthone, Revealed by an In Vivo Yeast Phenotypic Assay. *Planta Med.* **2002a**, 68, 1039-1041.
- Saraiva, L.; Fresco, P.; Pinto, E.; Sousa, E.; Pinto, M.; Gonçalves, J. Synthesis and *In Vivo* Modulatory Activity of Protein Kinase C of Xanthone Derivatives. *Bioorg. Med. Chem.* **2002b**, 10, 3219-3227.
- Saraiva, L.; Fresco, P.; Pinto, E.; Sousa, E.; Pinto, M.; Gonçalves, J. Inhibition of Protein Kinase C by Synthetic Xanthone Derivatives. *Bioorg. Med. Chem.* **2003**, 11, 1215-1225.
- Schwaebe, M. K.; Moran, T. J.; Whitten, J. P. Total synthesis of psorospermin. *Tetrahedron Lett.* **2005**, 46, 827–829.
- Seo, E. J.; Curtis-Long, M. J.; Lee, B. W.; Kim, H. Y.; Ryu, Y. B.; Jeong, T.-S.; Leec, W. S.; Parka, K. H. Xanthonones from *Cudrania Tricuspidata* displaying potent α -glucosidase inhibition. *Bioorg. Med. Chem. Lett.* **2007**, 17, 6421–6424.
- Shadid, K. A.; Shaari, K.; Abas, F.; Israf, D. A.; Hamzah, A. S.; Syakroni, N.; Saha, K.; Lajis, N. Hj. Cytotoxic caged-polyprenylated xanthonoids and a xanthone from *Garcinia cantleyana*. *Phytochemistry* **2007**, 68, 2537-2544.
- Sheldon, R. A.; Arends, I.; Hanefeld, U. *Em Green Chemistry and Catalysis*. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2007**.
- Shi, D.; Wu, N.; Zhuang, Q. KF-Montmorillonite-catalyzed Michael Addition Reaction of Malononitrile to α,β -Unsaturated Ketones. *Chinese J. Chem.* **2009**, 27, 169—173.
- Silva, A. M. S.; Pinto, D. C. G. A. Structure Elucidation of Xanthone Derivatives: Studies of Nuclear Magnetic Resonance Spectroscopy. *Curr. Med. Chem.* **2005**, 12, 2481-2497.
- Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Levai, A.; Patonay, T. Synthesis and reactivity of styrylchromones. *ARKIVOC* **2004**, vii, 106-123.
- Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Em Spectrometric Identification of Organic Compounds*. John Wiley & Sons, Inc., Singapore, 5^aed., **1991**.
- Singh, P.; Natani, K.; Jain, S.; Arya, K. ; Dandia, A. Microwave-assisted rapid cyclization of lapachol, a main constituent of *Heterophragma adenophyllum*. *Nat. Prod. Res.* **2006**, 20(2), 207–212.
- Sousa, M. E. S. P. Derivados de Xanten-9-ona: Síntese, Determinação Estrutural e Avaliação de Atividades Biológicas. *Tese de doutoramento, Faculdade de Farmácia da Universidade do Porto, Porto*, **2003**.

- Sousa, M. E.; Pinto, M. M. M. Synthesis of Xanthones: An Overview. *Curr. Med. Chem.* **2005**, *12*, 2447-2479.
- Spitaler, M.; Cantrell, D. A. Protein kinase C and beyond. *Nat. Immunol.* **2004**, *5*, 785-790.
- Subba Rao, G. S. R.; Raghavan, S. Synthetic studies on morellin. Part 4: Synthesis of 2,2-dimethyl-12-[3-methylbut-2-enyl]-2H,6H-pyrano[3,2-b]xanthen-6-one. *J. Indian Inst. Sci.* **2001**, *81*, 393-401.
- Sultanbawa, M. U. S. Xanthonoids of Tropical Plants. *Tetrahedron* **1980**, *36*, 1465-1506.
- Tala, M. F.; Krohn, K.; Hussain, H.; Kouam, S. F.; Wabo, H. K.; Tane, P.; Schulz, B.; Hu, Q. Laurentixanthone C: A New Antifungal and Algicidal Xanthone from Stem Bark of *Vismia laurentii*. *Z. Naturforsch.* **2007**, *62b*, 565-568.
- Tao, S.-J.; Guan, S.-H.; Wang, W.; Lu, Z.-Q.; Chen, G.-T.; Sha, N.; Yue, Q.-X.; Liu, X.; Guo, D.-A. Cytotoxic Polyprenylated Xanthonoids from the Resin of *Garcinia hanburyi*. *J. Nat. Prod.* **2009**, *72*, 117-124.
- Tchamo, D. N.; Dijoux-Franca, M.G.; Mariotte, A. M.; Tsamo, E.; Daskiewicz, J. B.; Bayet, C.; Barron, D.; Conseil G.; Di Pietro, A. Prenylated Xanthonoids as Potential P-Glycoprotein Modulators. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1343-1345.
- Teixeira, C. M. B. Nanopartículas Poliméricas de Derivados Xantônicos. *Tese de doutoramento, Faculdade de Farmácia da Universidade do Porto, Porto*, **2008**.
- Teixeira, M.; Cerqueira, F.; Barbosa, C. M.; Nascimento, M. S. J.; Pinto, M. Improvement of the inhibitory effect of xanthonoids on NO production by encapsulation in PLGA nanocapsules. *J. Drug Targeting* **2005**, *13*(2), 129-135.
- Teixeira, S. C. M. Modificação Molecular de Xantonas por Prenilação. *Relatório de Estágio, Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa e Faculdade de Farmácia da Universidade do Porto*, **2005**.
- Usyatinsky, A. Y.; Khmel'nitsky, Y. L. Microwave-assisted synthesis of substituted imidazoles on a solid support under solvent-free conditions. *Tetrahedron Lett.* **2000**, *41*, 5031-5034.
- Vaccari, A. Clays and catalysis: a promising future. *Appl. Clay Sci.* **1999**, *14*, 161-198.
- Vaccari, A. Preparation and catalytic properties of cationic and anionic clays. *Catal. Today* **1998**, *41*, 53-71.
- Varma, R. S. Clay and clay-supported reagents in organic synthesis. *Tetrahedron* **2002**, *58*, 1235-1255.
- Varma, R. S. Solvent-free accelerated organic syntheses using microwaves. *Pure Appl. Chem.* **2001**, *73*(1), 193-198.

- Varma, R. S. Solvent-free accelerated organic syntheses using microwaves. *Pure Appl. Chem.* **2001**, 73(1), 193–198.
- Varma, R. S. Solvent-free organic syntheses using supported reagents and microwave irradiation. *Green Chem.* **1999**, 43–55.
- Varma, R. S.; Kumar, D.; Liesen, P. J. Solid state synthesis of 2-arylbenzo[b]furans, 1,3-thiazoles and 3-aryl-5,6-dihydroimidazo[2,1-b][1,3]thiazoles from α -tosyloxyketones using microwave irradiation. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4093–4096.
- Viegas Jr, C.; Bolzani, V. S.; Barreiro, E. J. Os Produtos Naturais E A Química Medicinal Moderna. *Quim. Nova* **2006**, 29(2), 326–337.
- Vieira, L. M. M.; Kijjoa, A. Naturally-Occurring Xanthenes: Recent Developments; *Curr. Med. Chem.* **2005**, 12, 2413–2446.
- Vijayakumar, B.; Nagendrappa, G.; Prakash, B. S. J. Acid Activated Indian Bentonite, an Efficient Catalyst for Esterification of Carboxylic Acids. *Catal. Lett.* **2009**, 128, 183–189.
- Wang, L. C. S.; Ching, L.-M.; Paxton, J. W.; Kestell, P.; Sutherland, R.; Zhuang, L.; Baguley, B. C. Enhancement of the action of the antivasular drug 5,6-dimethylxanthenone-4-acetic acid (DMXAA; ASA404) by non-steroidal anti-inflammatory drugs. *Invest. New Drugs* **2008a**, *Short Report*.
- Wang, L. L.; Li, Z. L.; Xu, Y. P.; Liu, X. Q.; Pei, Y. H.; Jing, Y. K.; Hua, H. M. A new cytotoxic caged polyprenylated xanthone from the resin of *Garcinia hanburyi*. *Chinese Chem. Lett.* **2008b**, 19, 1221–1223.
- Wang, T.; Wei, J.; Qian, X.; Ding, Y.; Yu, L.; Liu, B. Gambogic acid, a potent inhibitor of survivin, reverses docetaxel resistance in gastric cancer cells. *Cancer Lett.* **2008c**, 262, 214–222.
- Webb, B. L. J.; Hirst, S. J.; Giembyez, M. A. Protein Kinase C Isoenzymes: a Review of Their Structure, Regulation and Role in Regulating Airways Smooth Muscle Tone and Mitogenesis. *British J. Pharmacol.* **2000**, 130, 1433–1452.
- Wei, P.; Zhang, X.; Tu, S.; Yan, S.; Ying, H.; Ouyang, P. New potential inhibitors of DNA topoisomerase. Part II: Design and synthesis of α -lapachone derivatives under microwave irradiation. *Bioorg. Med. Chem. Lett.* **2009**, 19, 828–830.
- Wen, L.; Lin, Y. C.; She, Z. G.; Du, D. S.; Chan, W. L.; Zheng, Z. H. Paeciloxanthone, a new cytotoxic xanthone from the marine mangrove fungus *Paecilomyces* sp. (Tree1-7). *J. Asian Nat. Prod. Res.*, **2008**, 10(2), 133–137.
- Wilairat, R.; Manosroi, J.; Manosroi, A.; Kijjoa, A.; Nascimento, M.S.J.; Pinto, M.; Silva, A.M.S.; Eaton, G.; Herz, W. Cytotoxicities of xanthenes and cinnamate esters from *Hypericum hookerianum*. *Planta Med.* **2005**, 71 (7), 680–682.

- Wu, H.-C.; Huang, C.-T.; Chang, D.-K. Anti-Angiogenic Therapeutic Drugs for Treatment of Human Cancer. *J. Cancer Mol.* **2008**, 4(2), 37-45.
- Xiao, Q.; Zeng, Y.-B.; Mei, W.-L.; Zhao, Y.-X.; Deng Y.-Y.; Dai, H.-F. Cytotoxic prenylated xanthenes from *Calophyllum inophyllum*. *J. Asian Nat. Prod. Res.* **2008**, 10(10), 993–997.
- Xu, G.; Feng, C.; Zhou, Y.; Han, Q.-B.; Qiao, C.-F.; Huang, S.-X.; Chang, D. C.; Zhao, Q.-S.; Luo, K. Q.; Xu, H.-X. Bioassay and Ultraperformance Liquid Chromatography/Mass Spectrometry Guided Isolation of Apoptosis-Inducing Benzophenones and Xanthone from the Pericarp of *Garcinia Yunnanensis* Hu. *J. Agric. Food Chem.* **2008**
- Yang, N.-Y.; Han, Q.-B.; Cao, X.-W.; Qiao, C.-F.; Song, J.-Z.; Chen, S.-L.; Yang, D.-J.; Yiu, H.; Xu, H.-X. Two New Xanthenes from the Stem Bark of *Garcinia lancilimba*. *Chem. Pharm. Bull.* **2007**, 55(6), 950-952.
- Yu, L.; Zhao, M.; Yang, B.; Zhao, Q.; Jiang, Y. Phenolics from hull of *Garcinia mangostana* fruit and their antioxidant activities. *Food Chem.* **2007**, 104, 176-181.
- Zare, A.; Hasaninejad, A.; Beyzavi, M. H.; Zare, A. R. M.; Khalafi-Nezhad, A.; Asadi, F.; Baramaki, L.; Jomhori-Angali, S.; Ghaleh-Golabi, R. KF/Al₂O₃ as a Highly Efficient, Green, Heterogeneous, and Reusable Catalytic System for the Solvent-Free Synthesis of Carboacyclic Nucleosides via Michael Addition Reaction. *Synth. Commun.* **2009**, 39, 139–157.
- Zelefack, F.; Guilet, D.; Fabre, N.; Bayet, C.; Chevalley, S.; Ngouela, S.; Lenta, B. N.; Valentin, A.; Tsamo, E.; Dijoux-Franca, M.-G. Cytotoxic and Antiplasmodial Xanthenes from *Pentadesma butyracea*. *J. Nat. Prod.* **2009**.
- Zhang, L.; Zhang, J. Y. Microwave-Assisted, Boron Trichloride Mediated Acylation of Phenols-Synthesis of (o-Hydroxyaryl)(Aryl)methanones and Xanthenes. *J. Comb. Chem.* **2006**, 8, 361-367.
- Zhong, F. F.; Chen, Y.; Mei, Z. N.; Yang, G. Z. Xanthenes from the bark of *Garcinia Xanthochymus*. *Chinese Chem. Lett.* **2007**, 18, 849–851.
- Zhong, F.; Chen, Y.; Wang, P.; Feng, H.; Yang, G. Xanthenes from the Bark of *Garcinia xanthochymus* and Their 1,1-Diphenyl-2-picrylhydrazyl Radical-Scavenging Activity. *Chin. J. Chem.* **2009**, 27, 74-80.
- Zhong, F.-F.; Chen, Y.; Song, F.-J.; Yang, G.-Z. Three new xanthenes from *Garcinia xanthochymus*. *Yaoxue Xuebao* **2008a**, 43(9), 938-941.
- Zhong, F.-F.; Chen, Y.; Yang, G.-Z. Chemical Constituents from the Bark of *Garcinia xanthochymus* and their 1,1-Diphenyl-2-picrylhydrazyl (DPPH) Radical-Scavenging Activities. *Helv. Chim. Acta* **2008b**, 91, 1695-1703.

Zhou, Y.; Han, Q.-B.; Song, J.-Z.; Qiao, C.-F.; Xu, H.-X. Characterization of polyprenylated xanthenes in *Garcinia xipshuanbannaensis* using liquid chromatography coupled with electrospray ionization quadrupole time-of-flight tandem mass spectrometry. *J. Chromatogr. A* **2008**, 1206, 131-139.

ANEXOS

ANEXO I

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Natural Prenylated Xanthenes: Chemistry and Biological Activities

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ABSTRACT

Xanthenes or 9H-xanthen-9-ones comprise an important class of oxygenated heterocycles. Among naturally occurring xanthenes, the prenylated derivatives are the most abundant group and possess a pleiade of very important pharmacological activities. Mangostin and gambogic acid are good examples of this group. Our literature survey, covering the period of January 1963 to December 2006, has shown that a total of 518 naturally occurring prenylated xanthenes have been described and among these 23 were obtained by synthesis.

Biosynthesis of the xanthenes and their prenylated derivatives from higher plants is also mentioned highlighting the aspects of incorporation study of the labelled precursors as well as characterization of the enzymes catalyzing the key steps of biosynthetic pathway in the cell cultured system. Moreover, the biomimetic syntheses of the prenylated caged xanthenes involving a tandem Claisen/Diels-Alder rearrangement were also discussed.

Finally, biological activities of prenylated xanthenes and their structure-activity relationship (SAR) are also discussed, with an emphasis on antitumor activity leading to the discovery and development of apoptosis inducers as potential new anticancer agents. An attention is also paid to the prenyl moieties, which, besides the oxygenation pattern, play an important role in the definition of the different activities as well as in the specificity for a biological target.

Keywords: Prenylated xanthenes, Prenyl, Biosynthesis, NMR, X-Ray, Chemopreventive, Antitumor, Cytotoxic, Antimicrobial, Antifungal, Antibacterial, Trypanocidal, Antimycobacterial, Apoptosis, Moraceae, Guttiferace, Gentianaceae, Geranyls, Cyclic, Caged, Gambogic acid, Mangostin, Lipophilicity, Structure-activity relationship (SAR), Platelet activation factor (PAF).

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1. INTRODUCTION

Xanthenes are secondary metabolites produced by a few families of higher plants, fungi and lichens. Their high taxonomic value (Vieira and Kijjoo, 2005) in such families allied with their interesting pharmacological properties have recently roused a great interest for this class of compounds (Pinto et al., 2005).

Chemically, xanthenes (9H-xanthen-9-ones) are heterocyclic compounds with a scaffold based on dibenzo- γ -pyrone (**Figure 1**) and naturally occurring xanthenes can be further subdivided, depending on the nature of the substituents in the dibenzo- γ -pyrone scaffold, into: simple oxygenated, glycosylated, prenylated and their derivatives, xanthone dimers, xanthonolignoids and miscellaneous (Pinto et al., 2005), being prenylated xanthenes the most abundant group of naturally occurring xanthenes. It is important to point out also that prenylated xanthenes are considered as chemotaxonomic markers for some higher plant families, especially Guttiferae (Clusiaceae) and Gentianaceae.

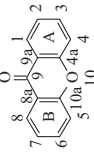


Fig. 1 Xanthone Scaffold and Its Numbering

Although a number of reviews on natural xanthenes has appeared in the literature in the past years (Vieira and Kijjoo, 2005; Mandal et al., 1992; Sultanbawa, 1980; Bennett and Lee,

1989; Peres et al., 1997a, b, 2000; Pinto and Sousa, 2003), the more recent ones are restricted to natural compounds isolated from a specific genus (Han et al., 2003; Brahmachari et al., 2004) or family (Bennett and Lee, 1989) or concerned with a specific chemical group of xanthenes (Peres et al., 1997a, b, 2000; Pinto and Sousa, 2003). However, none of these reviews have focused on the prenylated derivatives as a separate group.

In spite of a wide range of pharmacological activities exhibited by prenylated xanthenes (such as antibacterial, anti-inflammatory, antifungal, cytotoxic and antitumor activities), the recent reviews on xanthenes have systematically referred only briefly to their biological activities (Vieira and Kijjoo, 2005; Pinto et al., 2005). Consequently, we now report, besides natural sources and biosynthesis, the biological activities exhibited by prenylated xanthenes in the period of 1963 to 2006, with an emphasis on the aspects, which have not been referred in the previous reviews.

2. NATURAL PRENYLATED AND RELATED XANTHENES REPORTED DURING THE PERIOD 1963-2006

From the literature survey in the period of January 1963 to December 2006, a total of 518 naturally occurring prenylated xanthenes have been cited (**Table 1, 1-518**) and among these, 23 were also obtained by synthesis (**25, 26, 48, 55, 71, 115, 126, 127, 133, 141, 142, 155, 254, 255, 293, 363, 364, 367, 370, 371, 374, 376, 406**).

Table 1 Prenylated and related xanthenes isolated from natural sources from 1963-2006

Nº	Name of the compounds	Structure	Origin	References
1	Variecoxanthone A		<i>Aspergillus varicolor</i> (Fungus)	Chexal et al., 1975
2	Variecoxanthone B		<i>Aspergillus varicolor</i> (Fungus)	Chexal et al., 1975
3	Variecoxanthone C		<i>Aspergillus varicolor</i> (Fungus)	Chexal et al., 1975
4	Apetalinone A		<i>Calophyllum apetalum</i> (Guttiferae)	Iinuma et al., 1997
5	Cudraxanthone P		<i>Cudrania cochinchinensis</i> (Moraceae)	Hou et al., 2001

Table 1 Contd.

Table 1 Contd.

6	Cudratricusxanthone G		<i>Cudrania tricuspidata</i> (Moraceae)	Zou et al., 2004
7	Isoemicellin		<i>Fungus Emericella varicolor</i>	Bringmann et al., 2003
8	1,8-Dihydroxy-3-isoprenyloxy-6-methylxanthone		<i>Vismia guineensis</i> (Guttiferae)	Bilia et al., 2000
9	3-Geranyloxy-1,8-dihydroxy-6-methylxanthone		<i>Vismia guineensis</i> (Guttiferae)	Bilia et al., 2000
10	7-Geranyloxy-1,3-dihydroxyxanthone		<i>Cratogeomys cochinchinense</i> (Guttiferae)	Brahmachari, 2004; Nguyen, 1998
11	1,8-Dihydroxy-3-(2-methoxy-3-methylbut-3-enyloxy)-6-methylxanthone		<i>Vismia guineensis</i> (Guttiferae)	Bilia et al., 2000
12	1,8-Dihydroxy-6-methyl-3-(3,7-dimethyl-7-methoxyoct-2-enyloxy)-xanthone		<i>Vismia guineensis</i> (Guttiferae)	Bilia et al., 2000
13	1,8-Dihydroxy-3-(E-3-hydroxymethylbut-2-enyloxy)-6-methylxanthone		<i>Vismia guineensis</i> (Guttiferae)	Bilia et al., 2000
14	1,8-Dihydroxy-3-(3-hydroxymethyl-4-hydroxybut-2-enyloxy)-6-methylxanthone		<i>Vismia guineensis</i> (Guttiferae)	Bilia et al., 2000

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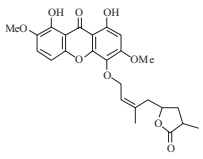
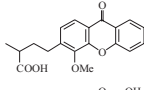
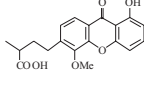
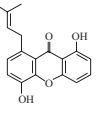
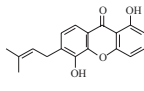
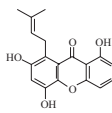
15	1,8-Dihydroxy-3,7-dimethoxy-4-O-[3'-methyl-4'-(3"-methyl-2,"H, 5"H-2"-oxofuran-5-yl)-2-butenyl]xanthone		<i>Tectona grandis</i> (Verbenaceae)	Singh et al., 2004
16	Teysmannic acid		<i>Calophyllum teysmannii</i> var. <i>Inophylloide</i> (Guttiferae)	Vieira, 2005; Kijjoa, 2000
17	Scriblitifolic acid		<i>Calophyllum teysmannii</i> var. <i>Inophylloide</i> (Guttiferae)	Vieira, 2005; Kijjoa, 2000
18	Isoguanandin		<i>Calophyllum brasiliense</i> (Guttiferae)	Gottlieb et al., 1968
19	Guanandin		<i>Calophyllum brasiliense</i> (Guttiferae)	Gottlieb et al., 1968
20	1,5,7-Trihydroxy-8-isoprenylxanthone (or 2,4,8-Trihydroxy-1-isoprenylxanthone)		<i>Tovomita krukovii</i> (Guttiferae)	Zhang et al., 2002

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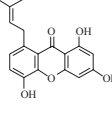
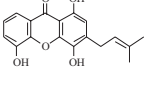
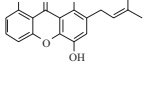
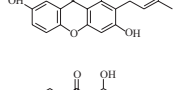
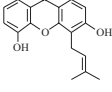
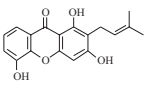
21	1,3,5-Trihydroxy-8-isoprenylxanthone		<i>Tovomita krukovii</i> (Guttiferae)	Zhang et al., 2002
22	1,4,5-Trihydroxy-3-(3-methylbut-2-enyl)xanthone		<i>Garcinia livingstonei</i> (Guttiferae)	Diserens, 1992; Brühlmann, 2004; Núñez, 2004; Marston, 1993; Mbwambo, 2006; Ji, 2006
23	Bangangxanthone B		<i>Garcinia polyantha</i> (Guttiferae)	Lannang et al., 2005
24	1,3,7-Trihydroxy-2-prenylxanthone (1,3,7-trihydroxy-2-(3-methylbut-2-enyl)xanthone)		<i>Cudrania cochinchinensis</i> (Moraceae); <i>Tovomita krukovii</i> , <i>Garcinia dulcis</i> , <i>Calophyllum paniciflorum</i> , <i>Kielmeyera coriacea</i> , <i>Garcinia afzelii</i> , <i>Hypericum chinense</i> (Guttiferae).	Ito, 1996, 1997, 1998; Fukai, 2004, 2005; Hou, 2001; Zhang, 2002; Chang, 1994; Cortez, 1998; Waffo, 2006; Tanaka, 2006
25	1,3,5-Trihydroxy-4-prenylxanthone		<i>Anaxagorea luzonensis</i> A. Gray (Annonaceae); <i>Synthesis</i>	Helesbeux, 2004; Hay, 2004b; Oger, 2003; Gonda, 2000; Ji, 2006
26	1,3,5-Trihydroxy-2-prenylxanthone (1,3,5-trihydroxy-2-(3,3-dimethylallyl)xanthone)		<i>Anaxagorea luzonensis</i> A. Gray (Annonaceae); <i>Calophyllum brasiliense</i> , <i>Calophyllum inophyllum</i> , <i>Calophyllum cuneifolium</i> , <i>Kielmeyera coriacea</i> (Guttiferae); <i>Synthesis</i>	Jantan, 2001, 2002; Helesbeux, 2004; Chairungsrikerd, 1996; Chilpa, 1997; Hay, 2004b; Oger, 2003; Gonda, 2000; Noldin, 2006

Table 1 Contd.

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27	1,3,6-Trihydroxy-4-prenylxanthone		<i>Anaxagorea luzonensis</i> A. Gray (<i>Annonaceae</i>)	Gonda et al., 2000
28	Caledonixanthone K		<i>Calophyllum caledonicum</i> (<i>Guttiferae</i>)	Morel et al., 2002
29	1,3,5,7-Tetrahydroxy-8-isoprenylxanthone		<i>Tovomita krukovii</i> (<i>Guttiferae</i>)	Zhang et al., 2002
30	Ugaxanthone (1,3,5,6-Tetrahydroxy-4-prenylxanthone)		<i>Garcinia dulcis</i> , <i>Hypericum japonicum</i> Thumb. (<i>Guttiferae</i>)	Ito, 1997; Wu, 1998; Fu, 2004
31	Assiguxanthone B (1,3,6,7-tetrahydroxy-2-prenylxanthone)		<i>Garcinia assigu</i> , <i>Kielmeyera variabilis</i> , <i>Hypericum androsaemum</i> , <i>Hypericum perforatum</i> (<i>Guttiferae</i>)	Pineiro, 2003a, b; Dias, 2000, 2001; Ito, 1997
32	1,3,6,7-Tetrahydroxy-8-(3-methylbut-2-enyl)xanthone (or 2,3,6,8-tetrahydroxy-1-isoprenylxanthone)		<i>Garcinia assigu</i> , <i>Hypericum scabrum</i> , <i>Garcinia mangostana</i> , <i>Hypericum patulum</i> , <i>Hypericum androsaemum</i> , <i>Hypericum perforatum</i> (<i>Guttiferae</i>)	Ishiguro, 1995; Schmidt, 2000; Dias, 2000, 2001; Ito, 1997; Huang, 2001; Tanaka, 2004
33	1,3,5,6-Tetrahydroxy-2-(3,3-dimethylallyl)xanthone		<i>Calophyllum brasiliense</i> , <i>Hypericum sampsonii</i> , <i>Calophyllum inophyllum</i> , <i>Garcinia dulcis</i> ,	Abe, 2004; Jantan, 2001, 2002; Pineiro, 2003a, b; Schmidt, 2000; Dias, 2000, 2001;

Table 1 Contd.

Table 1 Contd.

34	Morusignin A		<i>Hypericum androsaemum</i> , <i>Hypericum perforatum</i> , <i>Kielmeyera variabilis</i> (<i>Guttiferae</i>)	Ito, 1997; Chilpa, 1997; Yasunaka, 2005; Don, 2004; Wu, 2003; Noldin, 2006
35	Morusignin B		<i>Morus insignis</i> (<i>Moraceae</i>)	Nomura and Hano, 1994
36	Garcinianone A		<i>Garcinia multiflora</i> (<i>Guttiferae</i>)	Chiang et al., 2003
37	Globulixanthone D		<i>Garcinia linii</i> , <i>Symphonia globulifera</i> (<i>Guttiferae</i>)	Nkengfack, 2002; Chen, 2004
38	Linixanthone C		<i>Garcinia linii</i> (<i>Guttiferae</i>)	Chen et al., 2004
39	1,7-Dihydroxy-3-methoxy-2-(3-methyl-2-butenyl)xanthone		<i>Garcinia dulcis</i> , <i>Garcinia mangostana</i> , <i>Garcinia nigrolineata</i> (<i>Guttiferae</i>)	Suksamram, 2003; Rukachaisirikul, 2003a; Chairungsrikerd, 1996; Huang, 2001; Deachathai, 2005; 2006; Iinuma, 1996c
40	1,5-Dihydroxy-3-methoxy-4-prenylxanthone		<i>Chrysochlamys tenuis</i> (<i>Guttiferae</i>)	Molinar-Toribio et al., 2006

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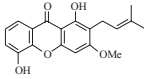
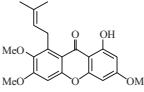
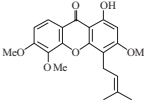
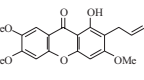
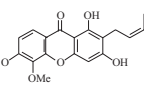
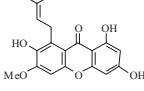
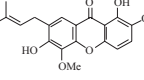
41	1,5-Dihydroxy-2-(3,3-dimethylallyl)-3-methoxyxanthone		<i>Calophyllum brasiliensis</i> , <i>Garcinia mangostana</i> , <i>Garcinia nigrolineata</i> (Guttiferae)	Rukachaisirikul, 2003a; Chilpa, 1997; Huang, 2001; Iinuma, 1996c
42	1-Hydroxy-3,6,7-trimethoxy-8-(3-methylbut-2-enyl)-xanthone		Methylation of <i>Dulxanthone D</i>	Nilar et al., 2005
43	Dimethyl ether <i>Dulxanthone A</i>		Methylation of <i>Dulxanthone A</i>	Ito et al., 1997
44	1-Hydroxy-3,6,7-trimethoxy-2-(3-methylbut-2-enyl)xanthone (Trimethylated Assiguxanthone B)		Methylation of 1,6-dihydroxy-3,7-dimethoxy-2-(3-methylbut-2-enyl)xanthone; Methylation of <i>Assiguxanthone B</i>	Nilar, 2002; Ito, 1997
45	Morusignin D		<i>Hypericum patulum</i> (Guttiferae)	Ishiguro, 1995; Nomura, 1994
46	1,3,7-Trihydroxy-6-methoxy-8-prenylxanthone		<i>Hypericum androsaemum</i> , <i>Hypericum perforatum</i> (Guttiferae)	Dias, 2000, 2001
47	1,2,6-Trihydroxy-5-methoxy-7-(3-methylbut-2-enyl)xanthone		<i>Garcinia xanthochymus</i> (Guttiferae)	Chanmahasathien, 2003a; Ohizumi, 2004

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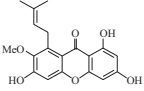
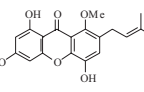
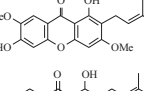
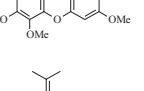
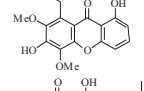
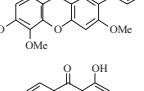
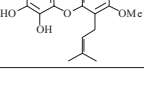
48	<i>Dulxanthone D</i> (1,3,6-Trihydroxy-7-methoxy-8-prenylxanthone)		<i>Garcinia mangostana</i> , <i>Garcinia dulcis</i> , <i>Hypericum androsaemum</i> , <i>Garcinia parvifolia</i> (Guttiferae); Synthesis	Dias, 2000; Hamada, 2003; Ito, 2005; Nilar, 2005; Rukachaisirikul, 2006
49	<i>Azelixanthone A</i>		<i>Garcinia afzelii</i> (Guttiferae)	Waffo et al., 2006
50	<i>Cowagarcinone B</i> (or 1,6-Dihydroxy-3,7-dimethoxy-2-(3-methylbut-2-enyl)xanthone)		<i>Garcinia cowa</i> , <i>Garcinia dulcis</i> , <i>Garcinia mangostana</i> (Guttiferae)	Nilar, 2002; Mahabusarakam, 2005; Deachathai, 2005; Panthong, 2006
51	<i>Cowagarcinone C</i>		<i>Garcinia cowa</i> (Guttiferae)	Mahabusarakam, 2005
52	5-O-Methylcelebixanthone		<i>Cratoxylum cochinchinense</i> (Guttiferae)	Laphookhieo, 2006
53	<i>Cowaxanthone A</i>		<i>Garcinia cowa</i> (Guttiferae)	Panthong et al., 2006
54	<i>Dulxanthone A</i>		<i>Garcinia dulcis</i> , <i>Garcinia cowa</i> (Guttiferae)	Ito, 1997, 1998; Shen, 2006

Table 1 Contd.

Table 1 Contd.

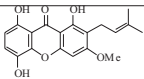
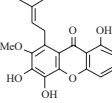
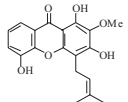
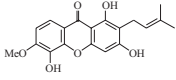
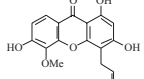
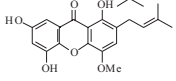
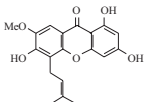
55	1,5,8-Trihydroxy-3-methoxy-2-(3-methyl-2-butenyl)xanthone		<i>Garcinia dulcis</i> (Guttiferae); Synthesis	Bennett, 1990; Deachathai, 2005
56	Celebixanthone		<i>Cratogeomys celebicum</i> , <i>Cratogeomys cochinchinense</i> (Guttiferae)	Stout, 1963; Mahabusakam, 2006; Laphookhieo, 2006
57	Caledonixanthone D		<i>Calophyllum caledonicum</i> (Guttiferae)	Morel, 2000, 2002; Noldin, 2006
58	1,3,5-Trihydroxy-6-methoxy-2-prenylxanthone		<i>Anaxagorea luzonensis</i> A. Gray (Annonaceae)	Gonda et al., 2000
59	1,3,6-Trihydroxy-5-methoxy-4-prenylxanthone		<i>Anaxagorea luzonensis</i> A. Gray (Annonaceae)	Gonda et al., 2000
60	Umbilicaxanthone A		Enzymatic hydrolysis of Umbilicaxanthoside A	Rezanka et al., 2003
61	Morusignin K		<i>Morus insignis</i> (Moraceae)	Hano, 1993; Nomura, 1994

Table 1 Contd.

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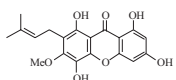
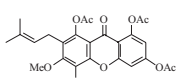
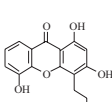
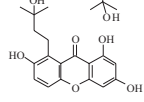
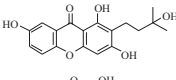
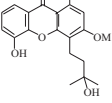
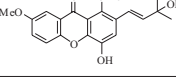
62	Hyperxanthone		<i>Hypericum sampsonii</i> (Guttiferae)	Don et al., 2004
63	Hyperxanthone tetraacetate		Acetylation of Hyperxanthone with acetic anhydride and pyridine	Don et al., 2004
64	1,3,5-Trihydroxy-4-(3-hydroxy-3-methylbutyl)xanthone		<i>Anaxagorea luzonensis</i> A. Gray (Annonaceae); <i>Garcinia nigrolineata</i> (Guttiferae)	Rukachaisirikul, 2003d; Gonda, 2000
65	Nigrolineaxanthone D		<i>Garcinia nigrolineata</i> (Guttiferae)	Rukachaisirikul et al., 2003
66	1,3,7-Trihydroxy-2-(3-hydroxy-3-methylbutyl)xanthone		<i>Garcinia nigrolineata</i> , <i>Kielmeyera coriacea</i> (Guttiferae)	Rukachaisirikul, 2003d; Cortez, 1998
67	Nigrolineaxanthone A		<i>Garcinia nigrolineata</i> (Guttiferae)	Rukachaisirikul et al., 2003
68	Azelixanthone B		<i>Garcinia afzelii</i> (Guttiferae)	Waffo et al., 2006

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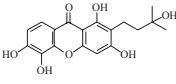
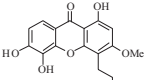
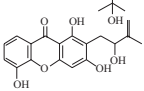
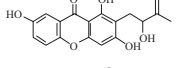
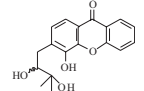
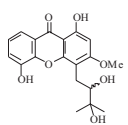
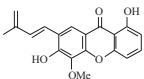
69	1,3,5,6-Tetrahydroxy-2-(3-hydroxy-3-methylbutyl)xanthone		<i>Calophyllum brasiliense</i> , <i>Calophyllum inophyllum</i> (Guttiferae)	Abe, 2004; Jantan, 2001; Reyes-Chilpa, 2006
70	1,5,6-Trihydroxy-3-methoxy-4-(3-hydroxy-3-methylbutyl)xanthone		<i>Garcinia cowa</i> (Guttiferae)	Shen and Yang, 2006
71	(±)-Caledol		<i>Calophyllum caledonicum</i> (Guttiferae); Synthesis	Helesbeux, 2004; Oger, 2003
72	1,3,7-Trihydroxy-2-(2-hydroxy-3-methyl-3-butenyl)xanthone		<i>Hypericum chinense</i> (Guttiferae)	Tanaka and Takaishi, 2006
73	Caledonixanthone G		<i>Calophyllum caledonicum</i> (Guttiferae)	Morel et al., 2002
74	Nigrolineaxanthone C		<i>Garcinia nigrolineata</i> (Guttiferae)	Rukachaisirikul et al., 2003
75	Globulixanthone A		<i>Symphonia globulifera</i> (Guttiferae)	Nkengfack et al., 2002

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Table 1 Contd.

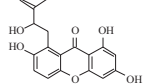
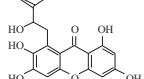
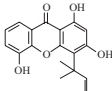
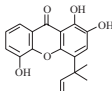
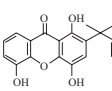
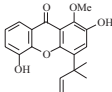
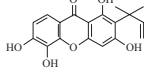
76	Hyperxanthone D		<i>Hypericum scabrum</i> (Guttiferae)	Tanaka et al., 2004
77	Hyperxanthone C		<i>Hypericum scabrum</i> (Guttiferae)	Tanaka et al., 2004
78	Pancixanthone A		<i>Garcinia assigu</i> , <i>Calophyllum paniciflorum</i> , <i>Garcinia vieillardii</i> (Guttiferae)	Ito, 1996, 1997, 1998; Hay, 2004b
79	Globuxanthone		<i>Garcinia subelliptica</i> , <i>Garcinia vilsersiana</i> , <i>Garcinia dulcis</i> (Guttiferae)	Tosa, 1997; Nguyen, 2000; Fukuyama, 1991; Iinuma, 1995c, 1996a; Minami, 1994
80	1,4,5-Trihydroxy-2-(1,1-dimethyl-2-propenyl)xanthone (12b-hydroxy-des-D-garcigerrin A)		<i>Garcinia subelliptica</i> , <i>Garcinia xanthochymus</i> , <i>Garcinia vilsersiana</i> , <i>Garcinia livingstonei</i> , <i>Garcinia Gerrardii</i> , <i>Garcinia dulcis</i> (Guttiferae)	Chanmahasathien, 2003a; Diserens, 1989, 1992; Abe, 2003; Brühlmann, 2004; Nguyen, 2000; Ohizumi, 2004; Núñez, 2004; Marston, 1993; Iinuma 1995c, 1996a,c; Fukuyama, 1991; Ji, 2006
81	1-O-Methylglobuxanthone		<i>Garcinia vilsersiana</i> (Guttiferae)	Nguyen and Harrison, 2000
82	Cudraxanthone S		<i>Cudrania fruticosa</i> , <i>Cudrania cochinchinensis</i> (Moraceae)	Fukai, 2003, 2004, 2005; Wang, 2005

Table 1 Contd.

Table 1 Contd.

83	Isocudranianthone A or Assiguxanthone A		<i>Cudrania fruticosa</i> (Moraceae); <i>Garcinia vieillardii</i> , <i>Garcinia assigu</i> (Guttiferae)	Hay, 2004a, b; Ito, 1997, 1998; Wang, 2005
84	Subelliptenone F		<i>Garcinia subelliptica</i> , <i>Garcinia dulcis</i> (Guttiferae)	Tosa, 1997; Iinuma, 1995a, 1996a, c
85	Symphoxanthone		<i>Garcinia subelliptica</i> , <i>Garcinia vilsersiana</i> (Guttiferae)	Nguyen, 2000; Minami, 1996
86	Cudranianthone		<i>Cudrania cochinchinensis</i> (Moraceae)	Chang, 1989b, 1994
87	Isocudranianthone B		<i>Cudrania tricuspidata</i> (Moraceae); <i>Garcinia vieillardii</i> , <i>Cratogeomys formosum</i> ssp. <i>pruniflorum</i> (Guttiferae)	Hay, 2004b; Lee, 2005b; Boonnak, 2006b; Park, 2006
88	Garcinianthone H		<i>Garcinia subelliptica</i> (Guttiferae)	Minami et al., 1996
89	1-O-Methylsymphoxanthone		<i>Garcinia subelliptica</i> (Guttiferae)	Minami et al., 1996

Table 1 Contd.

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90	Vieillardianthone		<i>Garcinia vieillardii</i> (Guttiferae)	Hay et al., 2004a
91	Mangostinone		<i>Garcinia cowa</i> , <i>Garcinia mangostana</i> , <i>Garcinia parvifolia</i> (Guttiferae)	Suksamram, 2002, 2003, 2006; Mahabusarakam, 2005; Jung, 2006; Rukachaisirikul, 2006
92	Fuscaxanthone E		<i>Garcinia fusca</i> (Guttiferae)	Ito et al., 2003b
93	Fuscaxanthone F		<i>Garcinia fusca</i> (Guttiferae)	Ito et al., 2003b
94	1,3,5-Trihydroxy-4-(3',7'-dimethylocta-2',6'-dienyl)xanthone		<i>Montrouziera sphaeroidea</i> , <i>Garcinia livingstonei</i> (Guttiferae)	Diserens, 1992; Brühlmann, 2004; Núñez, 2004; Ito, 2000; Mbawambo, 2006; Ji, 2006
95	Montrouxanthone		<i>Montrouziera sphaeroidea</i> (Guttiferae)	Ito et al., 2000
96	Smeathxanthone A		<i>Garcinia smeathmannii</i> , <i>Garcinia mangostana</i> (Guttiferae)	Komguem, 2005; Jung, 2006

Table 1 Contd.

Table 1 Contd.

97 Rubraxanthone		<i>Garcinia cowa</i> , <i>Garcinia dioica</i> , <i>Garcinia fusca</i> , <i>Allanblackia monticola</i> , <i>Garcinia parvifolia</i> (<i>Guttiferae</i>)	Jantan, 2002; Ito, 2003b; linuma, 1996c,d; Azebaze, 2004, 2006; Wahyuni, 2004; Kardono, 2006; Rukachaisirikul, 2006
98 Cowaxanthone		<i>Garcinia dulcis</i> , <i>Garcinia Cowa</i> , <i>Garcinia fusca</i> (<i>Guttiferae</i>)	Ito, 2003b; Mahabusarakam, 2005; Deachathai, 2005; Pattalung, 1994; Deachathai, 2006; Panthong, 2006
99 Parvixanthone E		<i>Garcinia parvifolia</i> (<i>Guttiferae</i>)	Xu et al., 2001
100 Calycinanthone D (1,3,5,6-tetrahydroxy-4-lavandulyxanthone)		<i>Hypericum roeperanum</i> (<i>Guttiferae</i>)	Rath et al., 1996
101 Roeperanone (1,3,5,6-tetrahydroxy-4-trans-sesquilandulyxanthone)		<i>Hypericum roeperanum</i> (<i>Guttiferae</i>)	Rath et al., 1996

Table 1 Contd.

Table 1 Contd.

102 1,3,6-Trihydroxy-8-(7-hydroxy-3,7-dimethyl-2,5-octadienyl)-7-methoxyxanthone		<i>Garcinia dioica</i> (<i>Guttiferae</i>)	linuma et al., 1996d
103 1,3,6-Trihydroxy-8-(6,7-epoxy-3,7-dimethyl-2-octenyl)-7-methoxyxanthone		<i>Garcinia dioica</i> (<i>Guttiferae</i>)	linuma et al., 1996d
104 Parvixanthone C		<i>Garcinia parvifolia</i> (<i>Guttiferae</i>)	Xu et al., 2001
105 Parvixanthone D		<i>Garcinia parvifolia</i> (<i>Guttiferae</i>)	Xu et al., 2001
106 Parvixanthone F		<i>Garcinia parvifolia</i> (<i>Guttiferae</i>)	Xu et al., 2001
107 Parvixanthone G		<i>Garcinia parvifolia</i> (<i>Guttiferae</i>)	Xu et al., 2001

Table 1 Contd.

Table 1 Contd.

108	Parvixanthone H		<i>Garcinia parvifolia</i> (Guttiferae)	Xu et al., 2001
109	Apetalinone D		<i>Calophyllum apetalum</i> (Guttiferae)	linuma et al., 1997
110	Tomentonone		<i>Calophyllum apetalum</i> , <i>Calophyllum tomentosum</i> (Guttiferae)	linuma, 1997; Banerji, 1994
111	Patulone (or 1,2-Dihydro-3,6,8- trihydroxy-1,1-bis(3- methylbut-2-enyl)- xanthen-2,9-dione)		<i>Hypericum patulum</i> (Guttiferae)	Ishiguro, 1997; Yamakuni, 2006
112	6-Deoxy-γ-mangostin (1,3,7-Trihydroxy-2,8-bis (3,3-dimethylallyl) xanthone)		<i>Calophyllum thwaitesii</i> , <i>Calophyllum caledonicum</i> , <i>Garcinia mangostana</i> (Guttiferae)	Dharmaratne, 1996, 1999; Hay, 2004b; Mahabusarakam, 1987; Noldin, 2006
113	Cudraxanthone H Gerontoxanthone H		<i>Cudrania fruticosa</i> , <i>Cudrania cochinchinensis</i> , <i>Cudrania tricuspidata</i> (Moraceae)	Zou, 2004; Fukai, 2004, 2005; Hou, 2001; Wang, 2005; Chang, 1989b, 1994; An, 2006; Nomura, 1994
114	1,3,7-Trihydroxy-2,4-di- (3-methylbut-2-enyl) xanthone		<i>Garcinia dioica</i> , <i>Cratoxylum cochinchinense</i> , <i>Chrysoclamys tenuis</i> (Guttiferae)	Tosa, 1997; linuma, 1996d; Mahabusarakam, 2006b; Laphookhieo, 2006; Molinar-Toribio, 2006

Table 1 Contd.

Table 1 Contd.

115	8-Desoxygartanin (1,3,5-Trihydroxy-2, 4-bis(3-methylbut-2- enyl)xanthone)		<i>Garcinia dulcis</i> , <i>Garcinia intermedia</i> ; <i>Garcinia nigrolineata</i> , <i>Calophyllum brasiliense</i> , <i>Garcinia mangostana</i> , <i>Garcinia merguensis</i> , <i>Garcinia speciosa</i> , <i>Chrysoclamys tenuis</i> (Guttiferae); <i>Maclura tinctoria</i> (Moraceae); <i>Rheedia brasiliensis</i> (Martius); Synthesis	Abe, 2004; Rukachaisirikul, 2003a, b; Ito, 2002, 2003a; Groweiss, 2000; Ho, 2002; Helesbeux, 2004; Chairungsrikerd, 1996; Nguyen, 2003; Huang, 2001; Hay, 2004b; Oger, 2003; Deachathai, 2005; Monache, 1984b; Govindachari, 1971; Suksamram, 2006; Jung, 2006; Noldin, 2006; Molinar-Toribio, 2006
116	Garcinone A		<i>Garcinia mangostana</i> (Guttiferae)	Sen et al., 1982
117	1,3,5-Trihydroxy-4, 8-di(3-methylbut-2- enyl)xanthone		<i>Garcinia merguensis</i> , <i>Garcinia quadrifaria</i> (Guttiferae)	Nguyen, 2003; Waterman, 1982
118	Garcinaxanthone C		<i>Garcinia subelliptica</i> (Guttiferae)	Minami et al., 1994
119	Cudraxanthone G		<i>Calophyllum paniciflorum</i> , <i>Garcinia mangostana</i> , <i>Mesua daphnifolia</i> (Guttiferae)	Ito, 1996, 1998; Ee, 2006b; Jung, 2006; Nomura, 1994

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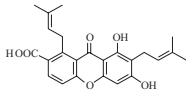
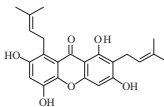
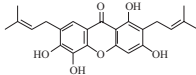
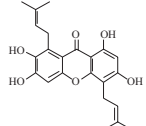
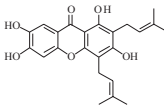
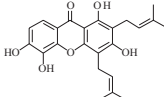
120	7-Carboxy-1,3-dihydroxy-2,8-diisoprenylxanthone		<i>Garcinia mangostana</i> (<i>Guttiferae</i>)	Gopalakrishnan and Balaganesan, 2000
121	Cratoxyarborenone B		<i>Cratoxylum sumatranum</i> (<i>Guttiferae</i>)	Seo, 2002; Kinghorn, 2003; Balunas, 2006
122	Toxyloxanthone D		<i>Cudrania fruticosa</i> (<i>Moraceae</i>)	Wang et al., 2005
123	Cudraticusxanthone B		<i>Cudrania tricuspidata</i> (<i>Moraceae</i>)	Zou et al., 2004
124	Cudraticusxanthone E		<i>Cudrania tricuspidata</i> (<i>Moraceae</i>)	Zou et al., 2004
125	Xanthone V _{1a}		<i>Cudrania tricuspidata</i> (<i>Moraceae</i>)	Zou et al., 2004

Table 1 Contd.

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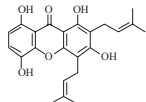
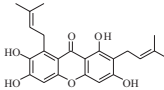
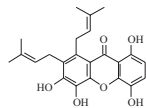
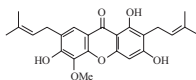
126	Gartanin		<i>Garcinia dulcis</i> , <i>Garcinia mangostana</i> (<i>Guttiferae</i>); <i>Maclura tinctoria</i> (<i>Moraceae</i>); Synthesis	Groweiss, 2000; Bennett, 1990b; Ho, 2002; Chairungsrield, 1996; Huang, 2001; Deachathai, 2005; Iinuma, 1996c; Mahabusarakam, 1987; Suksamram, 2006; Jung, 2006; Gopalakrishnan, 1997
127	γ-Mangostin		<i>Garcinia mangostana</i> , <i>Hypericum androsaemum</i> , <i>Hypericum patulum</i> (<i>Guttiferae</i>); Synthesis	Nakatani, 2002, 2004; Suksamram, 2003, 2006; Tosa, 1997; Nilar, 2002; Jinsart, 1992; Ho, 2002; Schmidt, 2000; Vlietinck, 1998; Chen, 1996; Chairungsrield, 1996, 1998; Jefferson, 1970; Matsumoto, 2005; Dias, 2000; Huang, 2001; Dharmaratne, 2005; Iinuma, 1996c; Yamakuni, 2006; Sen, 1982; Mahabusarakam, 1987; Jung, 2006; Gopalakrishnan, 1997
128	1,4,5,6-Tetrahydroxy-7,8-di (3-methylbut-2-enyl) xanthone (or 3,4,5,8-tetrahydroxy-1,2-diisoprenylxanthone)		<i>Garcinia xanthochymus</i> (<i>Guttiferae</i>)	Chanmahasathien, 2003a; Ohizumi, 2004
129	Cudraxanthone F		<i>Calophyllum brasiliense</i> (<i>Guttiferae</i>)	Ito, 2002, 2003a; Nomura, 1994; Noldin, 2006

Table 1 Contd.

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130	Dulcisxanthone B		<i>Garcinia dulcis</i> (<i>Guttiferae</i>)	Deachathai et al., 2005
131	8-Hydroxycudraxanthone G		<i>Garcinia mangostana</i> (<i>Guttiferae</i>)	Jung et al., 2006
132	Parvifolixanthone B		<i>Garcinia parvifolia</i> (<i>Guttiferae</i>)	Rukachaisirikul et al., 2006
133	Fuscaxanthone C (Dimethylmangostin or Methoxy- β -mangostin)		<i>Cratoxylum arborencens</i> (<i>Cratoxylaceae</i>) <i>Garcinia fusca</i> , <i>Garcinia mangostana</i> , <i>Garcinia cowa</i> (<i>Guttiferae</i>); <i>Synthesis</i>	Nilar, 2002; Jefferson, 1970; Ito, 2003b; Matsumoto, 2005; Pattanapratee, 2005; Dharmaratne, 2005; Panthong, 2006; Lee, 1981
134	Cratoxyarbornone C		<i>Cratoxylum sumatranum</i> (<i>Guttiferae</i>)	Seo, 2002; Kinghorn, 2003
135	Cowaxanthone B (or 1,3-Dihydroxy-6,7-dimethoxy-2,8-diprenylxanthone)		<i>Cratoxylum arborencens</i> , <i>Garcinia cowa</i> (<i>Guttiferae</i>)	Pattanapratee, 2005; Panthong, 2006

Table 1 Contd.

Table 1 Contd.

136	Cratoxyarbornone E		<i>Cratoxylum sumatranum</i> , <i>Cratoxylum arborencens</i> (<i>Guttiferae</i>)	Seo, 2002; Kinghorn, 2003; Reutrakul, 2006
137	Umbilicaxanthone B		<i>Enzymatic hydrolysis of Umbilicaxanthoside B</i>	Rezanka et al., 2003
138	Dulxanthone B		<i>Garcinia dulcis</i> (<i>Guttiferae</i>)	Ito, 1997, 1998
139	Dulxanthone C		<i>Garcinia dulcis</i> (<i>Guttiferae</i>)	Ito, 1997, 1998
140	1,3,6-Trihydroxy-7-methoxy-2,5-bis(3-methyl-2-butenyl)xanthone		<i>Garcinia dulcis</i> , <i>Garcinia cowa</i> (<i>Guttiferae</i>)	Mahabusarakam, 2005; Deachathai, 2005, 2006; Pattalung, 1994
141	α -Mangostin		<i>Garcinia mangostana</i> , <i>Garcinia fusca</i> , <i>Garcinia dulcis</i> , <i>Cratoxylum cochinchinensis</i> , <i>Garcinia speciosa</i> ,	Suksamram, 2006, 2003, 2002; Tosa, 1997; Lu, 1998; Malathi, 2000; Okudaira, 2000; Nilar, 2002; Jinsart, 1992; Ho,

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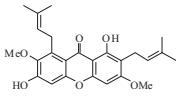
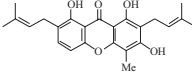
		<i>Allanblackia monticola</i> , <i>Garcinia cowa</i> , <i>Cratoxylum</i> <i>formosum</i> ssp. <i>pruniflorum</i> (<i>Guttiferae</i>); <i>Synthesis</i>	2002; Vlietinck, 1998; Chen, 1996; Iikubo, 2002; Jefferson, 1970; Matsumoto, 2004, 2005; Chairungsrikerd, 1996; Ito, 2003b; Huang, 2001; Bennett, 1993; Deachathai, 2005, 2006; Dharmaratne, 2005; Iinuma, 1996c; Mahabusarakam, 1987, 2006a, 2006b; Azebaze, 2006; Sen, 1982; Govindachari, 1971; Panthong, 2006; Laphookhieo, 2006; Jung, 2006; Boonnak, 2006b; Gopalakrishnan, 1997
142 β -Mangostin		<i>Garcinia mangostana</i> , <i>Garcinia fusca</i> , <i>Cratoxylum</i> <i>cochinchinense</i> , <i>Cratoxylum formosum</i> , <i>Garcinia cowa</i> , <i>Garcinia</i> <i>dulcis</i> (<i>Guttiferae</i>); <i>Synthesis</i>	Suksamram, 2002, 2003, 2006; Tosa, 1997; Nilar, 2002; Jefferson, 1970; Matsumoto, 2005; Ito, 2003b; Huang, 2001; Bennett, 1993; Dharmaratne, 2005; Iinuma, 1996c; Mahabusarakam, 1987, 2006b; Deachathai, 2006; Govindachari, 1971; Panthong, 2006; Laphookhieo, 2006; Chantrapromma, 2006; Boonnak, 2006b; Gopalakrishnan, 1997; Lee, 1981
143 1,3,8-Trihydroxy-4-methyl-2,7-di-(3-methylbut-2-enyl)xanthone		<i>Garcinia mangostana</i> (<i>Guttiferae</i>)	Gopalakrishnan and Balaganesan, 2000

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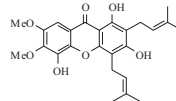
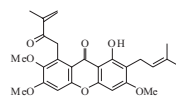
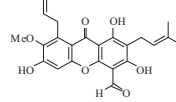
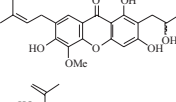
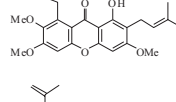
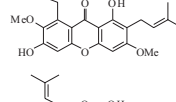
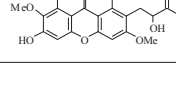
144 Globuliferin		<i>Symphonia globulifera</i> (<i>Guttiferae</i>)	Ngouela, 2005a, 2006
145 1-Hydroxy-3,6,7-trimethoxy-2-(3-methylbut-2-enyl)-8-(2-oxo-3-methylbut-3-enyl)xanthone		<i>Methylation of 1,6-dihydroxy-3,7-dimethoxy-2-(3-methylbut-2-enyl)-8-(2-oxo-3-methylbut-3-enyl)xanthone</i>	Nilar, 2002
146 Cowaxanthone E		<i>Garcinia cowa</i> (<i>Guttiferae</i>)	Panthong et al., 2006
147 Brasixanthone G		<i>Calophyllum brasiliense</i> (<i>Guttiferae</i>)	Ito, 2002, 2003a; Noldin, 2006
148 1-Hydroxy-8-(2-hydroxy-3-methylbut-3-enyl)-3,6,7-trimethoxy-2-(3-methylbut-2-enyl)xanthone		<i>Garcinia mangostana</i> (<i>Guttiferae</i>)	Nilar, 2002
149 1,6-Dihydroxy-8-(2-hydroxy-3-methylbut-3-enyl)-3,7-dimethoxy-2-(3-methylbut-2-enyl)xanthone		<i>Garcinia mangostana</i> (<i>Guttiferae</i>)	Nilar, 2002
150 1,6-Dihydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-3,7-dimethoxy-8-(3-methylbut-2-enyl)xanthone		<i>Garcinia mangostana</i> (<i>Guttiferae</i>)	Nilar, 2002

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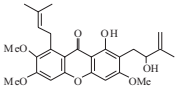
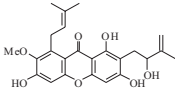
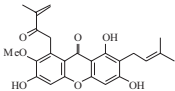
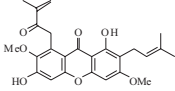
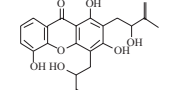
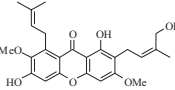
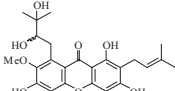
151	1-Hydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-3,6,7-trimethoxy-8-(3-methylbut-2-enyl)xanthone		<i>Garcinia mangostana</i> (Guttiferae)	Nilar, 2002
152	Mangostenol (1,3-Dihydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-6,7-dimethoxy-8-(3-methylbut-2-enyl)xanthone)		<i>Garcinia dulcis</i> , <i>Garcinia mangostana</i> (Guttiferae)	Suksamram, 2002, 2003; Nilar, 2002; Deachathai, 2005
153	Mangostingone (or 1,3,6-trihydroxy-7-methoxy-2-(3-methyl-2-butenyl)-8-(3-methyl-2-oxo-3-butenyl)xanthone)		<i>Garcinia mangostana</i> (Guttiferae)	Jung et al., 2006
154	1,6-Dihydroxy-3,7-dimethoxy-2-(3-methylbut-2-enyl)-8-(2-oxo-3-methylbut-3-enyl)xanthone		<i>Garcinia mangostana</i> (Guttiferae)	Nilar, 2002
155	(±)-Dicaledol		<i>Calophyllum caledonicum</i> (Guttiferae); Synthesis	Helesbeux, 2004; Oger, 2003
156	Fuscaxanthone D		<i>Garcinia fusca</i> (Guttiferae)	Ito et al., 2003b
157	Mangostenone E		<i>Garcinia mangostana</i> (Guttiferae)	Suksamram et al., 2006

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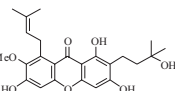
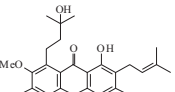
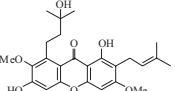
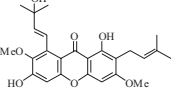
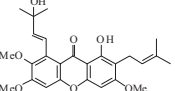
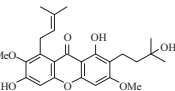
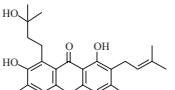
158	Cratoxylone (1,3,6-trihydroxy-2-(3-hydroxy-3-methylbutyl)-7-methoxy-8-(3,3-dimethylallyl)xanthone)		<i>Garcinia dulcis</i> , <i>Cratoxylum cochinchinense</i> (Guttiferae)	Bennett, 1993; Deachathai, 2005
159	Garcinone D		<i>Garcinia dulcis</i> , <i>Garcinia mangostana</i> , <i>Cratoxylum cochinchinense</i> (Guttiferae)	Suksamram, 2003, 2006; Huang, 2001; Bennett, 1993; Deachathai, 2005; Mahabusarakam, 2006b; Jung, 2006; Gopalakrishnan, 1997
160	Pruniflorone C		<i>Cratoxylum formosum</i> ssp. <i>pruniflorum</i> (Guttiferae)	Boonnak et al., 2006b
161	(16E)-1,6-Dihydroxy-8-(3-hydroxy-3-methylbut-1-enyl)-3,7-dimethoxy-2-(3-methylbut-2-enyl)xanthone		<i>Garcinia mangostana</i> (Guttiferae)	Nilar, 2002
162	(16E)-1-Hydroxy-8-(3-hydroxy-3-methylbut-1-enyl)-3,6,7-trimethoxy-2-(3-methylbut-2-enyl)xanthone		<i>Garcinia mangostana</i> (Guttiferae)	Nilar, 2002
163	Pruniflorone E		<i>Cratoxylum formosum</i> ssp. <i>pruniflorum</i> (Guttiferae)	Boonnak et al., 2006b
164	Garcinone C		<i>Garcinia mangostana</i> (Guttiferae)	Sen, 1982; Suksamram, 2006

Table 1 Contd.

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165 Nigrolineaxanthone N		<i>Garcinia nigrolineata</i> (Guttiferae)	Rukachaisirikul et al., 2003a
166 Nigrolineaxanthone O		<i>Garcinia nigrolineata</i> (Guttiferae)	Rukachaisirikul et al., 2003a
167 Pruniflorone D		<i>Cratoxylum formosum</i> ssp. <i>pruniflorum</i> (Guttiferae)	Boonnak et al., 2006b
168 Nigrolineaxanthone P		<i>Garcinia nigrolineata</i> (Guttiferae)	Rukachaisirikul et al., 2003a
169 Cudraticusaxanthone M		<i>Cudrania tricuspidata</i> (Moraceae)	Hwang et al., 2007
170 Umbilicaxanthoside A		<i>Lichens Umbilicaria proboscidea</i>	Rezanka et al., 2003

Table 1 Contd.

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171 Umbilicaxanthoside B		<i>Lichens Umbilicaria proboscidea</i>	Rezanka et al., 2003
172 Allanxanthone A		<i>Allanblackia monticola</i> , <i>Allanblackia floribunda</i> , <i>Calophyllum caledonicum</i> (Guttiferae)	Nkengfack, 2002a; Hay, 2003; Ngouela, 2005b
173 Garciniaxanthone A		<i>Garcinia subelliptica</i> , <i>Garcinia dulcis</i> (Guttiferae)	Abe, 2003; Fukuyama, 1991; Minami, 1994; Iinuma, 1996a
174 Gerontoxanthone I		<i>Cudrania fruticosa</i> , <i>Cudrania cochinchinensis</i> (Moraceae); <i>Cratoxylum formosum</i> (Guttiferae)	Fukai, 2004, 2005; Hou, 2001; Wang, 2005; Chang, 1989b, 1994; Boonsri, 2006; Nomura, 1994; Boonnak, 2006a, b
175 Alvaxanthone		<i>Cudrania fruticosa</i> , <i>Cudrania cochinchinensis</i> , <i>Maclura pomifera</i> (Moraceae)	Costa, 2000; Fukai, 2004, 2005; Teixeira, 2005; Hou, 2001; Wang, 2005; Monache, 1984a; Costa, 1999
176 Isoalvaxanthone		<i>Cudrania fruticosa</i> , <i>Cudrania cochinchinensis</i> (Moraceae)	Fukai, 2004, 2005; Hou, 2001; Wang, 2005
177 Cudraxanthone L		<i>Cudrania tricuspidata</i> (Moraceae)	Hano, 1991a; Zou, 2005; Lee, 2005a, b; Nomura, 1994; Park, 2006

Table 1 Contd.

Table 1 Contd.

178	Cudraticusxanthone A (1,3,6,7-tetrahydroxy-4-(1,1-dimethyl-2-propenyl)-8-prenylxanthone)		<i>Cudrania tricuspidata</i> (Moraceae)	Zou, 2004; Lee, 2005b; Park, 2006
179	2,3,6,8-tetrahydroxy-1-(3-methylbut-2-enyl)-5-(2-methylbut-3-en-2-yl)xanthone		<i>Cudrania tricuspidata</i> (Moraceae)	Lee, 2005a, b
180	Macluraxanthone C		<i>Cudrania tricuspidata</i> , <i>Maclura tinctoria</i> (Moraceae)	Groweiss, 2000; Zou, 2005; Perez, 2003
181	Macluraxanthone B		<i>Cudrania tricuspidata</i> , <i>Maclura tinctoria</i> (Moraceae)	Groweiss, 2000; Zou, 2004, 2005; Lee, 2005a, b; Perez, 2003; Park, 2006
182	Subelliptenone B		<i>Garcinia subelliptica</i> , <i>Garcinia vilsianiana</i> (Guttiferae)	Tosa, 1997; Abe, 2003; Nguyen, 2000; Iinuma, 1994a
183	1,3,5,6-Tetrahydroxy-4-(1,1-dimethylprop-2-enyl)-7-(3-methylbut-2-enyl)xanthone		<i>Rheedia brasiliensis</i> (Guttiferae)	Monache et al., 1984b

Table 1 Contd.

Table 1 Contd.

184	Cudraxanthone E		<i>Cudrania fruticosa</i> , <i>Cudrania tricuspidata</i> (Moraceae)	Zou, 2005; Wang, 2005; Nomura, 1994
185	Cudrafrutixanthone A		<i>Cudrania fruticosa</i> (Moraceae)	Wang et al., 2005
186	Cudraxanthone D		<i>Cudrania tricuspidata</i> (Moraceae)	Lee, 2005b; Park, 2006
187	Cudraxanthone C		<i>Cudrania tricuspidata</i> (Moraceae); <i>Calophyllum mucigerum</i> (Guttiferae)	Ee, 2004; Lee, 2005b; An, 2006; Park, 2006
188	Nigrolineaxanthone E (1,5,6-Trihydroxy-3-methoxy-2-(3-methylbut-2-enyl)-4-(1,1-dimethylprop-2-enyl)xanthen-9(9H)-one)		<i>Garcinia nigrolineata</i> , <i>Garcinia cowa</i> (Guttiferae)	Rukachaisirikul, 2003d; Wahyuni, 2004
189	Bracteaxanthone I		<i>Garcinia bracteata</i> (Guttiferae)	Thoisson et al., 2005
190	2-Geranyl-1,3,7-trihydroxy-4-(3,3-dimethylallyl) xanthone		<i>Cratoxylum cochinchinense</i> (Guttiferae)	Bennett et al., 1993

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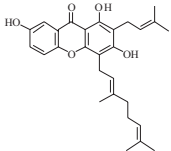
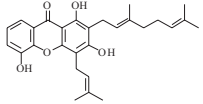
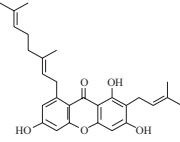
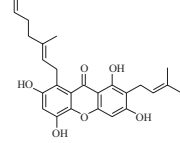
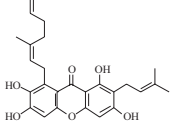
191	Cochinchinone A (1,3,7-Trihydroxy-2-(3-methyl-2-butenyl)-4-(3,7-dimethyl-2,6-octadienyl)xanthone)		<i>Cratoxylum cochinchinense</i> (Guttiferae)	Mahabusarakam, 2006b; Laphookhieo, 2006
192	Formoxanthone A		<i>Cratoxylum formosum</i> (Guttiferae)	Boonsri, 2006; Boonnak, 2006b
193	Pruniflorone I		<i>Cratoxylum formosum</i> ssp. <i>pruniflorum</i> (Guttiferae)	Boonnak et al., 2006b
194	Cratoxyarborenone A		<i>Cratoxylum sumatranum</i> (Guttiferae)	Seo, 2002; Kinghorn, 2003
195	Norcowanin		<i>Garcinia cowa</i> , <i>Garcinia fusca</i> , <i>Allanblackia monticola</i> (Guttiferae)	Ito, 2003b; Pattalung, 1994; Azebaze, 2006

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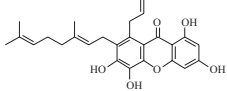
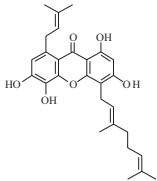
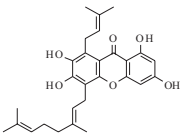
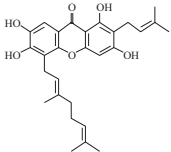
196	Garciniaxanthone E		<i>Garcinia subelliptica</i> , <i>Garcinia xanthochymus</i> (Guttiferae)	Chanmahasathien, 2003b; Abe, 2003; Ohizumi, 2004
197	Virgataxanthone A		<i>Garcinia virgata</i> (Guttiferae)	Merza et al., 2004
198	Dulciol A		<i>Garcinia dulcis</i> (Guttiferae)	Iinuma et al., 1996a
199	Cochinchinone B (1,3,6,7-Tetrahydroxy-2-(3-methyl-2-butenyl)-5-(3,7-dimethyl-2,6-octadienyl)xanthone)		<i>Cratoxylum cochinchinense</i> (Guttiferae)	Mahabusarakam et al., 2006b

Table 1 Contd.

Table 1 Contd.

200	Dulcisxanthone E		<i>Garcinia dulcis</i> (Guttiferae)	Deachathai et al., 2006
201	Isocowanol		<i>Garcinia parvifolia</i> (Guttiferae)	Jantan et al., 2002
202	Cowanin		<i>Garcinia dulcis</i> , <i>Garcinia cowa</i> , <i>Garcinia dioica</i> , <i>Garcinia fusca</i> , <i>Garcinia speciosa</i> (Guttiferae)	Tosa, 1997; Okudaira, 2000; Ito, 2003b; Mahabusarakam, 2005; Deachathai, 2005; Pattalung, 1994; Panthong, 2006
203	Cuneifolin		<i>Garcinia cuneifolia</i> (Guttiferae)	Vieira and Kijjoa, 2005

Table 1 Contd.

Table 1 Contd.

204	Parvifolixanthone C		<i>Garcinia parvifolia</i> (Guttiferae)	Rukachaisirikul et al., 2006
205	Fuscaxanthone H		<i>Garcinia fusca</i> (Guttiferae)	Ito et al., 2003b
206	Parvixanthone A		<i>Garcinia parvifolia</i> (Guttiferae)	Xu, 2001; Kardono, 2006
207	Cowanol		<i>Garcinia Cowa</i> , <i>Garcinia fusca</i> , <i>Garcinia speciosa</i> (Guttiferae)	Okudaira, 2000; Ito, 2003b; Mahabusarakam, 2005; Pattalung, 1994; Panthong, 2006
208	Cowagarcinone E		<i>Garcinia Cowa</i> (Guttiferae)	Mahabusarakam et al., 2005

Table 1 Contd.

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209	Parvixanthone B		<i>Garcinia parvifolia</i> (Guttiferae)	Xu et al., 2001
210	Garcinianone B		<i>Garcinia multiflora</i> (Guttiferae)	Chiang et al., 2003
211	Apetalinone C		<i>Calophyllum apetalum</i> (Guttiferae)	linuma et al., 1997
212	Allanxanthone C		<i>Allanblackia monticola</i> (Guttiferae)	Azebaze et al., 2006
213	Zeyloxanthone		<i>Calophyllum apetalum</i> , <i>Calophyllum tomentosum</i> , <i>Calophyllum zeylanicum</i> (Guttiferae)	linuma, 1997; Banerji, 1994; Gunasekera, 1981
214	Garcinone E		<i>Garcinia mangostana</i> (Guttiferae)	Ho, 2002; Chairungsrikerd, 1996; Huang, 2001; Dharmaratne, 2005; linuma, 1996c; Suksamran, 2006; Jung, 2006
215	Isogarcinixanthone E (or 1,3,5,6-Tetrahydroxy-4,7, 8-tri(3-methyl-2-butenyl) xanthone		<i>Garcinia subelliptica</i> , <i>Garcinia xanthochymus</i> (Guttiferae)	Chanmahasathien, 2003b; Abe, 2003; Ohizumi, 2004

Table 1 Contd.

Table 1 Contd.

216	Parvifolixanthone A		<i>Garcinia parvifolia</i> (Guttiferae)	Rukachaisirikul et al., 2006
217	7-O-Methylgarcinone		<i>Garcinia fusca</i> , <i>Garcinia cowa</i> (Guttiferae)	Ito, 2003b; Panthong, 2006
218	Subelliptenone A		<i>Garcinia subelliptica</i> (Guttiferae)	Abe, 2003; linuma, 1994a
219	Dulciol B		<i>Garcinia dulcis</i> (Guttiferae)	linuma et al., 1996a
220	Nervosaxanthone		<i>Garcinia nervosa</i> (Guttiferae)	Mahabusarakam, 2006b; Ampofo, 1986

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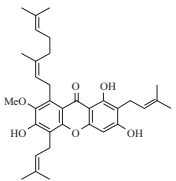
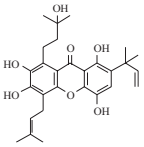
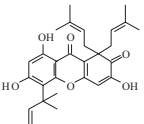
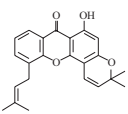
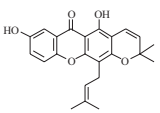
221	Cowagarcinone A		<i>Garcinia Cowa</i> (<i>Guttiferae</i>)	Mahabusarakam et al., 2005
222	Dulciol C		<i>Garcinia dulcis</i> (<i>Guttiferae</i>)	linuma et al., 1996a
223	1,2-Dihydro-3,6,8-trihydroxy-1,1-bis(3-methylbut-2-enyl)-5-(1,1-dimethylprop-2-enyl)xanthen-2,9-dione		<i>Hypericum erectum</i> (<i>Guttiferae</i>)	An et al., 2002
224	Laurentixanthon A		<i>Vismia laurentii</i> (<i>Guttiferae</i>)	Nguemaving et al., 2006
225	Brasixanthon B or Cudraxanthon Q		<i>Calophyllum brasiliense</i> (<i>Guttiferae</i>); <i>Cudrania cochinchinensis</i> (<i>Moraceae</i>)	Ito, 2002, 2003a; Hou, 2001; Noldin, 2006

Table 1 Contd.

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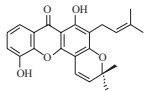
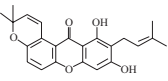
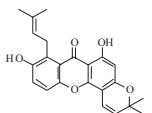
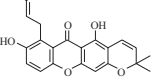
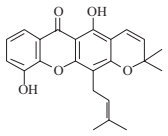
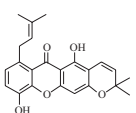
226	Ananixanthon		<i>Calophyllum caledonicum</i> , <i>Garcinia nigrolineata</i> , <i>Symphonia globulifera</i> , <i>Mesua daphnifolia</i> , <i>Chrysochlamys tenuis</i> (<i>Guttiferae</i>)	Rukachaisirikul, 2003a; Bayma, 1998; Morel, 2002b; Ee, 2006b; Molinar-Toribio, 2006
227	Calothwaitesixanthon		<i>Calophyllum thwaitesii</i> , <i>Calophyllum caledonicum</i> (<i>Guttiferae</i>)	Hay, 2003; Dharmaratne, 1996, 1999, 2002; Hay, 2004b; Noldin, 2006
228	Cudraxanthon I		<i>Cudrania cochinchinensis</i> (<i>Moraceae</i>)	Chang, 1994; Nomura, 1994
229	Demethylcalabaxanthon		<i>Garcinia mangostana</i> , <i>Calophyllum caledonicum</i> , <i>Calophyllum thwaitesii</i> (<i>Guttiferae</i>)	Suksamram, 2003, 2006; Dharmaratne, 1996; Hay, 2004b; Mahabusarakam, 1987; Noldin, 2006
230	Trapezifolixanthon or Toxyloxanthon A		<i>Garcinia mangostana</i> , <i>Calophyllum paniciflorum</i> , <i>Calophyllum thwaitesii</i> , <i>Tovomita brevistaminea</i> , <i>Calophyllum brasiliense</i> , <i>Calophyllum trapezifolium</i> , <i>Chrysochlamys tenuis</i> (<i>Guttiferae</i>)	Suksamram, 2002, 2003; Seo, 1999; Ito, 1996, 1998, 2002, 2003a; Dharmaratne, 1996, 1999; Somanathan, 1974; Noldin, 2006; Molinar-Toribio, 2006
231	Nigrolineaxanthon K		<i>Garcinia nigrolineata</i> (<i>Guttiferae</i>)	Rukachaisirikul et al., 2003a

Table 1 Contd.

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232 Mergueneone		<i>Garcinia merguensis</i> (<i>Guttiferae</i>)	Nguyen et al., 2003
233 Caloxanthone A		<i>Calophyllum inophyllum</i> (<i>Guttiferae</i>)	Tosa, 1997; Yimdjo, 2004; Iinuma, 1994c, 1996c; Noldin, 2006
234 Morusignin I		<i>Calophyllum paniciflorum</i> (<i>Guttiferae</i>); <i>Morus insignis</i> (<i>Moraceae</i>)	Ito, 1996, 1998; Hano, 1993; Nomura, 1994
235 Paxanthone B		<i>Hypericum patulum</i> (<i>Guttiferae</i>)	Ishiguro et al., 1995a
236 Cudraticusxanthone D		<i>Cudrania tricuspidata</i> (<i>Moraceae</i>)	Zou et al., 2004
237 Xanthone VI		<i>Garcinia dulcis</i> , <i>Cratogeomys formosum</i> (<i>Guttiferae</i>)	Ito, 1997, 1998; Boonsri, 2006; Boonnak, 2006b; Chantrapromma, 2005

Table 1 Contd.

Table 1 Contd.

238 Morusignin J		<i>Garcinia dulcis</i> (<i>Guttiferae</i>); <i>Morus insignis</i> (<i>Moraceae</i>)	Deachathai, 2005, 2006; Hano, 1993; Nomura, 1994
239 Garcinone B		<i>Garcinia dulcis</i> , <i>Garcinia mangostana</i> , <i>Calophyllum brasiliense</i> , <i>Hypericum patulum</i> , <i>Hypericum androsaemum</i> , <i>Cratogeomys cochinchinense</i> (<i>Guttiferae</i>)	Suksamran, 2002, 2003, 2006; Ito, 2002, 2003a; Ishiguro, 1995a; Dias, 2000; Huang, 2001; Deachathai, 2005, 2006; Mahabusarakam, 2006b; Yamakuni, 2006; Sen, 1982
240 Latisxanthone D		<i>Garcinia latissima</i> , <i>Garcinia nigrolineata</i> (<i>Guttiferae</i>)	Rukachaisirikul, 2003d; Ito, 1997
241 Calabaxanthone		<i>Calophyllum thwaitesii</i> , <i>Calophyllum zeylanicum</i> , <i>Garcinia mangostana</i> , <i>Calophyllum trapezifolium</i> (<i>Guttiferae</i>)	Dharmaratne, 1999; Gunasekera, 1981; Mahabusarakam, 1987; Somanathan, 1974
242 Brasixanthone A		<i>Calophyllum brasiliense</i> (<i>Guttiferae</i>)	Ito, 2002, 2003a; Noldin, 2006
243 5-O-Methylxanthone V ₁		<i>Garcinia bracteata</i> (<i>Guttiferae</i>)	Thoisson et al. 2005

Table 1 Contd.

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244	Brasixanthone E		<i>Calophyllum brasiliense</i> (Guttiferae)	Ito, 2002, 2003a; Noldin, 2006
245	1,6-Dihydroxy-8-isoprenyl-7-methoxy-6',6'-dimethylpyrano-(2'',3':3,2)xanthone (or 5,9-Dihydroxy-8-methoxy-2,2-dimethyl-7-(3-methylbut-2-enyl)-2H,6H-pyrano-[3,2-b]xanthen-6-one)		<i>Garcinia mangostana</i> (Guttiferae)	Suksamram, 2003, 2006; Nilar, 2002; Chairungsrikerd, 1996; Huang, 2001
246	Manglexanthone		<i>Tovomita brevistaminea</i> (Guttiferae)	Seo et al., 1999
247	1,5-dihydroxy-3-methoxy-6',6'-dimethylpyrano (2',3':6,7)-4-(3-methylbut-2-enyl)xanthone		<i>Garcinia cowa</i> (Guttiferae)	Shen and Yang, 2006
248	Cowaxanthone D or Dulcixanthone F		<i>Garcinia cowa</i> , <i>Garcinia dulcis</i> , <i>Cratogeomys formosum</i> ssp. <i>Pruniflorum</i> (Guttiferae)	Deachathai, 2006; Panthong, 2006; Boonnak, 2006b
249	Symphonin [2-(3,3-dimethylallyl)-1,5-dihydroxy-6,7-dimethoxy-2'',2'-dimethylpyrano(5'',6'':3,4)xanthone]		<i>Symphonia globulifera</i> (Guttiferae)	Lenta, 2004; Ngouela, 2006

Table 1 Contd.

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250	Gaboxanthone		<i>Symphonia globulifera</i> (Guttiferae)	Ngouela et al., 2006
251	Nigrolineaxanthone Q		<i>Garcinia nigrolineata</i> (Guttiferae)	Rukachaisirikul et al., 2003a
252	Nigrolineaxanthone J		<i>Garcinia nigrolineata</i> (Guttiferae)	Rukachaisirikul et al., 2003a
253	Mangostenone D		<i>Garcinia mangostana</i> (Guttiferae)	Suksamram et al., 2006
254	1-Isomangostin		<i>Garcinia mangostana</i> (Guttiferae); Synthesis	Mahabusarakam, 1987, 1998; Huang, 2001; Jung, 2006
255	3-Isomangostin (or 1,6-Dihydroxy-7-methoxy-8-(3-methyl-2-butenyl)-2'',2'-dimethylchromeno [5',6':2,3] xanthone)		<i>Garcinia mangostana</i> , <i>Garcinia dulcis</i> , <i>Cratogeomys formosum</i> ssp. <i>pruniflorum</i> (Guttiferae); Synthesis	Mahabusarakam, 1987, 1998; Nilar, 2002; Huang, 2001; Deachathai, 2005, 2006; Boonnak, 2006b

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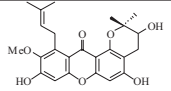
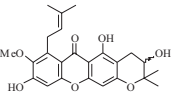
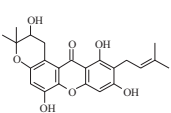
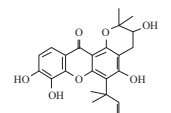
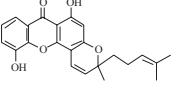
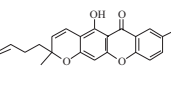
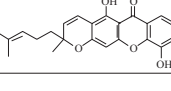
256	11-Hydroxy-1-isomangostin		<i>Cratoxylum cochinchinense</i> , <i>Garcinia mangostana</i> (Guttiferae)	Sia, 1995; Suksamrarn, 2006
257	Mangostanol		<i>Garcinia mangostana</i> (Guttiferae)	Suksamrarn, 2002, 2003, 2006; Lu, 1998; Chairungsilert, 1996; Huang, 2001
258	Garcimangosone C		<i>Garcinia mangostana</i> (Guttiferae)	Huang et al., 2001
259	Bracteaxanthone II		<i>Garcinia bracteata</i> (Guttiferae)	Thoisson et al., 2005
260	6,11-Dihydroxy-3-methyl-3-(4-methylpent-3-enyl)-3H,7H-pyrano [2,3-c] xanthen-7-one		<i>Garcinia livingstonei</i> (Guttiferae)	Diserens, 1992; Brühlmann, 2004; Mbwambo, 2006
261	1,7-Dihydroxy-6'-methyl-6'-(4-methyl-3-pentenyl)-pyrano (2', 3':3,2) xanthone		<i>Kielmeyera lathrophyton</i> (Guttiferae)	Cruz et al., 2001
262	1,5-Dihydroxy-6'-methyl-6'-(4-methyl-3-pentenyl)-pyrano (2', 3':3,2) xanthone		<i>Kielmeyera lathrophyton</i> , <i>Garcinia merguensis</i> (Guttiferae)	Cruz, 2001; Nguyen, 2003

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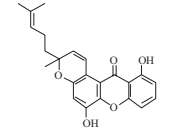
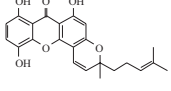
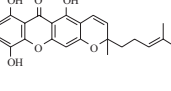
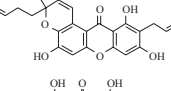
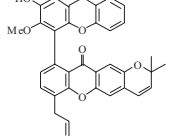
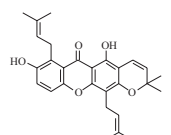
263	Globulixanthone B		<i>Symphonia globulifera</i> (Guttiferae)	Nkengfack et al., 2002
264	Bangangxanthone A		<i>Garcinia polyantha</i> (Guttiferae)	Lannang et al., 2005
265	Smeathxanthone B		<i>Garcinia smeathmannii</i> (Guttiferae)	Komguem et al., 2005
266	Cowagarcinone D (6,8,12-Trihydroxy-7-(3-methyl-2-butenyl)-2-methyl-2-(4-methyl-3-pentenyl)pyrano (2',3':7,8) xanthone)		<i>Garcinia Cowa</i> , <i>Garcinia dulcis</i> (Guttiferae)	Mahabusarakam, 2005; Deachathai, 2005
267	Globulixanthone E		<i>Symphonia globulifera</i> (Guttiferae)	Nkengfack et al., 2002c
268	Dombakinoxanthone		<i>Calophyllum caledonicum</i> , <i>Calophyllum moonii</i> (Guttiferae)	Dharmaratne, 1997; Hay, 2004b; Noldin, 2006

Table 1 Contd.

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269	Batukinaxanthone		<i>Calophyllum thwaitesii</i> (Guttiferae)	Dharmaratne et al., 1999
270	Dulcisxanthone A		<i>Garcinia dulcis</i> (Guttiferae)	Deachathai et al., 2005
271	Tovophyllin A (or 1,3,6-Trihydroxy-6',6'- dimethylpyrano(2',3':7,8)- 2,5-di(3-methylbut-2-enyl) xanthone)		<i>Garcinia dulcis</i> , <i>Garcinia mangostana</i> , <i>Allanblackia monticola</i> , <i>Cratoxylum cochinchinense</i> , <i>Tovomita macrophylla</i> , <i>Tovomita pyrifolium</i> (Guttiferae)	Ho, 2002; Azebaze, 2004, 2006; Huang, 2001; Bennett, 1993; Deachathai, 2005; Nagem, 1997; Jung, 2006
272	Latisxanthone C		<i>Garcinia latissima</i> , <i>Calophyllum brasiliense</i> (Guttiferae)	Ito, 1997, 1998, 2002, 2003a; Noldin, 2006
273	Caloxanthone J		<i>Calophyllum apetalum</i> (Guttiferae)	Lloyd, 1997
274	Cowaxanthone C		<i>Garcinia cowa</i> (Guttiferae)	Panthong et al., 2006

Table 1 Contd.

Table 1 Contd.

275	Caloxanthone		<i>Calophyllum blancoi</i> (Guttiferae)	Shen, 2005; Noldin, 2006
276	Calophinone		<i>Calophyllum inophyllum</i> (Guttiferae)	Cheng, et al., 2004
277	Dulcisxanthone D		<i>Garcinia dulcis</i> (Guttiferae)	Deachathai et al., 2006
278	Calophinone-6- O-acetate		<i>Calophyllum inophyllum</i> (Guttiferae)	Cheng, et al., 2004
279	Caloxanthone I		<i>Calophyllum inophyllum</i> , <i>Calophyllum apetalum</i> (Guttiferae)	Cheng, 2004; Lloyd, 1997
280	Latisxanthone A		<i>Garcinia latissima</i> (Guttiferae)	Ito, 1997, 1998

Table 1 Contd.

Table 1 Contd.

281	Mangostenone A		<i>Garcinia mangostana</i> (<i>Guttiferae</i>)	Suksamram, 2002, 2003
282	Tovophyllin B (or 1,6-Dihydroxy-5-(3-methylbut-2-enyl)-6',6'-dimethylpyrano (2',3':7,8)-6'',6''-dimethylpyrano (2'',3'':3,2)xanthone)		<i>Garcinia mangostana</i> , <i>Tovomita macrophylla</i> , <i>Tovomita pyrifolium</i> (<i>Guttiferae</i>)	Suksamram, 2002, 2003; Huang, 2001; Nagem, 1997
283	Mangostenone B		<i>Garcinia mangostana</i> (<i>Guttiferae</i>)	Suksamram et al., 2002
284	Garcimangosone A		<i>Garcinia mangostana</i> (<i>Guttiferae</i>)	Huang et al., 2001
285	Apetalinone B		<i>Calophyllum apetalum</i> (<i>Guttiferae</i>)	linuma et al., 1997
286	Nigrolineaxanthone M		<i>Garcinia nigrolineata</i> (<i>Guttiferae</i>)	Rukachaisirikul et al., 2003a

Table 1 Contd.

Table 1 Contd.

287	Nigrolineaxanthone B		<i>Garcinia nigrolineata</i> (<i>Guttiferae</i>)	Rukachaisirikul et al., 2003
288	Nigrolineaxanthone L		<i>Garcinia nigrolineata</i> (<i>Guttiferae</i>)	Rukachaisirikul et al., 2003a
289	Nigrolineaxanthone R		<i>Garcinia nigrolineata</i> (<i>Guttiferae</i>)	Rukachaisirikul et al., 2003a
290	Pruniflorone A		<i>Cratoxylum formosum</i> ssp. <i>pruniflorum</i> (<i>Guttiferae</i>)	Boonnak et al., 2006b
291	Pruniflorone B		<i>Cratoxylum formosum</i> ssp. <i>pruniflorum</i> (<i>Guttiferae</i>)	Boonnak et al., 2006b
292	Latisxanthone B		<i>Garcinia latissima</i> (<i>Guttiferae</i>)	Ito et al., 1997

Table 1 Contd.

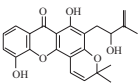
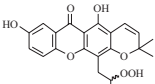
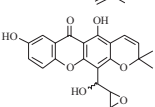
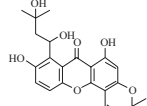
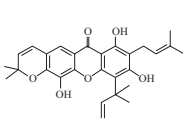
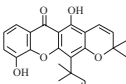
293	6,11-Dihydroxy-5-(2-hydroxy-3-methylbut-3-enyl)-3,3-dimethyl-3H-pyrano[2,3-c]-xanthen-7-one		<i>Calophyllum caledonicum</i> (Guttiferae); Synthesis	Helesbeux, 2004; Hay, 2004b; Oger, 2003
294	Brasixanthone C		<i>Calophyllum brasiliense</i> (Guttiferae)	Ito, 2002, 2003a; Noldin, 2006
295	Brasixanthone D		<i>Calophyllum brasiliense</i> (Guttiferae)	Ito, 2002, 2003a; Noldin, 2006
296	Cudraxanthone N		<i>Cudrania tricuspidata</i> (Moraceae)	Hano, 1991a; Nomura, 1994
297	1,3,5-Trihydroxy-6',6'-dimethylpyrano (2',3':6,7)-2-(3-methylbut-2-enyl)-4-(1,1-dimethylprop-2-enyl)xanthone		<i>Garcinia opaca</i> (Guttiferae)	Goh et al., 1992
298	Caloxanthone C or Inoxanthone (or 1,5-Dihydroxy-4-(1,1-dimethylallyl)-6',6'-dimethylpyrano (2',3':2,3) xanthone)		<i>Calophyllum caledonicum</i> , <i>Calophyllum inophyllum</i> (Guttiferae)	Tosa, 1997; Yimdjo, 2004; Hay, 2004b; Iinuma, 1994b

Table 1 Contd.

Table 1 Contd.

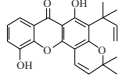
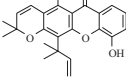
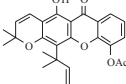
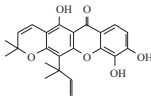
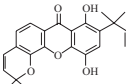
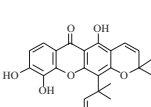
299	Inophyllin A		<i>Calophyllum inophyllum</i> (Guttiferae)	Ee et al., 2006a
300	Blancoxanthone		<i>Calophyllum blancoi</i> (Guttiferae)	Shen, 2005; Noldin, 2006
301	Acetyl Blancoxanthone		<i>Calophyllum blancoi</i> (Guttiferae)	Shen, 2005; Noldin, 2006
302	3-Hydroxyblancoxanthone		<i>Calophyllum blancoi</i> (Guttiferae)	Shen, 2005; Noldin, 2006
303	Garciniaxanthone B		<i>Garcinia subelliptica</i> , <i>Garcinia dulcis</i> (Guttiferae)	Chanmahasathien, 2003a; Abe, 2003; Fukuyama, 1991; Minami, 1994; Iinuma, 1996a
304	Macluraxanthone		<i>Calophyllum inophyllum</i> , <i>Garcinia opaca</i> , <i>Rheedia brasiliensis</i> , <i>Rheedia gardneriana</i> , <i>Rheedia benthamiana</i> , <i>Calophyllum caledonicum</i> , <i>Cratogeomys formosum</i> , <i>Cratogeomys cochinchinense</i> (Guttiferae); <i>Maclura pomifera</i> , <i>Cudrania cochinchinensis</i> (Moraceae)	Tosa, 1997; Jantan, 2001, 2002; Costa, 1999, 2000; Yimdjo, 2004; Hay, 2004b; Teixeira, 2005; Hou, 2001; Chang, 1989b; Monache, 1981, 1983, 1984b; Wu, 2003; Iinuma, 1994b, 1994c, 1996b, 1996c; Mahabusarakam, 2006b; Goh, 1992; Boonsri, 2006; Noldin, 2006; Fun, 2006

Table 1 Contd.

Table 1 Contd.

305	Gerontoxanthone B		<i>Cudrania fruticosa</i> , <i>Cudrania cochinchinensis</i> (Moraceae)	Fukai, 2004, 2005; Hou, 2001; Wang, 2005; Chang, 1989a, 1989b; Nomura, 1994; Boonnak, 2006b
306	Cudraticusxanthone H		<i>Cudrania tricuspidata</i> (Moraceae)	Zou, 2004, 2005
307	Cudraxanthone K		<i>Cudrania tricuspidata</i> (Moraceae); <i>Hypericum androsaemum</i> (Guttiferae)	Schmidt, 2000; Zou, 2005; Nomura, 1994
308	Cudraxanthone B		<i>Cudrania tricuspidata</i> (Moraceae)	An et al., 2006
309	1,3,5-Trihydroxy-6,6'-dimethylpyrano-(2',3':6,7)-4-(1,1-dimethylprop-2-enyl)xanthone		<i>Garcinia opaca</i> , <i>Rheedea brasiliensis</i> , <i>Calophyllum inophyllum</i> (Guttiferae)	Jantan, 2001, 2002; Nilar, 2005; Monache, 1984b; Goh, 1992; Noldin, 2006
310	1,3,7-Trihydroxy-4-(1,1-dimethyl-2-propenyl)-5,6-(2,2-dimethylchromeno)xanthone		<i>Cudrania tricuspidata</i> (Moraceae)	Lee, 2005b; Park, 2006
311	Isocudraxanthone K		<i>Cudrania tricuspidata</i> (Moraceae)	An et al., 2006

Table 1 Contd.

Table 1 Contd.

312	Subelliptenone H		<i>Garcinia subelliptica</i> , <i>Garcinia merguensis</i> , <i>Garcinia vilersiana</i> (Guttiferae)	linuma, 1995b; Abe, 2003; Nguyen, 2000, 2003
313	Linixanthone A		<i>Garcinia linii</i> (Guttiferae)	Chen et al., 2004
314	10-O-Methylmacluraxanthone		<i>Garcinia linii</i> , <i>Cratoxylum formosum</i> ssp. <i>pruniflorum</i> (Guttiferae)	Chen, 2004; Boonnak, 2006b; Boonnak et al.,
315	Pruniflorone G		<i>Cratoxylum formosum</i> ssp. <i>pruniflorum</i> (Guttiferae)	2006b
316	Pruniflorone H		<i>Cratoxylum formosum</i> ssp. <i>pruniflorum</i> (Guttiferae)	Boonnak et al., 2006b
317	Subelliptenone I		<i>Garcinia subelliptica</i> (Guttiferae)	linuma et al., 1995b
318	Garcigerrin A		<i>Garcinia gerrardii</i> (Guttiferae)	Brühlmann, 2004; Diserens, 1989

Table 1 Contd.

Table 1 Contd.

319	Garcigerrin B		<i>Garcinia Gerrardii</i> (Guttiferae)	Diserens et al., 1989
320	Subelliptenone E		<i>Garcinia subelliptica</i> (Guttiferae)	Tosa, 1997; Iinuma, 1995a
321	Caloxanthone L		<i>Calophyllum caledonicum</i> (Guttiferae)	Hay et al., 2003
322	8-Prenyltoxyloxanthone		<i>Maclura pomifera</i> (Moraceae)	Teixeira and Costa, 2005
323	8-Prenyltoxyloxanthone C		<i>Maclura pomifera</i> , <i>Cudrania fruticosa</i> (Moraceae)	Costa, 1999, 2000; Wang, 2005; Monache, 1984a
324	Gerontoxanthone C		<i>Cudrania fruticosa</i> , <i>Cudrania cochinchinensis</i> (Moraceae)	Wang, 2005; Chang, 1989a, 1989b, 1994; Nomura, 1994

Table 1 Contd.

Table 1 Contd.

325	Gerontoxanthone G		<i>Cudrania fruticosa</i> , <i>Cudrania cochinchinensis</i> (Moraceae)	Fukai, 2004, 2005; Hou, 2001; Wang, 2005; Chang, 1989b, 1994; Nomura, 1994
326	Cudraticusxanthone F		<i>Cudrania tricuspidata</i> (Moraceae)	Zou, 2004, 2005
327	Cudraxanthone M		<i>Cudrania tricuspidata</i> (Moraceae)	Hano, 1991a; Zou, 2004; Lee, 2005b; Nomura, 1994; Park, 2006
328	Formoxanthone C		<i>Cratoxylum formosum</i> (Guttiferae)	Boonsri et al., 2006
329	Caloxanthone B		<i>Calophyllum inophyllum</i> (Guttiferae)	Tosa, 1997; Yimdojo, 2004; Iinuma, 1994c; Noldin, 2006
330	Gerontoxanthone E		<i>Cudrania fruticosa</i> , <i>Cudrania cochinchinensis</i> (Moraceae)	Wang, 2005; Chang, 1989b, 1994; Nomura, 1994

Table 1 Contd.

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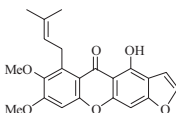
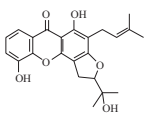
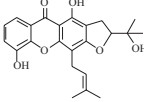
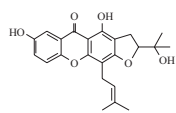
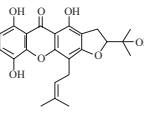
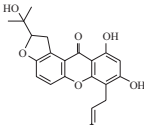
331	Garciniafuran		<i>Allanblackia monticola</i> , <i>Garcinia mangostana</i> (Guttiferae)	Nilar, 2002; Azebaze, 2004, 2006
332	Morusignin H		<i>Morus insignis</i> (Moraceae)	Hano, 1991b; Nomura, 1994
333	Morusignin G		<i>Garcinia merguensis</i> (Guttiferae); <i>Morus</i> <i>insignis</i> (Moraceae)	Nguyen, 2003; Nilar, 2005; Hano, 1993; Nomura, 1994
334	Mangoxanthone		<i>Garcinia mangostana</i> (Guttiferae)	Nilar et al., 2005
335	Morusignin E		<i>Morus insignis</i> (Moraceae)	Nilar, 2002; Hano, 1993; Nomura, 1994
336	Cudraxanthone J		<i>Cudrania tricuspidata</i> (Moraceae)	Hano, 1991a; Nomura, 1994

Table 1 Contd.

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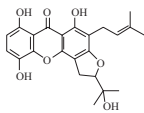
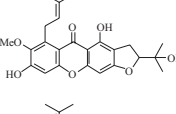
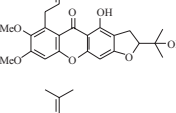
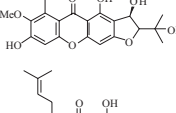
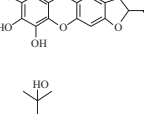
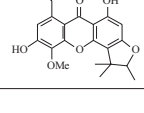
337	Morusignin F		<i>Morus insignis</i> (Moraceae)	Hano, 1991b; Nomura, 1994
338	Mangostanin		<i>Garcinia mangostana</i> , <i>Garcinia cowa</i> (Guttiferae)	Suksamram, 2003, 2006; Nilar, 2002; Panthong, 2006
339	6-O-Methylmangostanin		<i>Garcinia mangostana</i> , <i>Garcinia cowa</i> (Guttiferae)	Nilar, 2002; Panthong, 2006
340	Mangostenone C		<i>Garcinia mangostana</i> (Guttiferae)	Suksamram et al., 2006
341	Cratoxyarborenone D		<i>Cratoxylum</i> <i>sumatranum</i> (Guttiferae)	Seo, 2002; Kinghorn, 2003
342	Caloxanthone M		<i>Calophyllum inophyllum</i> (Guttiferae)	Wu et al., 2003

Table 1 Contd.

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343	Cudraticusxanthone C		<i>Cudrania tricuspidata</i> (Moraceae)	Zou et al., 2004
344	Rheediaxanthone B		<i>Rheedia brasiliensis</i> ; <i>Rheedia benthamiana</i> , <i>Rheedia gardneriana</i> (Guttiferae)	Thoison, 2000; Monache, 1981, 1983, 1984b
345	Isorheediaxanthone B (4',5'-dihydro-1,5, 6-trihydroxy-4',5', 5'-trimethylfurano(2', 3':3,2)-4-(1,1- dimethylprop-2- enyl)xanthone)		<i>Rheedia brasiliensis</i> , <i>Rheedia gardneriana</i> (Guttiferae)	Monache, 1983, 1984b
346	Garciniaxanthone F		<i>Garcinia subelliptica</i> (Guttiferae)	Minami et al., 1996
347	Garciniaxanthone D		<i>Garcinia subelliptica</i> , <i>Garcinia dulcis</i> (Guttiferae)	Minami, 1996; Iinuma, 1996a
348	Cudraxanthone R		<i>Cudrania cochinchinensis</i> (Moraceae)	Hou et al., 2001

Table 1 Contd.

Table 1 Contd.

349	Garciniaxanthone G or Dulciol D		<i>Garcinia subelliptica</i> , <i>Garcinia dulcis</i> (Guttiferae)	Minami, 1996; Iinuma, 1996a
350	Subelliptenone C		<i>Garcinia subelliptica</i> , <i>Garcinia dulcis</i> (Guttiferae)	Tosa, 1997; Iinuma, 1995c, 1996a
351	Subelliptenone D (or 1,2,5-Trihydroxy- 4-(1,1-dimethylallyl)- furano (2,3:6,7) xanthone)		<i>Garcinia subelliptica</i> , <i>Garcinia dulcis</i> (Guttiferae)	Tosa, 1997; Iinuma, 1995c, 1996a
352	4'',5''-Dihydro-1, 5-dihydroxy-6'',6''- dimethylpyrano (2',3':6,7)-2-(3- methylbut-2-enyl)- 4'',4'',5''-trimethylfurano (2'',3':3,4) xanthone		<i>Garcinia opaca</i> (Guttiferae)	Goh et al., 1992
353	Formoxanthone B		<i>Cratogeomys formosum</i> (Guttiferae)	Boonsri, 2006; Boonnak, 2006b
354	Allanxanthone B		<i>Allanblackia monticola</i> (Guttiferae)	Azebaze et al., 2004
355	Virgataxanthone B		<i>Garcinia virgata</i> (Guttiferae)	Merza et al., 2004

Table 1 Contd.

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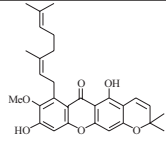
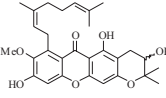
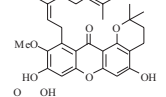
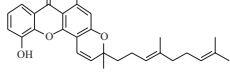
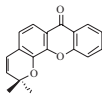
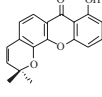
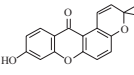
356	Fuscaxanthone A (1,6-dihydroxy-7-methoxy-8-(3,7-dimethyl-2,6-octadienyl)-2',2'-dimethylpyrano[3,2-b]xanthen-9-one)		<i>Garcinia Cowa</i> , <i>Garcinia fusca</i> , <i>Garcinia dulcis</i> (<i>Guttiferae</i>)	Ito, 2003b; Mahabusarakam, 2005; Deachathai, 2005
357	Fuscaxanthone B		<i>Garcinia fusca</i> (<i>Guttiferae</i>)	Ito et al., 2003b
358	Fuscaxanthone G		<i>Garcinia fusca</i> (<i>Guttiferae</i>)	Ito et al., 2003b
359	Nigrolineaxanthone S		<i>Garcinia nigrolineata</i> (<i>Guttiferae</i>)	Rukachaisirikul et al., 2003a
360	Caledonixanthone B		<i>Calophyllum caledonicum</i> (<i>Guttiferae</i>)	Morel, 2000, 2002b; Noldin, 2006
361	Dehydrocycloguanandin		<i>Calophyllum caledonicum</i> , <i>Calophyllum brasiliense</i> (<i>Guttiferae</i>)	Morel, 2000, 2002b; Gottlieb, 1968
362	Hyperireflexin		<i>Hypericum reflexum</i> (<i>Guttiferae</i>)	Cardona et al., 1990

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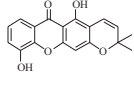
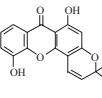
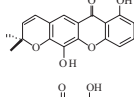
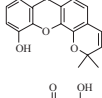
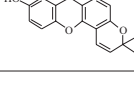
363	6-Deoxyjacareubin (6-desoxyjacareubin or 1,5-Dihydroxy-6',6'- dimethylpyrano[2',3':3,2] xanthone)		<i>Calophyllum brasiliense</i> , <i>Calophyllum inophyllum</i> , <i>Vismia latifolia</i> , <i>Calophyllum brasiliense</i> , <i>Garcinia nigrolineata</i> , <i>Garcinia merguensis</i> , <i>Calophyllum zeylanicum</i> , <i>Kielmeyera speciosa</i> , <i>Calophyllum fragrans</i> , <i>Cratogeomys formosum</i> ssp. <i>pruniflorum</i> (<i>Guttiferae</i>); <i>Cudrania</i> <i>cochinchinensis</i> (<i>Moraceae</i>); Synthesis	Abe, 2004; Tosa, 1997; Jantan, 2001, 2002; Ito, 2002, 2003a; Rukachaisirikul, 2003d; Cheng, 2004; Chilpa, 1997; Nguyen, 2003; Hou, 2001; Yasunaka, 2005; Locksley, 1971; Gunasekera, 1981; Wu, 2003; Doriguetto, 2001; Iinuma, 1994b; Gottlieb, 1968; Reyes-Chilpa, 2006; Noldin, 2006; Boonnak, 2006b
364	6-Deoxyisojacareubin		<i>Calophyllum caledonicum</i> , <i>Hypericum japonicum</i> , <i>Hypericum wightianum</i> , <i>Calophyllum brasiliense</i> , <i>Garcinia merguensis</i> , <i>Vismia laurentii</i> (<i>Guttiferae</i>); Synthesis	Helesbeux, 2004; Nguyen, 2003; Wu, 1998; Morel, 2002b; Ito, 2003a; Fu, 2004; Tao, 2004; Ngumeeving, 2006
365	Rheediachromenoxanthone (1,5-dihydroxy-6',6'- dimethylpyrano[3,2-c] xanthone)		<i>Garcinia linii</i> , <i>Garcinia</i> <i>merguensis</i> , <i>Rheedia</i> <i>brasiliensis</i> , <i>Rheedia</i> <i>gardneriana</i> (<i>Guttiferae</i>)	Nguyen, 2003; Chen, 2004; Monache, 1983, 1984b
366	6,11-Dihydroxy-2,2- dimethylpyrano[3,2-c] xanthen-7(2H)-one		<i>Garcinia livingstonei</i> (<i>Guttiferae</i>)	Diserens et al., 1992
367	Nigrolineaxanthone F		<i>Garcinia nigrolineata</i> (<i>Guttiferae</i>); Synthesis	Rukachaisirikul, 2003d; Mondal, 2006

Table 1 Contd.

368	Nigrolineaxanthone H		<i>Garcinia nigrolineata</i> (<i>Guttiferae</i>)	Rukachaisirikul et al., 2003
369	Tovoxanthone		<i>Garcinia nigrolineata</i> (<i>Guttiferae</i>)	Rukachaisirikul et al., 2003
370	Osajaxanthone		<i>Maclura pomifera</i> , <i>Cudrania cochinchinensis</i> (<i>Moraceae</i>); <i>Kielmeyera</i> <i>sp.</i> , <i>Kielmeyera corymbosa</i> , <i>Calophyllum nervosum</i> (<i>Guttiferae</i>); <i>Synthesis</i>	Costa, 2000; Teixeira, 2005; Chang, 1989a; Gottlieb, 1968; Taher, 2005; Mondal, 2006
371	Jacareubin		<i>Calophyllum brasiliense</i> , <i>Calophyllum inophyllum</i> , <i>Garcinia dulcis</i> , <i>Calophyllum brasiliensis</i> , <i>Kielmeyera coriacea</i> , <i>Calophyllum zeylanicum</i> (<i>Guttiferae</i>); <i>Synthesis</i>	Abe, 2004; Ito, 1997, 1998; Chilpa, 1997; Yasunaka, 2005; Jefferson, 1996; Gunasekera, 1981; Cortez, 1998; Wu, 2003; Gottlieb, 1968; Reyes-Chilpa, 2006
372	Morusignin C		<i>Garcinia nigrolineata</i> (<i>Guttiferae</i>)	Rukachaisirikul, 2003d; Nomura, 1994
373	Isojacareubin		<i>Hypericum japonicum</i> Thumb., <i>Hypericum roeperanum</i> (<i>Guttiferae</i>)	Rath, 1996; Wu, 1998; Fu, 2004
374	Toxyloxanthone B		<i>Hypericum sampsonii</i> , <i>Garcinia assigu</i> , <i>Garcinia dulcis</i> , <i>Hypericum subulatum</i> , <i>Hypericum scabrum</i> , <i>Hypericum androsaemum</i> , <i>Hypericum perforatum</i> , <i>Hypericum chinense</i> (<i>Guttiferae</i>); <i>Synthesis</i>	Dias, 2000, 2001; Ito, 1997, 1998; Chen, 1989; Tanaka, 2004, 2006; Cotterill, 1980; Don, 2004; Iinuma, 1996a

Table 1 Contd.

Table 1 Contd.

375	1,3,5-Trihydroxy-6', 6'-dimethyl-2 <i>H</i> -pyran (2',3':6,7)xanthone		<i>Rheedia brasiliensis</i> , <i>Garcinia mangostana</i> , <i>Garcinia cowa</i> (<i>Guttiferae</i>)	Nilar, 2005; Monache, 1984b; Shen, 2006
376	Atroviridin		<i>Garcinia atroviridis</i> (<i>Guttiferae</i>); <i>Synthesis</i>	Tisdale et al., 2003
377	Globulixanthone C		<i>Symphonia globulifera</i> (<i>Guttiferae</i>)	Nkengfack et al., 2002c
378	Caloxanthone K		<i>Calophyllum apetalum</i> (<i>Guttiferae</i>)	Lloyd, 1997
379	Linixanthone B		<i>Garcinia linii</i> (<i>Guttiferae</i>)	Chen et al., 2004
380	Brasixanthone F		<i>Calophyllum brasiliense</i> (<i>Guttiferae</i>)	Ito, 2002, 2003a; Noldin, 2006
381	Caledonixanthone E		<i>Calophyllum caledonicum</i> (<i>Guttiferae</i>)	Larcher, 2004; Morel, 2002b; Noldin, 2006
382	Forbexanthone		<i>Garcinia vieillardii</i> (<i>Guttiferae</i>)	Hay et al., 2004a
383	Paxanthone		<i>Hypericum perforatum</i> , <i>Hypericum androsaemum</i> , <i>Hypericum patulum</i> (<i>Guttiferae</i>)	Dias, 2000, 2001; Pasqua, 2003; Ferrari, 2005

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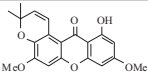
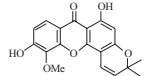
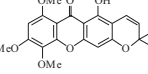
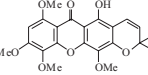
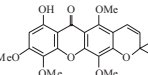
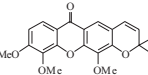
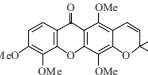
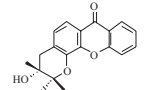
384	3-O-Methylpaxanthone		<i>Hypericum perforatum</i> (Guttiferae)	Ferrari et al., 2005
385	5-O-Methylisojacareubin		<i>Hypericum roeperanum</i> (Guttiferae)	Rath et al., 1996
386	Dulxanthone F		<i>Garcinia dulcis</i> , <i>Garcinia porrecta</i> (Guttiferae)	Kosela, 2000; Kardono, 2006
387	Dulxanthone G		<i>Garcinia dulcis</i> , <i>Garcinia porrecta</i> (Guttiferae)	Kosela, 2000; Kardono, 2006
388	Dulxanthone H		<i>Garcinia dulcis</i> (Guttiferae)	Kosela et al., 2000
389	Porxanthone A		<i>Garcinia porrecta</i> (Guttiferae)	Kardono et al., 2006
390	Dulxanthone E		<i>Garcinia dulcis</i> , <i>Garcinia porrecta</i> (Guttiferae)	Kosela, 1999; Kardono, 2006
391	Caledonixanthone A		<i>Calophyllum caledonicum</i> (Guttiferae)	Morel, 2000, 2002b; Noldin, 2006

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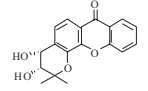
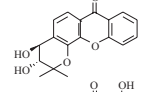
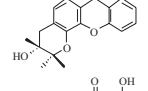
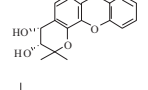
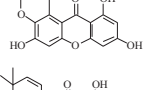
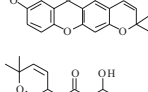
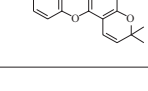
392	Caledonixanthone H		<i>Calophyllum caledonicum</i> (Guttiferae)	Morel et al., 2002
393	Caledonixanthone I		<i>Calophyllum caledonicum</i> (Guttiferae)	Morel et al., 2002
394	Caloxanthone G		<i>Calophyllum caledonicum</i> (Guttiferae)	Morel, 2000, 2002b
395	Caledonixanthone J		<i>Calophyllum caledonicum</i> (Guttiferae)	Morel et al., 2002
396	Hyperxanthone E		<i>Hypericum scabrum</i> (Guttiferae)	Tanaka et al., 2004
397	Thwaitesixanthone		<i>Calophyllum thwaitesii</i> , <i>Garcinia mangostana</i> (Guttiferae)	Dharmaratne, 1996, 1999, 2002; Suksamram, 2006; Noldin, 2006
398	Cudraxanthone A		<i>Cudrania cochinchinensis</i> (Moraceae)	Chang, 1989a, 1994

Table 1 Contd.

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399	Pyranojacareubin		<i>Calophyllum blancoi</i> , <i>Garcinia latissima</i> , <i>Calophyllum inophyllum</i> , <i>Calophyllum brasiliense</i> , <i>Rheedia brasiliensis</i> (Guttiferae)	Ito, 1997, 1998, 2002, 2003a; Cheng, 2004; Shen, 2005; Monache, 1984b; Noldin, 2006
400	Padiaxanthone (Brasilixanthone B)		<i>Cudrania fruticosa</i> (Moraceae); <i>Hypericum sampsonii</i> , <i>Hypericum patulum</i> , <i>Calophyllum inophyllum</i> , <i>Tovomita brasiliensis</i> (Guttiferae)	Ishiguro, 1996; Cheng, 2004; Marques, 2000; Wang, 2005; Don, 2004
401	Nigrolineaxanthone I		<i>Garcinia nigrolineata</i> (Guttiferae)	Rukachaisirikul et al., 2003
402	Brasilixanthone A		<i>Garcinia nigrolineata</i> , <i>Tovomita brasiliensis</i> (Guttiferae)	Rukachaisirikul, 2003d; Marques, 2000
403	Rheediaxanthone A		<i>Rheedia brasiliensis</i> , <i>Rheedia gardneriana</i> , <i>Rheedia benthamiana</i> , <i>Garcinia nigrolineata</i> , <i>Garcinia merguensis</i> , <i>Garcinia staudtii</i> , <i>Garcinia dulcis</i> (Guttiferae)	Rukachaisirikul, 2003d; Nguyen, 2003; Monache, 1981, 1983, 1984b; Deachathai, 2006; Waterman, 1982
404	4-Hydroxybrasilixanthone B		<i>Garcinia subelliptica</i> (Guttiferae)	Abe et al., 2003
405	BR-xanthone A		<i>Garcinia dulcis</i> , <i>Garcinia mangostana</i> (Guttiferae)	Deachathai, 2005, 2006; Balasubramanian, 1988; Gopalakrishnan, 1997

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406	Isonormangostin		<i>Garcinia dulcis</i> (Guttiferae); Synthesis	Deachathai, 2005; Lee, 1981
407	Pruniflorone F		<i>Cratoxylum formosum</i> ssp. <i>pruniflorum</i> (Guttiferae)	Boonnak et al., 2006b
408	Calozeyloxanthone		<i>Calophyllum moonii</i> , <i>Calophyllum lankensis</i> , <i>Calophyllum tomentosum</i> , <i>Calophyllum caledonicum</i> , <i>Calophyllum apetalum</i> , <i>Calophyllum zeylanicum</i> (Guttiferae)	Pinheiro, 2003b; Iinuma, 1997; Hay, 2003, 2004b; Dharmaratne, 1997, 1999, 2002; Banerji, 1994; Gunasekera, 1981; Noldin, 2006
409	11,12-Dihydrothwaitesixanthone		<i>Calophyllum thwaitesii</i> (Guttiferae)	Dharmaratne, 1996; Noldin, 2006
410	Nigrolineaxanthone G (or 1,5-Dihydroxy-6',6'- dimethyl-2H-pyran(2',3':6,7)- 6'',6''-dimethyl-2H,4H- pyran(2'',3'':2,3)xanthone)		<i>Garcinia nigrolineata</i> , <i>Rheedia brasiliensis</i> (Guttiferae)	Rukachaisirikul, 2003d; Monache, 1984b
411	1,5-Dihydroxy-6',6'- dimethyl-2H-pyran (2',3':6,7)-6'',6''- dimethyl-2H,4H- pyran(2'',3'':3,4)xanthone		<i>Rheedia brasiliensis</i> (Guttiferae)	Monache et al., 1984b
412	3,5-Dihydroxy-6',6'- dimethyl-2H-pyran (2',3':6,7)-6'',6''-dimethyl -2H,4H-pyran(2'',3'':1,2) xanthone		<i>Rheedia brasiliensis</i> (Guttiferae)	Monache et al., 1984b

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413	Garcimangosone B		<i>Garcinia mangostana</i> (Guttiferae)	Huang, 2001; Jung, 2006
414	Caledonixanthone L		<i>Calophyllum caledonicum</i> (Guttiferae)	Morel et al., 2002
415	Artobioxanthone		<i>Artocarpus nobilis</i> (Moraceae)	Sultanbawa and Surendrakumar, 1989
416	Varixanthone		<i>Fungus Emericella</i> <i>varicolor</i>	Malmström et al., 2002
417	Tajixanthone		<i>Aspergillus varicolor</i> (Fungus)	Chexal et al., 1974
418	Tajixanthone hydrate		<i>Fungus Emericella</i> <i>varicolor</i>	Malmström, 2002; Pompakakul, 2006

Table 1 Contd.

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419	14-Methoxytajixanthone-25-acetate		<i>Fungus Emericella</i> <i>varicolor</i>	Pompakakul et al., 2006
420	Tajixanthone methanoate		<i>Fungus Emericella</i> <i>varicolor</i>	Pompakakul et al., 2006
421	Shamixanthone		<i>Fungus Emericella</i> <i>varicolor</i> , <i>Aspergillus</i> <i>varicolor</i> , <i>Emericella</i> <i>nidulans</i>	Malmström, 2002; Bringmann, 2003; Chexal, 1974; Pompakakul, 2006; Kralj, 2006
422	4",5"-Dihydro-1,5-dihydroxy-6',6'-dimethylpyrano(2',3':6,7)-4",4",5"-trimethylfuran(2",3":3,4) xanthone		<i>Rheedia brasiliensis</i> , <i>Garcinia scortechinii</i> (Guttiferae)	Monache, 1984b; Rukachaisirikul, 2005
423	Gerontoxanthone A		<i>Cudrania fruticosa</i> , <i>Cudrania cochinchinensis</i> , <i>Cudrania tricuspidata</i> (Moraceae)	Fukai, 2004, 2005; Hou, 2001; Wang, 2005; Chang, 1989a, 1994; An, 2006; Nomura, 1994
424	Caledonixanthone M		<i>Calophyllum caledonicum</i> (Guttiferae)	Hay et al., 2003

Table 1 Contd.

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425	Cudraxanthone O		<i>Cudrania tricuspidata</i> (Moraceae)	Hano, 1991a; Nomura, 1994
426	Artoindonesianin C		<i>Artocarpus teysmanii</i> , <i>Artocarpus rigidus</i> (Moraceae)	Makmur, 2000; Namdaung, 2006
427	Artonol B		<i>Artocarpus rigidus</i> (Moraceae)	Namdaung et al., 2006
428	Pancixanthone B		<i>Calophyllum</i> <i>paniculatum</i> (Guttiferae)	Ito, 1996, 1998
429	Dulciol E		<i>Garcinia dulcis</i> (Guttiferae)	Iinuma et al., 1996a
430	Garbogiol		<i>Garcinia fusca</i> (Guttiferae)	Vieira, 2005; Ito, 2003b
431	Toxyloxanthone C		<i>Cudrania fruticosa</i> , <i>Cudrania cochinchinensis</i> , <i>Cudrania tricuspidata</i> , <i>Maclura pomifera</i> (Moraceae)	Costa, 2000; Fukai, 2003, 2004, 2005; Zou, 2004; Teixeira, 2005; Hou, 2001; Wang, 2005; Monache, 1984a

Table 1 Contd.

Table 1 Contd.

432	2-Deprenylr- heediexanthone B (or 1,5,6-Trihydroxy- 4',5'-dihydro-4',4', 5'-trimethylfurano- (2',3':3,4) xanthone)		<i>Garcinia vieillardii</i> , <i>Hypericum roeperanum</i> , <i>Calophyllum caledonicum</i> (Guttiferae)	Rath, 1996; Hay, 2004b; Morel, 2000
433	1,5,6-Trihydroxy-4', 5'-dihydro-4',4',5'- trimethylfurano(2',3': 4,5) xanthone		<i>Hypericum japonicum</i> Thunb. (Guttiferae)	Wu et al., 1998
434	Cudratricusxanthone I		<i>Cudrania tricuspidata</i> (Moraceae)	Zou et al., 2005
435	Gerontoxanthone J		<i>Cudrania cochinchinensis</i> (Moraceae)	Chang et al., 1995
436	6-O-Methyl-2- deprenylrheediexanthone B		<i>Garcinia vieillardii</i> (Guttiferae)	Hay et al., 2004a
437	5-O-Methyl-2- deprenylrheediexanthone B		<i>Garcinia vieillardii</i> , <i>Hypericum roeperanum</i> (Guttiferae)	Rath, 1996; Hay, 2004a
438	Gerontoxanthone D		<i>Cudrania cochinchinensis</i> (Moraceae)	Chang, 1989a, b, 1994; Nomura, 1994
439	Caledonixanthone C		<i>Calophyllum caledonicum</i> (Guttiferae)	Morel, 2000, 2002b; Noldin, 2006

Table 1 Contd.

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440	Caloxanthone F		<i>Calophyllum caledonicum</i> (Guttiferae)	Morel, 2000, 2002b
441	1,7-Dihydroxy-2,3-[2-(1-hydroxy-1-methylethyl)-dihydrofurano]xanthone		<i>Hypericum chinense</i> (Guttiferae)	Tanaka and Takaishi, 2006
442	Hyperxanthone A		<i>Hypericum scabrum</i> (Guttiferae)	Tanaka et al., 2004
443	Hyperxanthone B		<i>Hypericum scabrum</i> (Guttiferae)	Tanaka et al., 2004
444	Hyperxanthone F		<i>Hypericum scabrum</i> (Guttiferae)	Tanaka et al., 2004
445	Caledonixanthone F		<i>Calophyllum caledonicum</i> (Guttiferae)	Morel, 2002b; Noldin, 2006
446	1,3,5-Trihydroxy-2-(2',2'-dimethyl-4'-isopropenyl)cyclopentanylxanthone (6-deoxy-5-O-demethylpaxanthonin)		<i>Hypericum styphelioides</i> (Guttiferae)	Turro et al., 2004

Table 1 Contd.

Table 1 Contd.

447	5-O-Demethylpaxanthonin		<i>Hypericum styphelioides</i> , <i>Hypericum patulum</i> , <i>Hypericum roeperanum</i> (Guttiferae)	Rath, 1996; Ishiguro, 1996; Turro, 2004; Yamakuni, 2006
448	Paxanthonin		<i>Hypericum patulum</i> (Guttiferae)	Ishiguro, 1995b, 1996
449	Rheediaxanthone C		<i>Rheedia brasiliensis</i> , <i>Rheedia gardneriana</i> , <i>Rheedia benthamiana</i> (Guttiferae)	Monache, 1981, 1983, 1984b
450	Cratoxyxanthone		<i>Cratoxylum cochinchinense</i> (Guttiferae)	Sia et al., 1995
451	Griffipavixanthone		<i>Garcinia virgata</i> (Guttiferae)	Merza et al., 2004

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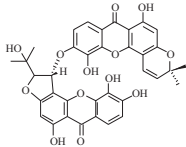
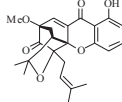
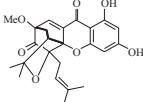
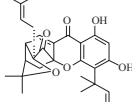
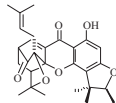
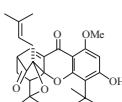
452	Bijaponicaxanthone		<i>Hypericum japonicum</i> Thumb. (Guttiferae)	Wu, 1998; Fu, 2004
453	Cochinchinone C		<i>Cratoxylum</i> <i>cochinchinense</i> (Guttiferae)	Mahabusarakam, 2006b; Laphookhieo, 2006
454	Cochinchinone D		<i>Cratoxylum</i> <i>cochinchinense</i> (Guttiferae)	Mahabusarakam et al., 2006b
455	Bractatin		<i>Garcinia bracteata</i> (Guttiferae)	Thoison, 2000; Nicolaou, 2001
456	Isobractatin		<i>Garcinia bracteata</i> (Guttiferae)	Thoison et al., 2000
457	1-O-Methylbractatin		<i>Garcinia bracteata</i> (Guttiferae)	Thoison, 2000; Nicolaou, 2001

Table 1 Contd.

Table 1 Contd.

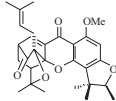
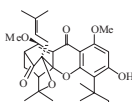
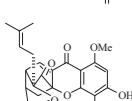
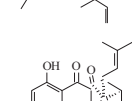
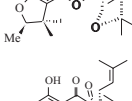
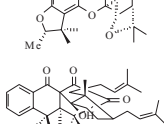
458	1-O-Methylisobractatin		<i>Garcinia bracteata</i> (Guttiferae)	Thoison et al., 2000
459	1-O-Methyl-8-methoxy-8,8a-dihydrobractatin		<i>Garcinia bracteata</i> (Guttiferae)	Thoison et al., 2000
460	1-O-Methylnobractatin		<i>Garcinia bracteata</i> (Guttiferae)	Thoison, 2000; Nicolaou, 2001
461	Neoisobractatin A		<i>Garcinia bracteata</i> (Guttiferae)	Thoison et al., 2005
462	Neoisobractatin B		<i>Garcinia bracteata</i> (Guttiferae)	Thoison et al., 2005
463	Garcibracteone		<i>Garcinia bracteata</i> (Guttiferae)	Thoison et al., 2005

Table 1 Contd.

Table 1 Contd.

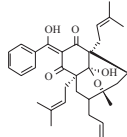
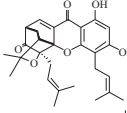
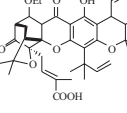
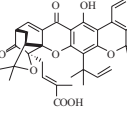
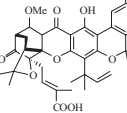
464	Xerophenone C		<i>Garcinia bracteata</i> (Guttiferae)	Thoison et al., 2005
465	Forbesione		<i>Garcinia forbesii</i> (Guttiferae)	Nicolaou, 2001; Cao, 1998
466	Gaudichaudiic acid F		<i>Garcinia gaudichaudii</i> (Guttiferae)	Xu et al., 2000
467	Gaudichaudiic acid G		<i>Garcinia gaudichaudii</i> (Guttiferae)	Xu et al., 2000
468	Gaudichaudiic acid H		<i>Garcinia gaudichaudii</i> (Guttiferae)	Xu et al., 2000

Table 1 Contd.

Table 1 Contd.

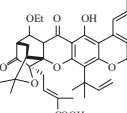
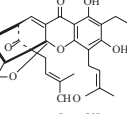
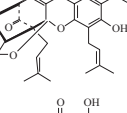
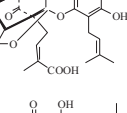
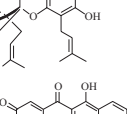
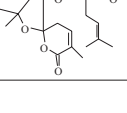
469	Gaudichaudiic acid I		<i>Garcinia gaudichaudii</i> (Guttiferae)	Xu et al., 2000
470	Gaudichaudione A		<i>Garcinia gaudichaudii</i> (Guttiferae)	Wu et al., 2002
471	Deoxygaudichaudione A		<i>Garcinia hanburyi</i> (Guttiferae)	Han et al., 2006a
472	Gaudichaudic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Han et al., 2006a
473	Isogambogenic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Han et al., 2006a
474	Gaudispirolactone		<i>Garcinia gaudichaudii</i> (Guttiferae)	Wu et al., 2001

Table 1 Contd.

Anexo I

Table 1 Contd.

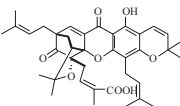
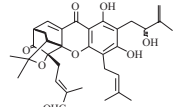
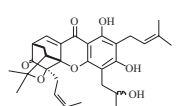
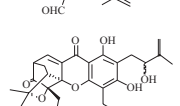
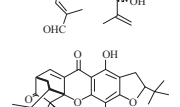
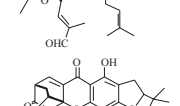
475	7-Isoprenylmorellic acid		<i>Garcinia gaudichaudii</i> (Guttiferae)	Wu et al., 2001
476	Gaudichaudione B		<i>Garcinia gaudichaudii</i> (Guttiferae)	Cao et al., 1998
477	Gaudichaudione C		<i>Garcinia gaudichaudii</i> (Guttiferae)	Cao et al., 1998
478	Gaudichaudione I		<i>Garcinia gaudichaudii</i> (Guttiferae)	Vieira and Kijjoa, 2005
479	Gaudichaudione D		<i>Garcinia gaudichaudii</i> (Guttiferae)	Cao et al., 1998
480	Gaudichaudione E		<i>Garcinia gaudichaudii</i> (Guttiferae)	Cao et al., 1998

Table 1 Contd.

Table 1 Contd.

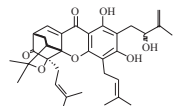
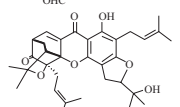
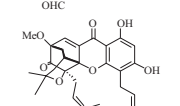
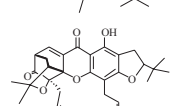
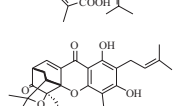
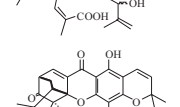
481	Gaudichaudione F		<i>Garcinia gaudichaudii</i> (Guttiferae)	Cao et al., 1998
482	Gaudichaudione G		<i>Garcinia gaudichaudii</i> (Guttiferae)	Cao et al., 1998
483	Gaudichaudione H		<i>Garcinia gaudichaudii</i> (Guttiferae)	Cao et al., 1998
484	Gaudichaudiic acid A		<i>Garcinia gaudichaudii</i> (Guttiferae)	Cao et al., 1998
485	Gaudichaudiic acid B		<i>Garcinia gaudichaudii</i> (Guttiferae)	Cao et al., 1998
486	Gaudichaudiic acid C		<i>Garcinia gaudichaudii</i> (Guttiferae)	Cao et al., 1998

Table 1 Contd.

Table 1 Contd.

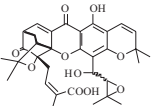
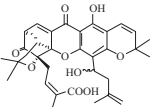
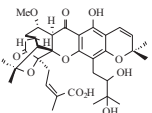
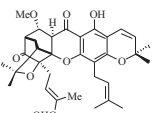
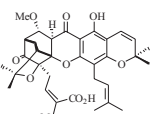
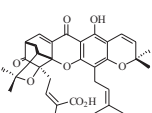
487	Gaudichaudiic acid D		<i>Garcinia gaudichaudii</i> (Guttiferae)	Cao et al., 1998
488	Gaudichaudiic acid E		<i>Garcinia gaudichaudii</i> (Guttiferae)	Wu, 2001; Cao, 1998
489	Hanburinone		<i>Garcinia hanburyi</i> (Guttiferae)	Sukpondma et al., 2005
490	Isomoreollin B		<i>Garcinia hanburyi</i> (Guttiferae)	Sukpondma et al., 2005
491	Moreollic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Sukpondma et al., 2005
492	Morellic acid		<i>Garcinia hanburyi</i> , <i>Garcinia gaudichaudii</i> (Guttiferae)	Wu, 2001; Sukpondma, 2005; Han, 2006a

Table 1 Contd.

Table 1 Contd.

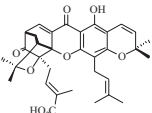
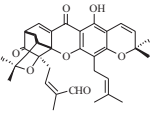
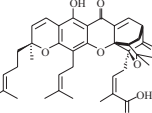
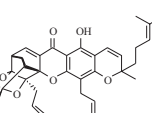
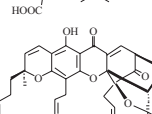
493	Isomorellic acid		<i>Garcinia gaudichaudii</i> , <i>Garcinia hanburyi</i> (Guttiferae)	Wu, 2001; Han, 2006a
494	Morellin		<i>Garcinia hanburyi</i> , <i>Garcinia Morella</i> (Guttiferae)	Weakley, 2001; Nicolau, 2001; Sukpondma, 2005
495	Gambogic acid		<i>Garcinia hurburyi</i> (Guttiferae)	Zhang, 2004; Lin, 1993; Weakley, 2001; Han, 2006a; Guo, 2006; Han, 2006b
496	Isogambogic acid		<i>Garcinia hurburyi</i> (Guttiferae)	Lin, 1993; Han, 2006a
497	30-Hydroxygambogic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Han et al., 2006c

Table 1 Contd.

Table 1 Contd.

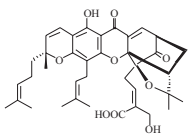
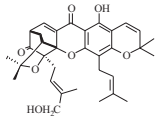
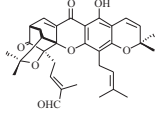
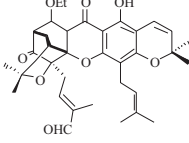
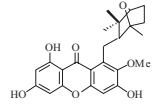
498	30-Hydroxyepigambogic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Han et al., 2006c
499	Isomorellinol		<i>Garcinia hurburyi</i> , <i>Garcinia gaudichaudii</i> (Guttiferae)	Lin, 1993; Wu, 2001; Han, 2006a
500	Isomorellin		<i>Garcinia hurburyi</i> , <i>Garcinia gaudichaudii</i> (Guttiferae)	Wu, 2001; Weakley, 2001
501	Isomoreollin		<i>Garcinia gaudichaudii</i> (Guttiferae)	Vieira, 2005; Wu, 2001
502	Parvixanthone I		<i>Garcinia parvifolia</i> (Guttiferae)	Xu et al., 2001

Table 1 Contd.

Table 1 Contd.

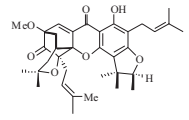
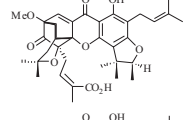
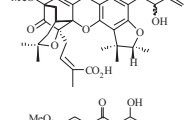
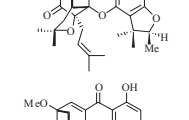
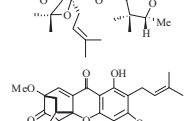
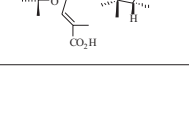
503	Scortechinone A		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul, 2000, 2003c, 2005
504	Scortechinone B		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul, 2000, 2003c, 2005
505	Scortechinone C		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul et al., 2000
506	Scortechinone D		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul, 2003c, 2005
507	Scortechinone E		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul et al., 2003c
508	Scortechinone F		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul, 2003c, 2005

Table 1 Contd.

Table 1 Contd.

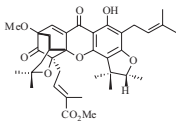
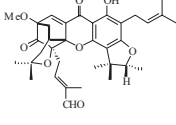
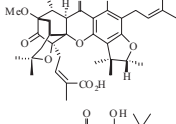
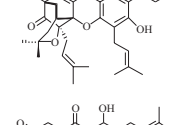
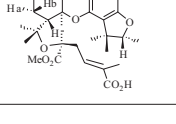
509	Scortechinone G		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul et al., 2003c
510	Scortechinone H		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul et al., 2003c
511	Scortechinone I		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul, 2003c, 2005
512	Scortechinone J		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul, 2003c, 2005
513	Scortechinone K		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul et al., 2003c

Table 1 Contd.

Table 1 Contd.

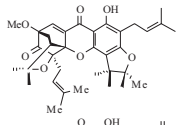
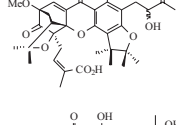
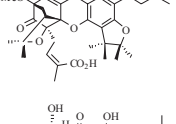
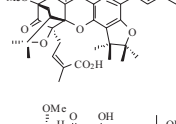
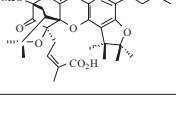
514	Scortechinone L		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul et al., 2005
515	Scortechinone M		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul et al., 2005
516	Scortechinone N		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul et al., 2005
517	Scortechinone O		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul et al., 2005
518	Scortechinone P		<i>Garcinia scortechinii</i> (Guttiferae)	Rukachaisirikul et al., 2005

Figure 2 shows the main prenyl substituents (C_5 group) which include the commonly found 3-methylbut-2-enyl or isoprenyl group (A) and the less frequent 3-hydroxy-3-methylbutyl group (B) as well as 1,1-dimethylprop-2-enyl or 1,1-dimethylallyl group (C). Besides these substituents, the products of cyclization of the substituents A and C with the *ortho* hydroxyl group of the benzene ring, such as 2,2-dimethylpyrano (D), 2,2,3-trimethylfuran (E) and the rare 2-isopropenyldihydrofuran (F) groups are also found. Substituents with higher number of carbons such as geranyl (C_{10}) (G) is frequently found while farnesyl (C_{15}) (H) is less common. Modifications of these side chains by hydroxylation, hydrogenation, epoxidation and lactonization can also happen. Interestingly, the more complex structures with the caged scaffold (e.g. 495 in Table 1) have become a very important subgroup of the naturally occurring prenylated xanthenes.

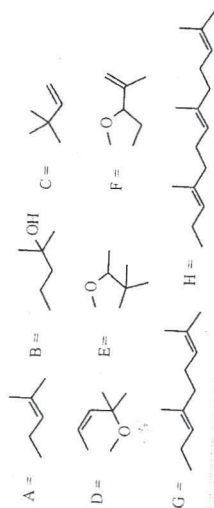


Fig. 2 Main Substituents (C_5 group) found in Prenylated Xanthenes

Table 1 lists the name of the compounds, their structures and natural sources together with the references. The content of Table 1 is organized according to the increasing complexity of the structure as mono-, di-, and triprenylated (Figure 2, A, B, C, G, H), cyclic (Figure 2, D, E, F) and caged xanthenes, respectively. All of these prenylated xanthenes are further subdivided into two categories as *O*-prenylated and *C*-prenylated. Although the *C*-prenylated derivatives are much more represented in nature (16-518), oxyprenylated compounds (1-15) are also found and among these only 6 occur concomitantly as *O*- and *C*-prenylated (2-7). Curiously, these substituents could be found in any position of the carbon skeleton of the xanthone scaffold though there are preferred positions (Figure 3). For example, 3-methylbut-2-enyl (A) and/or 1,1-dimethylprop-2-enyl (B)

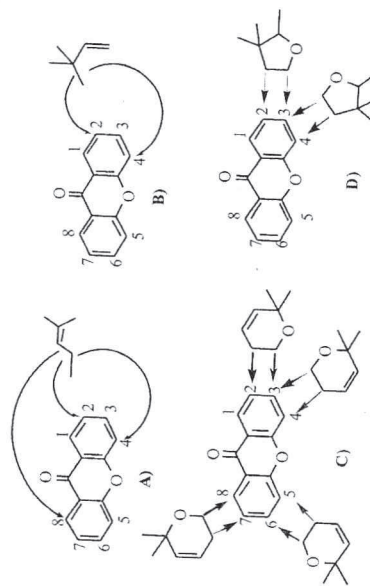


Fig. 3 Preferred Positions for Prenylation

substituents are normally at C-2 and C-4 though the former can also be found on C-8. The 2,2-dimethylpyrano group (C) is frequently located at C-2-C3, C3-C4, C5-C6 and C7-C8, while 2,2,3-trimethylfuran (D) are normally found at C2-C3 or C3-C4.

Most of the prenylated xanthenes are also oxygenated and they can be found mono- to hexaoxygenated (Vieira and Kijjoo, 2005). Thus, Table 1 shows seven mono- (16, 75, 360, 391-393, 439), twenty two di- (1-3, 7, 17-19, 120, 224, 361-362, 394-395, 416-421, 426-427, 440), one hundred and twenty six tri- (4, 8-14, 20-28, 37-41, 64-68, 71-72, 74-76, 78-81, 91-94, 109-110, 112-119, 143, 155, 165-166, 168, 172-173, 190-193, 211, 213, 225-232, 241, 251-252, 260-263, 268-270, 285-286, 288-289, 293-296, 299-301, 303, 318-319, 321-322, 332-334, 336, 346-347, 349, 353, 359, 363-370, 379, 397-398, 408-409, 424-425, 428-429, 441, 446), two hundred and seventy nine tetra- (5-6, 29-36, 42-61, 69-70, 77, 82-90, 95-108, 111, 121-142, 145-154, 156-164, 167, 169-171, 174-189, 194-210, 212, 214-223, 233-240, 242-248, 253-259, 264-266, 271-284, 287, 290-292, 297, 302, 304-312, 314-317, 320, 323-331, 335, 337-345, 348, 350-352, 354-358, 371-378, 380-385, 389, 396, 399-403, 405-407, 410-414, 422-423, 430-437, 442-445, 447-449), twelve penta- (15, 62-63, 144, 249, 250, 267, 313, 386, 390, 404, 438), two hexaoxygenated (387-388) and sixty seven caged prenylated xanthenes (415, 453-518). From Table 1, it is obvious that tetraoxygenated prenylated xanthenes isolated so far have outnumbered the rest of the prenylated xanthenes with different degree of oxygenation. It is noteworthy observing also that the plants of the family Guttiferae, especially *Garcinia* and *Calophyllum*, provide all different degree of oxygenation of the prenylated xanthenes. However, the dioxygenated derivatives were also reported from the marine-derived fungi *Emericella varicolor* (1, 2, 3) and *Aspergillus varicolor* (1). For their parts, trioxxygenated and tetraoxxygenated prenylated xanthenes have also been isolated from the plants of the families Annonaceae (*Anaxagorea luzonensis* specie) and Moraceae while the pentaoxxygenated prenylated xanthone 15 was reported from *Tectona grandis*, a member of the family Verbenaceae. Interestingly, all the caged prenylated xanthenes reported to date have been isolated only from the members of the family Guttiferae.

It is interesting to observe also that some of the xanthenes presented in Table 1 possess unique substituents. Thus, teysmannic acid (16) and scriblitifolic acid (17), both isolated from *Calophyllum teysmannii* var. *inophylloide* are the only naturally occurring xanthenes with the 3-carboxybutyl substituent (Vieira and Kijjoo, 2005; Kijjoo et al., 2000). Xanthone 446, isolated from the leaves of *Hypericum styphelioides* possesses a (2,2-dimethyl-4-isopropenyl)cyclopentanyl substituent (Turro et al., 2004) while brasixanthone C (294), isolated from the stem bark of *Calophyllum brasiliense*, has a 2-hydroperoxyl-3-methylbut-3-enyl side chain (Ito et al., 2002, 2003a; Noldin et al., 2006). On the other hand, vieillardixanthone (90), having a 1-isopropenylethenyl substituent on C-4, was reported from the stem bark of *Garcinia vieillardii* (Hay et al., 2004a,b; Ji et al., 2005) whereas parvixanthone I (502) from *Garcinia parvifolia* deserves special attention as it has an unusual 7-oxabicyclo [2.2.1] hept-2-ylmethyl side chain (Xu et al., 2001). Curiously, the configuration of the double bond of the geranyl substituent of garcinianone B (210), isolated from the stems of *G. multiflora* (Chiang et al., 2003), was 2Z instead of the commonly found 2E. In turn, a new xanthone with a lactonized geranyloxyl side chain (15) was isolated from *Tectona grandis* (Verbenaceae) (Singh et al., 2004) and it is the only prenylated pentaoxxygenated xanthone isolated from higher plant family other than Guttiferae. Geminal diprenylation with a concomitant loss of aromaticity of one of the benzene rings in apetalinone D

(109), tomentonone (110) and patulone (111) represent another interesting examples of structure modification by prenylation of xanthenes.

3. BIOSYNTHESIS

The biosynthesis of xanthenes from higher plants has been discussed extensively by several authors. In the book “*Organic Chemistry of Secondary Plant Metabolism*”, Geissman and Crout (1969) have suggested the biosynthetic origin of plant xanthenes by observation of the hydroxylation pattern in ring A and ring B of a number of xanthenes isolated from higher plants from the families Guttiferae and Gentianaceae (Figure 1). They have found that, in the great majority of xanthenes, one ring (arbitrarily designated ring A) had a clear 1,3,5 oxygenation pattern analogous to the archetypal hydroxylation pattern in ring A of the flavonoids while the substitution pattern of the other ring (designated ring B) was a source of great variation in this group where a coherent pattern of oxygenation was not found, even among members of the same family. However, after analysis of the oxygenation pattern of ring B, they had observed the tendency for the oxygen substituents to have an *ortho* or *para* relationship, as opposed to the predominantly *meta* relationship in ring A.

Based on these observations, they have proposed the biosynthetic origin of xanthenes from higher plants as being an extension of a C₆-C₁ aromatic acid (as the coenzyme A ester), condensation with three active acetate (malonate) units. From this hypothesis, it was clear that the 1,3,5 oxygenation pattern of ring A could emerge automatically from this pathway. However, the chronology of the hydroxylation of ring B could not be as readily predicted. They also hypothesized that the introduction of additional hydroxyl groups might precede cyclization or equally this may represent a terminal step in the pathway, taking place after ring closure.

The other important feature of the proposed pathway was the cyclization step, which resulted in the formation of the heterocyclic ring. They have suggested that this cyclization could occur by an oxidative phenol coupling process, analogous to the laboratory cyclization of the benzophenone derivative as shown in Figure 4.

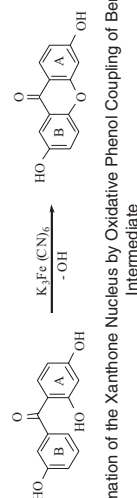


Fig. 4 Formation of the Xanthone Nucleus by Oxidative Phenol Coupling of Benzophenone Intermediate

The coupling steps shown in Figure 5 imposed the requirement for a phenolic hydroxyl group to be present at the *meta* position in the aromatic ring postulated to rise from shikimic acid. This hydroxyl group would finally appear at either position 5 or 7 in the completed xanthone structure, depending on whether the coupling proceeded through an *ortho* or *para* dienone intermediate (Figure 5).

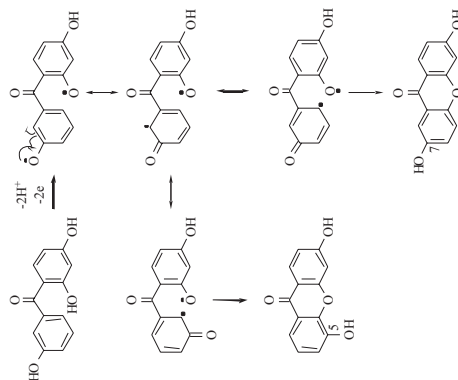


Fig. 5 Oxidative Phenolic Couplings of Hydroxybenzophenone via Dienone Intermediates

The available evidence to support the proposed pathway was obtained from two investigations carried out on the biosynthesis of the 1,3,5-trioxygenated xanthenes of *Gentiana lutea* (Gentianaceae). Floss and Retig (1964) found that 98% of the label from [1-¹⁴C]acetate was located in the 1,3-dioxygenated ring of gentisin. Gupta and Lewis (1971) also obtained a similar result on feeding of [2-¹⁴C]acetate. [U-¹⁴C]phenylalanine was also well incorporated, and the absence of activity in the phloroglucinol ring of gentisin led them to suggest the involvement of a phenylalanine-derived C₆C₁ unit (Figure 6).

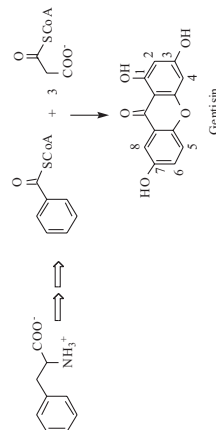


Fig. 6 Biosynthetic Pathway of Gentisin

On the other hand, Fujita and Inoue (1980), on investigating the biosynthesis of the *C*-glucosylxanthone mangiferin in *Anemarrhena asphodeloides* (Liliaceae), have found that, besides two malonate units, all the carbon atoms of phenylalanine as well as of cinnamic and *p*-coumaric acid were incorporated into mangiferin, and benzoic acid apparently did not involve in this pathway (Figure 7).

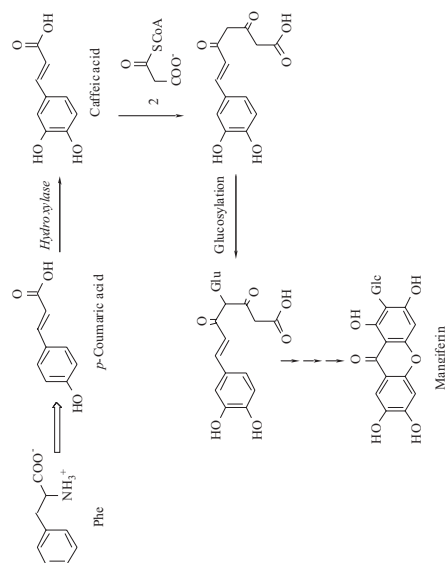


Fig. 7 Biosynthetic Pathway of Mangiferin

Bennett et al. (1990a) have studied the biosynthesis of mangostin (**141**) by feeding of the ^{14}C - and ^{13}C -labelled precursors to the *Garcinia mangostana* seedlings. They have found that when fed with $[2\text{-}^{14}\text{C}]$ malonic acid, the label primarily located in the phloroglucinol ring. Surprisingly, they have also found that though $[1\text{-}^{14}\text{C}]$ phenylalanine and $[U\text{-}^{14}\text{C}]$ phenylalanine were less well utilized by the plant, a proportion of the label was also detected in the phloroglucinol ring in both cases. $[3\text{-}^{14}\text{C}]$ Cinnamic acid was also a good precursor of mangostin but the phloroglucinol ring was devoid of activity. On the contrary, $[2\text{-}^{14}\text{C}]$ cinnamic acid was similarly well incorporated and the label was almost totally present in the phloroglucinol ring. These results implied the incorporation of an intact C_6C_3 unit, pointing out to a route similar to that found in mangiferin (Figure 7). However, in contrast to biosynthesis of mangiferin, $[2\text{-}^{14}\text{C}]$ *p*-coumaric acid was poorly incorporated while $[\text{carboxy-}^{14}\text{C}]$ benzoic acid was a very efficient precursor. This pointed to the involvement of C_6C_1 unit as proposed for the biosynthesis of gentisin (Figure 6). In order to differentiate between C_6C_3 and C_6C_1 routes, feeding experiments with ^{13}C -labelled precursors and the observation of couplings of the ^{13}C signals in the ^{13}C NMR spectra of dimethyl derivative of mangostin (**141**) were carried out. Feeding of $[2,3\text{-}^{13}\text{C}]$ cinnamic acid did not give coupling between C-9 and C-9a of 3,6-

di-*O*-methylmangostin (**133**). Based on this observation, the probable explanation for the observed incorporation of $[1\text{-}^{14}\text{C}]$ phenylalanine and $[2\text{-}^{14}\text{C}]$ cinnamic acid was that β cleavage of these compounds had occurred and that the two carbon fragments lost were incorporated as $[1\text{-}^{14}\text{C}]$ and $[2\text{-}^{14}\text{C}]$ acetate, respectively, into the phloroglucinol ring of mangostin (**141**). Also, when $[\text{carboxy-}^{14}\text{C}]$ benzoic acid was fed, the ^{13}C NMR spectrum of the resultant 3,6-di-*O*-methylmangostin (**133**) displayed a carboxyl peak more than three times natural abundance intensity. This led to the conclusion that the carbonyl and ring B were derived from benzoate or C_6C_1 unit. Figure 8 summarizes the biosynthetic route of mangostin (**141**), resulting from the feeding experiments with ^{14}C and ^{13}C -labelled precursors.

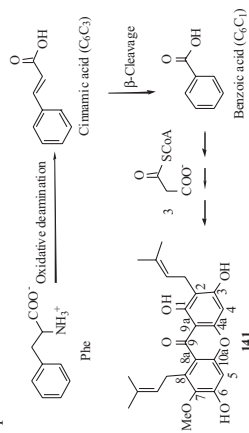


Fig. 8 Biosynthetic Route to the Formation of Mangostin Skeleton (**141**)

In contrast to the incorporation study of labelled precursors, the enzymology of xanthone biosynthesis in higher plants was in lesser extent and the majority of the work in this field was carried out by the group of Beerhues.

Barrilas and Beerhues (1997), have detected the activity of 3-hydroxybenzoate:CoA ligase which catalysed the activation of 3-hydroxybenzoate. 3-Hydroxybenzoate:CoA ligase was separated from another enzyme, 4-coumarate:CoA ligase, by fractionated ammonium sulphate precipitation and hydrophobic interaction chromatography of the cultured cell extract of *Centaurium erythraea*. It was found that 3-hydroxybenzoate:CoA ligase activated only benzoic acids being 3-hydroxybenzoic acid as the preferred substrate. Contrary to 4-coumarate:CoA ligase, 3-hydroxybenzoate:CoA ligase lacked affinity for cinnamic acids.

Beerhues (1996) has detected the activity of benzophenone synthase also in the cultured cells of *Centaurium erythraea*. This enzyme was found to catalyze the stepwise condensation of 3-hydroxybenzoyl CoA with three molecules of malonyl CoA to form 2,3',4,6-tetrahydroxybenzophenone. Besides 3-hydroxybenzoyl CoA as the preferred substrate, benzophenone synthase was also found to convert benzoyl CoA with half-maximal activity. In contrast, neither 2-hydroxybenzoyl CoA nor 4-hydroxybenzoyl CoA was found to serve as substrates for this enzyme.

For the final step in xanthone biosynthesis, the cyclization of the benzophenone intermediate to form a heterocyclic ring in the xanthone skeleton, Peters et al. (1998) have isolated and characterized the enzyme xanthone synthase also from the cultured cells of *Centaurium erythraea*.

This enzyme catalyzed an intramolecular regioselective cyclization of 2,3',4,6-tetrahydroxybenzophenone to give 1,3,5-trihydroxyxanthone. In contrast to benzophenone synthase and 3-hydroxybenzoate:CoA ligase, xanthone synthase is a cytochrome P₄₅₀ enzyme, probably a cytochrome P₄₅₀ oxidase. This membrane-bound enzyme was found to be dependent on oxygen and nicotinamide adenine dinucleotide phosphate-reduced form (NADPH) and strongly reduced by established P₄₅₀ inhibitors. Besides, this enzyme was appreciably inhibited by carbon monoxide in the dark and its activity was restored by illumination with white and blue light. The mechanism proposed for the regioselective intramolecular cyclization of the benzophenone was probably oxidative phenol coupling involving two one-electron oxidation steps (Figure 9).

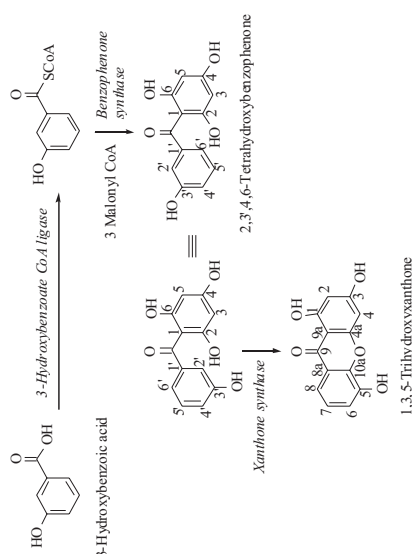


Fig. 9 Proposed Biosynthetic Route to 1,3,5-Trihydroxyxanthone in the Cell Culture of *Centaurea erythraea*

The first one electron transfer and proton abstraction would result in a phenoxyl radical which, after electrophilic attack at C-2', resulted in cyclization of the benzophenone. The hydroxycyclohexadienyl radical intermediate was then converted, by the loss of one electron and one proton, to 1,3,5-trihydroxyxanthone. This mechanism was strongly favoured by the *ortho*-*para*-directing 3-hydroxyl group on the ring B which was supported by the substrate specificities of benzophenone synthase and 3-hydroxybenzoate:CoA ligase which converted most efficiently the 3-hydroxylated substrates.

The same authors (Peters et al., 1998) have also examined the enzymology of the cultured cells of *Hypericum androsaemum* (Hypericaceae). They have found that the enzyme benzophenone synthase had, however, different substrate specificity from that of benzophenone synthase detected in *Centaurea erythraea*. The benzophenone synthase from *Hypericum androsaemum* was found

to convert most efficiently benzoyl CoA while 3-hydroxybenzoyl CoA only gave half-maximal activity. It was also found that 3-hydroxybenzoic acid was the preferred substrate for 3-hydroxybenzoate:CoA ligase from the cultured cells of *Hypericum androsaemum*. However, this enzyme acted relatively efficiently on benzoic acid. On the other hand, benzoic acid was found to be a poor substrate for 3-hydroxybenzoate:CoA ligase from the cell culture of *Centaurea erythraea*. Another enzyme, benzophenone 3-hydroxylase, was also detected in the cultured cells of *Hypericum androsaemum*. This enzyme catalyzed 3-hydroxylation of 2,4,6-trihydroxybenzophenone. It was detected in a microsomal fraction and was described as a cytochrome P₄₅₀ oxygenase. This enzyme did not hydroxylate the 3-position of benzoic acids and cinnamic acids and thus was not involved in the early steps of xanthone biosynthesis. The substrate specificities of 3-hydroxybenzoate:CoA ligase and benzophenone synthase together with the existence of benzophenone-3-hydroxylase suggested that there were alternative pathways for the formation of 2,3',4,6-tetrahydroxybenzophenone in the cultured cells of *Hypericum androsaemum*. However, it is still unclear if the 3'-hydroxyl group was introduced either at the benzophenone level or at earlier stage in the xanthone biosynthetic pathway. Another interesting aspect of the biosynthetic pathway of *Hypericum androsaemum* is that it produced 1,3,7-trihydroxyxanthone instead of 1,3,5-trihydroxyxanthone found in the cultured cells of *Centaurea erythraea* (Figure 10). It is evident that the formation of 1,3,7-trihydroxyxanthone in *Hypericum androsaemum* was also by regioselective intramolecular cyclization of 2,3',4,6-tetrahydroxybenzophenone, via the *para*-position to the 3'-hydroxyl group instead of the *ortho*-position as proposed for the formation of 1,3,5 trihydroxyxanthone found in *Centaurea erythraea* (Figure 9).

On the other hand, Dias et al. (2000) reported the identification of xanthones with a 1,3,5,6-oxygenation pattern from the suspended cells of *Hypericum androsaemum*. They suggested these cell cultures had the biosynthetic capability of producing 5-oxygenated xanthones and concluded that the discrepancy of their results from those obtained by Peters et al. (1998) could be due to different culture conditions used.

Interestingly, Wang et al. (2003), by using quantitative ¹³C NMR analysis of 1,3,5,8-tetrahydroxyxanthone, isolated from the root cultures of *Sweetia chirata* (Gentianaceae), grown with supplements of [1-¹³C]glucose, [U-¹³C₆]glucose or [carboxy-¹³C]shikimic acid, have concluded that it was derived from a shikimate pathway intermediate before the biosynthetic level of phenylpyruvate and not via phenylalanine and cinnamate. They have proposed a hypothetical mechanism for the conversion of shikimic acid into 3-hydroxybenzoate via the vinylogous elimination of phosphate from shikimic acid-3-phosphate. Dehydration of the resulting diene intermediate would afford the aromatic ring system of 3-hydroxybenzoate. The CoA ester of 3-hydroxybenzoate could then provide the starter unit for the downstream steps of the polyketide-type biosynthesis of 1,3,5,8-tetrahydroxyxanthone (Figure 11).

Contrary to the biosynthesis of the xanthone skeleton, the enzymology and reaction mechanism of prenylation of plant secondary metabolites, especially xanthones, are sparse. This is partly due to the fact that only a small number of aromatic prenyltransferases responsible for prenyl group attachment have been recently isolated and characterized (Pojer et al., 2003; Edwards and Gerwick, 2004; Kuzuyama et al., 2005). By analogy to other classes of prenylated secondary metabolites, the xanthone skeletons are constructed before the prenyl group is attached.

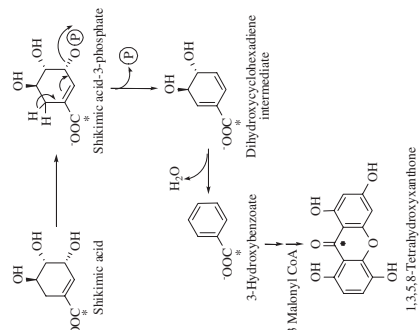


Fig. 10 Alternative Pathways of Xanthone Biosynthesis in Cell Cultures of *Hypericum androsaemum*

The biosynthetic pathway of the new prenylated xanthones apetalinone A (**4**), apetalinone B (**285**), apetalinone C (**211**) and the known zeyloxanthone (**213**) and calzeyxanthone (**408**), isolated from the roots of *Callophyllum apetalum* was proposed by Iinuma et al. (1997) (Figure 13).

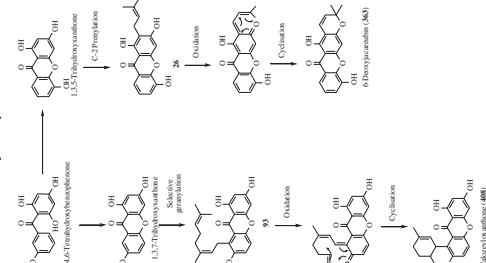


Fig. 12 Proposed Biosynthetic Routes for Calozeoylozanthone (408) and 6-Deoxyjacareubin (363)

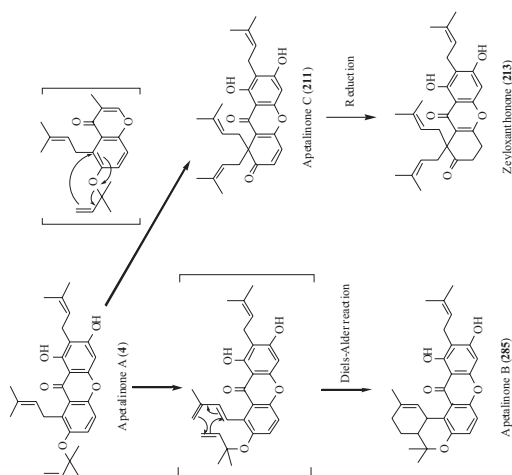


Fig. 13 Apetalinone A (4) as Building Block for Apetalinone B (285), Apetalinone C (211) and Zeyloxanthone (213)

Figure 13 depicts the mechanism of Claisen rearrangement of a 1,1-dimethylallyloxy moiety on C-8 of apetalinone A (4) to form apetalinone C (211) which, after reduction of the double bond, gives zeyloxanthone (213). On the other hand, apetalinone B (285) was synthesized by Diels-Alder reaction from apetalinone A (4).

The ever growing secondary metabolites isolated from the genus *Garcinia* (Guttiferae) whose structure is based on the unique 4-oxa-tricyclo[4.3.1.0]dec-8-en-2-one scaffold are one of the most interesting prenylated xanthones not only due to their interesting biological activities but also by biosynthetic point of view. The structures of these "caged xanthones" are shown in **Figure 14**.

It has been suggested that the caged scaffold could arise in nature by means of a tandem Claisen/Diels-Alder rearrangement (Tisdale et al., 2004). By using mesuaxanthone B as a starting material, Quillinan and Scheinmann (1971) successfully prepared and tested their hypothesis on 5,6-bis(allyloxy)-1-hydroxy-9*H*-xanthen-9-one (I). They showed that by heating mesuaxanthone B in boiling decalin induced the Claisen and subsequently, the Diels-Alder rearrangement, to create the caged structure. As can be observed, there is a possible concomitant allylation at both the C-5 and C-6 centres giving intermediates II and IV, which then yield the regular caged scaffold (III) and its constitutional isomer, the so called neoscaffold (V), respectively.

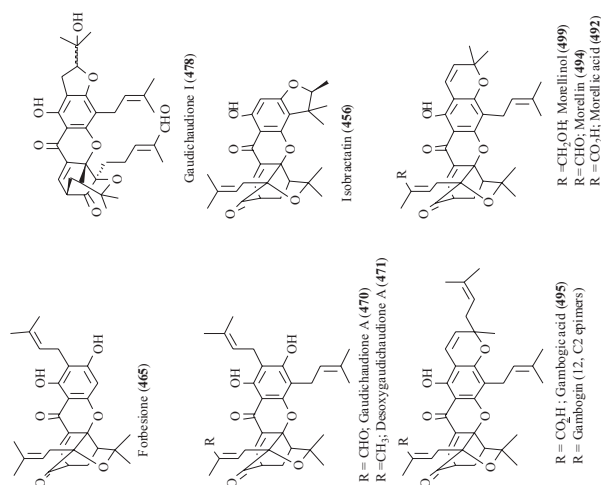


Fig. 14 Structures of Caged Xanthones

Based on the biomimetic synthesis of forbesione (465) by using a site selective Claisen/Diels-Alder /Claisen reaction cascade, Tisdale et al. (2004) have proposed the Claisen/Diels-Alder /Claisen rearrangement of the allyloxy intermediates (VIa-c) as shown in **Figure 16**.

It was found that the substituent on C-1 exerted a strong influence on the formation of the regular cage scaffold or neoscaffold. When C-1 substituent was a hydroxyl group (R = H), the regular caged scaffold was exclusively formed (IXa). However, when the substituent on C-1 was methoxyl or acetyl, both regular (IXb-c) and neo scaffolds (IXb,c) were formed. The explanation of this finding was based on the fact that the hydroxyl group on C-1 could increase the electron deficiency of the carbonyl group (C-9) by hydrogen bonding, and thus weakening the bond between the oxygen and C-18. This resulted in a formation of the intermediate VIIa, which, after a Diels-Alder rearrangement by C-21-C-22 dienophilic attack, gave rise to the product of the regular caged scaffold (IXa). On the contrary, if the methoxyl or acetyl group was on C-1, the electron deficiency on the carbonyl carbon (C-9) was not strong enough to weaken preferentially the oxygen and C-18

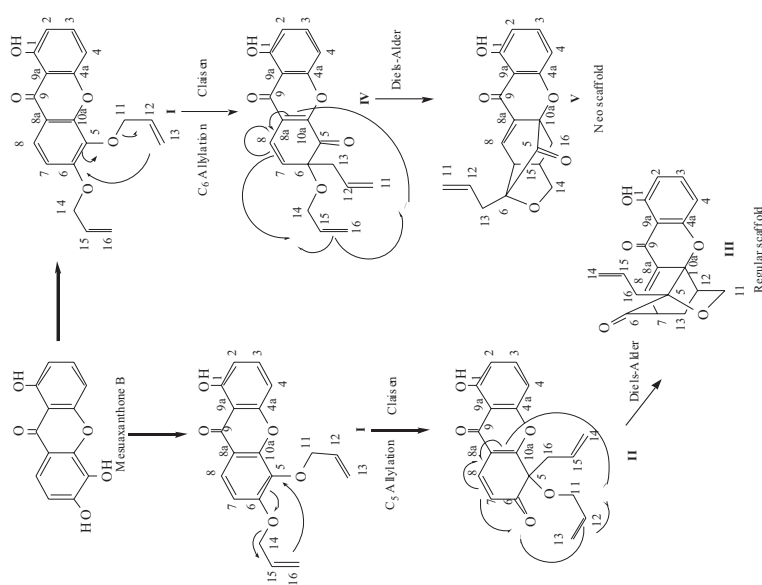


Fig. 15 Formation of Caged Scaffold by Claisen/Diels-Alder Rearrangement of Mesuaxanthone B

bond. As a result, either C-18-O or C-23-O could be broken in the Claisen rearrangement, leading to a formation of both intermediates (VIIb,c or VIIIb,c). The Diels-Alder rearrangement of these intermediates would give rise to both regular (IXb,c) and neo caged scaffolds (Xb,c).

Using ¹H NMR technique to study the timing of the Claisen/Diels-Alders/Claisen reaction cascade, Tisdale et al. (2004) have found that the Claisen/Diels-Alder rearrangement of the ring B leading to a formation of the 4-oxatricyclo[4.3.1.0]dec-8-en-2-one system occurred before the A-ring Claisen rearrangement.

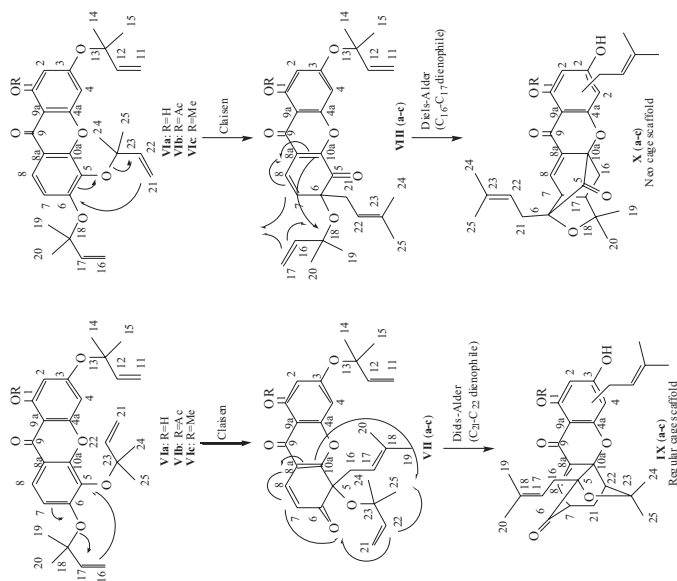


Fig. 16 Claisen/Diels –Alder Rearrangement of the Intermediate VII

The fact that the prenyl substituents are equally found in position 2 or 4 of the ring A of the xanthone scaffold has aroused the attention to understand the mechanism by which these substituents are attached during the process of biosynthesis. Knowing before hand that the Claisen rearrangement in ring A occurred after the caged scaffold is formed, Tisdale et al. (2004) have used several models to study the selectivity of the Claisen rearrangement in ring A. They have found that when the substituent on C-1 was a hydroxyl group, the prenylation occurred equally on C-2 and C-4 (Figure 17).

However, when the substituent on C-1 was methoxyl, prenylation occurred predominantly on C-4 (Figure 18). These results could be explained on the basis of increased steric hindrance by methoxyl group during C-2 prenylation. When the substituent on C-1 is hydroxyl group, the

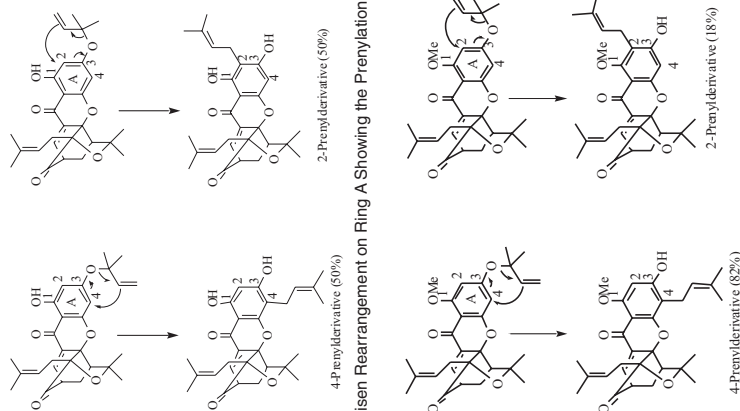


Fig. 17 Claisen Rearrangement on Ring A Showing the Prenylation on C-2 and C-4

Fig. 18 Steric Hindrance of Methoxyl Group on C-1 Hinders the Prenylation of C-2

phenolic hydrogen is bonded to the carbonyl group thus does not hinder the [3,3]-sigmatropic rearrangement at C-2.

A majority of caged xanthenes isolated from *Garcinia* species possess a regular caged scaffold as in forbesione (**465**) except for 1-*O*-methylneobractatin (**460**), which has the "neo caged" scaffold. 1-*O*-methylneobractatin (**460**) was isolated as a minor constituent along with bractatin (**455**) and 1-*O*-methylbractatin (**457**) from the extract of dried powdered leaves of *Garcinia bracteata* (Figure 19).

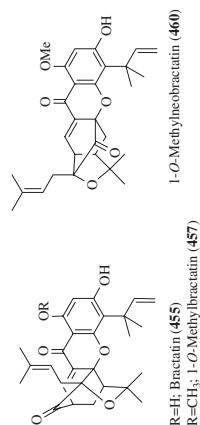


Fig. 19 Structures of Bractatin (**455**) and *O*-Methyl Derivatives

The co-occurrence of 1-*O*-methylbractatin (**457**) and 1-*O*-methylneobractatin (**460**), both with methoxyl group on C-1, could indicate that the 1-*O*-methyl group was incorporated by nature prior to the tandem Claisen/Diels-Alder/Claisen rearrangement to produce the regular and caged scaffolds.

It is interesting to observe that the tandem Claisen/Diels-Alder/Claisen rearrangement mechanism proposed for the genesis of the caged scaffold of the natural xanthenes in *Garcinia* species implied the existence of the prenyloxy intermediates in the biosynthetic pathway. As expected, a small number of prenyloxy xanthenes have been reported from natural sources. Examples of these are 7-geranyloxy-1,3-dihydroxyxanthone (**10**), isolated from *Cratogeomys cochinchinensis* (Nguyen and Harrison, 1998) as well as six prenyloxy xanthenes (**8-9**, **11-14**), isolated from *Vismia guianensis* (Bilia et al., 2000) (Figure 20).

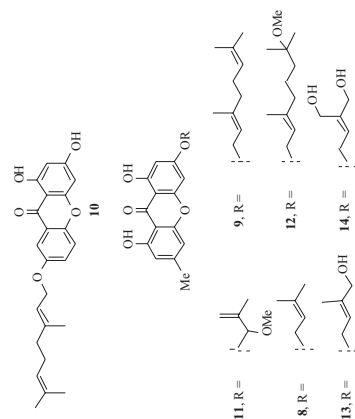


Fig. 20 Naturally Occurring Prenyloxy Xanthenes (**8-14**)

The biosynthesis of prenyloxy xanthenes can occur by nucleophilic attack of Dimethylallyl Pyrophosphate (DMPP) or Geranyl Pyrophosphate (GPP) by the phenolic hydroxyl groups of xanthone nucleus formed in the earlier stage of the biosynthetic route as depicted in **Figure 21**.

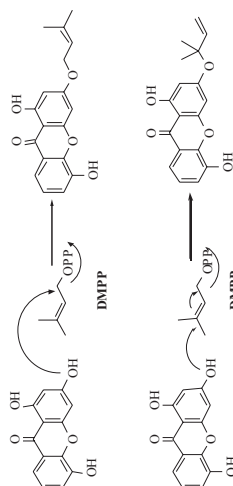


Fig. 21 Examples of Formation of the Prenyloxy Side Chains. DMPP = Dimethylallyl Pyrophosphate

4. ISOLATION AND STRUCTURE ELUCIDATION

The methods of isolation and structure elucidation of xanthenes have been widely covered in some recent reviews (Vietra and Kijjoa, 2005; Peres et al., 1997a,b, 2000; Pinto and Sousa, 2003; Fernandes et al., 1998). ^1H and ^{13}C NMR spectroscopic methods are the most useful tools in the structure elucidation of naturally occurring and synthetic prenylated xanthenes. The 2D NMR techniques such as COSY, NOESY, HSQC and HMBC (Rukachaisirikul et al., 2003a, d; Thoison et al., 2000; Pinheiro et al., 2003b; Chammahathien et al., 2003a; Nkengack et al., 2002a; Abe et al., 2003; Ito et al., 2003b; Nguyen et al., 2003; Xu et al., 2000, 2001; Huang et al., 2001; Zhang et al., 2002; Malmström et al., 2002; Wahyuni et al., 2004; Silva and Pinto, 2005) as well as X-ray diffraction (Gales and Damas, 2005) have been widely used to establish unambiguously the complex structures of prenylated xanthenes.

Silva and Pinto (2005), in a recent review on the ^1H and ^{13}C NMR for structure elucidation of xanthone derivatives, have discussed the characteristic proton and carbon chemical shift values of the commonly found prenyl substituents as summarized in **Figure 22**.

The ^1H NMR spectrum can be used as a first approach to identify the type of the prenyl substituents shown in **Figure 22** as well as their positions on the xanthone nucleus. For example, the ^1H NMR spectrum of the 3,3-dimethyl-2-propenyl substituent (**A**, **Figure 22**) can be very useful to assign its position on the xanthone nucleus, showing the signal of the methylene protons adjacent to the aromatic ring as a doublet at δ 3.2-3.6. However, when this substituent is on C-1 or C-8, the chemical shifts of the methylene protons appear at higher frequencies at δ 4.0-4.2, due to the deshielding effect of the neighbouring carbonyl group.

For the 1,1-dimethyl-2-propenyl substituent (**B**, **Figure 22**), the ^1H NMR spectrum usually exhibits three signals of the olefinic protons, appearing as doublets at δ 6.5-6.6 (CH) and at

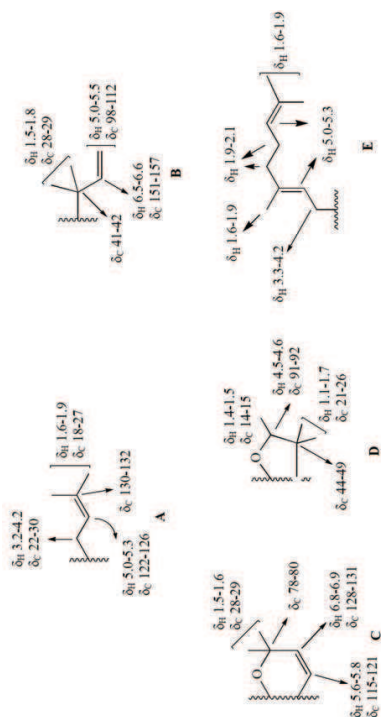


Fig. 22 Characteristic Chemical Shifts of the Commonly Found Prenyl Substituents

δ 5.0-5.5 (CH_2), the latter show coupling constants characteristic of a *cis-trans* system. The 2,2-dimethyl-3-propenyl substituent (**C**, **Figure 22**) can be identified by the two doublets of the *cis*-coupled olefinic protons, respectively at δ 5.6-5.8 and δ 6.8-6.9, and a singlet of the two methyl groups at δ 1.5-1.6. However, when the 2,2-dimethyl-3-propenyl substituent (**C**) is on C7-C8, the olefinic proton on the carbon adjacent to the aromatic ring is found to resonate at higher frequencies appearing at δ 8.0. The higher chemical shift of this olefinic proton is also attributed to the deshielding effect of the neighbouring carbonyl group. In the case of the dihydrofuran fused ring (**D**, **Figure 22**), one of the three methyl groups appears as a doublet at δ 1.4-1.5, whereas the signal of the methine proton appears as a quartet at δ 4.5-4.6. For the geranyl substituent (**E**, **Figure 22**), its location on the xanthone nucleus can be identified in the same fashion as that of the 3,3-dimethyl-2-propenyl substituent (**A**), with the chemical shifts of the methylene protons adjacent to the aromatic nucleus generally appear as a doublet ($J=6-7$ Hz) at δ 3.3-3.6. However, when it is on C-1 or C-8, the methylene protons appear at higher frequencies (δ 4.1-4.2). The other methylene protons appear at δ 1.9-2.1 while the two vinylic protons resonate at δ 5.0-5.3. The protons of the three methyl groups appear around δ 1.6-1.9.

The proton chemical shifts can be further useful to distinguish between the C-prenylated and O-prenylated derivatives. In the case of prenyloxy and geranyloxy substituents, the oxymethylene protons are strongly deshielded relatively to those of the prenyl and geranyl groups of the C-prenylated derivatives, appearing as a doublet at δ 4.4-4.6 ppm (Castanheiro et al., 2007).

The chemical shifts observed in ^{13}C NMR spectrum, and in conjunction with DEPTs' spectra, can be very useful to confirm the type of the prenyl substituents and their position on the xanthone nucleus, identified by the ^1H NMR spectrum. For the 3,3-dimethyl-2-propenyl substituent (**A**, **Figure 22**), the chemical shift value of the methylene carbon is normally at δ 22. However,

when this substituent is on C-1 or C-8 of the xanthone nucleus, the methylene carbon appears at *ca.* δ 27. The chemical shift values of the olefinic carbons also can be useful to determine the positions of this substituent. They normally appear at δ 121–122 (CH=) and 135–136 (C=), respectively. However, when this substituent is on C-1 or C-8, one of the olefinic carbons appears at higher frequencies at *ca.* δ 123–124 (CH=) whereas the other shows up at lower frequencies at δ 132–133 (C=), respectively. Generally, the two methyl carbons of this substituent show the characteristic chemical shifts values at *ca.* δ 18 and 26, irrespective of its position on the xanthone nucleus. It is important to note also that this generalization also applies to the carbon chemical shift values of the geranyl substituent (E). For its parts, the 2,2-dimethylpyrano substituent (C) gives the characteristic ^{13}C NMR spectrum. Besides the signal of the oxygen bearing quaternary carbon at *ca.* δ 80, there are two olefinic carbons (CH=) at *ca.* δ 121 and 131, respectively being the lower frequencies carbon attached to the aromatic ring. The two methyl carbons appear at the same frequencies showing at *ca.* δ 25–26.

The 2D NMR techniques proved to be essential to established unequivocally the structure of the prenylated xanthones especially the HMBC spectrum which is frequently used to locate not only the position of the methoxyl and hydroxyl substituents in the xanthone nucleus but also the position to which the prenyl substituent is attached (Zou et al., 2004; Nkengfack et al., 2002a). By observing the correlation of the signal of the methylene protons (at *ca.* δ 3.2–3.6 or 4.0–4.2) of the 3,3-dimethyl-2-propenyl substituent and the aromatic carbons of the xanthonic nucleus, the position of this substituent can be confirmed. For the 2,2-dimethylpyrano substituent (C), the crosspeaks between the olefinic proton at *ca.* δ 6.8–6.9 (or *ca.* δ 8.0) and the signal of aromatic carbons can be very elucidative to determine its position.

X-ray crystallography has become a very interesting technique to elucidate the crystal structure of xanthones and the review recently published by Gales and Damas (2005) has provided important data and references for this subject. Essentially, the 9*H*-xanthen-9-one shows a planar crystal structure except for the oxygen atom of the carbonyl group, with a deviation of 0.13° from the plane. This is probably due to the crystallographic packing of the xanthone molecules, which may lead to repulsion between this oxygen atom of one molecule and C-6 of another adjacent molecule. The planes containing the aromatic rings form angles of 3.7° and 2.0° with the plane of the pyranoid ring, adopting a much flattened boat conformation. It seems that the p_z electrons of the oxygen atom of the ether linkage can be used for conjugation with the carbonyl (C-9) to confer the aromatic character to the central pyranoid ring which, in turn, makes the molecular skeleton planar. The two benzene rings are not regular hexagons, but these distortions seem to be symmetric with the whole molecule exhibiting an approximate C_{2v} symmetry. The X-ray diffraction data also showed that the isoprenyl side chain was out of the main plane of the xanthone scaffold even when it was not stacked by adjacent substituents. Examples of this steric behaviour can be found in compounds **2**, **239** and **421** (Figure 23) with the corresponding dihedral angle of 111.8° in varicoxanthone B (**2**), 95.4° in shamixanthone (**421**) and 111.5° in garcinone B (**239**).

For compounds with two isoprenyl side chains such as mangostin (**141**) (Figure 23), and its acetate derivative, they are found to possess distinct overall conformations. Although the isoprenyl side chains are planar in both compounds, they form a dihedral angle of 130.4° in mangostin (**141**) while in mangostin acetate the corresponding angle is 159.8°.

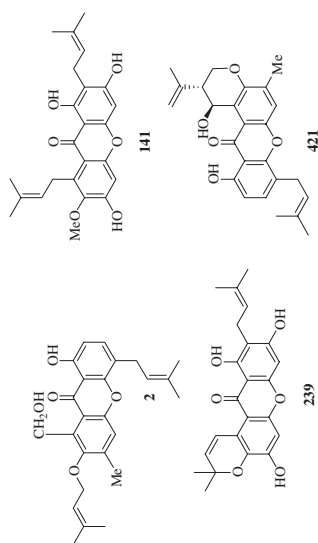


Fig. 23 Structure of Varicoxanthone B (**2**), Mangostin (**141**), Garcinone (**239**) and Shamixanthone (**421**)

Cyclization of the prenyl side chain with the *ortho* hydroxyl group of the xanthone nucleus can result in an extra pyran ring whose orientation can be linear as in compounds **363** and **390** (Figure 24) or angular as in compounds **239** and **373** (Figure 24). In both cases, the planes of the benzenoid rings define angles lower than 8°, thus making the xanthone skeleton almost planar. In these compounds (**363**, **390** and **239**, **373**), the γ -pyran ring assumes a half chair conformation.

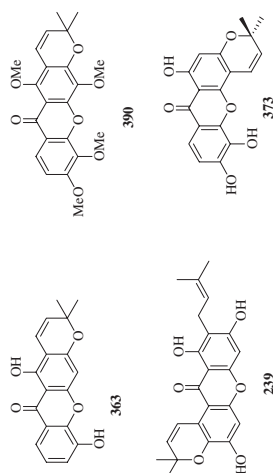


Fig. 24 Structures of Linear Pyranoxanthones (**363**, **390**) and Angular Pyranoxanthones (**239**, **373**)

5. BIOLOGICAL ACTIVITIES

Although a number of reviews on naturally occurring and synthetic xanthone derivatives (Dean, 1973; Afzal and Al-Hassan, 1980; Sultanbawa, 1980; Bennett and Lee, 1989; Mandal et al.; 1992,

Petes et al., 1997a, b; Vieira and Kijjoa, 2005) have included biological activities of some xanthones, they were concerned only with their preliminary studies. Though a recent review on biological activities of xanthones by Pinto et al. (2005) has covered all classes of these compounds, it also referred only briefly the prenylated derivatives. However, there is no in depth report on biological activities of prenylated xanthones as a separate group. For this reason, various aspects of biological activities of prenylated xanthones are reported here.

Table 2 indicates biological activities and their targets of some xanthones listed in **Table 1**. From the analysis of these data it can be inferred that prenylated xanthones exhibit a wide range of biological and pharmacological activities. It is interesting to point out that, in the majority of cases, compounds with isoprenoid side chains exhibit biological activities distinct from their non-prenylated precursors. It is worth emphasizing that the presence of the prenyl groups is, on one hand, essential for biological activities and, on the other hand, for improvement of potency and selectivity. The influence of the prenyl groups is found to be associated with their positions on the xanthone scaffold and can be considered as dual since the prenyl groups can interfere with physicochemical properties such as lipophilicity of the compounds as well as on their three-dimensional properties especially the steric effects on the interaction with biological receptors.

Among the biological activities described in **Table 2**, the *in vitro* growth inhibitory effect on the tumor cell lines appeared to be noteworthy since these compounds exert their effect on a broad range of different tumor cell lines ranging from leukemia to oral squamous cell, colon, breast, ovarian, uterine, lung, hepatocellular, gastric and nasopharynx epidermoid carcinomas.

6. STRUCTURE –ACTIVITY-RELATIONSHIP STUDIES (SAR)

Up to now structure-activity relationship studies are confined to only few pharmacological activities such as chemopreventive activity against chemical induced carcinogenesis, cytotoxic, antitumor, antimicrobial, antifungal, trypanocidal activities and inhibitory effect on platelet-activating factor (PAF). Taking into account the importance of these biological/pharmacological activities, the respective "hit compounds" together with the hypothesized putative pharmacophoric data are presented.

6.1 Chemopreventive Activity

Epstein-Barr virus (EBV) is a human virus that infects 90% of adult population worldwide as a largely non-pathogenic infection being maintained under latent condition by an efficient host immune response. However EBV has a potential oncogenic nature and is associated with a variety of cancers in humans, including Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease. EBV is also a causative agent in lymphoproliferative disorders in immunocompromised individuals. The mechanism by which latently infected cells can be activated into the virus productive (lytic) cycle is still poorly defined.

Table 2. Principal Biological Activities of Prenylated Xanthones

Nº Name of the compounds	Activities	References
6 Cudraticusxanthone G	Inhibitory effects on four kinds of human digestive apparatus tumor cell lines (HCT-116, SMMC-7721, SGC-7901 and BGC-823)	Zou et al., 2004
12 1,8-Dihydroxy-6-methyl-3-(3,7-dimethyl-7-methoxyoct-2-enyloxy)xanthone	Antimitotic activity	Bilia et al., 2000
21 1,3,5-Trihydroxy-8-isoprenylxanthone	Inhibitory effects against <i>Candida albicans</i> secreted aspartic proteases	Zhang et al., 2002
22 1,4,5-Trihydroxy-3-(3-methylbut-2-enyl)xanthone	Antifungal activity against <i>Cladosporium cucumerinum</i> ; Active against <i>Trypanosoma brucei</i> and <i>cruzi</i> ; Activity against <i>Leishmania infantum</i> and <i>Plasmodium falciparum</i> ; Monoamine oxidase A (MAO A) inhibition	Diserens et al., 1992; Brühlmann et al., 2004; Núñez et al., 2004; Marston et al., 1993; Mbwambo et al., 2006; Ji and Zhang, 2006
23 Bangangxanthone B	Weak Antioxidant	Lannang et al., 2005
24 1,3,7-Trihydroxy-2-(3-methylbut-2-enyl)xanthone	Weak antibacterial against five vancomycin-resistant <i>Enterococci</i> (VRE) strains (Van A, van B, van C) and against methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) strains; Antifungal activity against <i>Cladosporium cucumerinum</i> and <i>Candida albicans</i> ; Inhibition of EBV-early antigen activation	Ito et al., 1998; Fukai et al., 2004, 2005; Hou et al., 2001; Zhang et al., 2002; Chang et al., 1994; Cortez et al., 1998
25 1,3,5-Trihydroxy-4-prenylxanthone	Weak antioxidant activity; Antimalarial against chloroquine-resistant strains of <i>Plasmodium falciparum</i> ; Monoamine oxidase B (MAO B) and Acetylcholinesterase E inhibition	Hay et al., 2004b; Gonda et al., 2000; Ji and Zhang, 2006
26 1,3,5-Trihydroxy-2-(3,3-dimethylallyl)xanthone	Weak antioxidant activity; Antifungal activity against the brown rot fungus <i>Postia placenta</i> ; Strong inhibition of PAF receptor binding; Antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i>	Jantan et al., 2001, 2002; Hay et al., 2004b; Chairungsilert et al., 1996; Chilpa et al., 1997; Gonda et al., 2000
27 1,3,6-Trihydroxy-4-prenylxanthone	Weak antioxidant activity	Gonda et al., 2000
29 1,3,5,7-Tetrahydroxy-8-isoprenylxanthone	Inhibitory effect against <i>Candida albicans</i> secreted aspartic proteases	Zhang et al., 2002
31 Assiguxanthone B	Antibacterial activity against <i>Bacillus subtilis</i>	Pinheiro et al., 2003b

Table 2 Contd.

Table 2 Contd.

32	1,3,6,7-Tetrahydroxy-8-(3-methylbut-2-enyl)xanthone	Active as inhibitors of human tumor cell replication: A549 and MCF-7	Tanaka et al., 2004
33	1,3,5,6-Tetrahydroxy-2-(3,3-dimethylallyl)xanthone	Active against <i>Staphylococcus aureus</i> ; moderate activity against <i>Escherichia coli</i> ; Trypanocidal activity against epimastigotes and trypomastigotes of <i>Trypanosoma cruzi</i> ; Antifungal activity against the brown rot fungus <i>Postia placenta</i> ; Inhibition of PAF receptor binding	Abe et al., 2004; Jantan et al., 2001, 2002; Pinheiro et al., 2003b; Chilpa et al., 1997; Yasunaka et al., 2005; Wu et al., 2003
36	Garciniane A	Toxic to brine shrimp	Chiang et al., 2003
37	Globulixanthone D	Cytotoxicity against P-388 and HT-29 cell lines; Antibacterial activity against <i>Staphylococcus aureus</i> and <i>Bacillus subtilis</i>	Nkengfack et al., 2002; Chen et al., 2004
38	Linixanthone C	Cytotoxicity against P-388 and HT-29 cell lines	Chen et al., 2004
39	1,7-Dihydroxy-3-methoxy-2-(3-methyl-2-butenyl) xanthone	Antibacterial activity against MRSA; Antiproliferative activity against human leukemia HL60 cells	Suksamram et al., 2003; linuma et al., 1996c; Rukachaisirikul et al., 2003a; Matsumoto et al., 2003; Chairungsrikerd et al., 1996; Deachathai et al., 2005, 2006; Molinar-Toribio et al., 2006
40	1,5-Dihydroxy-3-methoxy-4-prenylxanthone	Activity against chloroquine-resistant strain of <i>Plasmodium falciparum</i>	
47	1,2,6-Trihydroxy-5-methoxy-7-(3-methylbut-2-enyl) xanthone	Activity of neurite outgrowth on PC12D cells	Chanmahasathien et al., 2003a; Ohizumi and Li, 2004
49	Afzelixanthone A	Antioxidant activity based on the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free-radical- scavenging	Waffo et al., 2006
52	5-O-Methylcelebixanthone	Antimalarial activity against <i>Plasmodium falciparum</i>	Laphookhieo et al., 2006
56	Celebixanthone	Cytotoxic activity against the NCI-H187 cell line; Antimalarial activity against <i>Plasmodium falciparum</i> ; Potent Antioxidant DPPH radical scavenging activity	Mahabusarakam et al., 2006; Laphookhieo et al., 2006
58	1,3,5-Trihydroxy-6-methoxy-2-prenylxanthone	Weak antioxidant activity	Gonda et al., 2000
59	1,3,6-Trihydroxy-5-methoxy-4-prenylxanthone	Weak antioxidant activity	Gonda et al., 2000
64	1,3,5-Trihydroxy-4-(3-hydroxy-3-methylbutyl) xanthone	Weak antioxidant activity	Gonda et al., 2000

Table 2 Contd.

Table 2 Contd.

68	Afzelixanthone B	Antioxidant activity based on the DPPH free-radical-scavenging	Waffo et al., 2006
69	1,3,5,6-Tetrahydroxy-2-(3-hydroxy-3-methylbutyl) xanthone	Inhibited dog gastric H ⁺ , K ⁺ -ATPase activity	Abe et al., 2004; Jantan et al., 2001; Reyes-Chilpa et al., 2006
71	(±)-Caledol	Antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i>	Oger et al., 2003
75	Globulixanthone A	Cytotoxic activity against the KB cell line	Nkengfack et al., 2002
77	Hyperxanthone C	Active as inhibitor of human tumor cell replication: A549 and MCF-7	Tanaka et al., 2004
78	Pancixanthone A	Antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i>	Ito et al., 1998; Hay et al., 2004b
79	Globuxanthone	Inhibitory effect against topoisomerase II	Tosa et al., 1997; Fukuyama et al., 1991; Minami et al., 1994
80	12b-Hydroxy-des-D-garcigerrin A	Trypanocidal activity against trypomastigotes of <i>Trypanosoma cruzi</i> ; Antibacterial activity against MRSA and methicillin-sensitive <i>Staphylococcus aureus</i> (MSSA); Activity of neurite outgrowth on PC12D cells; Antifungal activity against <i>Cladosporium cucumerinum</i> ; MAO A inhibition; Inhibition of growth of Co115 colon carcinoma cells	Tosa et al., 1997; Abe et al., 2003; Chanmahasathien et al., 2003a; Diserens et al., 1989, 1992; Brühlmann et al., 2004; Ohizumi and Li, 2004; Núñez et al., 2004; Marston et al., 1993; linuma et al., 1996c; Fukuyama et al., 1991; Ji and Zhang et al., 2006
82	Cudraxanthone S	Cytotoxicity against HCT-116, SMMC-7721, SGC-7901 and BGC-823 cell lines; Weak antibacterial activity against MRSA strains; Antifungal activity against <i>Cryptococcus neoformans</i> , <i>Aspergillus fumigatus</i> , <i>A. nidulans</i> , and <i>Candida glabrata</i>	Fukai et al., 2003, 2004, 2005; Wang et al., 2005
83	Isocudranixanthone A or Assiguxanthone A	Cytotoxicity against HCT-116, SMMC-7721, SGC-7901 and BGC-823 cell lines; Antioxidant activity based on the DPPH free-radical-scavenging; Antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i>	Hay et al., 2004a, b; Ito et al., 1998; Wang et al., 2005; Ji et al., 2005
84	Subelliptenone F	Inhibitory effect against topoisomerases I and II	Tosa et al., 1997; linuma et al., 1996c
85	Symphoxanthone	Antioxidant activity; Inhibitory activity of lipid peroxidation; O ₂ ⁻ scavenging activity; Scavenging activity of DPPH radical	Minami et al., 1996

Table 2 Contd.

Table 2 Contd.

86	Cudranixanthone	Antilipid peroxidative activity in the rat liver homogenate	Chang et al., 1994
87	Isocudranixanthone B	Strong scavenging effect on the DPPH radical; Antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i> ; Antioxidant activity against LDL oxidation; Inhibit cholesterol acyltransferase (hACAT) type 1 and 2	Hay et al., 2004b; Lee et al., 2005b; Boonnak et al., 2006b; Park et al., 2006
88	Garcinixanthone H	Antioxidant activity; Inhibitory activity of lipid peroxidation; O ₂ ⁻ scavenging activity	Minami et al., 1996
90	Vieillardixanthone	Antioxidant activity based on the DPPH free-radical- scavenging	Hay et al., 2004a; Ji et al., 2005
91	Mangostinone	Antiproliferative activity against human leukemia HL60 cells	Suksamrarn et al., 2003, 2006; Matsumoto et al., 2003; Mahabusarakam et al., 2005; Jung et al., 2006; Rukachaisirikul et al., 2006
94	1,3,5-Trihydroxy-4-(3',7'-dimethylocta-2',6'-dienyl)xanthone	Growth inhibitory activity against human colon carcinoma cell lines: Co 115, SW 480, SW 620; MAO A inhibition; Active against <i>Trypanosoma brucei</i> and <i>cruzi</i>	Diserens et al., 1992; Brühlmann et al., 2004; Núñez et al., 2004; Mbawambo et al., 2006; Ji and Zhang, 2006
96	Smeathxanthone A	Activity against a range of bacteria and yeasts; Antioxidant peroxynitrite scavenging activity	Komguem et al., 2005; Jung et al., 2006
97	Rubraxanthone	Strong antibacterial activity against MRSA and MSSA and moderate against <i>Staphylococcus aureus</i> ; Inhibitory activity on EBV-early antigen activation; Strong inhibition of PAF receptor binding; Cytotoxic activity against L1210 murine leukemia cell line	Jantan et al., 2002; Ito et al., 2003b; Iinuma et al., 1996c; Azebaze et al., 2004, 2006; Wahyuni et al., 2004; Kardono et al., 2006; Rukachaisirikul et al., 2006
98	Cowaxanthone	Antibacterial activity against <i>Staphylococcus aureus</i> ; Inhibitory activity on EBV- early antigen activation	Ito et al., 2003b; Mahabusarakam et al., 2005; Deachathai et al., 2005, 2006; Pattalung et al., 1994; Panthong et al., 2006

Table 2 Contd.

Table 2 Contd.

100	Calycinoxanthone D	Antifungal activity against <i>Candida albicans</i>	Rath et al., 1996
101	Roeperanone	Antifungal activity against <i>Candida albicans</i>	Rath et al., 1996
111	Patulone	Prevents A23187-induced prostaglandin E ₂ release	Yamakuni et al., 2006
112	6-Deoxy-γ-mangostin	Potent antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i>	Dharmaratne et al., 1999; Hay et al., 2004b
113	Cudraxanthone H Gerontoxanthone H	Antibacterial activity against five VRE strains (Van A, van B, van C) and growth inhibitory activity against MRSA strains and against a kind of MSSA; Cytotoxicity against SGC-7901 and BGC-823, SMMC-7721 cell lines	Zou et al., 2004; Fukai et al., 2004, 2005; Hou et al., 2001; Wang et al., 2005; Chang et al., 1994; An et al., 2006
114	1,3,7-Trihydroxy-2,4-di-(3-methylbut-2-enyl)xanthone	Activity against a chloroquine-resistant strain of <i>Plasmodium falciparum</i> ; Activity against <i>Trypanosoma cruzi</i>	Tosa et al., 1997; Mahabusarakam et al., 2006b; Laphookhieo et al., 2006; Molinar-Toribio et al., 2006
115	8-Desoxygartanin	Trypanocidal activity against epimastigotes and trypomastigotes of <i>Trypanosoma cruzi</i> ; Antibacterial activity against MRSA; Inhibitory activity against 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced EBV-early antigen activation in Raji cells; Antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i>	Abe et al., 2004; Rukachaisirikul et al., 2003a, b; Ito et al., 2002; Groweiss et al., 2000; Ho et al., 2002; Oger et al., 2003; Chairungsrilerd et al., 1996; Hay et al., 2004b; Deachathai et al., 2005; Suksamrarn et al., 2006; Jung et al., 2006; Molinar-Toribio et al., 2006
121	Cratoxyarborenone B	Cytotoxic activity against KB cell line	Seo et al., 2002; Kinghorn et al., 2003; Balunas et al., 2006
122	Toxyloxanthone D	Cytotoxicity against HCT-116, SMMC-7721, SGC-7901 and BGC-823 cell lines	Wang et al., 2005
123	Cudratricusxanthone B	Cytotoxicity against HCT-116, SMMC-7721 and SGC-7901 cell lines	Zou et al., 2004
124	Cudratricusxanthone E	Inhibitory effects on four kinds of human digestive apparatus tumor cell lines (HCT-116, SMMC-7721, SGC-7901 and BGC-823)	Zou et al., 2004
125	Xanthone V _{1a}	Cytotoxicity against HCT-116, SMMC-7721 and SGC-7901 cell lines	Zou et al., 2004
126	Gartanin	Cytotoxic activity against the human cancer cell line, NCI-H187; Antifungal activity against <i>Dreschlera oryzae</i> ; Antioxidant peroxynitrite scavenging activity	Groweiss et al., 2000; Bennett et al., 1990b; Ho et al., 2002; Iinuma et al., 1996c; Chairungsrilerd et al., 1996; Deachathai et al., 2005; Jung et al., 2006; Suksamrarn et al., 2006; Gopalakrishnan et al., 1997

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127	γ -Mangostin	Inhibition of cell growth of human colon cancer DLD-1 cells at 20mM; Inhibition of cyclooxygenase and prostaglandin E ₂ ; Inhibitory effect against <i>Mycobacterium tuberculosis</i> ; Inhibitory effect against topoisomerase II; Inhibition of k _B kinase activity and decrease of lipopolysaccharide-induced cyclooxygenase-2 gene expression in C6 rat glioma cells; antiproliferative activity against human leukemia HL60 cells; Inhibitory activity against cyclic adenosine monophosphate (cAMP) phosphodiesterase; Inhibition of protein kinases: CDPK(III-S), CDPK(MLCP), MLCK(MLCP), cAK(kemptide); Inhibitory activity on human immunodeficiency virus (HIV) protease; 5-Hydroxy tryptamine 2A receptor antagonist in the central nervous system; Cytotoxic activity against BC-1 cell line; Antifungal activity against <i>Fusarium oxysporum</i> vasinfectum, <i>Alternaria tenuis</i> and <i>Dreschlera oryzae</i> ; Antioxidant peroxynitrite scavenging activity	Nakatani et al., 2002, 2004; Suksamrarn et al., 2003, 2006; Tosa et al., 1997; Jinsart et al., 1992; Ho et al., 2002; Vlietinck et al., 1998; Chen et al., 1996; Chairungsriert et al., 1996, 1998; Jefferson et al., 1970; Matsumoto et al., 2003, 2005; Iinuma et al., 1996c; Yamakuni et al., 2006; Jung et al., 2006; Gopalakrishnan et al., 1997
128	1,4,5,6-Tetrahydroxy-7,8-di (3-methylbut-2-enyl) xanthone	Enhancing of the activity of neurite outgrowth on PC12D cells	Chanmahasathien et al., 2003a; Ohizumi and Li, 2004
131	8-Hydroxycudraxanthone G	Antioxidant peroxynitrite scavenging activity	Jung et al., 2006
132	Parvifolixanthone B	Antioxidant DPPH radical scavenging activity	Rukachaisirikul et al., 2006
134	Cratoxyarborenone C	Cytotoxic activity against KB cell line	Seo et al., 2002; Kinghorn et al., 2003
135	Cowaxanthone B	Activity against the human small cell lung cancer NCI-H187 cell line; Antibacterial activity against <i>Staphylococcus aureus</i> , both penicillin-sensitive strain ATCC 25923 and methicillin-resistant strain MRSA SK1	Pattanaprateeb et al., 2005; Panthong et al., 2006
136	Cratoxyarborenone E	Cytotoxic activity against KB cell line; Inhibition of HIV-1 reverse transcriptase	Seo et al., 2002; Kinghorn et al., 2003; Reutrakul et al., 2006
138	Dulxanthone B	Inhibit the EBV- early antigen activation	Ito et al., 1998
141	α -Mangostin	Inhibition of cell growth of human colon cancer DLD-1 cells at 20mM; Induction of apoptosis in human leukemia HL60 cells; Strong inhibitory effect against <i>Mycobacterium tuberculosis</i> ; Inhibitory effect against topoisomerase II; Antibacterial activity against <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> and <i>Streptococcus faecalis</i> , MRSA, MSSA and moderate activity against <i>Staphylococcus aureus</i> both penicillin-sensitive strain ATCC 25923 and methicillin-resistant strain MRSA SK1; Inhibitory activity on EBV- early antigen activation; Inhibitory activity against cAMP phosphodiesterase; Inhibition of protein kinases: CDPK(III-S), CDPK(MLCP), MLCK(MLCP), cAK(kemptide); Inhibitory activity on HIV protease; Inhibition of acidic sphingomyelinase;	Suksamrarn et al., 2006, 2003; Tosa et al., 1997; Lu et al., 1998; Ho et al., 2002; Okudaira et al., 2000; Jinsart et al., 1992; Vlietinck et al., 1998; Chen et al., 1996; Iikubo et al., 2002; Jefferson et al., 1970; Matsumoto et al., 2003, 2004, 2005; Ito et al., 2003b; Chairungsriert et al., 1996; Deachathai et al., 2005, 2006;

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		Cytotoxic activity against the NCI-H187, BC-1, KB, MCF-7, HeLa, HT-29 cell lines and weak cytotoxicity against A375 cells; Antifungal activity against <i>Dreschlera oryzae</i> ; Antiplasmodial activity against two strains of <i>Plasmodium falciparum</i> F32 and FcM29; Antioxidant peroxynitrite scavenging activity; Inhibition of 7,12-dimethylbenz[a]anthracene-induced preneoplastic lesions in a mouse mammary organ culture assay	Iinuma et al., 1996c; Azebaze et al., 2006; Mahabusarakam et al., 2006a, 2006b; Panthong et al., 2006; Laphookhieo et al., 2006; Jung et al., 2006; Boonnak et al., 2006b; Gopalakrishnan et al., 1997
142	β -Mangostin	Inhibition of growth of human colon cancer DLD-1 cells at 20M; Inhibitory effect against <i>Mycobacterium tuberculosis</i> ; Antiproliferative activity against human leukemia HL60 cells; Inhibitory activity on EBV- early antigen activation; Cytotoxic activity against the NCI-H187, MCF-7, HeLa, HT-29 and KB cell lines; Antimalarial activity against <i>Plasmodium falciparum</i> ; Antibacterial activity against <i>Staphylococcus aureus</i> , both penicillin-sensitive strain ATCC 25923 and methicillin-resistant strain MRSA SK1	Suksamrarn et al., 2003, 2006; Tosa et al., 1997; Jefferson et al., 1970; Matsumoto et al., 2003, 2005; Ito et al., 2003b; Iinuma et al., 1996c; Mahabusarakam et al., 2006b; Deachathai et al., 2006; Panthong et al., 2006; Laphookhieo et al., 2006; Boonnak et al., 2006b; Lee et al., 1981; Gopalakrishnan et al., 1997
144	Globuliferin	Antimicrobial activity against <i>Staphylococcus aureus</i> , <i>Streptococcus faecalis</i> , <i>Klebsiella pneumonia</i> and <i>Escherichia coli</i> ; Antiplasmodial activity against W2 strain of <i>Plasmodium falciparum</i> ; Antioxidant DPPH radical scavenging activity	Ngouela et al., 2005a, 2006
155	($\pm$)-Dicaledol	Antifungal activity against <i>Aspergillus fumigatus</i>	Oger et al., 2003
159	Garcinone D	Inhibitory effect against <i>Mycobacterium tuberculosis</i> ; Antifungal activity against <i>Dreschlera oryzae</i>	Suksamrarn et al., 2003, 2006; Deachathai et al., 2005; Mahabusarakam et al., 2006b; Jung et al., 2006; Gopalakrishnan et al., 1997
160	Pruniflorone C	Antibacterial activity against <i>Bacillus subtilis</i> and <i>Staphylococcus aureus</i>	Boonnak et al., 2006b
163	Pruniflorone E	Antibacterial activity against <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> and <i>Streptococcus faecalis</i>	Boonnak et al., 2006b
165	Nigrolineaxanthone N	Antibacterial activity against MRSA	Rukachaisirikul et al., 2003a
172	Allanxanthone A	Cytotoxic activity against the KB cell line	Nkengfack et al., 2002a; Hay et al., 2003
173	Garciniaxanthone A	Trypanocidal activity against trypomastigotes of <i>Trypanosoma cruzi</i>	Abe et al., 2003; Fukuyama et al., 1991; Minami et al., 1994

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Anexo I

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174	Gerontoxanthone I	Cytotoxicity against HCT-116, SMMC-7721, SGC-7901 and BGC-823 cell lines, particularly strong against MCF-7, HeLa, HT-29 and KB cell lines; Antibacterial activity against <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus faecalis</i> , <i>Salmonella typhi</i> , <i>Shigella sonnei</i> , <i>Pseudomonas aeruginosa</i> , but weaker against five VRE strains (Van A, van B, van C) and MRSA strains; Anti-lipid peroxidative activity in the rat liver homogenate	Fukai et al., 2004, 2005; Hou et al., 2001; Wang et al., 2005; Chang et al., 1994; Boonsri et al., 2006; Boonnak et al., 2006b
175	Alvaxanthone	Cytotoxicity against HCT-116, SMMC-7721, SGC-7901 and BGC-823, HSC-2 and HGF cell lines; Antibacterial activity against five VRE strains (Van A, van B, van C)	Fukai et al., 2004, 2005; Hou et al., 2001; Wang et al., 2005
176	Isoalvaxanthone	Cytotoxicity against HCT-116, SMMC-7721, SGC-7901 and BGC-823, HSC-2 and HGF cell lines; Antibacterial activity against five VRE strains (Van A, van B, van C)	Fukai et al., 2004, 2005; Hou et al., 2001; Wang et al., 2005
177	Cudraxanthone L	Cytotoxicity against A549 and SK-OV3 cell lines, particularly strong against AGS; Strong scavenging effect on the DPPH radical and significant antioxidant activity against LDL oxidation; Inhibit hACAT-2 and hACAT-1	Zou et al., 2005; Lee et al., 2005a, b; Park et al., 2006
178	Cudratricusxanthone A	Cytotoxicity against BGC-823 cells; Strong scavenging effect on the DPPH radical and significant antioxidant activity against LDL oxidation; Inhibition preferentially of hACAT-2 than hACAT-1	Zou et al., 2004; Lee et al., 2005b; Park et al., 2006
179	2,3,6,8-Tetrahydroxy-1-(3-methylbut-2-enyl)-5-(2-methylbut-3-en-2-yl) xanthone	Cytotoxicity against SK-OV3 cell lines	Lee et al., 2005a, b
180	Macluraxanthone C	Inhibitory effects on 4 kinds of human digestive tumor cell lines (HCT-116, SMMC-7721, SGC-7901 and BGC-823); HIV inhibitory activity	Groweiss et al., 2000; Zou et al., 2005; Perez et al., 2003
181	Macluraxanthone B	Inhibitory effects on 4 kinds of human digestive tumor cell lines (HCT-116, SMMC-7721, SGC-7901 and BGC-823) and against A549 and SK-OV3 cell lines; Strong scavenging effect on the DPPH radical and antioxidant activity against LDL oxidation; HIV inhibitory activity; Inhibit hACAT-2 and hACAT-1	Groweiss et al., 2000; Zou et al., 2004, 2005; Lee et al., 2005a, b; Perez et al., 2003; Park et al., 2006
182	Subelliptenone B	Trypanocidal activity against epimastigotes and trypomastigotes of <i>Trypanosoma cruzi</i>	Tosa et al., 1997; Abe et al., 2003
184	Cudraxanthone E	Inhibitory effects on 4 kinds of human digestive tumor cell lines (HCT-116, SMMC-7721, SGC-7901 and BGC-823)	Zou et al., 2005; Wang et al., 2005
185	Cudrafrutixanthone A	Cytotoxicity against HCT-116, SMMC-7721, SGC-7901 and BGC-823 cell lines	Wang et al., 2005
186	Cudraxanthone D	Cytotoxic activity against AGS cell lines; Scavenging effect on the DPPH radical and antioxidant activity against LDL oxidation; Inhibit hACAT-2 and hACAT-1	Lee et al., 2005b; Park et al., 2006

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187	Cudraxanthone C	Superoxide and hydroxyl radical scavenging activities; Inhibition preferentially of hACAT-2 than hACAT-1	Lee et al., 2005b; An et al., 2006; Park et al., 2006
191	Cochinchinone A	Cytotoxic activity against the NCI-H187 cell line	Mahabusarakam et al., 2006b; Laphookhieo et al., 2006
194	Cratoxyarborenone A	Cytotoxic activity against KB cell line.	Seo et al., 2002; Kinghorn et al., 2003
195	Norcowanin	Inhibitory activity on EBV- early antigen activation; Antiplasmodial activity against two strains of <i>Plasmodium falciparum</i> F32 and FcM29; Cytotoxicity against human melanoma cells	Ito et al., 2003b; Pattalung et al., 1994; Azebaze et al., 2006
196	Garcinixanthone E	Trypanocidal activity against trypomastigotes of <i>Trypanosoma cruzi</i> ; Elicited marked enhancement of nerve growth factor-mediated neurite outgrowth in PC12D cells	Chanmahasathien et al., 2003b; Abe et al., 2003; Ohizumi and Li, 2004
197	Virgataxanthone A	Antioxidant activity based on the DPPH free-radical- scavenging	Merza et al., 2004
199	Cochinchinone B	Potent Antioxidant DPPH radical scavenging activity	Mahabusarakam et al., 2006b
202	Cowanin	Inhibitory effect against topoisomerase II; Inhibitory activity on EBV- early antigen activation; Inhibit the acidic sphingomyelinase; Antibacterial activity against <i>Staphylococcus aureus</i> , both penicillin-sensitive strain ATCC 25923 and methicillin-resistant strain MRSA SK1	Tosa et al., 1997; Okudaira et al., 2000; Ito et al., 2003b; Mahabusarakam et al., 2005; Deachathai et al., 2005; Pattalung et al., 1994; Panthong et al., 2006
206	Parvixanthone A	Cytotoxic activity against L1210 murine leukemia cell line	Kardono et al., 2006
207	Cowanol	Antibacterial activity against <i>Staphylococcus aureus</i> , both penicillin-sensitive strain ATCC 25923 and methicillin-resistant strain MRSA SK1; Inhibitory activity on EBV-early antigen activation; Inhibition of acidic sphingomyelinase	Okudaira et al., 2000; Ito et al., 2003b; Mahabusarakam et al., 2005; Pattalung et al., 1994; Panthong et al., 2006
210	Garciniane B	Toxic to brine shrimp	Chiang et al., 2003
212	Allanxanthone C	Antiplasmodial activity against two strains of <i>Plasmodium falciparum</i> F32 and FcM29; Cytotoxicity against human melanoma cells	Azebaze et al., 2006
214	Garcinone E	Antiproliferative activity against human leukemia HL60 cells and potent cytotoxic effect on all HCC cell lines, lung cancer cell lines, gastric cancer cell lines and cytotoxic against KB and BC-1 cell lines	Ho et al., 2002; Matsumoto et al., 2003; Chairungsilard et al., 1996; Iinuma et al., 1996c; Suksamram et al., 2006; Jung et al., 2006
215	Isogarcinixanthone E	Trypanocidal activity against trypomastigotes of <i>Trypanosoma cruzi</i> ; Elicited marked enhancement of nerve growth factor-mediated neurite outgrowth in PC12D cells	Chanmahasathien et al., 2003b; Abe et al., 2003; Ohizumi and Li, 2004

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216	Parvifolixanthone A	Antioxidant DPPH radical scavenging activity	Rukachaisirikul et al., 2006
217	7-O-Methylgarcinone	Inhibitory activity on EBV- early antigen activation; Antibacterial activity against <i>Staphylococcus aureus</i> , both penicillin-sensitive strain ATCC 25923 and methicillin-resistant strain MRSA SK1	Ito et al., 2003b; Panthong et al., 2006
218	Subelliptenone A	Trypanocidal activity against trypomastigotes of <i>Trypanosoma cruzi</i>	Abe et al., 2003
224	Laurentixanthone A	Antibacterial and Antifungal activities against <i>Streptococcus faecalis</i> and <i>Candida glabrata</i> , respectively	Nguemaving et al., 2006
225	Brasixanthone B or Cudraxanthone Q	Inhibitory activity against TPA-induced EBV- early antigen activation in Raji cells	Ito et al., 2002; Hou et al., 2001
226	Ananixanthone	Antibacterial activity against MRSA; Activity against a chloroquine-resistant strain of <i>Plasmodium falciparum</i> ; Activity against <i>Trypanosoma cruzi</i>	Rukachaisirikul et al., 2003a; Morel et al., 2002b; Molinar-Toribio et al., 2006
227	Calothwaitesixanthone	Potent antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i>	Hay et al., 2003; Dharmaratne et al., 1999, 2002; Hay et al., 2004b
229	Demethylcalabaxanthone	Inhibitory effect against <i>Mycobacterium tuberculosis</i> ; Potent antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i>	Suksamrarn et al., 2003, 2006; Hay et al., 2004b
230	Trapezifolixanthone or Toxyloxanthone A	Inhibitory effect against <i>Mycobacterium tuberculosis</i> ; Cytotoxic activity against KB cell line; Activity against a chloroquine-resistant strain of <i>Plasmodium falciparum</i>	Suksamrarn et al., 2003; Seo et al., 1999; Ito et al., 1998, 2002; Dharmaratne et al., 1999; Molinar-Toribio et al., 2006
233	Caloxanthone A	Antibacterial activity against MSSA and <i>Staphylococcus aureus</i>	Tosa et al., 1997; Yimdo et al., 2004; Iinuma et al., 1996c
236	Cudraticusxanthone D	Cytotoxicity against HCT-116, SMMC-7721 and SGC-7901 cell lines	Zou et al., 2004
237	Xanthone VI	Antibacterial activity against <i>Pseudomonas aeruginosa</i> , <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus faecalis</i> , <i>Salmonella typhi</i> ; Cytotoxic against HeLa, HT-29 and KB cell lines	Ito et al., 1998; Boonsri et al., 2006; Boonnak et al., 2006b; Chantapromma et al., 2005
239	Garcinone B	Strong inhibitory effect against <i>Mycobacterium tuberculosis</i> ; Reduction of prostaglandin E ₂ release and NF- κ B-mediated transcription in C6 rat glioma cells	Suksamrarn et al., 2003, 2006; Ito et al., 2002; Deachathai et al., 2005, 2006; Mahabusarakam et al., 2006b; Yamakuni et al., 2006

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242	Brasixanthone A	Inhibitory activity against TPA-induced EBV- early antigen activation in Raji cells	Ito et al., 2002
245	1,6-Dihydroxy-8-isoprenyl-7-methoxy-6',6'-dimethylpyrano[2',3':3,2]xanthone	Inhibitory effect against <i>Mycobacterium tuberculosis</i>	Suksamrarn et al., 2003, 2006; Chairungsilord et al., 1996
246	Manglexanthone	Cytotoxic activity against KB cell line	Seo et al., 1999
249	Symphonin	Antimicrobial activity against <i>Staphylococcus aureus</i> , <i>Streptococcus faecalis</i> , <i>Klebsiella pneumonia</i> and <i>Escherichia coli</i> ; Anti-plasmodial activity against W2 strain of <i>Plasmodium falciparum</i> ; Antioxidant DPPH radical scavenging activity	Lenta et al., 2004; Ngouela et al., 2006
250	Gaboxanthone	Antiplasmodial activity against W2 strain of <i>Plasmodium falciparum</i> ; Antioxidant DPPH radical scavenging activity	Ngouela et al., 2006
253	Mangostenone D	Cytotoxic activity against BC-1 cell line	Suksamrarn et al., 2006
257	Mangostanol	Inhibitory activity against cAMP phosphodiesterase; Cytotoxic activity against the human cancer cell line, NCI-H187	Suksamrarn et al., 2003, 2006; Lu et al., 1998; Chairungsilord et al., 1996
260	6,11-Dihydroxy-3-methyl-3-(4-methylpent-3-enyl)-3H,7H-pyrano[2,3-c] xanthen-7-one	Growth inhibitory activity against human colon carcinoma cell lines: Co 115, SW 480, SW 620; Active against <i>Trypanosoma brucei</i> and <i>cruzi</i>	Diserens et al., 1992; Brühlmann et al., 2004; Mbwambo et al., 2006
263	Globulixanthone B	Cytotoxic activity against the KB cell line	Nkengfack et al., 2002
264	Bangangxanthone A	Antioxidant DPPH radical scavenging activity	Lannang et al., 2005
265	Smeathxanthone B	Antimicrobial activity (antibacterial and antifungal)	Komguem et al., 2005
267	Globulixanthone E	Antimicrobial activity against <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> and <i>Vibrio anguillarum</i>	Nkengfack et al., 2002c
268	Dombakinaxanthone	Antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i>	Hay et al., 2004b
272	Latisxanthone C	Inhibition of EBV- early antigen activation	Ito et al., 1998, 2002
274	Cowaxanthone C	Antibacterial activity against <i>Staphylococcus aureus</i> , both penicillin-sensitive strain ATCC 25923 and methicillin-resistant strain MRSA SK1	Panthong et al., 2006
281	Mangostenone A	Inhibitory effect against <i>Mycobacterium tuberculosis</i>	Suksamrarn et al., 2003
282	Tovophyllin	Inhibitory effect against <i>Mycobacterium tuberculosis</i>	Suksamrarn et al., 2003

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294	Brasixanthone C	Inhibitory activity against TPA-induced EBV- early antigen activation in Raji cells	Ito et al., 2002
295	Brasixanthone D	Inhibitory activity against TPA-induced EBV- early antigen activation in Raji cells	Ito et al., 2002
298	Caloxanthone C or Inoxanthone	Antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i>	Tosa et al., 1997; Yimdjo et al., 2004; Hay et al., 2004b
299	Inophyllin A	Toxic activity against the larvae of <i>Aedes aegypti</i>	Ee et al., 2006a
300	Blancoxanthone	Anti-coronavirus activity	Shen et al., 2005
303	Garciniaxanthone B	Trypanocidal activity against epimastigotes and trypomastigotes of <i>Trypanosoma cruzi</i> ; Enhancement of choline acetyltransferase activity in a cultured neuronal cell of foetal rat brain hemisphere	Chanmahasathien et al., 2003a; Abe et al., 2003; Fukuyama et al., 1991; Minami et al., 1994
304	Macluraxanthone	Strong inhibition of PAF receptor binding; Antibacterial activity against <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus faecalis</i> , <i>Salmonella typhi</i> and against MSSA; Antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i> ; Potent antioxidant DPPH radical scavenging activity	Tosa et al., 1997; Jantan et al., 2001, 2002; Yimdjo et al., 2004; Hay et al., 2004b; Hou et al., 2001; Wu et al., 2003; Iinuma et al., 1996c; Boonsri et al., 2006; Mahabusarakam et al., 2006b
305	Gerontoxanthone B	Cytotoxicity against HCT-116, SMMC-7721, SGC-7901 and BGC-823 cell lines	Fukai et al., 2004, 2005; Hou et al., 2001; Wang et al., 2005; Boonnak et al., 2006b
306	Cudraticusxanthone H	Significant inhibitory effects on 4 kinds of human digestive tumor cell lines (HCT-116, SMMC-7721, SGC-7901 and BGC-823)	Zou et al., 2004, 2005
309	1,3,5-Trihydroxy-6,6'-dimethylpyrano-(2',3':6,7)-4-(1,1-dimethylprop-2-enyl)xanthone	Inhibition of PAF receptor binding	Jantan et al., 2001, 2002;
310	1,3,7-Trihydroxy-4-(1,1-dimethyl-2-propenyl)-5,6-(2,2-dimethylchromeno)xanthone	Superoxide and hydroxyl radical scavenging activities and significant antioxidant activity against LDL oxidation; Inhibit preferentially of hACAT-2 than hACAT-1	Lee et al., 2005b; Park et al., 2006
324	Gerontoxanthone C	Cytotoxicity against HCT-116, SMMC-7721, SGC-7901 and BGC-823 cell lines; Anti-lipid peroxidative activity in the rat liver homogenate	Wang et al., 2005; Chang et al., 1994

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325	Gerontoxanthone G	Cytotoxicity against HCT-116, SMMC-7721, SGC-7901 and BGC-823 cell lines	Fukai et al., 2004, 2005; Hou et al., 2001; Wang et al., 2005; Chang et al., 1994
326	Cudraticusxanthone F	Inhibitory effects on 4 kinds of human digestive tumor cell lines (HCT-116, SMMC-7721, SGC-7901 and BGC-823)	Zou et al., 2004, 2005
327	Cudraxanthone M	Strong scavenging effect on the DPPH radical and significant antioxidant activity against LDL oxidation; Inhibitory effects on human digestive tumor cell lines (HCT-116, SMMC-7721, SGC-7901 and BGC-823) and strong cytotoxicity against AGS; Inhibition preferentially of hACAT-2 than hACAT-1	Zou et al., 2004; Lee et al., 2005b; Park et al., 2006
328	Formoxanthone C	Antibacterial activity against <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus faecalis</i> , <i>Salmonella typhi</i> ; Cytotoxicity against MCF-7, HeLa, HT-29 and KB cell lines	Boonsri et al., 2006
338	Mangostanin	Inhibitory effect against <i>Mycobacterium tuberculosis</i> ; Strong antibacterial activity against <i>Staphylococcus aureus</i> , both penicillin-sensitive strain ATCC 25923 and methicillin-resistant strain MRSA SK1	Suksamram et al., 2003, 2006; Panthong et al., 2006
340	Mangostenone C	Cytotoxic activity against 3 human cancer cell lines: KB, BC-1 and NCI-H187	Suksamram et al., 2006
341	Cratoxyborenone D	Cytotoxic activity against KB cell line	Seo et al., 2002; Kinghorn et al., 2003
343	Cudraticusxanthone C	Cytotoxicity against SMMC-7721 and HCT-116 cell lines	Zou et al., 2004
344	Rheedixanthone B	Cytotoxic activity against KB cell line	Thoisson et al., 2000
346	Garciniaxanthone F	Antioxidant activity; Inhibitory activity of lipid peroxidation	Minami et al., 1996
347	Garciniaxanthone D	Antioxidant activity; Inhibitory activity of lipid peroxidation; O ₂ ⁻ scavenging activity	Minami et al., 1996
349	Garciniaxanthone G	Antioxidant activity; Inhibitory activity of lipid peroxidation	Minami et al., 1996
363	6-Deoxyjacareubin	Trypanocidal activity against epimastigotes and trypomastigotes of <i>Trypanosoma cruzi</i> ; Inhibition of PAF receptor binding; Inhibition of dog gastric H ⁺ , K ⁺ -ATPase activity; Antibacterial activity against <i>Staphylococcus aureus</i>	Abe et al., 2004; Tosa et al., 1997; Jantan et al., 2001, 2002; Ito et al., 2002; Chilpa et al., 1997; Hou et al., 2001; Yasunaka et al., 2005; Locksley et al., 1971; Wu et al., 2003; Doriguetto et al., 2001; Reyes-Chilpa et al., 2006; Boonnak et al., 2006b

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364	6-Deoxyisojacareubin	Antifungal activity against <i>Aspergillus fumigatus</i>	Wu et al., 1998; Morel et al., 2002b; Nguemaving et al., 2006
365	Rheediachromenoxanthone	Cytotoxicity against P-388 cell line	Chen et al., 2004
371	Jacareubin	Activity against <i>Staphylococcus aureus</i> ; moderate activity against <i>Escherichia coli</i> ; Trypanocidal activity against epimastigotes and trypomastigotes of <i>Trypanosoma cruzi</i> ; Antifungal activity against the brown rot fungus <i>Postia placenta</i> and against <i>Cladosporium cucumerinum</i> and <i>Candida albicans</i> ; Inhibited dog gastric H ⁺ , K ⁺ -ATPase activity	Abe et al., 2004; Ito et al., 1998; Chilpa et al., 1997; Yasunaka et al., 2005; Jefferson and Scheinmann, 1996; Cortez et al., 1998; Wu et al., 2003; Reyes-Chilpa et al., 2006
373	Isojacareubin	Anticoagulation of activated partial thromboplastin time	Rath et al., 1996; Wu et al., 1998
377	Globulixanthone C	Antimicrobial activity against <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i>	Nkengfack et al., 2002c
379	Linixanthone B	Cytotoxicity against P-388 and HT-29 cell lines	Chen et al., 2004
381	Caledonixanthone E	Activity against the human pathogenic fungus <i>Aspergillus fumigatus</i> and <i>A. flavus</i>	Larcher et al., 2004; Morel et al., 2002b
385	5-O-Methylisojacareubin	Antifungal activity against <i>Candida albicans</i>	Rath et al., 1996
386	Dulxanthone F	Cytotoxic activity against L1210 murine leukemia cell line	Kardono et al., 2006
387	Dulxanthone G	Cytotoxic activity against L1210 murine leukemia cell line	Kardono et al., 2006
390	Dulxanthone E	Cytotoxic activity against L1210 murine leukemia cell line	Kardono et al., 2006
396	Hyperxanthone E	Activity as inhibitors of human tumor cell replication: A549 and MCF-7 cell lines	Tanaka et al., 2004
399	Pyranojacareubin	Anti-coronavirus activity	Ito et al., 1998, 2002; Shen et al., 2005
408	Calozeyloxanthone	Activity against MRSA; Antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i>	Pinheiro et al., 2003b; Hay et al., 2003, 2004b; Dharmaratne et al., 1999, 2002
416	Varixanthone	Antimicrobial activity against Gram positive and Gram negative bacteria	Malmström et al., 2002
418	Tajixanthone hydrate	Cytotoxic activity against KATO3, SW620, BT474, HEP-G2 and CHAGO cell lines	Malmström et al., 2002; Pornpakakul et al., 2006
419	14-Methoxytjixanthone-25-acetate	Cytotoxic activity and selectivity against KATO3, SW620 and BT474 cell lines	Pornpakakul et al., 2006
420	Tajixanthone methanoate	Cytotoxic activity and selectivity against KATO3, SW620 and BT474 cell lines	Pornpakakul et al., 2006

Table 2 Contd.

Table 2 Contd.

421	Shamixanthone	Cytotoxic activity and selectivity against KATO3, SW620 and BT474 cell lines	Malmström et al., 2002; Bringmann et al., 2003; Kralj et al., 2006; Pornpakakul et al., 2006
423	Gerontoxanthone A	Hepatoprotective effect against tacrine-induced cytotoxicity in Hep G2 cells	Fukai et al., 2004, 2005; Hou et al., 2001; Wang et al., 2005; Chang et al., 1994; An et al., 2006
426	Artoindonesianin C	Antimycobacterial activity against <i>Mycobacterium tuberculosis</i> ; Cytotoxic against the KB, BC and NCI-H187 cells	Namdaung et al., 2006
427	Artonol B	Antimycobacterial activity against <i>Mycobacterium tuberculosis</i> ; Cytotoxic against the NCI-H187 cell	Namdaung et al., 2006
431	Toxyloxanthone C	Cytotoxicity against HCT-116, SMMC-7721, SGC-7901 and BGC-823 cell lines; Antifungal activity against <i>Cryptococcus neoformans</i> , <i>Aspergillus fumigatus</i> , <i>A. nidulans</i> , <i>Candida glabrata</i> and <i>Candida albicans</i> ; Antibacterial activity against MRSA strains	Fukai et al., 2003, 2004, 2005; Zou et al., 2004; Hou et al., 2001; Wang et al., 2005
432	2-Deprenylrheediexanthone B	Antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i> ; Antifungal activity against <i>Candida albicans</i>	Rath et al., 1996; Hay et al., 2004b
434	Cudratricusxanthone I	Cytotoxicity against gastric carcinoma cell lines: SGC-7901 and BGC-823	Zou et al., 2005
437	5-O-Methyl-2-deprenylrheediexanthone B	Antifungal activity against <i>Candida albicans</i>	Rath et al., 1996; Hay et al., 2004a; Ji et al., 2005
438	Gerontoxanthone D	Antilipid peroxidative activity, in the rat liver homogenate	Chang et al., 1994
440	Caloxanthone F	Antifungal activity against <i>Aspergillus fumigatus</i>	Morel et al., 2002b
446	1,3,5-Trihydroxy-2-(2',2'-dimethyl-4'-isopropenyl)cyclopentanylxanthone	Antioxidant activity based on the DPPH free-radical-scavenging	Turro et al., 2004
447	5-O-Deethylpaxanthonin	Antioxidant activity based on the DPPH free-radical-scavenging; Antifungal activity against <i>Candida albicans</i>	Rath et al., 1996; Turro et al., 2004; Yamakuni et al., 2006
451	Griffipavixanthone	Antioxidant activity based on the DPPH free-radical-scavenging	Merza et al., 2004
453	Cochinchinone C	Cytotoxic activity against the NCI-H187 cell line; Antimalarial activity against <i>Plasmodium falciparum</i>	Mahabusarakam et al., 2006b; Laphookhieo et al., 2006
455	Bractatin	Cytotoxic activity against KB cell line and FPTase	Thoisson et al., 2000; Nicolaou and Li, 2001
456	Isobractatin	Cytotoxic activity against KB cell line and FPTase	Thoisson et al., 2000

Table 2 Contd.

Table 2 Contd.

457	1-O-Methylbractatin	Cytotoxic activity against KB cell line	Thoisson et al., 2000; Nicolaou and Li, 2001
458	1-O-Methylsobractatin	Cytotoxic activity against KB cell line	Thoisson et al., 2000
459	1-O-Methyl-8-methoxy-8,8a-dihydrobractatin	Cytotoxic activity against KB cell line	Thoisson et al., 2000
460	1-O-Methylnobractatin	Cytotoxic activity against KB cell line	Thoisson et al., 2000; Nicolaou and Li, 2001
461	Neoisobractatin A	Cytotoxic activity on KB cell line	Thoisson et al., 2005
462	Neoisobractatin B	Cytotoxic activity on KB cell line	Thoisson et al., 2005
466	Gaudichaudiic acid F	Cytotoxicity to the P388 cell line	Xu et al., 2000
467	Gaudichaudiic acid G	Cytotoxicity to the P388, P388/DOX and to the Messa cell lines	Xu et al., 2000
468	Gaudichaudiic acid H	Cytotoxicity to the P388, P388/DOX and to the Messa cell lines	Xu et al., 2000
469	Gaudichaudiic acid I	Cytotoxicity to the P388, P388/DOX and to the Messa cell lines	Xu et al., 2000
470	Gaudichaudione A	Growth inhibitory effect against Jurkat human leukemic cells, parental murine leukemic P388 and P388/DOX-resistant cell lines and cytotoxicity against P388/DOX as well as P388, WEHI1640, MOLT4, HePG2 and LL/2 cell lines	Wu et al., 2002
471	Deoxygaudichaudione A	Cytotoxicity against human leukemia K562 and K562/ADR cell lines	Han et al., 2006a
472	Gaudichaudiic acid	Cytotoxicity against human leukemia K562 and K562/ADR cell lines	Han et al., 2006a
473	Isogambogenic acid	Cytotoxicity against human leukemia K562 and K562/ADR cell lines	Han et al., 2006a
476	Gaudichaudione B	Cytotoxic activity against P388, WEHI1640, MOLT4, HePG2 and LL/2 cell lines	Cao et al., 1998
477	Gaudichaudione C	Cytotoxic activity against P388, WEHI1640, MOLT4, HePG2 and LL/2 cell lines	Cao et al., 1998
479	Gaudichaudione D	Cytotoxic activity against P388, WEHI1640, MOLT4, HePG2 and LL/2 cell lines	Cao et al., 1998
480	Gaudichaudione E	Cytotoxic activity against P388, WEHI1640, MOLT4, HePG2 and LL/2 cell lines	Cao et al., 1998
481	Gaudichaudione F	Cytotoxic activity against P388, WEHI1640, MOLT4, and LL/2 cell lines	Cao et al., 1998
482	Gaudichaudione G	Cytotoxic activity against P388, WEHI1640, MOLT4, HePG2 and LL/2 cell lines	Cao et al., 1998
484	Gaudichaudiic acid A	Cytotoxic activity against P388, WEHI1640, MOLT4, HePG2 and LL/2 cell lines	Cao et al., 1998

Table 2 Contd.

Table 2 Contd.

488	Gaudichaudiic acid E	Cytotoxic activity against P388, WEHI1640, MOLT4, HePG2 and LL/2 cell lines	Cao et al., 1998
489	Hanburinone	Antibacterial activity against methicillin-resistant <i>Staphylococcus aureus</i>	Sukpondma et al., 2005
490	Isomoreollin B	Antibacterial activity against methicillin-resistant <i>Staphylococcus aureus</i>	Sukpondma et al., 2005
491	Morellic acid	Antibacterial activity against methicillin-resistant <i>Staphylococcus aureus</i>	Sukpondma et al., 2005
492	Morellic acid	Antibacterial activity against methicillin-resistant <i>Staphylococcus aureus</i> ;	Sukpondma et al., 2005;
		Cytotoxicity against human leukemia K562 and K562/ADR cell lines	Han et al., 2006a
493	Isomorellic acid	Cytotoxicity against human leukemia K562 and K562/ADR cell lines	Han et al., 2006a
494	Morellin	Antibacterial activity against methicillin-resistant <i>Staphylococcus aureus</i>	Nicolaou and Li, 2001;
			Sukpondma et al., 2005
495	Gambogic acid	Potent apoptosis inducer by a HTS assay; Cytotoxic against KB, drug-resistant KB-V1 and human leukemia K562 and K562/R cell lines; Inhibition of human telomerase reverse transcriptase gene expression in human hepatoma SMMC-7721 cells	Zhang et al., 2004; Lin et al., 1993; Han et al., 2006a,b; Guo et al., 2006
496	Isogambogic acid	Cytotoxic against KB and drug-resistant KB-V1 cell lines	Lin et al., 1993; Han et al., 2006a
497	30-Hydroxygambogic acid	Cytotoxicity against the human leukemia K562 and K562/R cell lines	Han et al., 2006c
498	30-Hydroxyepigambogic acid	Cytotoxicity against the human leukemia K562 and K562/R cell lines	Han et al., 2006c
499	Isomorellinol	Cytotoxic against KB, drug-resistant KB-V1 and human leukemia K562 and K562/R cell lines	Lin et al., 1993; Han et al., 2006a
504	Scortechinone B	Antibacterial activity against MRSA	Rukachaisirikul, 2000, 2005
505	Scortechinone C	Antibacterial activity against MRSA	Rukachaisirikul et al., 2000

Abbreviations: ATCC = American Type Culture Collection; cAMP = cyclic adenosine monophosphate; DPPH = 2,2-diphenyl-1-picrylhydrazyl; hACAT = Human Acyl-CoA: cholesterol acyltransferase; HIV = Human immunodeficiency virus; LDL = Low-density lipoprotein; MAO A = Monoamine oxidase A; MAO B = Monoamine oxidase B; MRSA = Methicillin-Resistant *Staphylococcus aureus*; MSSA = Methicillin-Sensitive *Staphylococcus aureus*; TPA = 12-O-tetradecanoylphorbol-13-acetate; VRE = Vancomycin-Resistant *Enterococci*. **Cell lines:** A375 = Human melanoma; A549 = Human lung cancer; AGS = Human gastric cancer; BC-1 = Breast cancer; BGC-823 = Gastric carcinoma; BT474 = Breast carcinoma; CHAGO = Lung carcinoma; HCC = Liver carcinoma; HCT-116 = Human colon carcinoma; HeLa = Human uterine carcinoma; HEP-G2 = Human hepatocellular carcinoma; HGF = Human gingival fibroblasts; HSC-2 = Human oral squamous cell carcinoma; HT-29 = Human colon carcinoma; K562 = Human leukemia; K562/ADR = Human adriamycin-resistant leukemia; K562/R = Human resistant leukemia; KATO3 = Gastric carcinoma; KB = Human epidermoid carcinoma of the nasopharynx; LL/2 = Lewis lung carcinoma; MCF-7 = Breast adenocarcinoma; Messa = Human leukemia; MOLT4 = Human lymphoblastic leukemia; NCI-H187 = National cancer institute human small cell lung cancer; P-388 = Mouse lymphocytic leukemia; P-388/DOX = Mouse doxorubicin-resistant lymphocytic leukemia; PC12D = pheochromocytoma; SGC-7901 = Gastric carcinoma; SK-OV3 = Human ovarian cancer; SMMC-7721 = Hepatocellular carcinoma; SW620 = Colon carcinoma; WEHI1640 = Fibrosarcoma

Ito et al. (1998), on screening for the inhibitory effects on EBV-early antigen activation induced by 12-*O*-tetradecanoylphorbol-13-acetate in Raji cells of 20 xanthones isolated from the plants of the Gutierrez family, have found that 1,3,7-trihydroxy-2-(3-methyl-2-butenyl)xanthone (**24**), dulxanthone-B (**138**) and laisxanthone-C (**272**) (**Figure 25**) were significantly active, indicating that these compounds might be valuable antitumor promoters.

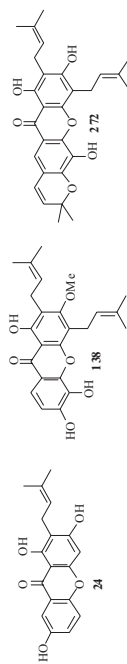


Fig. 25 Structures of 1,3,7-Trihydroxy-2-(3-methyl-2-butenyl)xanthone (**24**), Dulxanthone-B (**138**) and Laisxanthone-C (**272**)

From the structure-activity relationship point of view, the presence of the 1,3-dioxygenated xanthone skeleton with a prenyl group either at C-2 or at both C-2 and C-4 is required for the more potent inhibitory activity (Ito et al., 1998). Further studies with eight xanthones isolated as major components from *Garcinia fusca*, resulted in a discovery of more three potent derivatives (Ito et al., 2003b). Among these, 7-*O*-methylgarcinone (**217**), having three prenyl substituents at C-2, C-5, and C-8, exhibited the most potent inhibitory activity, followed by β -mangostin (**142**) and α -mangostin (**141**), both with two prenyl substituents at C-2 and C-8 of the xanthone scaffold. It is interesting to observe that all the three xanthones possess the methoxy group on C-7.

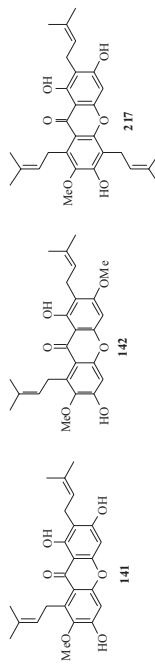


Fig. 26 Structure of α -Mangostin (**141**), β -Mangostin (**142**) and 7-*O*-Methylgarcinone (**217**)

As can be observed, besides the presence of hydroxyl group at C-6 and methoxyl group at C-7, all of these xanthones (**141**, **142**, **217**) also possess the oxygenated substituents at C-1 and C-3 as well as a prenyl group on C-2, a common structural feature found in the active xanthones previously studied (**24**, **138** and **272**) by Ito et al., 1998.

From the SAR studies by Ito et al. (1998, 2003b), some structural features associated with the decrease of activity are:

- The presence of only 1,1-dimethylallyl group at C-4 of the 1,3-dihydroxyxanthone nucleus;
- A dimethylpyran ring fused with the 1-hydroxy-2-(3-methyl-2-butenyl)xanthone nucleus at C-3 /C-4;

- A dimethylpyran ring or a dihydrofuran ring fused with the xanthone nucleus at C-2/C-3 or C-3/C-4.

From the SAR studies, we propose the putative pharmacophoric data for inhibitory effects on EBV are shown in **Figure 27**:

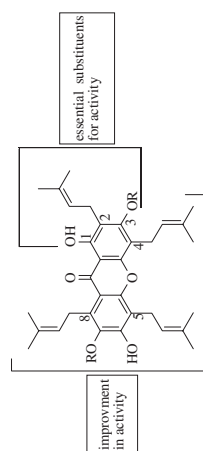


Fig. 27 Putative Pharmacophoric Data for Inhibitory Effects on EBV

6.2 Cytotoxic Activity

The capacity of the compounds to inhibit the *in vitro* growth of several human tumor cell lines, usually referred as cytotoxic effect, is normally used to evaluate their potential antitumor effect which may be due to an interference with several biological processes.

The cytotoxic activity of several prenylated xanthones, isolated from *Cudrania tricuspidata* (Moraceae) (**Figure 28**), have been investigated for their inhibitory effects on four types of human digestive apparatus tumor cell lines, including human colon carcinoma (HCT-116), hepatocellular carcinoma (SMC-7721) and gastric carcinomas (SGC-7901 and BGC-823) (Zou et al., 2004).

The results showed that:

- Xanthones **6**, **124**, **327**, and **431** exhibited significant inhibitory effects on all four types of tumor cell lines;
- Xanthones **123**, **125** and **236** displayed prominent cytotoxicity against HCT-116, SMMC-7721 and SGC-7901 but insignificant activity against BGC-823.

Some xanthones were found to exhibit selectivity for some tumor cell lines:

- Xanthone **113** exhibited higher cytotoxicity against SGC-7721 than BGC-823 and SMMC-7721 and no cytotoxicity against HCT-116;
- Xanthone **343** was potent against HCT-116 and SMMC-7721 but inactive against SGC-7901 and BGC-823;
- Xanthone **178** only exerted weak activity against BGC-823;

From the above-mentioned activities, some features for structure-activity relationship can be observed:

- Most active xanthones (**6**, **113**, **123**, **124**, **125**, **236** and **431**) have one or two hydrophobic groups (i.e. isoprenoid unit) on one aromatic ring and one or two hydrophilic groups (i.e. hydroxyl) on another aromatic domain;

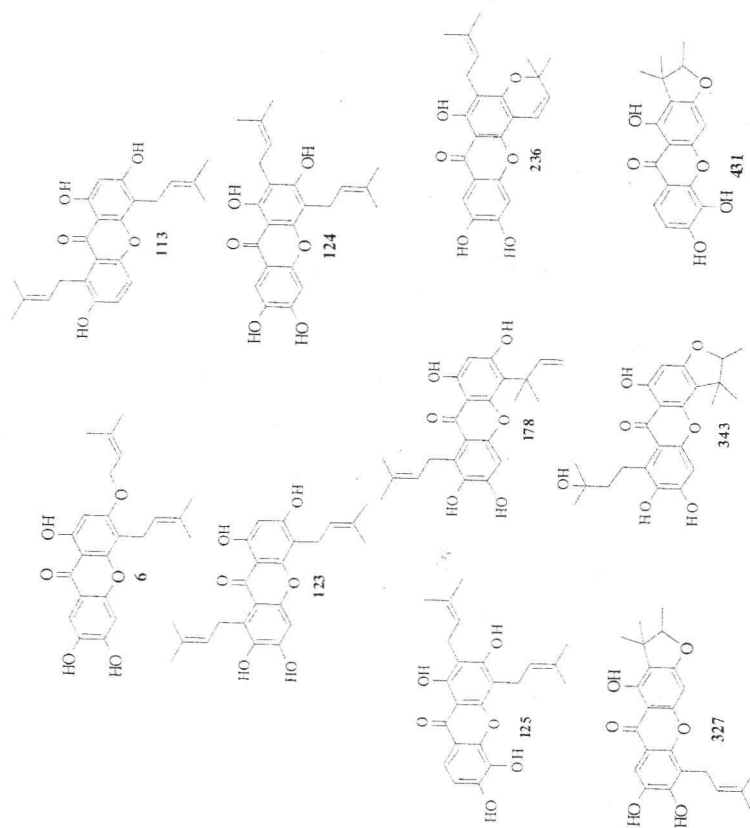


Fig. 28 Structure of the Xanthenes Isolated from *Cudrania tricuspidata* (Moraceae)

- The substituent at C-8 seems to have little or no effect on the cytotoxicity;
- Less active compounds (178 and 343) have the 1,1-dimethylallyl substituent at C-4 or a 2,3,3-trimethylfuran ring at C-3/C-4 (resulting from cyclization between a 1,1-dimethylallyl group and a hydroxyl group on the aromatic ring).

Further study on seven xanthenes, also from *Cudrania tricuspidata*, was carried out by Zou et al (2005) for the same tumor cell lines and it was found that the most active compounds were 180, 181, 306 and 326 (Figure 29). These results confirmed the SAR proposed previously by the same authors (Zou et al., 2004).

Anexo I

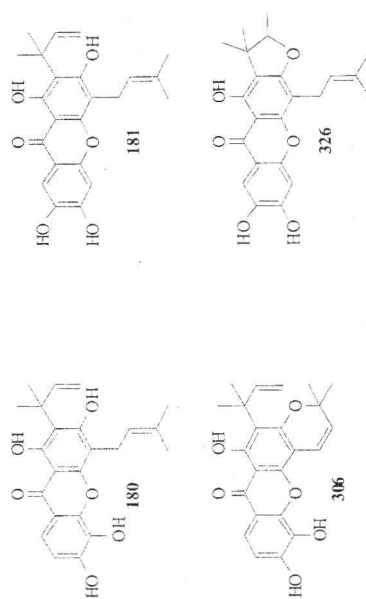


Fig. 29 Structure of Compounds 180, 181, 306 and 326, Isolated from *Cudrania tricuspidata*

Consequently, we propose the putative pharmacophoric data for cytotoxic activity as shown in Figure 30;

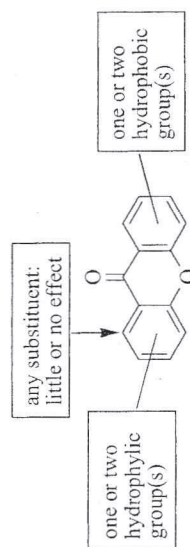


Fig. 30 Putative Pharmacophoric Data for Cytotoxic Activity of Prenylated Xanthenes

6.3 Apoptosis Induction

Apoptosis, or programmed cell death, is an important event in normal cell development and tissue homeostasis. Caspases play a crucial role in the execution of apoptosis being caspase 3 the key enzyme with an important role in both major pathways that activate apoptosis. It has been found that many cancer cells lack the capacity to undergo apoptosis because the inexistence of molecular machinery to activate the caspase cascade.

Interesting results for antitumor activity of prenylated xanthenes from *Garcinia* species were found to be related to complex caged structures with a peculiar mechanism of action on apoptosis induction. The isolation and cytotoxic activity of gaudichaudione A (470) and gambogic acid (495) (Figure 31), isolated from *Garcinia gaudichaudii* and the dry resin obtained from *Garcinia hanburyi* tree respectively, were reported in the 90's (Asano et al., 1996).

However, the studies of the mechanism of action of these compounds as antitumor agents were carried out some years later. Thus, gaudichaudione A (470) was reported to induce apoptosis in Jurkat cells through mitochondrial destabilization and caspase-3 activation (Wu et al., 2002) while gambogic acid (495) was shown to be a potent apoptosis inducer by a high throughput assay (Zhang et al., 2004).

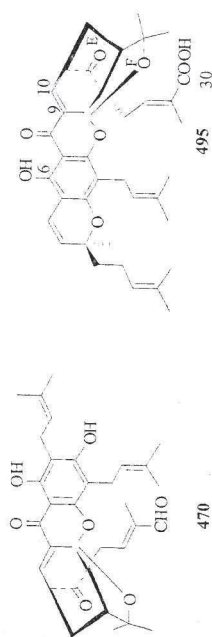


Fig. 31 Structure of Gaudichaudione A (470) and Gambogic Acid (495)

The extract of gamboge contains a group of compounds collectively known as gambogic acids with gambogic acid (495) as a main component. Gambogic acid (495) possesses a unique 4-oxatricyclo[4.3.1.0]decan-2-one ring system. The mechanism of action of gamboge extract was investigated by using the experimental tumor SMMC-7721 in nude mice and *in vitro* cell culture. Besides the growth inhibition of the tumor cells, other studies related to inhibition of the telomerase were carried out. It was found that gambogic acids drastically inhibited the telomerase activity of the human hepatoma cell line SMMC-7721. Interestingly, the proliferation of tumor cells can be reduced or even stopped by inhibition of telomerase suggesting that this is one of the mechanisms of action of gambogic acids for their antitumor effect (Guo et al., 2004; Wu et al., 2004). Further studies showed that gambogic acid (495) treatment of SMMC-7721 significantly reduced the expression of c-MYC, a ubiquitous transcription factor involved in the control of cell proliferation and differentiation, in a time- and concentration-dependent manner accompanied with the down-regulation of the human Telomerase Reverse Transcriptase (hTERT) transcription and the ultimate reduction in telomerase activity (Guo et al., 2006a; Yu et al., 2006). The authors concluded that human Telomerase Reverse Transcriptase was a target of c-MYC activity (Guo et al., 2006a; Yu et al., 2006).

Gambogic acid (495) was discovered by using caspase-based high-throughput screening assays, as a potent apoptosis inducer with a novel mechanism of action and independent of cell cycle. The apoptosis-inducing activity was further characterized by a nuclear fragmentation assay and flow cytometry analysis in human breast tumor cells T47D. Gambogic acid (495) was found to induce apoptosis and activate caspases in T47D cells. The level of its activation is one of the highest observed, indicating that this compound is highly effective in activating caspases in cells.

In order to study the structure-activity relationship (SAR) of gambogic acid (495), several derivatives of this compound were obtained (Zhang et al., 2004) by modifying functional groups in 6, 9, and 30 positions indicated in **Figure 32**. It is important to point out also that in this SAR study; only the induction of apoptosis through the caspase activation assay was considered (Zhang et al., 2004).

The results from the SAR studies of gambogic acid (495) revealed that:

- 6-Hydroxyl and C-30 carboxyl group can tolerate a variety of modifications. Though 6-hydroxyl group is not important for activity, it is involved in a strong intra-molecular hydrogen bonding with the C-8 carbonyl group;
- The carboxyl group was found to tolerate many modifications (esters, amides) and even large modifications are well tolerated. This is an indication that the carboxy moiety is not

probably involved in important interactions with biological targets. Besides, the carboxyl group is located on the "hydrophilic face" of the molecule. From these data it can be inferred that "hydrophilic face" is less important for biological activity than the "hydrophobic face" where the two prenyl chains and the rings E and F are positioned;

- The double bond between C-9 and C-10 of the α,β -unsaturated ketone is important for biological activity.

Compounds lacking the double bond between C-9 and C-10 are not active in T47D cells, indicating that this double bond in the α,β -unsaturated ketone is critical not only for cytotoxicity but also for apoptosis-inducing activity, leading to the conclusion that the caged molecular moiety is crucial for biological activity.

From these results, putative pharmacophoric data for cytotoxic activity and apoptosis induction are summarized in **Figure 32**:

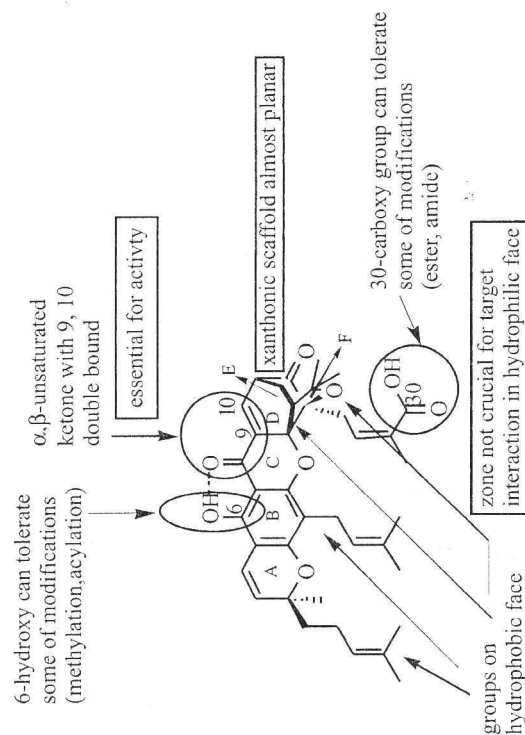


Fig. 32 Putative Pharmacophoric Data for Cytotoxic and Apoptosis Induction Activities for Derivatives of Gambogic Acid (495)

As gambogic acid (495) has a different mechanism of action from many of the current anticancer drugs, it is possible that gambogic acid (495) induces apoptosis in two steps.

After the interaction of gambogic acid (495) with molecular target(s), a nucleophile presented in the target could attack the carbon-carbon double bond in the α,β -unsaturated ketone. This type of Michael addition would result in a covalent attachment of gambogic acid (495) to its target which then activates the apoptosis signal and leads to the activation of caspase cascade and cell death.

As gambogic acid (**495**) showed a potential interest in therapeutics, evaluation on pharmacokinetics (Hao et al., 2005a,b) and toxicological studies on acute and chronic toxicity using albino mice and Beagle dogs as model animals of this compound have been performed (Guo et al., 2006b). The results showed that gambogic acid (**495**) could be administered via intraperitoneal injection, every two days, in a dose higher than that normally used for human trials, which is a good theoretical approach for future clinical application.

6.4 Antimicrobial Activity

Bacterial and fungal resistance to antibiotics has become a serious problem in the treatment of infectious diseases. Particularly worrying is the increase in incidences of the infections by opportunistic fungi, especially in patients whose immune systems are compromised by AIDS, cancer and diabetes, as well as by the multidrug-resistant organisms such as the methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci*.

Great concern is also associated with tropical diseases such as Chaga's disease and the increase of tuberculosis around the world, even in countries where this disease was considered eradicated.

Medicinal plants that have been used for a long time may be good sources of antimicrobial agents because of their active secondary metabolites, themselves, or working as raw models for new molecules with improved effects. It is possible to find some examples for prenylated xanthenes in these research fields.

6.4.1 Antifungal

Many antifungal compounds have been identified, but so far safe and effective antifungal drugs have not yet been developed. Several substances are in therapeutics for the antifungal activity, namely amphotericin B, miconazole, ketoconazole, fluconazole and itraconazole, but all of them present relevant side effects such as nephrotoxicity and hepatotoxicity or vomiting and impotence. These situations lead to a strong demand for drugs with fewer side effects. However, one of the difficulties associated with research and development of new active compounds is a high degree of similarity between fungi and mammalian cells.

In a search for naturally occurring antifungal compounds, bioassay-guided fractionation of the root extract of *Cudrania cochinchinensis* against *Cryptococcus neoformans*, *Aspergillus fumigatus*, *A. nidulans* and *Candida glabrata* resulted in the isolation of antifungal agents cudraxanthone S (**82**) and toxylloxanthone C (**431**) (Figure 33) (Fukai et al., 2003).

Xanthenes with antifungal activity were isolated also from *Calophyllum caledonicum* (Morel et al., 2002) and *Tovomita kruckovi* (Zhang et al., 2002). The most active compounds were **21**, **29** and caledonixanthone E (**381**) (Figure 34).

These compounds (**21**, **29**, **381**) exhibited antifungal activity against *Aspergillus fumigatus* and/or *Candida albicans* and were found to possess common structural features: a hydrophobic group on A ring and a hydroxyl group at C-5 or C-6. It is likely that antifungal xanthenes require a hydrophobic group on ring A and three or four hydroxyl groups in which one or two hydroxyl groups must be at C-5 and/or C-6.

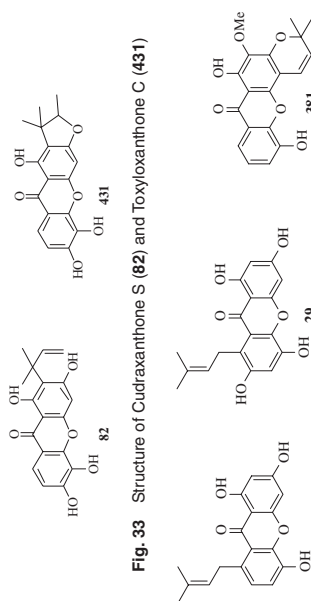


Fig. 33 Structure of Cudraxanthone S (**82**) and Toxylloxanthone C (**431**)

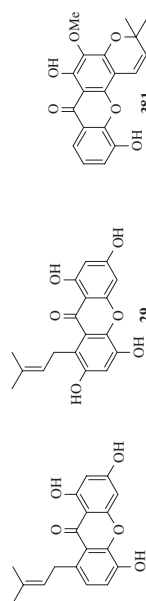


Fig. 34 Structure of Xanthenes **21**, **29** and Caledonixanthone E (**381**)

Thus, putative pharmacophoric data for antifungal activity can be summarized as in Figure 35:

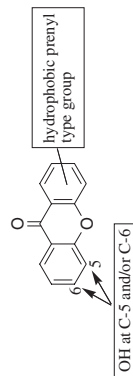


Fig. 35 Putative Pharmacophoric Data for Antifungal Activity of Prenylated Xanthenes

6.4.2 Antibacterial

Only a few anti-methicillin-resistant *Staphylococcus aureus* xanthenes with one or more isoprenoid groups have been reported (Inuma et al., 1996c; Dharmaratne et al., 1999; Rukachaisirikul et al., 2000). However, ten xanthenes with one or two isoprenoid groups isolated from roots of *Cudrania cochinchinensis* (Moraceae) were tested for their antimicrobial activities against *Bacillus subtilis* and methicillin-resistant *Staphylococcus aureus* (Fukai et al., 2004). Among these compounds, gerontoxanthone H (**113**) exhibited considerable antibacterial activity against *B. subtilis*, while gerontoxanthone I (**174**), toxylloxanthone C (**431**), cudraxanthone S (**82**), and 1,3,7-trihydroxy-2-prenylxanthone (**24**), showed weak antibacterial activity (Figure 36).

From this study, some conclusions can be drawn as follows:

- The antibacterial activity of xanthenes with one or two hydrophobic groups against methicillin-sensitive *Staphylococcus aureus* and methicillin-resistant *S. aureus* was similar to its anti-*Bacillus* potency;

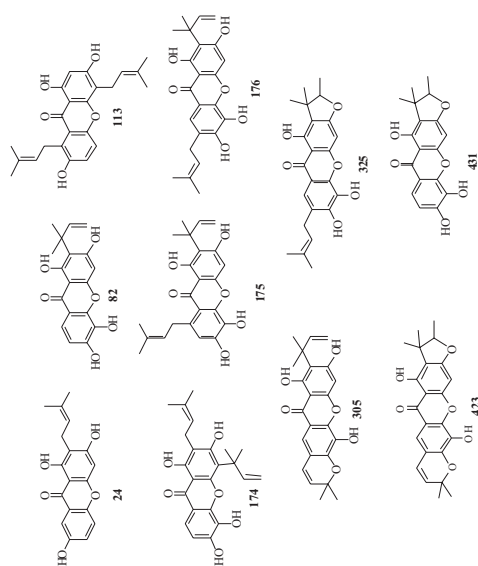


Fig. 36 Structure of Xanthone 24, Cudraxanthone S (82), Gerontoxanthone H (113), Gerontoxanthone I (174), 175, 176, 305, Gerontoxanthone G (325), 423, and Toxyloxanthone C (431)

- Gerontoxanthone H (113) also exhibited the highest growth inhibitory activity against ten methicillin-sensitive *S. aureus* strains as well as the activity against a kind of methicillin-sensitive *S. aureus*.

In a later study, xanthones with one or two isoprenoid groups were tested for their antimicrobial activities against vancomycin-resistant *Enterococci* (Fukai et al., 2005). Among these compounds, gerontoxanthone H (113) exhibited considerable antibacterial activity against five vancomycin-resistant *Enterococci* strains (VanA, VanB and VanC). 1,3,7-Trihydroxy-2-prenylxanthone (24), cudraxanthone S (82), gerontoxanthone I (174), alvaxanthone (175), isovalxanthone (176), gerontoxanthone G (325), and toxyloxanthone C (431) showed only weak antibacterial activity against these vancomycin-resistant *Enterococci*.

The results of this study lead to a conclusion that:

- It is likely that anti-vancomycin-resistant *Enterococci* xanthones require one or two hydrophobic sites (i.e. isoprenoid groups) and hydrophilic sites (i.e. hydroxyl groups), in which a hydroxyl group apart from the hydrophobic domains may potentiate the anti-vancomycin-resistant *Enterococci* activity.

Interestingly, it was found that the antibacterial effect of these isoprenoid-substituted xanthones may also be due to an action similar to that of some flavones, reducing the fluidity of the outer and

inner layers of membranes (Tsuchiya and Inuma, 2000) with the isolated hydroxyl groups as a kind of chemical lance to attack the lipidic bilayer or the hydrophobic residues of proteins of target microorganisms.

Consequently, gerontoxanthone H (113) could be considered as a potential candidate for vancomycin-resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus* infections. Though the *in vivo* effectiveness and the mode of action of this compound remain to be further investigated, the structure of this "hit compound" can be a valuable starting point for new potential antimicrobial agents.

6.4.3 Trypanocidal

The etiologic agent of Chagas' disease (American trypanosomiasis) is the epimastigote form of the protozoan *Trypanosoma cruzi*. It is transmitted to humans by triatomine bugs or through blood transfusion. The life cycle of *T. cruzi* is divided into three stages: epimastigote in the insect gut; trypomastigote, an infectious form in the mammalian blood stream; and amastigote, a proliferative form in mammalian cells.

Related to this parasite, nine prenylated xanthones isolated from the stem bark of *Garcinia subelliptica* (Guttiferae) (Figure 37): xanthone 80, garciniaxanthone A (173), subelliptenone B (182), garciniaxanthone E (196), 215, 218, garciniaxanthone B (303), subelliptenone H (312) and 404, were investigated for their trypanocidal activity against epimastigotes of *Trypanosoma cruzi*. Trypanocidal activity against trypomastigotes of these compounds as well as their cytotoxic activity was also investigated (Abe et al., 2003).

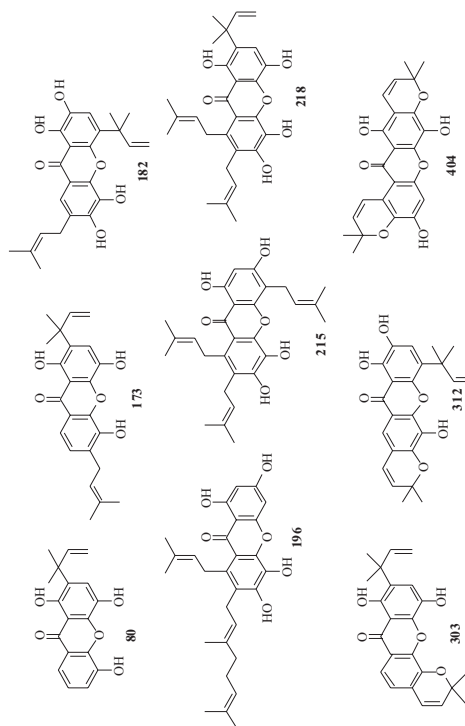


Fig. 37 Prenylated Xanthones Isolated from *Garcinia subelliptica*

All xanthenes studied exhibited stronger activity against trypanastigotes than against epimastigotes. Although the number of xanthenes examined might not be sufficient to clarify completely the structure-activity relationships, the effects of substitution patterns on the activity against trypanastigotes can be observed as follows:

- The compound with the strongest activity was **303**;
- Compounds **80**, **173** and **218** have the same substitution pattern in ring A as **303**. Substitution of one prenyl unit in ring B increases the activity, although two units decrease it.
- In compounds **215** and **218**, the difference in the substitution pattern in ring A had no influence on the activity. Isomers **196**, **215**, **218** which have three isoprenyl units and four hydroxyl groups in their structures, showed practically the same activity;
- The presence of a linear pyran ring to ring A or B (**404** or **312**) reduced significantly the activity.

It was also found that garcinaxanthone B (**303**), with one prenyl unit in both rings A and B, showed the highest activity and, due to its high trypanocidal activity and low cytotoxic activity, was proposed to be a candidate for further *in vivo* investigation.

Abe et al. (2004) have further investigated the constituents of the leaves of *Garcinia intermedia* and heartwood of *Calophyllum brasiliense* for their trypanocidal activity against epimastigotes of *Trypanosoma cruzi*. It was found that xanthone (**115**), together with jacareubin (**371**), 6-deoxyjacareubin (**363**), and 1,3,5,6-tetrahydroxy-2-(3-methyl-2-butenyl)xanthone (**33**) (**Figure 38**) exhibited a trypanocidal activity against trypanastigotes.

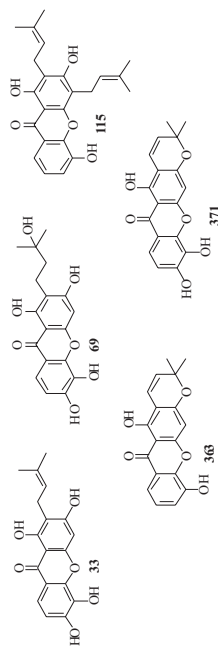


Fig. 38 Structure of Xanthenes **33**, **69**, **115**, **363** and **371**

From these studies some conclusions can be achieved:

- By comparing 6-deoxyjacareubin (**363**) with jacareubin (**371**), it was found that the presence of a pyrocatechol moiety caused a significant increase of the activity;
- Comparing compounds **33**, **69** and **371**, whose substitution pattern in ring B is similar, it was found that a decrease in the degree of insaturation of the side chain on ring A was accompanied by a decrease in activity.

Based on the structure-activity relationship, putative pharmacophoric data for trypanocidal activity can be proposed as shown in **Figure 39**:

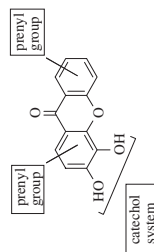


Fig. 39 Putative Pharmacophoric Data for Trypanocidal Activity of Prenylated Xanthenes

Admittedly, the lack of defence against oxidative stress in *T. cruzi* makes this parasite susceptible to substances that are able to generate reactive oxygen species such as quinones (Senvilveda and Cassels, 1996) and flavonoids (Ribeiro et al., 1997). Based on this fact, it is possible to assume that xanthenes, especially with the catechol system, can also influence the redox balance of *T. cruzi* leading to trypanocidal activity.

6.4.4 Antimycobacterial Activity

In spite of the fact that drugs for treatment of tuberculosis are known more than half a century, the increase of the disease worldwide and the coinfection with HIV, also associated with multidrug-resistance are enough reasons for search of new antimycobacterial drugs, even from natural origin. For this reason, many researchers have focused on screening plant secondary metabolites for their antimycobacterial activity. Consequently, fifteen prenylated xanthenes (**Figure 40**), isolated from seeds of *Garcinia mangostana*, were tested for their antituberculosis potential against *Mycobacterium tuberculosis*. Among these, α - and β -mangostins (**141** and **142**, respectively) and garcinone B (**239**) were found to exhibit a strong inhibitory effect (Suksumarn et al., 2003).

The results of this screening suggested that for a moderate to high antimycobacterial activity, the xanthenes nucleus should contain tri- or tetraoxygen functions with either di- C_5 units or with a C_5 and a modified C_3 groups in the aromatic rings. These structural features can be observed in the major constituent α -mangostin (**141**), β -mangostin (**142**) and garcinone B (**239**), which are 1,3,6,7-tetraoxygenated xanthenes bearing the C_5 units at C-2 and C-8 and exhibited the most potent activities. Interestingly, γ -mangostin (**127**), whose structure contains the hydroxyl groups on C-3 and C-7, exhibited lower inhibitory activity. This result leads to the suggestion that methylation of the 3-hydroxyl as well as the 7-hydroxyl groups resulted in increasing activity.

- A structure-activity comparison of **141** with **159** and mangostenol (**152**) revealed that modifications of the C_5 units in either at C-8 or C-2 caused an alteration of the activity;
- Furthermore, cyclization of the C_5 group at C-2 position resulted in a decreased inhibitory activity as exemplified by the xanthenes **245**, **338** and mangostanol (**257**);
- It is of interest to note that increment in polarity of the C_5 side chain reduced the activity and addition of the third C_5 moiety like in mangostenone A (**281**) and totophyllin B (**282**), with respect to **239** and **245**, affected the inhibitory activity;

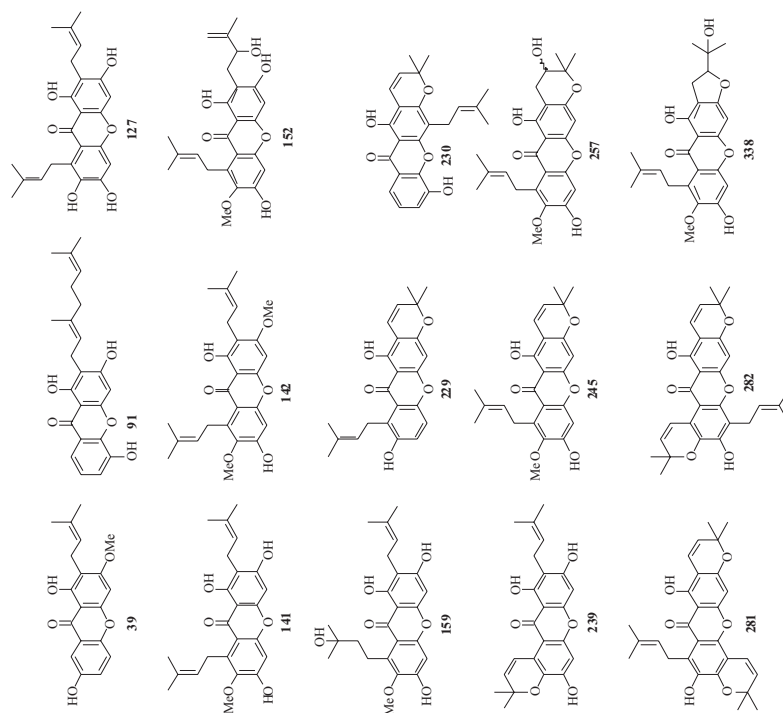


Fig. 40 Structure of Xanthenes **39**, **91**, **127**, **141**, **142**, **152**, **159**, **229**, **230**, **239**, **245**, **257**, **281**, **282**, **338**

- In the case of 1,3,7-trioxygenated compounds, the inactivity of **39**, the xanthone with only one C₅ group located at C-2, compared with the moderately active demethylcalabaxanthone (**229**), indicated the essential of the di-C₅ side chains in the nucleus;
- For 1,3,5-trioxygenated xanthenes, the more potent activity of trapezifolixanthone (**230**), when compared with mangostinone (**91**), further supported this fact.

In accordance with the structure-activity studied above mentioned, putative pharmacophoric data for antimycobacterial activity can be summarized as in **Figure 41**:

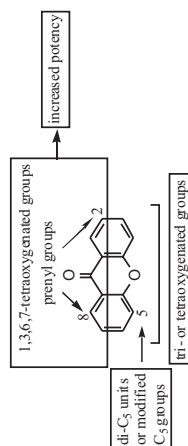


Fig. 41 Putative Pharmacophoric Data for Antimycobacterial Activity of Prenylated Xanthenes

6.5 Inhibitory Effects on Platelet Activating Factor (PAF)

1-Alkyl-2-acetyl-glycero-3-phosphocholine or platelet activating factor (PAF), a potent phospholipid activator and mediator of many leucocyte functions and with specific receptors in a variety of cell membranes is associated with aggregation and degranulation of platelets and leukocytes, increased vascular permeability hypotension and depression of cardiac function. These receptors can recognize a wide variety of ligands with antagonist effect and with a large diversity of chemical structures, from natural to synthetic origin, being these compounds potential valuable tools in many pathologies such as inflammation, allergy, asthma, cardiac anaphylaxis, gastrointestinal ulceration and thrombosis. Concerning this, nine naturally occurring xanthenes (**Figure 42**), isolated from the members of the family Gutierrezia (*Callophyllum inophyllum*, *Garcinia opaca*, *G. bancana*) were investigated for their platelet activating factor (PAF) receptor binding inhibitory effects using rabbit platelets (Jantan et al., 2001). It was found that 1,3,5-trihydroxy-2-(3-methylbut-2-enyl)xanthone (**26**), maculaxanthone (**304**), 1,3,5-trihydroxy-6,6'-dimethylpyrano-(2',3':6,7)-4-(1,1-dimethylprop-2-enyl)xanthone (**309**), 6-deoxyjacareubin (**363**) and 1,3,5,6-tetrahydroxy-2-(3-methylbut-2-enyl)xanthone (**33**) showed strong PAF receptors inhibition.

Structure-activity analysis of these compounds revealed that the presence of a prenyl group at C-2 was associated with a strong binding affinity to the receptor (e.g. compound **26**). However, the presence of a dimethylprop-2-enyl group at C-4 caused a slight increase in potency, indicating that this group may be involved in binding to the PAF receptor (e.g. compounds **309** and **304**). Some molecular moieties are also associated with an increase of the activity:

- The presence of hydroxyl group at C-6 as in compound **33**;
- Cyclization of the prenyl group in compound **26** to form a pyran ring substituted at C-2 and C-3 (compound **363**).

On contrary:

- Hydroxylation of the prenyl group resulted in significant loss in binding to the receptor (e.g. compound **69**). However, a hydroxyl group at C-5 was preferred in binding to the receptor;

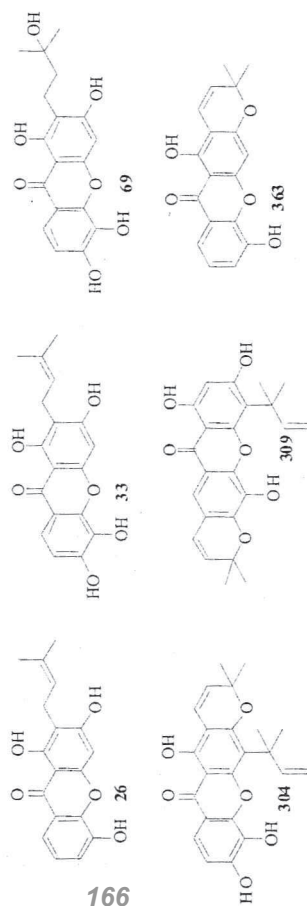


Fig. 42 Structure of Xanthenes 26, 33, 69, 304, 309 and 363

- The location of the pyran ring at C-6 and C-7, as in compound 309, resulted in a slight decrease of binding affinity.

Jantan et al. (2002) have also investigated inhibitory effects on PAF binding to rabbit platelets of rubraxanthone (97) and isocowanol (201) (Figure 43), isolated from *Garcinia parvifolia* Miq., and it was found that only rubraxanthone (97) showed a strong inhibition against PAF.

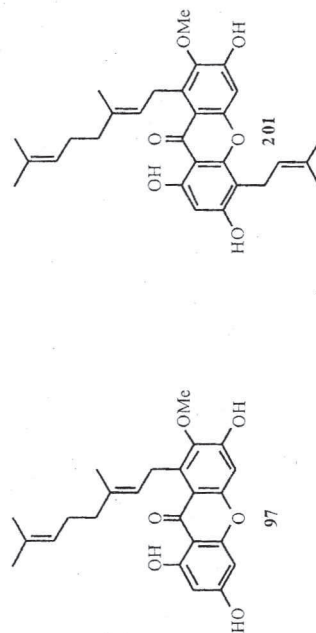


Fig. 43 Structures of Rubraxanthone (97) and Isocowanol (201)

The results revealed that prenylated xanthenes could represent a new class of natural products, which can bind strongly to PAF receptor being the prenyl group at C-2, the dimethylprop-2-enyl group at C-4 and the hydroxyl group at C-5 essential for this activity. Moreover, it was also observed that a geranyl group at C-8 improved the interaction while a hydroxylated prenyl group at C-4 resulted in a significant loss in binding to the PAF. The presence of the isoprenoid group at C-8 can indicate a possible hydrophobic interaction of this molecular moiety with the receptor (Figure 44):

Anexo I

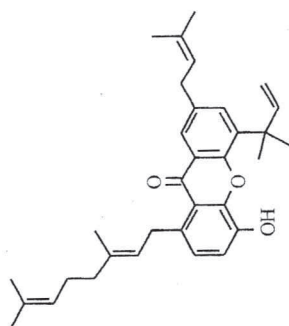


Fig. 44 Putative Pharmacophoric Data for PAF Receptor Binding Inhibition for Prenylated Xanthenes

7. CONCLUDING REMARKS

The present chapter provides the current knowledge on structure determination, biosynthesis and biological activities of prenylated xanthenes. The structural diversity allied with a myriad of biological and pharmacological activities of this class of compounds can make a research in this field more challenging. Interestingly, the main sources of these compounds are still from nature, plants from the Clusiaceae (Guttiferae) and Moraceae families.

Besides the potential pharmacological properties associated with the isolated compounds, the respective natural scaffold can act as very useful templates for molecular modifications in order to improve their physicochemical and biological properties. Furthermore, the findings from the SAR studies revealed that the relative location of a hydroxyl group and hydrophobic prenyl moieties on the xanthone nucleus might be important chemical attributes for the specificity of biological activities. All the knowledge achieved so far can contribute to a future rational design of the new bioactive compounds, more diverse and complex, based on the xanthone scaffold. Besides their own importance as potential therapeutics, prenylated xanthenes may constitute an excellent starting material for the development of efficient drugs in a near future.

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Abbreviations and Symbols

¹³C NMR = Carbon Nuclear Magnetic Resonance and replace
¹H NMR = Proton Nuclear Magnetic Resonance
 2D NMR = Two Dimension Nuclear Magnetic Resonance
 AIDS = Acquired Immune Deficiency Syndrome
 COSY = Correlated Spectroscopy
 DEPT = Distortionless Enhancement by Polarization Transfer

EBV = Epstein-Barr Virus
 HMBC = Heteronuclear Multiple-Bond Correlation
 HSQC = Heteronuclear Single-Quantum Correlation
 NOESY = Nuclear Overhauser Enhancement Spectroscopy
 PAF = Platelet Activating Factor
 SAR = Structure-Activity Relationship
 δ = Chemical Shift
 ppm = Parts per million

References

- Abe, F., Nagafuji, S., Okabe, H., Akahane, H., Estrada-Muniz, E., Huerta-Reyes, M., Reyes-Chilpa, R. (2004). *Trypanocidal Constituents in Plants 3. Leaves of Garcinia intermedia and Heartwood of Calophyllum brasiliense*; Biol Pharm Bull **27**(1), 141-143.
- Abe, F., Nagafuji, S., Okabe, H., Higo, H., Akahane, H. (2003). *Trypanocidal Constituents in Plants 2. Xanthones from the Stem Bark of Garcinia subelliptica*; Biol Pharm Bull **26**, 1730-1733.
- Afzal, M., Al-Hassan, J.M. (1980). *Synthesis and Biosynthesis of Phytotoxanthones*; Heterocycles **14**(8), 1173-1205.
- Ampofo, S.A., Waterman, P.G. (1986). *Xanthones from three Garcinia species*; Phytochemistry **25**(10), 2351-2355.
- An, R.-B., Sohn, D.-H., Kim, Y.-C. (2006). *Hepatoprotective Compounds of the Roots of Cudrania tricuspidata on Taurine-Induced Cytotoxicity in Hep G2 Cells*; Biol Pharm Bull **29**(4), 838-840.
- An, T.Y., Hu, L.H., Chen, Z.L. (2002). *A New Xanthone Derivative from Hypericum Erectum*; Chinese Chem Lett **13**(7), 623-624.
- Asano, J., Kazuhiro, C., Tada, M., Yoshii, T. (1996). *Cytotoxic Xanthones from Garcinia Handburyi*; Phytochemistry **41**, 815-820.
- Azebaze, A.G.B., Meyer, M., Bodo, B., Nkengfack, A.E. (2004). *Allanxanthone B, a polyisoprenylated xanthone from the stem bark of Allanblackia monticola Staner L. C*; Phytochemistry **65**, 2561-2564.
- Azebaze, A.G.B., Meyer, M., Valentin, A., Nguemfo, E.L., Fomum, Z.T., Nkengfack, A.E. (2006). *Prenylated Xanthone Derivatives with Antiplasmodial Activity from Allanblackia monticola Staner L.C.*; Chem Pharm Bull **54**(1), 111-113.
- Balasubramanian, K., Rajagopalan, K. (1988). *Novel xanthones from Garcinia mangostana, structures of Br-Xanthone A and Br-Xanthone B*; Phytochemistry **27**(5), 1552-1554.
- Balunas, M.J., Jones, W.P., Chin, Y.-W., Mi, Q., Farnsworth, N.R., Socjarto, D.D., Cordell, G.A., Swanson, S.M., Pezuto, J.M., Chai, H.-B., Kinghorn, A.D. (2006). *Relationships between Inhibitory Activity against a Cancer Cell Line Panel, Profiles of Plants Collected, and Compound Classes Isolated in an Anticancer Drug Discovery Project*; Chem & Biodiversity **3**, 897-915.
- Banerji, A., Deshpande, A.D., Prabhu, B.R., Pradhan, P. (1994). *Tomentonone, a new xanthanol from the stem bark of Calophyllum tomentosum*; J Nat Prod **57**(3), 396-399.
- Barillas, W., Beechues, L. (1997). *3-Hydroxybenzoate: coenzyme A ligase and 4-coumarate: coenzyme A ligase from cultured cells of Centaurea erythraea*; Planta **202**, 112-116.
- Bayma, J.C., Arruda, M.S.P., Neto, M.S. (1998). *A prenylated xanthone from the bark of Symphonia Globulifera*; Phytochemistry **49**(4), 1159-1160.
- Beethues, L. (1996). *Benzophenone synthase from cultured cells of Centaurea erythraea*; FEBS Lett **383**, 264-266.
- Beethues, L., Barillas, W., Peters, S., Schmidt, W. (1999). *Bioorganic Chemistry: Highlights and New Aspects*; pp. 322-328; Wiley-VCH, Weinheim.
- Bennett, G.J., Harrison, L.J., Sia, G.L., Sim, K.Y. (1993). *Triterpenoids, Tocotrienols and Xanthones from the bark of Cratogeomys cochinchinensis*; Phytochemistry **32**(5), 1245-1251.
- Bennett, G.J., Lee, H.H. (1989). *Xanthones from Gentiferae*; Phytochemistry **28**(4), 967-998.
- Bennett, G.J., Lee, H.H., Dash, N.P. (1990a). *Biosynthesis of Mangostin. Part 1: The Origin of the Xanthone Skeleton*; J Chem Soc Perkin Trans 1, 2671-2676.
- Bennett, G.J., Lee, H.H., Lee, L.P. (1990b). *Synthesis of minor Xanthones from Garcinia mangostana*; J Nat Prod **53**(6), 1463-1470.
- Bilia, A.R., Yusuf, A.W., Braca, A., Keita, A., Morelli, I. (2000). *New Prenylated Anthraquinones and xanthones from Vismia guianensis*; J Nat Prod **63**, 16-21.
- Boonmak, N., Chantapromma, S., Fun, H.-K. (2006a). *4-(1,1-Dimethylprop-2-enyl)-1,3,5,6-tetrahydroxy-2-(3-methylbut-2-enyl)-9H-xanthen-9-one monohydrate*; Acta Cryst E **16**(2), o2034-o2036.
- Boonmak, N., Karalai, C., Chantapromma, S., Ponglamanont, C., Fun, H.-K., Kanjana-Opas, A., Laplookhieo, S. (2006b). *Bioactive prenylated xanthones and anthraquinones from Cratogeomys formosum ssp. pruniflorum*; Tetrahedron **62**, 8850-8859.
- Boonsri, S., Karalai, C., Ponglamanont, C., Kanjana-Opas, A., Chantapromma, K. (2006). *Antibacterial and cytotoxic xanthones from the roots of Cratogeomys formosum*; Phytochemistry **67**, 723-727.
- Brahmachari, G., Mondal, S., Gangopadhyay, A., Gorai, D., Mukhopadhyay, B., Saha, S., Brahmachari, A.K. (2004). *Swerita (Gentianaceae): Chemical and Pharmacological Aspects*; Chem & Biodiversity **1**, 1627-1651.
- Bringmann, G., Lang, G., Steffens, S., Günther, E., Schaumann, K. (2003). *Evariquinone, isomerized, and stromenycin from a sponge derived strain of the fungus Emericella varicolor*; Phytochemistry **63**, 437-443.
- Brühlmann, C., Marston, A., Hostettmann, K., Carup, P.A., Testa, B. (2004). *Screening of Non-Alkaloidal Natural Compounds as Acetylcholinesterase Inhibitors*; Chem & Biodiversity **1**, 819-829.
- Cao, S.-G., Sing, V.H.L., Wu, X.-H., Sim, K.-Y., Tan, B.H.K., Pereira, J.T., Goh, S.H. (1998). *Novel Cytotoxic Polyisoprenylated Xanthones from Garcinia gaudichaudii (Guttiferae)*; Tetrahedron **54**, 10915-10924.
- Cardona, M.L., Fernández, I., Pedro, J.R., Serrano, A. (1990). *Xanthones from Hypericum reflexum*; Phytochemistry **29**(9), 3003-3006.
- Castanheiro, R.A.P., Pinto, M.M.M., Silva, A.M.S., Cravo, S.M.M., Gales, L., Damas, A.M., Nazareth, N., Nascimento, M.S.J., Eaton, G. (2007). *Dihydroxyxanthones Prenylated Derivatives: Synthesis, Structure Elucidation and Growth Inhibitory Activity on Human Tumor Cell Lines with Improvement of Selectivity for MCF-7*; Bioorg Med Chem **15**, 6080-6088.
- Chaurungsilerd, N., Furukawa, K.I., Tadano, T., Kisara, K., Ohizumi, Y. (1998). *Effect of α -mangostin through the inhibition of 5-hydroxy-tryptamine_{2A} receptors in 5-fluoro- α -methyltryptamine-induced head-twitch responses of mice*; Br J Pharmacol **123**, 855-862.
- Chaurungsilerd, N., Takeuchi, K., Ohizumi, Y., Nozoe, S., Ohta, T. (1996). *Mangostanol, a prenyl xanthone from Garcinia mangostana*; Phytochemistry **43**(5), 1099-1102.
- Chang, C.-H., Lin, C.-C., Hattori, M., Namba, T. (1989a). *Four prenylated xanthones from Cudrania cochinchinensis*; Phytochemistry **28**(2), 595-598.
- Chang, C.-H., Lin, C.-C., Kawata, Y., Hattori, M., Namba, T. (1989b). *Prenylated Xanthones from Cudrania Cochinchinensis*; Phytochemistry **28**(10), 2823-2826.

- Chang, C.-H., Lin, C.-C., Hattori, M., Namba, T. (1994). Effects on anti-lipid peroxidation of *Cudrania cochinchinensis* var. *geronotae*. J Ethnopharmacol **44**, 79-85.
- Chang, C.-H., Lin, C.-C., Kadota, S., Hattori, M., Namba, T. (1995). Flavonoids and a Prenylated Xanthone from *Cudrania Cochinchinensis* Var. *geronotae*. Phytochemistry **40**(3), 945-947.
- Channahasathien, W., Li, Y., Masuyuki, S., Oshima, Y., Ruangrungsri, N., Ohizumi, Y. (2003a). Prenylated Xanthones with NGF-potentiating activity from *Garcinia xanthochymus*; Phytochemistry **64**, 981-986.
- Channahasathien, W., Li, Y., Stakke, M., Oshima, Y., Ishibashi, M., Ruangrungsri, N., Ohizumi, Y. (2003b). Prenylated Xanthones from *Garcinia xanthochymus*; Chem Pharm Bull **51**(11), 1332-1334.
- Chantrapromma, S., Boonmak, N., Fun, H.-K., Anjum, S., Rahman, A. (2005). 5,9,10-Trihydroxy-2,2-dimethyl-12-(3-methylbut-2-enyl)-2H-pyran-6-one methanol solvate; Acta Cryst E **E61**, 62136-02138.
- Chantrapromma, S., Boonmak, N., Fun, H.-K., Karalai, C. (2006). 1,6-Dihydroxy-3,7-dimethoxy-2,8-bis(3-methyl-2-butenyl)-9H-xanthen-9-one; Acta Cryst E **E62**, 6360-0362.
- Chen, J.-J., Chen, I.-S., Duh, C.-Y. (2004). Cytotoxic Xanthones and Biphenyls from the Root of *Garcinia linnii*; Planta Med **70**, 1195-1200.
- Chen, M.T., Kuoh, Y.P., Wang, C.H., Kuoh, C.M. (1989). Additional Constituents of *Hypericum subulatum*; J Chinese Chem Soc **36**, 165-168.
- Chen, S.X., Wan, M., Loh, B.N. (1996). Active Constituents against HIV-1 Protease from *Garcinia mangostana*; Planta Med **62**, 381-382.
- Cheng, H.-C., Wang, L.-T., Khalil, A.T., Chang, Y.-T., Lin, Y.-C., Shen, Y.-C. (2004). Pyranoxanthones from *Calophyllum inophyllum*; J Chinese Chem Soc-Taipei **51**, 431-435.
- Cheval, K.K., Fouweather, C., Holker, J.S.E., Simpson, T.J., Young, K. (1974). The Biosynthesis of Fungal Metabolites. Part III. Structure of Shamixanthone and Tajixanthone. Metabolites of *Aspergillus varicolor*; J Chem Soc Perkin Trans 1, 1584-1593.
- Cheval, K.K., Holker, J.S.E., Simpson, T.J., Young, K. (1975). The Biosynthesis of Fungal Metabolites. Part V. Structure of Varicoxanthones A, B, and C. Metabolites of *Aspergillus varicolor*; Conversion of Varicoxanthone A into (*)-De-C-prenylshamixanthone; J Chem Soc Perkin Trans 1, 543-548.
- Chiang, Y.M., Kuo, Y.H., Oota, S., Fukuyama, Y. (2003). Xanthones and Benzophenones from the Stems of *Garcinia multiflora*; J Nat Prod **66**, 1070-1073.
- Chilpa, R.R., Estrada, M.J., Muñoz, E.E. (1997). Antifungal Xanthones from *Calophyllum brasiliensis* heartwood; J Chem Ecol **23**(7), 1901-1911.
- Cortez, D.A.G., Young, M.C.M., Marston, A., Wolfender, J.-L., Hostettmann, K. (1998). Xanthones, Triterpenes and a Biphenyl from *Kielmeyera coriacea*; Phytochemistry **47**(7), 1367-1374.
- Costa, C.T., Dalluge, J.J., Welch, M.J., Coxon, B., Margolis, S.A., Horton, D. (2000). Characterization of prenylated xanthones and flavanones by liquid chromatography/ atmospheric pressure chemical ionization mass spectrometry; J Mass Spectrom **35**, 540-549.
- Costa, C.T., Margolis, S.A., Bennett, Jr., B.A., Horton, D. (1999). Comparison of methods for extraction of flavanones and xanthones from the root bark of the osage orange tree using liquid chromatography; J Chromatogr A **831**, 167-178.
- Cotterill, P.J., Scheinmann, F. (1980). Studies in the Xanthone Series. Part 13. Structural and Synthetic Studies on Toxyloxanthone B; J Chem Soc Perkin Trans 1, 2353-2357.
- Cruz, F.G., Silva-Neto J.T., Guedes, M.L.S. (2001). Xanthones and Coumarins from *Kielmeyera lathrophyton*; J Braz Chem Soc **12**(1), 117-122.
- Deuchathai, S., Mahabusarakam, W., Phongpaichit, S., Taylor, W.C. (2005). Phenolic compounds from the fruit of *Garcinia dulcis*; Phytochemistry **66**, 2368-2375.
- Deuchathai, S., Mahabusarakam, W., Phongpaichit, S., Taylor, W.C., Zhang, Y.-J., Yang, C.-R. (2006). Phenolic compounds from the flowers of *Garcinia dulcis*; Phytochemistry **67**, 464-469.
- Dean, F.M. (1973). The Total Synthesis of Natural Products: Vol. 1, pp. 534-562; John Apsimon.
- Dhamaratne, H.R.W., Piyasena, K.G.N.P., Tennakoon, S.B. (2005). A Geranylated Biphenyl Derivative from *Garcinia mangostana*; Nat Prod Res **19**(3), 239-243.
- Dhamaratne, H.R.W., Tan, G.T., Marasinghe, G.P.K., Pezuto, J.M. (2002). Inhibition of HIV-1 Reverse Transcriptase and HIV-1 Replication by *Calophyllum coumarins* and Xanthones; Planta Med **68**, 86-87.
- Dhamaratne, H.R.W., Wanggasekera, W.M.A.P. (1996). Xanthones from the root bark of *Calophyllum thwaitesii*; Phytochemistry **42**(1), 249-250.
- Dhamaratne, H.R.W., Wijesinghe, W.M.N.M. (1997). A Trioxysgenated Diprenylated Chromenoxanthone from *Calophyllum moonii*; Phytochemistry **46**(7), 1293-1295.
- Dhamaratne, H.R.W., Wijesinghe, W.M.N.M., Thevanasem, V. (1999). Antimicrobial activity of xanthones from *Calophyllum* species, against methicillin-resistant *Staphylococcus aureus* (MRSA); J Ethnopharmacol **66**, 339-342.
- Dias, A.C.P., Seabra, R.M., Andrade, P.B., Ferreres, F., Ferreira, M.F. (2000). Xanthone biosynthesis and accumulation in calli and suspended cells of *Hypericum androsaemum*; Plant Sci **150**, 93-101.
- Dias, A.C.P., Seabra, R.M., Andrade, P.B., Ferreres, F., Ferreira, M.F. (2001). Xanthone production in calli and suspended cells of *Hypericum perforatum*; J Plant Physiol **158**, 821-827.
- Diserens, I.S., Marston, A., Hamburger, M., Rogers, C., Hostettmann, K. (1989). Novel Prenylated Xanthones from *Garcinia gerrardii* Harvey; Helv Chim Acta **72**, 1001-1007.
- Diserens, I.S., Rogers, C., Sordat, B., Hostettmann, K. (1992). Prenylated Xanthones from *Garcinia Livingstonei*; Phytochemistry **31**(1), 313-316.
- Don, M.-J., Huang, Y.-J., Huang, R.-L., Lin, Y.-L. (2004). New Phenolic Principles from *Hypericum sampsonii*; Chem Pharm Bull **52**, 866-869.
- Doriguello, A.C., Santos, M.H., Ellena, J.A., Nagem, T.J. (2001). 6-Deoxyjacarubin; Acta Cryst C **57**, 1095-1097.
- Edwards, D.J., Gerwick, W.H. (2004). Lyngbyatoxin Biosynthesis: Sequence of Biosynthetic Gene Cluster and Identification of a Novel Aromatic Prenyltransferase; J Am Chem Soc **126**, 11432-11433.
- Ee, G.C.L., Kua, A.S.M., Lim, C.K., Jong, V., Lee, H.L. (2006a). Inophyllin A, a new pyranoxanthone from *Calophyllum inophyllum* (Guttiferae); Nat Prod Res **20**(5), 485-491.
- Ee, G.C.L., Lim, C.K., Ong, G.P., Sukari, M.A., Lee, H.L. (2006b). Daphnifolin, a new xanthone from *Mesua daphnifolia* (Guttiferae); J Asian Nat Prod Res **8**(6), 567-570.
- Ee, G.C.L., Ng, K.N., Taufiq-Yap, Y.H., Rahmani, M., Ali, A.M., Muse, R. (2004). Mucigerin, a New Coumarin from *Calophyllum mucigerum* (Guttiferae); Nat Prod Res **18**, 123-128.
- Epifano, F., Genovesi, S., Menghini, L., Curini, M. (2007). Chemistry and pharmacology of oxyprenylated secondary plant metabolites; Phytochemistry **68**, 939-953.
- Fernandes, E.G.R., Silva, A.M.S., Cavaleiro, J.A.S., Silva, F.M., Borges, M.F.M., Pinto, M.M.M. (1998). ¹H and ¹³C NMR Spectroscopy of Mono-, Di-, Tri- and Tetrasubstituted Xanthones; Magn Res Chem **36**, 305-309.
- Ferrari, F., Pasqua, G., Monacelli, B., Cimino, P., Botta, B. (2005). Xanthones from *Calli of Hypericum perforatum* Subsp. *perforatum*; Nat Prod Res **19**(2), 171-176.
- Floss, H.G., Retti, A. (1964). Biosynthesis with Gentianaceae. I. Biosynthesis of gentisin; Z Naturforsch, Teil B **19**(12), 1103-1105.

- Fu, P., Li, T.-Z., Liu, R.-H., Zhang, W.-D., Chen, H.-S. (2004). *Studies on the of Hypericum japonicum* Thunb. ex Murray; Nat. Prod. Res. Dev. 16.
- Fujita, M., Inoue, T. (1980). *Biosynthesis of Mangiferin in Anemarrhena-Asphodeloides Bunge*. 1. The Origin of the Xanthone Nucleus; Chem. Pharm. Bull. 28(8), 2476-2481.
- Fukui, T., Oku, Y., Hou, A.J., Yonekawa, M., Terada, S. (2004). *Antimicrobial Activity of Hydrophobic Xanthones from Cudrania cochinchinensis against Bacillus subtilis and Methicillin-Resistant Staphylococcus aureus*; Chem. & Biodiversity 1, 1385-1390.
- Fukui, T., Oku, Y., Hou, A.J., Yonekawa, M., Terada, S. (2005). *Antimicrobial activity of isoprenoid-substituted xanthones from Cudrania cochinchinensis against vancomycin-resistant enterococci*; Phytomedicine 12, 510-513.
- Fukui, T., Yonekawa, M., Hou, A.-J., Nomura, T., Sun, H.-D., Uno, J. (2003). *Antifungal Agents from the Roots of Cudrania cochinchinensis against Candida, Cryptococcus and Aspergillus Species*; J. Nat. Prod. 66, 1118-1120.
- Fukuyama, Y., Kamiyama, A., Mima, Y., Kodama, M. (1991). *Prenylated xanthones from Garcinia subelliptica*; Phytochemistry 30(10), 3433-3436.
- Fun, H.-K., Ng, S.-L., Razak, I.A., Boonakb, N., Chantapromma, S. (2006). *12-(1,1-Dimethyl-2-propenyl)-5,9,10-trihydroxy-2,2-dimethyl-2H-pyran-1(3,2-b)-xanthene-6-one*; Acta Cryst. E 62, o130-o132.
- Gales, L., Damas, A.M. (2005). *Xanthones-A Structural Perspective*; Curr. Med. Chem. 12, 2499-2515.
- Geissman, T.A., Crout, D.H.G. (1969). *Organic Chemistry of Secondary Plant Metabolism*; pp. 373-391; Freeman, Cooper & Company; California, USA.
- Goh, S.H., Jantan, I., Gray, A.I., Waterman, P.G. (1992). *Prenylated xanthones from Garcinia opaca*; Phytochemistry 31(4), 1383-1386.
- Gonda, R., Takeda, T., Akiyama, T. (2000). *Studies on the Constituents of Anaxagorea luzonensis* A. Gray; Chem. Pharm. Bull. 48(8), 1219-1222.
- Gopalakrishnan, G., Balaganesan, B. (2000). *Two novel xanthones from Garcinia mangostana*; Fitoterapia 71, 607-609.
- Gopalakrishnan, G., Banumathi, B., Suresh, G. (1997). *Evaluation of the Antifungal Activity of Natural Xanthones from Garcinia mangostana and their Synthetic Derivatives*; J. Nat. Prod. 60, 519-524.
- Gottlieb, O.R., Magalhães, M.T., Pereira, M.O.S., Mesquita, A.A.L., Corrêa, D.B., Oliveira, G.G. (1968). *The Chemistry of Brazilian Guttiferæ-XII. Isoprenylated xanthones from Kalmeyera and Calophyllum species*; Tetrahedron 24, 1601-1610.
- Govindachari, T.R., Kalyanaram, P.S., Muthukumaraswamy, N., Pai, B.R. (1971). *Xanthones of Garcinia mangostana* Linn.; Tetrahedron 27(16), 3919-3926.
- Groweiss, A., Cardellina, II, J.H., Boyd, M.R. (2000). *HIV-Inhibitory Prenylated Xanthones and Flavones from Macleura victoriae*; J. Nat. Prod. 63, 1537-1539.
- Gunasekera, S., Sotheeswaran, S., Sultanbawa, M. (1981). *Two New Xanthones, Calozeyloxanthone and Zeyloxanthone, from Calophyllum zeylanicum (Guttiferæ)*; J. Chem. Soc. Perkin Trans. 1, 1831-1835.
- Guo, Q.-L., Lin, S.-S., You, Q.-D., Gu, H.-Y., Yu, J., Zhao, L., Qi, Q., Liang, F., Tan, Z., Wang, X. (2006a). *Inhibition of human telomerase reverse transcriptase gene expression by Gambogic acid in human hepatoma SMMC-7721 cells*; Life Sci. 78, 1238-1245.
- Guo, Q.-L., Qi, Q., You, Q.-D., Gu, H.-Y., Zhao, L., Wu, Z. (2006b). *Toxicological studies of Gambogic acid and its potential targets in experimental animals*; Basic Clin. Pharmacol. Toxicol. 99, 178-184.
- Guo, Q.-L., You, Q.-D., Wu, Z.-Q., Yuan, S.-T., Zhao, L. (2004). *Gambogic acids inhibited growth of human hepatoma SMMC-7721 in vitro and in nude mice*; Acta Pharmacol. Sin. 25(6), 769-774.
- Gupta, P., Lewis, J.R. (1971). *Biogenesis of Xanthones in Gentiana-Lutea*; J. Chem. Soc. C, 629-631.
- Hamada, M., Ikubo, K., Ishikawa, Y., Ikeda, A., Umezawa, K., Nishiyama, S. (2003). *Biological Activities of a-Mangostin Derivatives against Acid Sphingomyelinase*; Bioorg. Med. Chem. Lett. 13, 3151-3153.
- Han, C.-R., Song, X.-P., Chen, G.-Y. (2003). *Advances in the studies on chemical components of calophyllum and related pharmacological activities*; Chin. J. Org. Chem. 23, 212-219.
- Han, Q.-B., Wang, Y.-L., Yang, L., Tso, T.-F., Qiao, C.-F., Song, J.-Z., Xu, L.-J., Chen, S.-L., Yang, D.-J., Xu, H.-X. (2006a). *Cytotoxic Polyphenylated Xanthones from the Resin of Garcinia hanburyi*; Chem. Pharm. Bull. 54(2), 265-267.
- Han, Q., Yang, L., Liu, Y., Wang, Y., Qiao, C., Song, J., Xu, L., Yang, D., Chen, S., Xu, H. (2006b). *Gambogic Acid and EpiGambogic Acid, C-2 Epimers with Novel Anticancer Effects from Garcinia hanburyi*; Planta Med. 72, 281-284.
- Han, Q.-B., Yang, L., Wang, Y.-L., Qiao, C.-F., Song, J.-Z., Sun, H.-D., Xu, H.-X. (2006c). *A Pair of Novel Cytotoxic Polyphenylated Xanthone Epimers from Gamboges*; Chem. & Biodiversity 3, 101-105.
- Hano, Y., Matsumoto, Y., Shinohara, K., Sun, J.Y., Nomura, T. (1991a). *Structures of Four New Isoprenylated Xanthones, Cudraxanthones L, M, N, and O from Cudrania tricuspidata*; Planta Med. 57, 172-175.
- Hano, Y., Okamoto, T., Nomura, T. (1991b). *Components of the Root Bark of Moris insignis Bur. 2. Structures of Four New Isoprenylated Xanthones, Morisignins E, F, G and H; Heterocycles* 32(7), 1357-1364.
- Hano, Y., Okamoto, T., Suzuki, K., Negishi, M., Nomura, T. (1993). *Components of the Root Bark of Moris insignis Bur. 3. Structures of Three New Isoprenylated Xanthones, Morisignins I, J, and K and an Isoprenylated Flavone Morisignin L; Heterocycles* 36(6), 1359-1366.
- Hao, K., Liu, X.-Q., Wang, G.-J. (2005a). *Pharmacokinetics of Gambogic acid in dogs*; Chin. J. Nat. Med. (Zhongguo Tianran Yaowu) 3, 312-315.
- Hao, K., Liu, X.-Q., Wang, G.-J. (2005b). *Pharmacokinetics of Gambogic acid in rats*; J. Chin. Pharm. Uni. 36, 338-345.
- Hay, A.-E., Aumond, M.-C., Mallet, S., Dumontet, V., Litaudon, M., Rondeau, D., Richomme, P. (2004a). *Antioxidant Xanthones from Garcinia vieillardii*; J. Nat. Prod. 67, 707-709.
- Hay, A.-E., Hélesbeux, J.-J., Duval, O., Labaëd, M., Grellet, P., Richomme, P. (2004b). *Antimalarial xanthones from Calophyllum caldonicum and Garcinia vieillardii*; Life Sci. 75, 3077-3085.
- Hay, A.-E., Guillet, D., Morel, C., Larcher, G., Macherel, D., Le Ray, A.-M., Litaudon, M., Richomme, P. (2003). *Antifungal Chromans Inhibiting the Mitochondrial Respiratory Chain of Pea Seeds and New Xanthones from Calophyllum caldonicum*; Planta Med. 69, 1130-1135.
- Helesbeux, J.J., Duval, O., Dartiguelongue, C., Séraphin, D., Oger, J.M., Richomme, P. (2004). *Synthesis of 2-hydroxy-3-methyl-3-enyl substituted coumarins and xanthones as natural products. Application of the Schenck ene reaction of singlet oxygen with ortho-prenylphenol precursors*; Tetrahedron 60, 2293-2300.
- Ho, C.-K., Huang, Y.-L., Chen, C.-C. (2002). *Garcione E, a Xanthone Derivative, has Potent Cytotoxic Effect Against Hepatocellular Carcinoma Cell Lines*; Planta Med. 68, 975-979.
- Hou, A.J., Fukui, T., Shimazaki, M., Sakagami, H., Sun, H.D., Nomura, T. (2001). *Benzophenones and Xanthones with Isoprenoid Groups from Cudrania cochinchinensis*; J. Nat. Prod. 64, 903-906.
- Huang, Y.-L., Chen, C.-C., Chen, Y.-J., Huang, R.-L., Shieh, B.-J. (2001). *Three xanthones and a Benzophenone from Garcinia mangostana*; J. Nat. Prod. 64, 903-906.
- Hwang, J.H., Hong, S.S., Han, X.H., Hwang, J.S., Lee, D., Lee, H., Yun, Y.P., Kim, Y., Ro, J.S., Hwang, B.Y. (2007). *Prenylated Xanthones from the Root Bark of Cudrania tricuspidata*; J. Nat. Prod. 70(7), 1207-1209.
- Iikubo, K., Ishikawa, Y., Ando, N., Umezawa, K., Nishiyama, S. (2002). *The first direct synthesis of a-mangostin, a potent inhibitor of the acidic sphingomyelinase*; Tetrahedron Lett. 43, 291-293.

- Inuma, M., Ito, T., Tosa, H., Tanaka, T., Miyake, R., Chelladurai, V. (1997). Prenylated Xanthonoids from *Calophyllum Apetalum*; Phytochemistry **46**(8), 1423-1429.
- Inuma, M., Tosa, H., Tanaka, T., Shimano, R., Asai, F., Yonemori, S. (1994b). Two Xanthones from root bark of *Garcinia subelliptica*; Phytochemistry **35**(5), 1355-1360.
- Inuma, M., Tosa, H., Tanaka, T., Yonemori, S. (1994b). Two New Xanthones in the Underground Part of *Calophyllum inophyllum*; Heterocycles **37**(2), 833-838.
- Inuma, M., Tosa, H., Tanaka, T., Yonemori, S. (1994c). Two xanthones from root bark of *Calophyllum inophyllum*; Phytochemistry **35**(2), 527-532.
- Inuma, M., Tosa, H., Tanaka, T., Asai, F., Shimano, R. (1995a). Three xanthones from root bark of *Garcinia subelliptica*; Phytochemistry **38**(1), 247-249.
- Inuma, M., Tosa, H., Tanaka, T., Asai, F., Shimano, R. (1995b). Two xanthones with a 1,1-dimethylallyl group in root bark of *Garcinia subelliptica*; Phytochemistry **39**(4), 945-947.
- Inuma, M., Tosa, H., Tanaka, T., Asai, F., Shimano, R. (1995c). Two New Xanthones from the Root Bark of *Garcinia subelliptica*; Heterocycles **40**(1), 279-284.
- Inuma, M., Ito, T., Tosa, H., Tanaka, T. (1996a). Five New Xanthones from *Garcinia dulcis*; J Nat Prod **59**, 472-475.
- Inuma, M., Tosa, H., Ito, T., Tanaka, T., Madulid, D.A. (1996b). Two Xanthones from roots of *Cratogeomys formosanus*; Phytochemistry **42**(4), 1195-1198.
- Inuma, M., Tosa, H., Tanaka, T., Asai, F., Kobayashi, Y., Shimano, R., Miyauchi, K.-I. (1996c). Antibacterial Activity of Xanthones from Gutiferous Plants against Methicillin-resistant *Staphylococcus aureus*; J Pharm Pharmacol **48**, 861-865.
- Inuma, M., Tosa, H., Tanaka, T., Riswan, S. (1996d). Three New Xanthones from the Bark of *Garcinia dioica*; Chem Pharm Bull **44**(1), 232-234.
- Ishiguro, K., Fukumoto, H., Saitani, A., Nakajima, M., Itoi, K. (1996). Prenylated Xanthones from Cell Suspension Cultures of *Hypericum Patulum*; Phytochemistry **42**(2), 435-537.
- Ishiguro, K., Nagayama, N., Saitani, A., Fukumoto, H. (1997). A Prenylated Xanthone from Cell Suspension Cultures of *Hypericum Patulum*; Phytochemistry **44**(6), 1065-1066.
- Ishiguro, K., Nakajima, M., Fukumoto, H., Itoi, K. (1995a). Co-occurrence of Prenylated Xanthones and their Cyclization products in cell suspension cultures of *Hypericum Patulum*; Phytochemistry **38**(4), 867-869.
- Ishiguro, K., Nakajima, M., Fukumoto, H., Itoi, K. (1995b). A Xanthone Substituted with an Irregular Monoterpene in Cell Suspension Cultures of *Hypericum Patulum*; Phytochemistry **39**(4), 903-905.
- Ito, C., Itoigawa, M., Furukawa, H., Rao, K.S., Enjo, F., Bu, P., Takayasu, J., Tokuda, H., Nishino, H. (1998). Xanthones as inhibitors of Epstein-Barr virus activation; Cancer Lett **132**, 113-117.
- Ito, C., Itoigawa, M., Mishina, Y., Filho, V.C., Enjo, F., Tokuda, H., Nishino, H., Furukawa, H. (2003a). Chemical Constituents of *Calophyllum brasiliense*. 2. Structure of Three New Coumarins and Cancer Chemopreventive Activity of 4-Substituted Coumarins; J Nat Prod **66**, 368-371.
- Ito, C., Itoigawa, M., Takakura, T., Ruangrungrat, N., Enjo, F., Tokuda, H., Nishino, H. (2003b). Chemical constituents of *Garcinia lucas*: Structure Elucidation of Eight New Xanthones and Their Cancer Chemopreventive Activity; J Nat Prod **66**, 200-205.
- Ito, C., Itoigawa, M., Mishina, Y., Filho, V.C., Mukainaka, T., Tokuda, H., Nishino, H., Furukawa, H. (2002). Chemical Constituents of *Calophyllum brasiliensis*: Structure Elucidation of Seven New Xanthones and their Cancer Chemopreventive Activity; J Nat Prod **65**, 267-272.
- Ito, C., Mishina, Y., Litauon, M., Cosson, J.-P., Furukawa, H. (2000). Xanthone and dihydrocoumarin from *Monrocziera sphaerocarpa*; Phytochemistry **53**, 1043-1046.
- Ito, C., Miyamoto, Y., Nakayama, M., Kawai, Y., Rao, K.S., Furukawa, H. (1997). A Novel Depsidone and Some New Xanthones from *Garcinia Species*; Chem Pharm Bull **45**(9), 1403-1413.
- Ito, C., Miyamoto, Y., Rao, K.S., Furukawa, H. (1996). A Novel Dibenzofuran and Two New Xanthones from *Calophyllum pumiliflorum*; Chem Pharm Bull **44**(2), 441-443.
- Jantan, I., Juriyati, J., Warif, N.A. (2001). Inhibitory effects of xanthones on platelet activating factor receptor binding in vitro; J Ethnopharmacol **75**, 287-290.
- Jantan, I., Pissar, M.M., Idris, M.S., Taher, M., Ali, R.M. (2002). In Vitro Inhibitory Effect of Rubraxanthone Isolated from *Garcinia parvifolia* on Platelet-Activating Factor Receptor Binding; Planta Med **68**, 1133-1134.
- Jefferson, A., Quillinan, A.J., Scheinmann, F., Sim, K.Y. (1970). Studies in the xanthone series; Aust J Chem **23**, 2539-2543.
- Jefferson, A., Scheinmann, F. (1996). Studies in the Xanthone Series. Part VIII. An Unambiguous Synthesis of *Jacareubin*; J Chem Soc (C), 1751-178.
- Jensen, S.R., Schripsema, J. (2002). Gentianaceae: Systematics and Natural History; Chap. 6, Cambridge University Press.
- Ji, H.-F., Tang, G.-Y., Zhang, H.-Y. (2005). Theoretical Elucidation of DPPH Radical-Scavenging Activity Difference of Antioxidant Xanthones; QSAR Comb Sci **24**, 826-830.
- Ji, H.-F., Zhang, H.-Y. (2006). Theoretical evaluation of flavonoids as multipotent agents to combat Alzheimer's disease; J Mol Struct Theorchem **767**, 3-9.
- Jinsart, W., Ternai, B., Buddhasukh, D., Polya, G.M. (1992). Inhibition of wheat embryo calcium-dependent protein kinase and other kinases by Mangostin and α -Mangostin; Phytochemistry **31**(11), 3711-3713.
- Jung, H.-A., Su, B.-N., Keller, W.J., Mehta, R.G., Kinghorn, A.D. (2006). Antioxidant Xanthones from the Pericarp of *Garcinia mangostana* (Mangosteen); J Agric Food Chem **54**, 2077-2082.
- Kardono, L.B.S., Hanafi, M., Sherley, G., Kosela, S., Harrison, L.J. (2006). Bioactive Constituents of *Garcinia porrecta* and *G. parvifolia* Grown in Indonesia; Pak J Biol Sci **9**(3), 483-486.
- Kijjoa, A., Gonzalez, M.J., Alonso, C.M., Pinto, M.M.M., Anantachoke, C., Herz, W. (2000). Xanthones from *Calophyllum teysmannii* var. *inophyllode*; Phytochemistry **53**, 1021-1024.
- Kinghorn, A.D., Farnsworth, N.R., Soejarto, D.D., Cordell, G.A., Swanson, S.M., Pezzuto, J.M., Wani, M.C., Wall, M.E., Oberlies, N.H., Kroll, D.J., Kramer, R.A., Rose, W.C., Vite, G.D., Fairchild, C.R., Peterson, R.W., Wild, R. (2003). Novel Strategies for the Discovery of Plant-Derived Anticancer Agents; Pharmaceutical Biol **41**(6), 53-67.
- Konguem, J., Meli, A.L., Manfouo, R.N., Lonsi, D., Ngounou, F.N., Kuete, V., Kamdem, H.W., Tane, P., Ngadjui, B.T., Sondengam, B.L., Connolly, J.D. (2005). Xanthones from *Garcinia smeathmannii* (Oliver) and their antimicrobial activity; Phytochemistry **66**, 1713-1717.
- Kosela, S., Hu, L. H., Rachmatia, T., Hanafi, M., Sim, K.Y. (2000). Dulxanthones F-H, Three New Pyranoxanthones from *Garcinia dulcis*; J Nat Prod **63**, 406-407.
- Kosela, S., Hu, L.H., Yip, S.C., Rachmatia, T., Sukri, T., Daulay, T.S., Tan, G.K., Vittal, J.J., Sim, K.Y. (1999). Dulxanthone E: a pyranoxanthone from the leaves of *Garcinia dulcis*; Phytochemistry **52**, 1375-1377.
- Kralj, A., Kehraus, S., Krick, A., Eguereva, E., Kelter, G., Maurer, M., Wortmann, A., Fiebig, H.-H., König, G.M. (2006). *Arigovins G and H*: Prenylated Polyketides from the Marine-Derived Fungus *Emeticella nidulans* var. *arigovata*; J Nat Prod **69**, 995-1000.
- Kuzuyama, T., Noel, J.P., Richard, S.B. (2005). Structural basis for promiscuous biosynthetic prenylation of aromatic products I: Nature **435**(16), 983-987.
- Lannang, A.M., Konguem, J., Ngninzeke, F.N., Tangmouo, J.G., Lonsi, D., Ajaz, A., Choudhary, M.I., Rajjit, R., Devkota, K.P., Sondengam, B.L. (2005). *Banggangxanthone A and B*, two xanthones from the stem bark of *Garcinia polyantha* Olin.; Phytochemistry **66**, 2351-2355.

- Laphookhieo, S., Svers, J.K., Kiattansakul, R., Chantapromma, K. (2006). Cytotoxic and Antimalarial Prenylated Xanthones from *Cratoxylum cochinchinense*; Chem Pharm Bull **54**(5), 745-747.
- Larcher, G., Morel, C., Tronchin, G., Landreau, D., Séraphin, D., Richomme, P., Bouchara, J.-P. (2004). Investigation of the Antifungal Activity of Caledonian xanthone E and other Xanthones against *Aspergillus fumigatus*; Planta Med **70**, 569-571.
- Lee, B.W., Gal, S.W., Park, K.M., Park, K.H. (2005a). Cytotoxic Xanthones from *Cudrania tricuspidata*; J Nat Prod **68**, 456-458.
- Lee, B.W., Lee, J.H., Lee, S.-T., Lee, H.S., Jeong, T.-S., Park, K.H. (2005b). Antioxidant and cytotoxic activities of xanthones from *Cudrania tricuspidata*; Bioorg Med Chem Lett **15**, 5548-5552.
- Lee, H.-H. (1981). Synthesis of the Mangostins; J Chem Soc Perkin Trans 1, 3205-3213.
- Lenta B.N., Ngouela, S., Nougoué, D.T., Tsamo, E., Connolly J.D. (2004). *Symphonin*: A New Prenylated Pyranoxanthone with Antimicrobial Activity from the Seeds of *Symphonia globulifera* (Guttiferae); Bull Chem Soc Ethiop **18**(2), 175-180.
- Lin, L.J., Lin, L.Z., Pezzuto, J.M., Cordell, A. (1993). *IsoGambogic acid and Isomorellinol from Garcinia Hanburyi*; Magn Reson Chem **31**, 340-347.
- Lloyd, A.W. (1997). Novel Pyranoxanthones; DDT **2**(7), 301-306.
- Locksley, H.D., Quillinan, A.J., Scheinmann, F. (1971). Extractives from Guttiferae. Part XXIII. An Unambiguous Synthesis of 6-Deoxyacareubin and Related 3,3- and 1,1-Dimethylidyl and Amulated Xanthones; J Chem Soc (C), 3804-3814.
- Lu, Z.X., Hasmeda, M., Mahabusarakam, W., Ternai, B., Ternai P.C., Polya, J.M. (1998). Inhibition of eukaryote protein kinases and of a cyclic nucleotide-binding phosphatase by prenylated xanthones; Chem-Biol Interact **114**, 121-140.
- Mahabusarakam, W., Chairerk, P., Taylor, W.C. (2005). Xanthones from *Garcinia cowa* Roxb. latex; Phytochemistry **66**, 1148-1153.
- Mahabusarakam, W., Kuaha, K., Wilairat, P., Taylor, W.C. (2006a). Prenylated xanthones as potential antiparasitic substances; Planta Med **72**(10), 912-916.
- Mahabusarakam, W., Nuangmowarat, W., Taylor, W.C. (2006b). Xanthone derivatives from *Cratoxylum cochinchinense* roots; Phytochemistry **67**, 470-474.
- Mahabusarakam, W., Pakawatchai, C., Wiriyaichitra, P., Taylor, W.C., Skelton, B.W., White, A.H. (1998). *Bicyclomangostin: a New Acid Catalyzed Cyclization Product from Mangostin*; Aust J Chem **51**, 249-254.
- Mahabusarakam, W., Wiriyaichitra, P., Taylor, W.C. (1987). Chemical Constituents of *Garcinia mangostana*; J Nat Prod **50**(3), 474-478.
- Makmur, L., Tukiran, S., Achmad, S.A., Aimi, N., Hakim, E.H., Kitajima, M., Takayama, H. (2000). *Arindonesianin C, a New Xanthone Derivative from Arocarpus teysmanii*; J Nat Prod **63**, 243-244.
- Malathi, R., Kabaleeswaran, V., Rajan, S.S. (2000). Structure of mangostin; J Chem Crystallogr **30**(3), 203-205.
- Malmström, J., Christophersen, C., Barrero, A.F., Oltra, J.E., Justicia, J., Rosales, A. (2002). Bioactive Metabolites from a Marine-Derived Strain of the Fungus *Emericella varicolor*; J Nat Prod **65**, 364-367.
- Mandal, S., Das, P.C., Joshi, P.C. (1992). Naturally Occurring Xanthones from Terrestrial Flora; J Indian Chem Soc **69**, 611-636.
- Marques, V.L.L., de Oliveira, F.M., Conserva, L.M., Brito, R.G.L., Guillon, G.M.S.P. (2000). *Dichromenoxanthones from Tovomitia brasiliensis*; Phytochemistry **55**, 815-818.
- Marston, A., Maillard, M., Hostettmann, K. (1993). Search for antifungal, molluscicidal and larvicidal compounds from African medicinal plants; J Ethnopharmacol **38**, 215-223.
- Matsumoto, K., Akao, Y., Kobayashi, E., Ohguchi, K., Ito, T., Tanaka, T., Inuma, M., Nozawa, Y. (2003). Induction of Apoptosis by Xanthones from Mangosteen in Human Leukemia Cell Lines; J Nat Prod **66**, 1124-1127.
- Matsumoto, K., Akao, Y., Ohguchi, K., Ito, T., Tanaka, T., Inuma, M., Nozawa, Y. (2005). Xanthones induce cell-cycle arrest and apoptosis in human colon cancer DLD-1 cells; Bioorg Med Chem Lett **13**, 6064-6069.
- Matsumoto, K., Akao, Y., Yi, H., Ohguchi, K., Ito, T., Tanaka, T., Kobayashi, E., Inuma, M., Nozawa, Y. (2004). Preferential target is mitochondria in α -mangostin-induced apoptosis in human leukemia HL60 cells; Bioorg Med Chem **12**, 5799-5806.
- Mbwambo, Z.H., Kapingu, M.C., Moshi, M.J., Machumi, F., Apers, S., Côté, P., Ferreira, D., Marais, J.P.J., Beghe, D.V., Maes, L., Vlietinck, A., Pieters, L. (2006). Antiparasitic Activity of Some Xanthones and Biflavonoids from the Root Bark of *Garcinia livingstonei*; J Nat Prod **69**, 369-372.
- Merza, J., Aumond, M.-C., Rondeau, D., Dumontet, V., Le Ray, A.-M., Séraphin, D., Richomme, P. (2004). Prenylated Xanthones and Tocotrienols from *Garcinia virgata*; Phytochemistry **65**, 2915-2920.
- Minami, H., Kinoshita, M., Fukuyama, Y., Kodama, M., Yoshizawa, T., Sugitara, M., Nakagawa, K., Tago, H. (1994). Antioxidant Xanthones from *Garcinia subelliptica*; Phytochemistry **36**(2), 501-506.
- Minami, H., Kuwayama, A., Yoshizawa, T., Fukuyama, Y. (1996). Novel Prenylated Xanthones with Antioxidant Property from the Wood of *Garcinia subelliptica*; Chem Pharm Bull **44**(11), 2103-2106.
- Molinar-Toribio, E., González, J., Ortega-Barria, E., Capson, T.L., Coley, P.D., Kursar, T.A., McPhail, K., Cubilla-Rios, L. (2006). Antiproteasomal Activity against Plasmodium falciparum and Trypanosoma cruzi of Xanthones Isolated from *Chrysoclamys tenuis*; Pharmaceutical Biol **44**(7), 550-553.
- Monache, F.D., Botta, B., Nicoletti, M., Coelho, J.S.B., Lyra, F.D.A. (1981). Three New Xanthones and Maculaxanthone from *Rheedia benthamiana* Pl. Triana (Guttiferae); J Chem Soc Perkin Trans 1, 484-488.
- Monache, F.D., Ferrari, F., Pomponi, M. (1984a). Flavanones and Xanthones from *MacLura Pomifera*; Phytochemistry **23**(7), 1489-1491.
- Monache, G.D., Botta, B., Mello, J.F., Coelho, J.S.B., Menichini, F. (1984b). Chemical Investigation of the Genus *Rheedia*. IV. Three New Xanthones from *Rheedia brasiliensis*; J Nat Prod **47**(4), 620-625.
- Monache, G.D., Monache, F.D., Bettolo, G.B.M., Lima, R.A. (1983). Chemical Investigation of the Genus *Rheedia*. Prenylated Xanthones from *Rheedia Gardneriana*; J Nat Prod **46**(5), 655-659.
- Mondal, M., Puranik, V.G., Argade, N.P. (2006). Facile Synthesis of 1,3,7-Trihydroxyxanthone and its Regioselective Coupling Reactions with Prenyl: Simple and Efficient Access to Osgiaxanthone and Nigrolinexanthone F; J Org Chem **71**, 4992-4995.
- Morel, C., Hay, A.-E., Litaudon, M., Sévenet, T., Séraphin, D., Bruneton, J., Richomme, P. (2002a). Thirteen New Xanthone Derivatives from *Calophyllum caledonicum* (Clusiaceae); Molecules **7**, 38-50.
- Morel, C., Séraphin, D., Teyrouz, A., Larcher, G., Bouchara, J.-P., Litaudon, M., Richomme, P., Bruneton, J. (2002b). New and Antifungal Xanthones from *Calophyllum caledonicum*; Planta Med **68**, 41-44.
- Morel, C., Séraphin, D., Oger, J.-M., Litaudon, M., Sévenet, T., Richomme, P., Bruneton, J. (2000). New Xanthones from *Calophyllum caledonicum*; J Nat Prod **63**, 1471-1474.
- Nagem, T.J., Werle, A.A., Carvalho, M.G., Mesquita, A.A.L. (1997). The complete assignment of ^1H and ^{13}C -NMR of Prenylated Xanthones from *Tovomitia* spp. (Guttiferae); J Braz Chem Soc **8**(3), 285-288.
- Nakatani, K., Nakahata, N., Arakawa, T., Yasuda, H., Ohizumi, Y. (2002). Inhibition of cyclooxygenase and prostaglandin E_2 synthesis by α -mangosteen, a xanthone derivative in mangosteen, in C6 rat glioma cells; Biochem Pharmacol **63**, 73-79.

- Nakatani, K., Yamakuni, T., Kondo, N., Arakawa, T., Oosawa, K., Shimura, S., Inoue, H., Ohizumi, Y. (2004). *g-Mangosin Inhibits Inhibitor-1B Kinase Activity and Decreases Lipopolysaccharide-Induced Cyclooxygenase-2 Gene Expression in Co Rat Glioma Cells*; Mol Pharmacol **66**(3), 667-674.
- Nandaing, U., Aroonker, N., Suksumram, S., Danwisetkanjana, K., Suenboonrueng, J., Arjchomphu, W., Suksumram, A. (2006). *Bioactive Constituents of the Root Bark of Artocarpus rigidus subsp. rigidus*; Chem Pharm Bull **54**(10), 1433-1436.
- Nogueira, S., Lenta, B.N., Nougoué, D.T., Ngoupayo, J., Boyom, F.F., Tsamo, E., Gut, J., Rosenthal, P.J., Connolly, J.D. (2006). *Anti-plasmodial and antioxidant activities of constituents of the seed shells of Symphonia globulifera Linn f.*; Phytochemistry **67**, 302-306.
- Nogueira, S., Ndjakou, B.L., Tchamo, D.N., Zelefsack, F., Tsamo, E., Connolly, J.D. (2005a). *A Prenylated Xanthone with Antimicrobial Activity from the Seeds of Symphonia globulifera*; Nat. Prod. Res **19**(1), 23-27.
- Nogueira, S., Zelefsack, F., Lenta, B.N., Nguamegne, E.T., Tchamo, D.N., Tsamo, E., Connolly, J.D. (2005b). *Xanthones and other constituents of Allanblackia monticola (Guttiferaceae)*; Nat. Prod. Res **19**(7), 685-688.
- Ngumeving, J.R., Azebaze, A.G.B., Kuete, V., Carly, N.N.E., Beng, Y.P., Meyer, M., Blond, A., Bodo, B., Nkengfack, A.E. (2006). *Laurentianxanthones A and B, antimicrobial xanthones from Vismia laurentii*; Phytochemistry **67**, 1341-1346.
- Nguyen, L.H.D., Harrison, L.J. (1998). *Triterpenoid and xanthone constituents of Cratogeomys cochinchinense*; Phytochemistry **50**, 471-476.
- Nguyen, L.H.D., Harrison, L.J. (2000). *Xanthones and triterpenoids from the bark of Garcinia vilseniana*; Phytochemistry **53**, 111-114.
- Nguyen, L.H.D., Vo, H.T., Pham, H.D., Connolly, J.D., Harrison, L.J. (2003). *Xanthones from the bark of Garcinia meruensis*; Phytochemistry **63**, 467-470.
- Nicolaou, K.C., Li, J. (2001). *Biomimetic Cascade Reactions in Organic Synthesis: Construction of 4-Oxatricyclo-(4.3.1.0)decan-2-one Systems and Total Synthesis of 1-O-Methylforbesinone via Tandem Claisen Rearrangement/Diels-Alder Reactions*; Angew. Chem. Int. Ed. **40**(22), 4264-4268.
- Nilar, L.J.H. (2002). *Xanthones from the heartwood of Garcinia mangostana*; Phytochemistry **60**, 541-548.
- Nilar, L.H.D.N., Venkatraman, G., Sim, K.Y., Harrison, L.J. (2005). *Xanthones and benzophenones from Garcinia griffithii and Garcinia mangostana*; Phytochemistry **66**, 1718-1723.
- Nkengfack, A.E., Azebaze, G.A., Vardamides, J.C., Fomum, Z.T., Heerden, F.R.V. (2002a). *A prenylated xanthone from Allanblackia floribunda*; Phytochemistry **60**, 381-384.
- Nkengfack, A.E., Mkounga, P., Fomum, Z.T., Meyer, M., Bodo, B. (2002b). *Globalixanthones A and B, two new cytotoxic xanthones with isoprenoid groups from the root bark of Symphonia globulifera*; J. Nat. Prod. **65**, 734-736.
- Nkengfack, A.E., Mkounga, P., Meyer, M., Fomum, Z.T., Bodo, B. (2002c). *Globalixanthones C, D and E, three prenylated xanthones with antimicrobial properties from the root bark of Symphonia globulifera*; Phytochemistry **61**, 181-187.
- Noldin, V.F., Islas, D.B., Filho, V.C. (2006). *Gênero Calophyllum: Importância Química e Farmacológica*; Quim. Nova **29**(3), 549-554. (Brazilian).
- Nomura, T., Hano, Y. (1994). *Isoprenoid-substituted Phenolic Compounds of Moraceae Plants*; Nat. Prod. Rep. **205**-218.
- Núñez, M.B., Magaña, F.P., Okalik, N.B., Castro, E.A. (2004). *QSAR modeling of the MAO inhibitory activity of xanthones derivatives*; Bioorg. Med. Chem. Lett. **14**, 5611-5617.
- Oger, J.-M., Morel, C., Helesbeux, J.-I., Litaudon, M., Séraphin, D., Dartiguelongue, C., Larcher, G., Richomme, P., Duval, O. (2003). *First 2 Hydroxy-3-Methylbut-3-enyl substituted xanthones isolated from plants: Structure Elucidation, Synthesis and Antifungal Activity*; Nat. Prod. Res **17**, 195-199.
- Ohizumi, Y., Li, Y. (2004). *Search for Constituents with Neurotrophic Factor-Potentiating Activity from the Medicinal Plants of Paraguay and Thailand*; Yakugaku Zasshi **124**(7), 417-424.
- Okawa, H., Tokiwano, T. (2004). *Enzymatic catalysis of the Diels-Alder reaction in the biosynthesis of natural products*; Nat. Prod. Rep. **21**, 321-352.
- Okudaira, C., Ikeda, Y., Kondo, S., Hirabayashi, Y., Koyano, T., Saito, Y., Umezawa, K. (2000). *Inhibition of Acidic Sphingomyelinase by Xanthone Compounds Isolated from Garcinia speciosa*; J. Enzyme. Inhib. **15**, 129-138.
- Panthong, K., Pongcharoen, W., Phongpachit, S., Taylor, W.C. (2006). *Tetraoxygenated xanthones from the fruits of Garcinia cowa*; Phytochemistry **67**, 999-1004.
- Park, K.H., Park, Y.-D., Han, J.-M., Im, K.-R., Lee, B.W., Jeong, I.Y., Jeong, T.-S., Lee, W.S. (2006). *Anti-atherosclerotic and anti-inflammatory activities of catecholic xanthones and flavonoids isolated from Cudrania tricuspidata*; Bioorg. Med. Chem. Lett. **16**, 5580-5583.
- Pasqua, G., Avato, P., Monacelli, B., Santamaria, A.R., Argentieri, M.P. (2003). *Metabolites in cell suspension cultures, calli, and in vitro regenerated organs of Hypericum perforatum cv. Tapas*; Plant Sci. **165**, 977-982.
- Pattalung, P., Thongthearaparp, W., Wiriyachitra, P., Taylor, W.C. (1994). *Xanthones of Garcinia cowa*; Planta Med. **60**, 365-368.
- Pattanaaprateeb, P., Ruangrunsi, N., Cordell, G.A. (2005). *Cytotoxic Constituents from Cratogeomys arborescens*; Planta Med. **71**, 181-183.
- Peres, V., Nagem, T.J. (1997a). *Naturally Occurring Penta-oxygenated, Hexa-oxygenated and Dimeric Xanthones: A Literature Survey*; Quim. Nova **20**, 388-397.
- Peres, V., Nagem, T.J. (1997b). *Tri-oxygenated Naturally Occurring Xanthones*; Phytochemistry **44**, 191-214.
- Peres, V., Nagem, T.J., Oliveira, F.F. (2000). *Tetraoxygenated naturally occurring xanthones*; Phytochemistry **55**, 683-710.
- Perez G.R.M. (2003). *Antiviral Activity of Compounds Isolated From Plants*; Pharmaceutical Biol. **41**(2), 107-157.
- Peters, S., Schmidt, W., Beerhues, L. (1998). *Regioselective oxidative phenol couplings of 2,3',4,6'-tetrahydroxybenzophenone in cell cultures of Centaurea erythraea RAFN and Hypericum androsaemum L.*; Planta **204**, 64-69.
- Pinheiro, L., Cortez, D., Vidotti, G.I., Young, M., Ferreira, A.G. (2003a). *Estudo fitoquímico e avaliação da atividade moluscicida da kielmeyera variabilis Mart (Clusiaceae)*; Quim. Nova **26**(2), 157-160; (Brazilian).
- Pinheiro, L., Nakamura, C.V., Filho, B.P.D., Ferreira, A.G., Young, M.C.M., Cortez, D.A.G. (2003b). *Antibacterial Xanthones from Kielmeyera variabilis Mart. (Clusiaceae)*; Mem. Inst. Oswaldo Cruz **98**, 549-552.
- Pinto, M.M.M., Sousa, E.P. (2003). *Natural and Synthetic Xanthonolignoids: Chemistry and Biological Activities*; Curr. Med. Chem. **10**, 1-12.
- Pinto, M.M.M., Sousa, M.E., Nascimento, M.S.J. (2005). *Xanthone Derivatives: New Insights in Biological Activities*; Curr. Med. Chem. **12**, 2517-2538.
- Pojer, F., Wemakor, E., Kammerer, B., Chen, H.W., Wölsh, C.T., Li, S.M., Heide, L. (2003). *Cloq, a Prenyltransferase Involved in Chlorobacin Biosynthesis*; Proc. Natl. Acad. Sci. USA **100**(5), 2316-2321.
- Pornpakul, S., Liangsakul, J., Ngamrojanavanich, N., Roengsumman, S., Sihanonth, P., Piapukiew, J., Sangvichien, E., Puthong, S., Peisom, A. (2006). *Cytotoxic Activity of Four Xanthones from Emericella varicolor, an Endophytic Fungus Isolated from Crotan oblongifolius*; Arch. Pharm. Res **29**(2), 140-144.

- Quillinan, A.J., Scheinmann, F. (1971). *Application of the Claisen Rearrangement to the Synthesis of Heterocyclic Bicyclo[2.2.2]octenones: an Approach to the Morellins Based on New Biogenetic Suggestions*. *J Chem Soc Chem Commun* **16**, 966-967.
- Rath, G., Potterat, O., Mavi, S., Hostettmann, K. (1996). *Xanthones from Hypericum Roeperianum*; *Phytochemistry* **43**(2), 513-520.
- Reutrakul, V., Chnakul, W., Pohmakul, M., Jaipetch, T., Yoosook, C., Kasit, J., Napaswat, C., Santisak, T., Prabpai, S., Kongsere, P., Tuchinda, P. (2006). *Anti-HIV-1 Constituents from Leaves and Twigs of Cratoxylum arborescens*; *Planta Med* **72**, 1433-1435.
- Reyes-Chilpa, R., Baggio, C.H., Alvarez-Solano, D., Estrada-Muñoz, E., Kaufman, F.C., Sanchez, R.L., Mesia-Vela, S. (2006). *Inhibition of gastric H⁺ K⁺ ATPase activity by flavonoids, coumarins and xanthones isolated from Mexican medicinal plants*; *J Ethnopharmacol* **105**, 167-172.
- Rezaika, T., Jachymová, J., Dembitsky, V.M. (2003). *Prenylated Xanthone glucosides from Ural's lichen Umbilicaria proboidea*; *Phytochemistry* **62**, 607-612.
- Ribeiro, A., Pilo-Veloso, D., Romanha, A.J., Zani, C.L. (1997). *Trypanocidal Flavonoids from Trichia vauhierii*; *J Nat Prod* **60**, 836-838.
- Rukachaisirikul, V., Kaewnok, W., Koyomboon, S., Phongpaichit, S., Taylor, W.C. (2000). *Caged-Tetraprenylated Xanthones from Garcinia scorteichinii*; *Tetrahedron* **56**, 8539-8543.
- Rukachaisirikul, V., Kamkaew, M., Sukavisit, D., Phongpaichit, S., Sawangchote, P., Taylor, W.C. (2003a). *Antibacterial Xanthones from the Leaves of Garcinia nigrolineata*; *J Nat Prod* **66**, 1531-1535.
- Rukachaisirikul, V., Pallee, P., Hiranrat, A., Tuchinda, P., Yoosook, C., Kasit, J., Taylor, W.C., Reutrakul, V. (2003b). *Anti-HIV-1 Protostane Triterpenes and Diglycerylbenzophenone from Trunk Bark and Stems of Garcinia speciosa*; *Planta Med* **69**, 1141-1146.
- Rukachaisirikul, V., Panuphong, P., Sukpondma, Y., Koyomboon, S., Sawangchote, P., Taylor, W.C. (2003c). *Caged-Triprenylated and -Tetraprenylated Xanthones from the Latex of Garcinia scorteichinii*; *J Nat Prod* **66**, 933-938.
- Rukachaisirikul, V., Ritthiwigrom, T., Pinsa, A., Sawangchote, P., Taylor, W.C. (2003d). *Xanthones from the stem bark of Garcinia nigrolineata*; *Phytochemistry* **64**, 1149-1156.
- Rukachaisirikul, V., Naklue, W., Phongpaichit, S., Towatana, N.H., Maneenoon, K. (2006). *Phloroglucinols, depsidones and xanthones from the twigs of Garcinia parvifolia*; *Tetrahedron* **62**, 8578-8585.
- Rukachaisirikul, V., Phainuphong, P., Sukpondma, Y., Phongpaichit, S., Taylor, W.C. (2005). *Antibacterial Caged-Tetraprenylated Xanthones from the Stem Bark of Garcinia scorteichinii*; *Planta Med* **71**, 165-170.
- Schmidt, W., El-Mawla, A.M.A.A., Wolfender, J.-L., Hostettmann, K., Beerhues, L. (2000). *Xanthones in cell cultures of Hypericum androsaemum*; *Planta Med* **66**, 380-381.
- Sen, A.K., Sarkar, K.K., Mazumder, P.C., Banerji, N., Uusvuori, R., Hase, T.A. (1982). *The Structures of Garcinones A, B and C: Three new xanthones from Garcinia mangostana*; *Phytochemistry* **21**(7), 1747-1750.
- Seo, E.K., Kim, N.-C., Wani, M.C., Wall, M.E., Navarro, H.A., Burgess, J.P., Kawanishi, K., Kardono, L.B.S., Riswan, S., Rose, W.C., Fairchild, C.R., Farnsworth, N.R., Kinghorn, A.D. (2002). *Cytotoxic Prenylated Xanthones and the Unusual Compounds Anthraquinobenzophenones from Cratoxylum sumatranum*; *J Nat Prod* **65**, 299-305.
- Seo, E.K., Wall, M.E., Wani, M.C., Navarro, H., Mukherjee, R., Farnsworth, N.R., Kinghorn, A.D. (1999). *Cytotoxic constituents from the roots of Tovomita brevistaninaeae*; *Phytochemistry* **52**, 669-674.
- Sepúlveda-Boza, S., Cassels, B.K. (1996). *Plant metabolites active against Trypanosoma cruzi*; *Plant Med* **62**, 98-105.
- Shen, J., Yang, J.-S. (2006). *Two New Xanthones from the Stems of Garcinia cova*; *Chem Pharm Bull* **54**(1), 126-128.
- Shen, Y.-C., Wang, L.-T., Khalil, A.T., Chiang, L.-C., Cheng, P.-W. (2005). *Bioactive Pyranoxanthones from the Roots of Calophyllum blancoi*; *Chem Pharm Bull* **53**(2), 244-247.
- Sia, G.-L., Bennett, G.I., Harrison, L.J., Sim, K.-Y. (1995). *Minor Xanthones from the Bark of Cratoxylum Cochinchinense*; *Phytochemistry* **38**(6), 1521-1528.
- Silva, A.M.S., Pinto, D.C.G.A. (2005). *Structure Elucidation of Xanthone Derivatives: Studies of Nuclear Magnetic Resonance Spectroscopy*; *Curr Med Chem* **12**, 2481-2497.
- Singh, A., Srivastava, N., Purwar, C., Singh, J. (2004). *New Xanthone from the seeds of Tectona grandis*; *J Indian Chem Soc* **81**(2), 167-168.
- Somanathan, R., Sultanbawa, M.U.S. (1974). *Chemical Investigation of Ceylonese Plants. Part VIII. Trapezifolioxanthone, a New Di-isoprenylated Xanthone from the Bark of Calophyllum trapezifolium Thw. (Guttiferae)*; *J Chem Soc Perkin Trans 1*, 2515-2517.
- Stout, G.H., Stout, V.F., Welsh, M.J. (1963). *Celebixanthone: A Combined Chemical and Crystallographic Structure Proof*; *Tetrahedron* **19**, 667-676.
- Sukpondma, Y., Rukachaisirikul, V., Phongpaichit, S. (2005). *Antibacterial Caged-Tetraprenylated Xanthones from the Fruits of Garcinia hanburyi*; *Chem Pharm Bull* **53**(7), 850-852.
- Suksamran, S., Komutiban, O., Ratananukul, P., Chinnnoi, N., Lartpormatulee, N., Suksamran, A. (2006). *Cytotoxic Prenylated Xanthones from the Young Fruit of Garcinia mangostana*; *Chem Pharm Bull* **54**(3), 301-305.
- Suksamran, S., Suwannapoch, N., Phakhodee, W., Thanuhiranlert, J., Ratananukul, P., Chinnnoi, N., Suksamran, A. (2003). *Antimycobacterial Activity of Prenylated Xanthones from the Fruits of Garcinia mangostana*; *Chem Pharm Bull* **51**(7), 857-859.
- Suksamran, S., Suwannapoch, N., Ratananukul, P., Aroonlerk, N., Suksamran, A. (2002). *Xanthones from the Green Fruit Halls of Garcinia mangostana*; *J Nat Prod* **65**, 761-763.
- Sultanbawa, M.U.S. (1980). *Xanthonoids of tropical plants*; *Tetrahedron* **36**(11), 1465-1506.
- Sultanbawa, M.U.S., Surendrakumar, S. (1989). *Two Pyranodihydrobenzoxanthones from Artocarpus nobilis*; *Phytochemistry* **28**(2), 599-605.
- Taher, M., Idris, M.S., Ahmad, F., Arbain, D. (2005). *A polyisoprenylated ketone from Calophyllum nervosum*; *Phytochemistry* **66**, 723-726.
- Tanaka, N., Takaishi, Y. (2006). *Xanthones from Hypericum chinense*; *Phytochemistry* **67**, 2146-2151.
- Tanaka, N., Takaishi, Y., Shikishima, Y., Nakanishi, Y., Bastow, K., Lee, K.H., Honda, G., Ito, M., Takeda, Y., K. Kodzhimatov, O.K., Ashurmetov, O. (2004). *Prenylated Benzophenones and Xanthones from Hypericum scabrum*; *J Nat Prod* **67**, 1870-1875.
- Tao, S.-H., Wu F.-E. (2004). *Studies on chemical constituents of Hypericum wightianum*; *Nat Prod Res Dev* **16**, 26.
- Teixeira, D.M., Costa, C.T. (2005). *Novel methods to extract flavanones and xanthones from the root bark of Macleura pomifera*; *J Chromatogr A* **1062**, 175-181.
- Thoisson, O., Cuong, D.D., Gramain, A., Chiaroni, A., Hung, N.V., Sévenet, T. (2005). *Further rearranged prenylxanthones and benzophenones from Garcinia bracteata*; *Tetrahedron* **61**, 8529-8535.
- Thoisson, O., Fahy, J., Dumontet, V., Chiaroni, A., Riche, C., Tri, M.V., Sévenet, T. (2000). *Cytotoxic Prenylxanthones from Garcinia bracteata*; *J Nat Prod* **63**, 441-446.
- Tisdale, E.J., Kochman, D.A., Theodorakis, E.A. (2003). *Total synthesis of taraviridin*; *Tetrahedron Lett* **44**, 3281-3284.

- Tisdale, E.J., Slobodov, I., Theodorakis, E.A. (2004). Unified synthesis of caged *Garcinia* natural products based on a site-selective Claisen-Diels-Alder/Claisen rearrangement; *PNAS* **101**(33), 12030-12035.
- Tosa, H., Inuma, M., Tanaka, T., Nozaki, H., Ikeda, S., Tsutsui, K., Tsutsui, K., Yamada, M., Fujimori, S. (1997). Inhibitory Activity of Xanthone Derivatives Isolated from some *Gutierrezia* Plants against DNA Topoisomerases I and II; *Chem Pharm Bull* **45**(2), 418-420.
- Tsuchiya, H., Inuma, M. (2000). Reduction of membrane fluidity by antibacterial sophoroflavanone G isolated from *Sophora exigua*; *Phytomedicine* **7**, 161.
- Turro, D.G., Rubio, O.C., González, S.P., Simone, F., Passi, S., Rastrelli, L. (2004). Antioxidative Constituents from the Leaves of *Hypericum sphylioides*; *J Nat Prod* **67**, 869-871.
- Vieira, L.M.M., Kijjoa, A. (2005). Naturally-Occurring Xanthones: Recent Developments; *Curr Med Chem* **12**, 2413-2446.
- Vlitsinck, A.J., Bruyne, T., Apers, S., Pieters, L.A. (1998). Plant-Derived Leading Compounds for Chemotherapy of Human Immunodeficiency Virus (HIV) Infection; *Planta Med* **64**, 97-109.
- Waffo, A.F.K., Mulholland, D., Wansi, J.D., Mbaze, L.M., Powo, R., Mpondo, T.N., Fomum, Z.T., König, W., Nkengfack, A.E. (2006). Afzelixanthones A and B, Two New Prenylated Xanthones from *Garcinia afzelii* ENGL. (*Guttiferae*); *Chem Pharm Bull* **54**(4), 448-451.
- Wahyuny, F.S., Byrne, L.T., Dachryanus, Dianita, R., Jubahar, J., Lajis, N.H., Sargent, M.V. (2004). A New Ring-Reduced Tetraprenylolquinone and a Prenylated Xanthone from *Garcinia cowa*; *Aust J Chem* **57**, 223-226.
- Wang, C.-Z., Maier, U.H., Keil, M., Zenk, M.H., Bacher, A., Rohdich F., Eisenreich, W. (2003). Phenylalanine-independent biosynthesis of 1,3,5,8-tetrahydroxyxanthone a retrobiosynthetic NMR study with root cultures of *Swerletia chirata*; *Eur J Biochem* **270**, 2950-2958, and references therein.
- Wang, Y.H., Hou, A.J., Zhu, G.F., Chen, D.F., Sun, H.D. (2005). Cytotoxic and Antifungal Isoprenylated Xanthones and Flavonoids from *Cudrania fruticosae*; *Planta Med* **71**, 273-274.
- Waterman, P.G., Hussain, R.A. (1982). Major Xanthones from *Garcinia quadrifaria* and *Garcinia staudtii* stem barks; *Phytochemistry* **21**(8), 2099-2101.
- Weakley, T.J.R., Cai, S.X., Zhang, H.-Z., Keana, J.F.W. (2001). Crystal structure of the pyridine salt of *Gambogic acid*; *J Chem Crystallogr* **31**(11), 501-505.
- Wildermuth, M.C. (2006). Variations on a theme: synthesis and modification of plant benzocic acids; *Curr Opin Plant Biol* **9**, 288-296.
- Wu, J., Xu, Y.-J., Cheng, X.-F., Harrison, L.J., Sim, K.-Y., Goh, S.H. (2001). A highly rearranged tetraprenylxanthone from *Garcinia gaudichaudii* (*Guttiferae*); *Tetrahedron Lett* **42**, 727-729.
- Wu, Q.L., Wang, S.P., Du, L.J., Yang, J.S., Xiao, P.G. (1998). Xanthones from *Hypericum Japonicum* and *H. Henryi*; *Phytochemistry* **49**(5), 1395-1402.
- Wu, X., Cao, S., Goh, S., Hsu, A., Tan, B.K.H. (2002). Mitochondrial Destabilisation and Caspase-3 Activation are involved in the Apoptosis of Jurkat Cells Induced by *Gaudichaudone A*, a Cytotoxic Xanthone; *Planta Med* **68**, 198-203.
- Wu, Y., Zhang, P.-C., Chen, R.-Y., Yu, D.-Q., Liang, X.-T. (2003). Two New Xanthones from *Calophyllum inophyllum*; *Acta Chim Sin* **61**, 1047-1051, (Chinese).
- Wu, Z.-Q., Guo, Q.-L., You, Q.-D., Zhao, L., Gu, H.Y. (2004). *Gambogic acid* inhibits proliferation of human lung carcinoma SPC-AJ cells in vivo and in vitro and represses telomerase activity and telomerase reverse transcriptase mRNA expression in the cells; *Biol Pharm Bull* **27**(11), 1769-1774.
- Xu, Y.J., Lai, Y.-H., Imiyabir, Z., Goh, S.-H. (2001). Xanthones from *Garcinia parvifolia*; *J Nat Prod* **64**, 1191-1195.
- Xu, Y.J., Yip, S.C., Kosela, S., Fitri, E., Hana, M., Goh, S.H., Sim, K.Y. (2000). Novel Cytotoxic, Polyphenylated/Heptacyclic Xanthonoids from Indonesian *Garcinia gaudichaudii* (*Guttiferae*); *Org Lett* **2**(24), 3945-3948.
- Yamakuni, T., Aoki, K., Nakatani, K., Kondo, N., Oku, H., Ishiguro, K., Ohizumi, Y. (2006). *Garcinone B* reduces prostaglandin E_2 release and NF- κ B-mediated transcription in C6 rat glioma cells; *Neurosci Lett* **394**, 206-210.
- Yasunaka, K., Abe, F., Nagayama, A., Okabe, H., Lozada-Pérez, L., López-Villafraña, E., Muñoz, E. E., Aguilar, A., Reyes-Chilpa, R. (2005). Antibacterial activity of crude extracts from Mexican medicinal plants and purified coumarins and xanthones; *J Ethnopharmacol* **97**, 293-299.
- Yimdjo, M.C., Azabaze, A.G., Nkengfack, A.E., Meyer, A.M., Bodo, B., Fomum, Z.T. (2004). Antimicrobial and cytotoxic agents from *Calophyllum inophyllum*; *Phytochemistry* **65**, 2789-2795.
- Yu, J., Guo, Q.L., Lin, Q.D., X.S.S., Li, Z., Zhang, H.Y., G.H.W., Tan, Z., Wang, X. (2006). Repression of telomerase reverse transcriptase mRNA and hTERT promoter by gambogic acid in human gastric carcinoma cells; *Cancer Chemother Pharmacol* **58**, 434-443.
- Zhang, H.Z., Kasibhadda, S., Wang, Y., Herich, J., Guastella, J., Tseng, B., Drewe, J., Cai, S.X. (2004). Discovery, characterization and SAR of Gambogic acid as a potent apoptosis inducer by a HTS assay; *Bioorg Med Chem* **12**, 309-317.
- Zhang, Z., ElSohly, H.N., Jacob, M.R., Pasco, D.S., Walker, L.A., Clark, A.M. (2002). Natural Products Inhibiting *Candida albicans* Secreted Aspartic Proteases from *Toxomitia Krkovi*; *Planta Med* **68**, 49-54.
- Zou, Y.S., Hou, A.J., Zhu, G.F. (2005). Isoprenylated Xanthones and flavonoids from *Cudrania tricuspidata*; *Chem & Biodiversity* **2**, 131-138.
- Zou, Y.-S., Hou, A.-J., Zhu, G.-F., Chen, Y.-F., Sun, H.-D., Zhao, Q.-S. (2004). Cytotoxic Isoprenylated Xanthones from *Cudrania tricuspidata*; *Bioorg Med Chem* **12**, 1947-1953.

ANEXO II

Tabela 8. Xantonas Preniladas isoladas de fontes naturais no período de 2007-2009 (†)

Nº	Name of the compounds	Structure	Origin	Principal Biological Activities	References
519	1,3,5-Trihydroxy-6-O-prenylxanthone		<i>Hypericum ascyron</i> (Guttiferae)		Hashida et al., 2007
520	Polyanxanthone B		<i>Garcinia polyantha</i> Oliv. (Guttiferae)	Significant inhibition against AchE and BChE	Louh et al., 2008
521	Polyanxanthone A		<i>Garcinia polyantha</i> Oliv. (Guttiferae)	Weak inhibition against AchE and BChE	Louh et al., 2008
522	Polyanxanthone C		<i>Garcinia polyantha</i> Oliv. (Guttiferae)		Louh et al., 2008
523	Cochinchinone G		<i>Cratoxylum cochinchinense</i> (Guttiferae)		Mahabusarakam et al., 2008
524	Cochinchinone L		<i>Cratoxylum cochinchinense</i> (Guttiferae)	Antibacterial and Antifungal activity	Boonnak et al., 2009
525	Cochinxanthone A		<i>Cratoxylum cochinchinense</i> (Guttiferae)		Laphookhieo et al., 2008
526	Cochinxanthone B		<i>Cratoxylum cochinchinense</i> (Guttiferae)		Laphookhieo et al., 2008

† Atualização das Tabelas presentes no **Anexo I: Table 1. Prenylated and related xanthenes isolated from natural sources from 1963-2006** e **Table 2. Principal Biological Activities of Prenylated Xanthenes**, na qual é feita uma atualização das XP isoladas de fontes naturais no período de 2007-2009, bem como as actividades biológicas correspondentes.

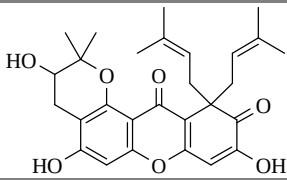
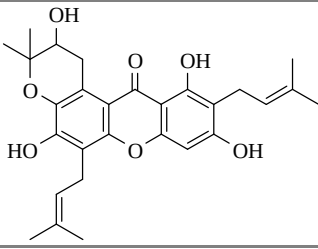
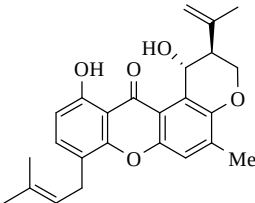
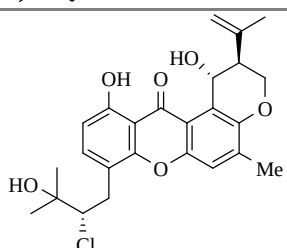
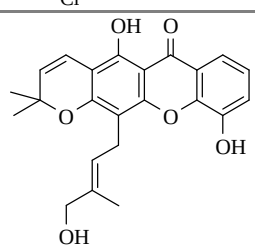
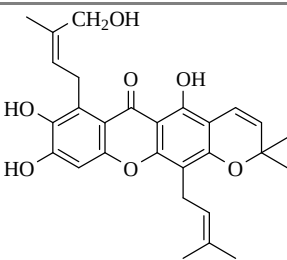
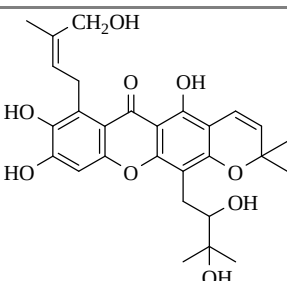
527	Cochinixanthone C		<i>Cratoxylum cochinchinense</i> (Guttiferae)		Laphookhieo et al., 2008
528	2,8-Dihydroxy-6-methoxy-5-(3-methylbut-2-enyl) xanthone		<i>Garcinia mangostana</i> (Guttiferae)		Ee et al., 2008
529	Paeciloxanthone		Fungus <i>Paecilomyces</i> sp.	Cytotoxic activity against hepG2 cell line; Inhibition of AChE; Antimicrobial activity	Wen et al., 2008
530	1,4,5,6-Tetrahydroxy-7-(3-methylbut-2-en-1-yl)xanthone		<i>Garcinia xanthochymus</i> (Guttiferae)	Moderate cytotoxicity against MDA-MB-435S and A549 cell lines	Han et al., 2007
531	Garcinexanthone C		<i>Garcinia xanthochymus</i> (Guttiferae)		Chen et al., 2008b
532	Cochinchinone F		<i>Cratoxylum cochinchinense</i> (Guttiferae)		Mahabusarakam et al., 2008
533	1,4,6-Trihydroxy-5-methoxy-7-(3-methylbut-2-en-1-yl)xanthone		<i>Garcinia xanthochymus</i> (Guttiferae)	Moderate cytotoxicity against MDA-MB-435S and A549 cell lines; Antioxidant activity	Han et al., 2007; Zhong et al., 2009
534	1,3,5-trihydroxy-6-methoxy-7-(3-methylbut-2-enyl)xanthone		<i>Garcinia lancilimba</i> (Guttiferae)		Han et al., 2008b
535	1,3-dihydroxy-5,6-dimethoxy-7-(3-methylbut-2-enyl)xanthone		<i>Garcinia lancilimba</i> (Guttiferae)		Han et al., 2008b
536	4,8-Dihydroxy-2,3-dimethoxy-1-(3-methylbut-2-enyl)xanthone		<i>Cratoxylum formosum</i> ssp. <i>pruniflorum</i> . (Guttiferae)		Boonnak et al., 2007

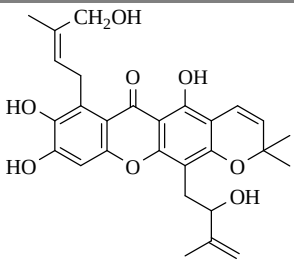
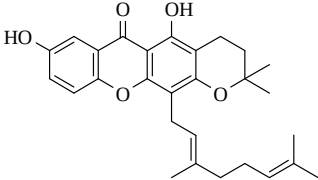
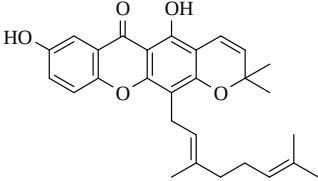
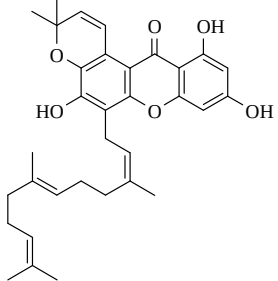
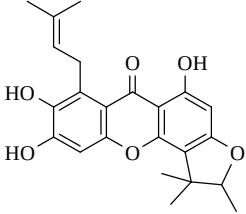
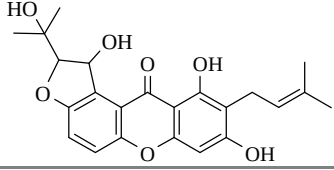
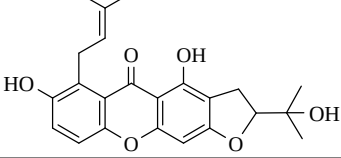
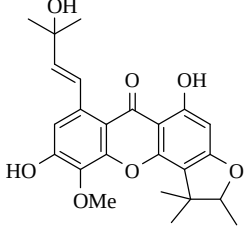
537	1,7-dihydroxyxanthone-8-(4'-hydroxyprenyl)		<i>Psorospermum molluscum</i> (Hypericaceae)		Leet et al., 2008
538	1,2,7-trihydroxy-4-(1,1-dimethylallyl)xanthone		<i>Garcinia xanthochymus</i> (Guttiferae)		Zhong et al., 2008a
539	Allanxanthone D		<i>Allanblackia gabonensis</i> (Guttiferae)	Antileishmanial and Antimicrobial activity	Azebaze et al., 2008
540	1,3,5,8-Tetrahydroxy-4-(1,1-dimethylprop-2-enyl) xanthone		<i>Garcinia cantleyana</i> , <i>Garcinia penangiana</i> (Guttiferae)	Weak cytotoxic activity against MDA-MB-231, MCF-7, CaOV-3, HeLa cell lines.	Shadid et al., 2007
541	Cudraticusxanthone L		<i>Cudrania tricuspidata</i> (Moraceae)		Hwang et al., 2007
542	1,6,7-Trihydroxy-2-(1,1-dimethyl-2-propenyl)-3-methoxyxanthone		<i>Cudrania fruticosa</i> Wight (Moraceae)		Liang et al., 2007
543	Vieillardixanthone B		<i>Garcinia vieillardii</i> (Guttiferae)		Hay et al., 2008
544	Vieillardixanthone C		<i>Garcinia vieillardii</i> (Guttiferae)		Hay et al., 2008
545	Bannaxanthone C		<i>Garcinia xipshuanbannaensis</i> (Guttiferae)		Han et al., 2008a
546	1,2,5,6-Tetrahydroxy-7-[(2E)-3,7-dimethylocta-2,6-dien-1-yl]xanthone		<i>Garcinia xanthochymus</i> (Guttiferae)	Moderate cytotoxicity against MDA-MB-435S and A549 cell lines	Han et al., 2007
547	Butyraxanthone D		<i>Pentadesma butyracea</i> (Guttiferae)	Cytotoxic activity against MCF-7 cell line.	Zelefack et al., 2009

548	1,3,6,7-Tetrahydroxy-2,8-(3-methyl-2-butenyl) xanthone		<i>Garcinia mangostana</i> (Guttiferae)	Antioxidant activity	Yu et al., 2007
549	1,3,6-Trihydroxy-3-methoxy-2,8-(3-methyl-2-butenyl)xanthone		<i>Garcinia mangostana</i> (Guttiferae)	Antioxidant activity	Yu et al., 2007
550	Cudraticusxanthone K		<i>Cudrania tricuspidata</i> (Moraceae)		Hwang et al., 2007
551	Cochinchinone E		<i>Cratoxylum cochinchinense</i> (Guttiferae)		Mahabusarakam et al., 2008
552	Pinetoxanthone		<i>Calophyllum pinetorum</i> (Guttiferae)		Alarcón et al., 2008
553	1,3,6,7-tetrahydroxy-2-(3-methylbut-2-enyl)-8-(2-methylbut-3-en-2-yl) xanthone		<i>Cudrania tricuspidata</i> (Moraceae)	Significant degree of α -glucosidase inhibition	Seo et al., 2007
554	Dulcisxanthone G		<i>Garcinia dulcis</i> (Guttiferae)		Deachathai et al., 2008
555	Bannaxanthone A		<i>Garcinia xipshuanbannaensis</i> (Guttiferae)		Han et al., 2008a
556	Bannaxanthone B		<i>Garcinia xipshuanbannaensis</i> (Guttiferae)	Low cytotoxic activity against HeLa cells	Han et al., 2008a
557	Garcinexanthone D		<i>Garcinia xanthochymus</i> (Guttiferae)		Chen et al., 2008b

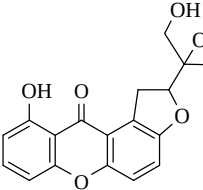
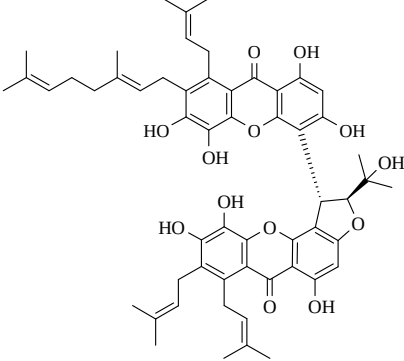
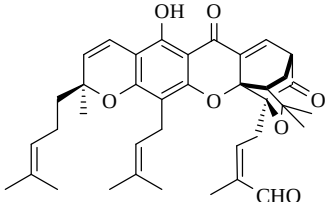
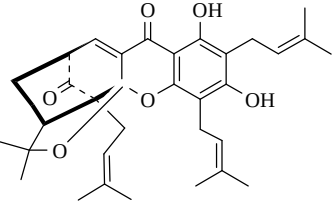
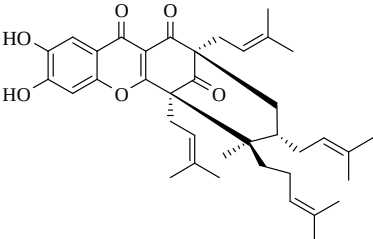
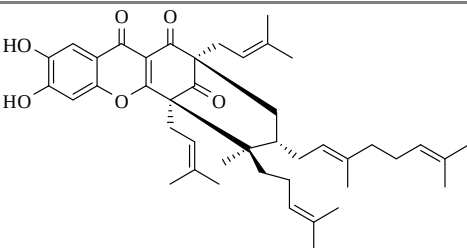
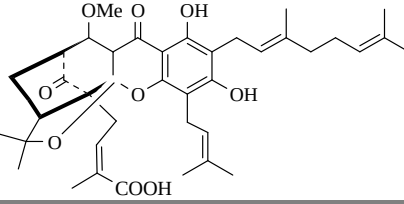
558	Oblongixanthone B		<i>Garcinia oblongifolia</i> (Guttiferae)		Huang et al., 2009
559	Oblongixanthone C		<i>Garcinia oblongifolia</i> (Guttiferae)	Apoptosis- inducing effect against HeLa-C3 cells.	Huang et al., 2009
560	Butyraxanthone A		<i>Pentadesma</i> <i>butyracea</i> (Guttiferae)	Antiplasmodial activity and cytotoxic activity against MCF-7 cell line.	Zeleafack et al., 2009
561	Garcinenone D		<i>Garcinia</i> <i>xanthochymus</i> (Guttiferae)	Antioxidant activity	Zhong et al., 2009
562	Garcinenone E		<i>Garcinia</i> <i>xanthochymus</i> (Guttiferae)	Antioxidant activity	Zhong et al., 2009
563	1,5,6-Trihydroxy-6',6'- dimethyl-2H-pyrano (2',3':3,4)-2-(3- methylbut-2- enyl)xanthone		<i>Garcinia lancilimba</i> (Guttiferae)	Moderate cytotoxic activity against MDA-MB- 435S cell line	Yang et al., 2007
564	1,6,7-Trihydroxy-6',6'- dimethyl-2H-pyrano (2',3':3,2)-4-(3- methylbut-2- enyl)xanthone		<i>Garcinia lancilimba</i> (Guttiferae)	Moderate cytotoxic activity against MDA-MB- 435S cell line	Yang et al., 2007
565	Termicalcicolanone A		<i>Terminalia calcicola</i> (Combretaceae)	Weak antiproliferative activity toward the A2780 cell line	Cao et al., 2007
566	Termicalcicolanone B		<i>Terminalia calcicola</i> (Combretaceae)	Weak antiproliferative activity toward the A2780 cell line	Cao et al., 2007

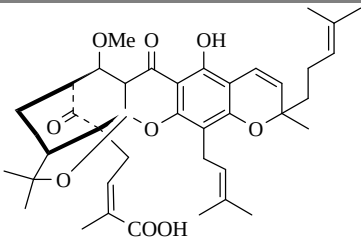
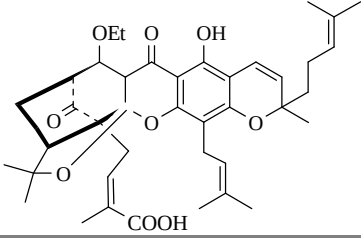
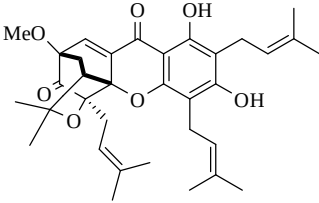
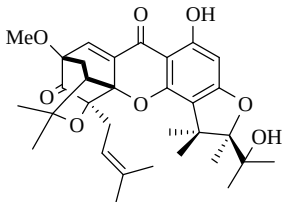
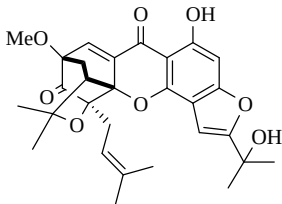
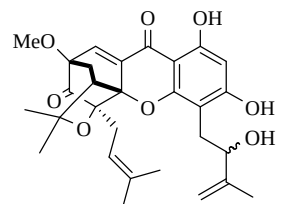
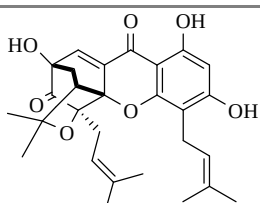
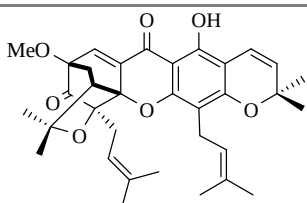
567	Cochinchinone J		<i>Cratogeomys cochinchinense</i> (Guttiferae)		Boonnak et al., 2009
568	Bannaxanthone D		<i>Garcinia xipshuanbannaensis</i> (Guttiferae)	Cytotoxic activity against HeLa cells	Han et al., 2008a
569	Laurentixanthone C		<i>Vismia laurentii</i> (Guttiferae)	Antibacterial and Algicidal activities	Tala et al., 2007
570	Membraxanthone A		<i>Calophyllum membranaceum</i> (Guttiferae)		Chen et al., 2008b
571	1,5,6-trihydroxy-7,8-di(3-methyl-2-butenyl)-6',6'-dimethylpyrano (2',3':3,4)xanthone		<i>Garcinia xanthochymus</i> (Guttiferae)		Zhong et al., 2008a
572	Butyraxanthone B		<i>Pentadesma butyracea</i> (Guttiferae)	Antiplasmodial activity and cytotoxic activity against MCF-7 cell line.	Zelefack et al., 2009
573	Garcinenone B		<i>Garcinia xanthochymus</i> (Guttiferae)	Antioxidant activity	Zhong et al., 2009
574	Garcinenone C		<i>Garcinia xanthochymus</i> (Guttiferae)	Antioxidant activity	Zhong et al., 2009

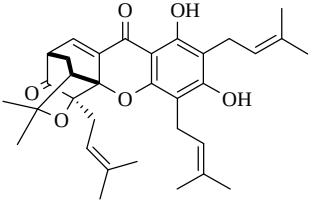
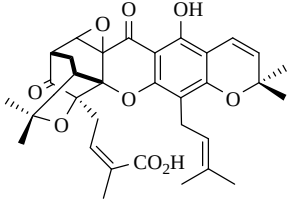
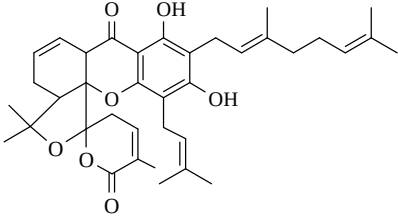
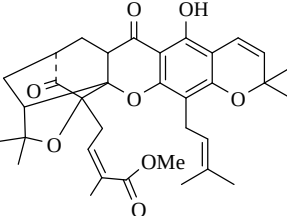
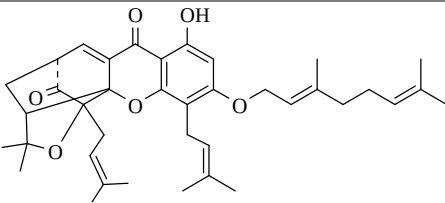
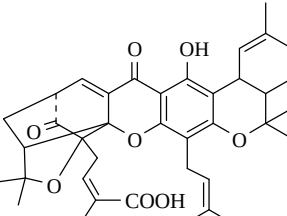
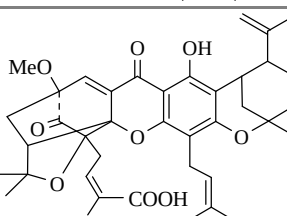
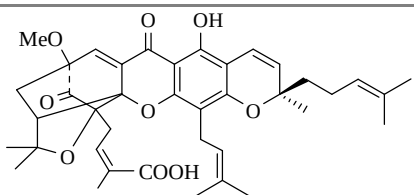
575	Bannaxanthone H		<i>Garcinia xipshuanbannaensis</i> (Guttiferae)		Han et al., 2008a
576	Butyraxanthone C		<i>Pentadesma butyracea</i> (Guttiferae)		Zeleafack et al., 2009
577	14-methoxytajibixanthone		<i>Fungus Emericella</i> sp.	CaM – inhibitors	Figuerola et al., 2009
578	15-chlorotajibixanthone hydrate		<i>Fungus Emericella</i> sp.	CaM – inhibitors	Figuerola et al., 2009
579	Garcinexanthone E		<i>Garcinia xanthochymus</i> (Guttiferae)		Chen et al., 2008b
580	Bannaxanthone E		<i>Garcinia xipshuanbannaensis</i> (Guttiferae)		Han et al., 2008a
581	Bannaxanthone F		<i>Garcinia xipshuanbannaensis</i> (Guttiferae)		Han et al., 2008a

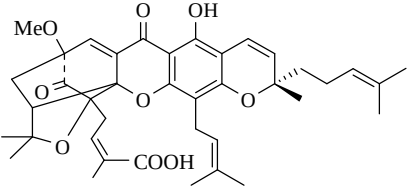
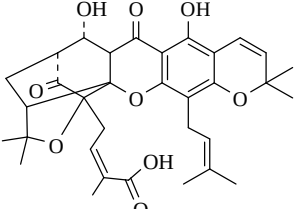
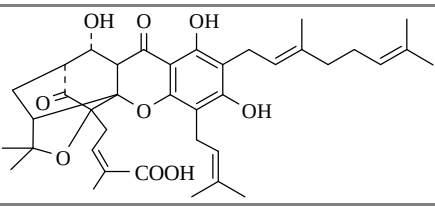
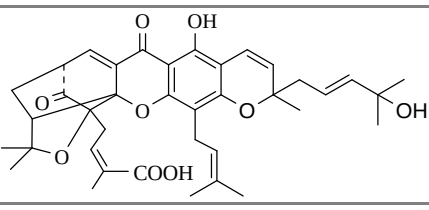
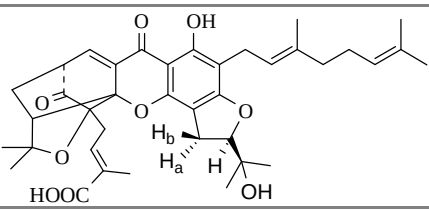
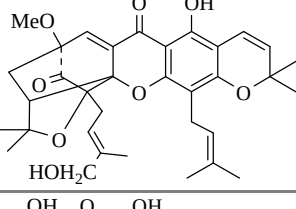
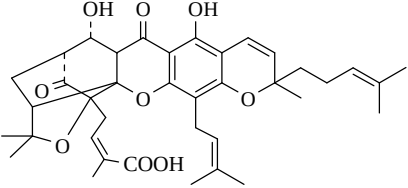
582	Bannaxanthone G		<i>Garcinia xipshuanbannaensis</i> (Guttiferae)		Han et al., 2008a
583	Cochinchinone K		<i>Cratoxylum cochinchinense</i> (Guttiferae)		Boonnak et al., 2009
584	Cochinchinone I		<i>Cratoxylum cochinchinense</i> (Guttiferae)		Boonnak et al., 2009
585	5-Farnesyltoxoxanthone B		<i>Garcinia merguensis</i> (Guttiferae)	Moderate cytotoxic activity against MCF-7, MDA-MB-231, NCI-H460, SF- 268 cell lines	Kijjoa et al., 2008
586	Cudraticusxanthone J		<i>Cudrania tricuspidata</i> (Moraceae)		Hwang et al., 2007
587	1,2-Dihydro-1,8,10-trihydroxy-2-(2-hydroxypropan-2-yl)-9-(3-methylbut-2-enyl)furo[3,2-a]xanthen-11-one		<i>Garcinia mangostana</i> (Guttiferae)	Quinone reductase- inducing activityin Hepa lcl7 cells	Chin et al., 2008
588	6-deoxy-7-demethylmangostanin		<i>Garcinia mangostana</i> (Guttiferae)	Quinone reductase- inducing activityin Hepa lcl7 cells	Chin et al., 2008
589	Caloxanthone N		<i>Calophyllum inophyllum</i> (Guttiferae)	Cytotoxic activity against K562 cell line	Xiao et al., 2008

590	Tetrandraxanthone [or 1,3-Dihydroxy-2',2'-dimethylpyrano(5',6':5,6) xanthone]		<i>Garcinia tetrandra</i> Pierre (<i>Guttiferae</i>)		Hartati et al., 2008
591	Oblongixanthone A		<i>Garcinia oblongifolia</i> (<i>Guttiferae</i>)		Huang et al., 2009
592	Garcinenone A		<i>Garcinia xanthochymus</i> (<i>Guttiferae</i>)	Antioxidant activity	Zhong et al., 2009
593	Garcinexanthone B		<i>Garcinia xanthochymus</i> (<i>Guttiferae</i>)		Chen et al., 2008b
594	Yahyaxanthone		<i>Garcinia rigida</i> (<i>Guttiferae</i>)	Cytotoxic activity against L1210 cell line	Elya et al., 2008
595	Garcinexanthone A		<i>Garcinia xanthochymus</i> (<i>Guttiferae</i>)		Chen et al., 2008b
596	3,4-dihydro-3,4,7,9,12-pentahydroxy-2,2-dimethyl-2H,6H-pyrano[3,2-b]xanthen-6-one		<i>Garcinia lancilimba</i> (<i>Guttiferae</i>)		Han et al., 2008b
597	O ¹ -demethyl-3',4'-deoxy-psorospermin-3',4'-diol		<i>Vismia laurentii</i> (<i>Guttiferae</i>)	Antimicrobial activity	Kuete et al., 2007
598	1,3,5-Trihydroxy-6,7-[2'-(1-methylethenyl)-dihydrofurano] xanthone		<i>Hypericum ascyron</i> (<i>Guttiferae</i>)		Hashida et al., 2007
599	1,3,5-Trihydroxy-6,7-[2'-(1-hydroxy-1-methylethyl)-dihydrofurano] xanthone		<i>Hypericum ascyron</i> (<i>Guttiferae</i>)		Hashida et al., 2007
600	3',4'-Deoxy-4'-chloropsoroxanthin-(3',5'-diol)		<i>Psorospermum molluscum</i> (<i>Hypericaceae</i>)	Cytotoxic activity against A2780, HCT-116, ABAE, SKBR3 cell lines (showed selectivity against ABAE)	Leet et al., 2008

601	Psoroxanthin		<i>Psorospermum molluscum</i> (Hypericaceae)	Cytotoxic activity against A2780, HCT-116, ABAE cell lines	Leet et al., 2008
602	Bigarcinenone A		<i>Garcinia xanthochymus</i> (Guttiferae)	Potent DPPH-Radical-Scavenging Activity (Antioxidant activity)	Zhong et al., 2008b
603	Gambogic aldehyde		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against P388 and P388/ADR cells	Wang et al., 2008b
604	Desoxymorellinin		<i>Resina Garciniae</i> (Guttiferae)	Potent cytotoxic activity against HL-60, SMMC-7721, BGC-823 cells	Feng et al., 2007
605	Oxy-guttiferone K		<i>Garcinia cambogia</i> (Guttiferae)		Masullo et al., 2008
606	Garciyunnanin B		<i>Garcinia yunnanensis</i> (Guttiferae)	Apoptosis-inducing activity against HeLa-C3 cells	Xu et al., 2008
607	10-methoxygambogenic acid		<i>Resina Garciniae</i> (Guttiferae)	Potent cytotoxic activity against HL-60, SMMC-7721, BGC-823 cells	Feng et al., 2007

608	10-methoxygambogic acid		<i>Resina Garcinia</i> (<i>Guttiferae</i>)	Potent cytotoxic activity against HL-60, SMMC-7721, BGC-823 cells	Feng et al., 2007
609	10-ethoxygambogic acid		<i>Resina Garcinia</i> (<i>Guttiferae</i>)	Potent cytotoxic activity against HL-60, SMMC-7721, BGC-823 cells	Feng et al., 2007
610	Cantleyanone A		<i>Garcinia cantleyana</i> (<i>Guttiferae</i>)	Moderate cytotoxic activity against MDA-MB-231 cell line and weak cytotoxic activity against MCF-7, CaOV-3, HeLa cell lines	Shadid et al., 2007
611	Cantleyanone B		<i>Garcinia cantleyana</i> (<i>Guttiferae</i>)	Strong cytotoxic activity against MDA-MB-231, MCF-7, CaOV-3, HeLa cell lines	Shadid et al., 2007
612	Cantleyanone C		<i>Garcinia cantleyana</i> (<i>Guttiferae</i>)	Strong cytotoxic activity against MDA-MB-231, MCF-7, CaOV-3, HeLa cell lines	Shadid et al., 2007
613	Cantleyanone D		<i>Garcinia cantleyana</i> (<i>Guttiferae</i>)	Strong cytotoxic activity against MCF-7, CaOV-3, HeLa cell lines and weak cytotoxic activity against MDA-MB-231 cell line	Shadid et al., 2007
614	7-Hydroxyforbesione		<i>Garcinia cantleyana</i> (<i>Guttiferae</i>)	Strong cytotoxic activity against MDA-MB-231, MCF-7, CaOV-3, HeLa cell lines	Shadid et al., 2007
615	7-Methoxydesoxymorellin		<i>Garcinia hanburyi</i> (<i>Guttiferae</i>)	Cytotoxic activity against P-388, KB, Col-2, BCA-1, Lu-1, ASK cell lines	Reutrakul et al., 2007

616	2-Isoprenylforbesione		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against P-388, KB, Col-2, BCA-1, Lu-1, ASK cell lines	Reutrakul et al., 2007
617	8,8a-epoxymorellic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against P-388, KB, Col-2, BCA-1, Lu-1, ASK cell lines; Anti-HIV activity	Reutrakul et al., 2007
618	Gambospiroene		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against HeLa cell line.	Tao et al., 2009
619	Methyl 8,8a-dihydromorellate		<i>Garcinia hanburyi</i> (Guttiferae)		Tao et al., 2009
620	3-O-Geranylforbesione		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against HeLa cell line.	Tao et al., 2009
621	Gambogefic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against HeLa cell line.	Tao et al., 2009
622	7-Methoxygambogellic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against HeLa cell line.	Tao et al., 2009
623	7-Methoxygambogic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against HeLa cell line.	Tao et al., 2009

624	7-Methoxyepigambogic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against HeLa cell line.	Tao et al., 2009
625	8,8a-Dihydro-8-hydroxymorellic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against HeLa cell line.	Tao et al., 2009
626	8,8a-Dihydro-8-hydroxygambogenic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against HeLa cell line.	Tao et al., 2009
627	Oxygambogic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against HeLa cell line.	Tao et al., 2009
628	Gambogenific acid		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against HeLa cell line.	Tao et al., 2009
629	7-Methoxyisomorellinol		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against HeLa cell line.	Tao et al., 2009
630	8,8a-Dihydro-8-hydroxygambogic acid		<i>Garcinia hanburyi</i> (Guttiferae)	Cytotoxic activity against HeLa cell line.	Tao et al., 2009

Abreviaturas: AchE = Acetylcholinesterase; BChE = Butyrylcholinesterase; CaM = Calmodulin; HIV = Human immunodeficiency virus.

Linhas Celulares: A2780 = Human ovarian cancer cell line; A549 = Human lung cancer; ABAE = Adult bovine aortic endothelial cells; SK-BR-3 = Human breast adenocarcinoma; ASK = Rat glioma; BCA-1 = Human breast cancer; BGC-823 = Gastric carcinoma; CaOV-3 = Human ovarian cancer; Col-2 = Human colon cancer; HCT-116 = Human colon carcinoma; HeLa = Human cervical cancer; HeLa-C3 = Human cervical cancer; Hepa 1c1c7 = Murine hepatoma; Hep-G2 = Human hepatocellular carcinoma; HL-60 = Human promyelocytic leukemia cells; K562 = Human leukemia; KB = Human oral nasopharyngeal carcinoma; L1210 = Murine leukemia cell line; Lu-1 = Human lung cancer; MCF-7 = Breast adenocarcinoma estrogen-dependent ER (+); MDA-MB-231 = Breast adenocarcinoma estrogen-independent ER (-); MDA-MB-435S = Human breast carcinoma; NCI-H460 = Non-small cell lung cancer; P-388 = Murine lymphocytic leukemia; P388/ADR = Murine adriamycin-resistant leukemia; SF-268 = Central nervous system cancer; SMMC-7721 = Hepatocellular carcinoma.

ANEXO III

Synthesis of Prenylated Xanthones: An Overview

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Abstract: Xanthenes or 9*H*-xanthen-9-ones (dibenzo- γ -pyrones) comprise an important class of oxygenated heterocycles, being prenylated derivatives the most abundant group. The prenylated xanthenes are found to possess a wide range of important biological and pharmacological activities. Because of this, synthetic strategies leading to new and more complex molecules have been widely explored in the past years. In our literature survey, from January 1963 to March 2009, a total of 93 synthetic prenylated xanthenes were described and 24 of which were firstly obtained from natural sources.

Thus, the main purpose of this review is to report synthetic methods to obtain prenylated xanthenes, such as simple prenylation, Claisen rearrangement and/or cyclization. We also discuss the application of new methodologies to the synthesis of prenylated derivatives, such as microwave assisted organic synthesis, heterogeneous catalysis with Montmorillonite K₁₀ Clay as catalyst and the combination of heterogeneous catalysis with microwave irradiation. Furthermore, different approaches and methodologies used to synthesize bioactive natural prenylated xanthenes, like α -mangostin, are also discussed.

Finally, biological activities of prenylated xanthenes are also briefly referred.

Keywords: Heterocycles, Xanthenes, Synthesis, Prenylation, Claisen Rearrangement, Cyclization, Microwave-assisted organic synthesis, Heterogeneous Catalysis.

1. INTRODUCTION: Xanthenes are secondary metabolites commonly occurring in a few higher plant families, fungi and lichens [1-4] with prenylated derivatives being the most abundant group of naturally occurring xanthenes. Prenylated xanthenes are not only valued as taxonomic markers in higher plant families, especially in *Guttiferae* [5-6] but also for their interesting pharmacological properties which have recently aroused great interest in the search for novel bioactive compounds [7-8].

Chemically, xanthenes (9*H*-xanthen-9-ones) are heterocyclic compounds with a dibenzo- γ -pyrone scaffold (Fig. (1)).

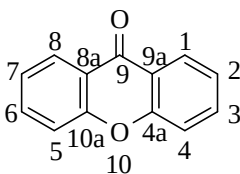


Fig. (1). Xanthone nucleus and numbering.

Despite the importance of prenylated xanthenes, a few works on their synthesis [9-11] and only one review mentioning briefly their synthesis [12] have been reported. Basically, the main objective of prenylated xanthenes synthesis is to obtain natural mimic compounds along with to develop new and more diverse and complex bioactive compounds to evaluate for their biological activity as well as to study their structure-activity-relationship (SAR). Consequently, this review describes several classical and non-classical methods for the synthesis of prenylated xanthenes such as prenylation of building blocks, molecular modification on xanthenes by direct prenylation, Claisen rearrangement and cyclization of prenylated precursors. However, when appropriate, some examples of total synthesis of natural prenylated xanthenes are also highlighted.

2. PRENYLATED XANTHONES: Prenylated xanthenes are the major group of naturally occurring xanthenes. In our literature survey covering from January 1963 to March 2009, a total of 93 synthetic prenylated xanthenes have been described and 24 of which were first obtained from natural sources.

The main substituents (C_5 group) found in synthetic prenylated xanthenes include the commonly 3-methylbut-2-enyl or isoprenyl group (A), the less frequent 2-hydroxy-3-methylbut-3-enyl group (B) and also the 1,1-dimethylprop-2-enyl or 1,1-dimethylallyl group (C). Compounds containing the 2,2-dimethyldihydropyrano (D), the 2,2-dimethylpyrano (E) and the 2,2,3-trimethyldihydrofurano (F) groups, which are the result of cyclization of the substituents A and C with the *ortho* hydroxyl group, can be also found. Modifications of these side chains by hydroxylation, hydrogenation, cyclization and Claisen rearrangement reactions can also occur (Fig. (2)) [8].

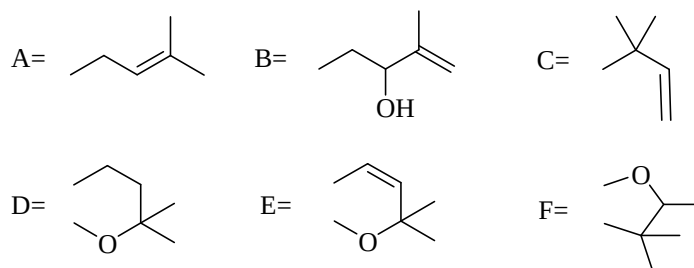


Fig. (2). Main substituents (C_5 group) found in synthetic prenylated xanthenes.

Though these substituents could be found on any carbons of the xanthonic scaffold, some positions are preferred as can be illustrated in Table 1. Generally, the 3-methylbut-2-enyl group is often found at positions 2, 4 and 8 of the xanthonic scaffold (see Table 1). Both 2,2-dimethyldihydropyran and 2,2-dimethylpyran groups are frequently located at C_2 - C_3 and C_3 -

C₄, while the 2,2,3-trimethyldihydrofuran group are normally fused with C₁-C₂, C₂-C₃ or C₃-C₄ (Fig. (3)) [8].

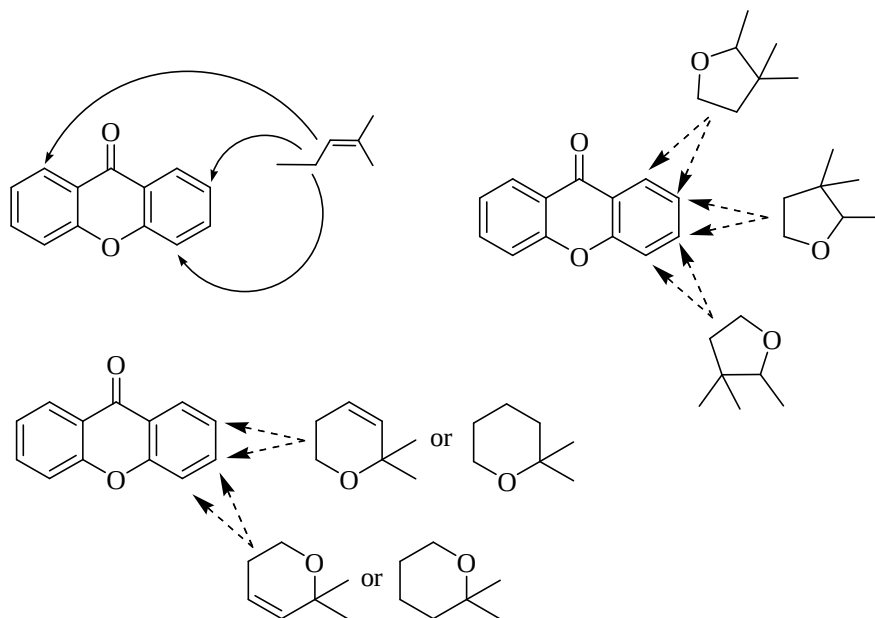


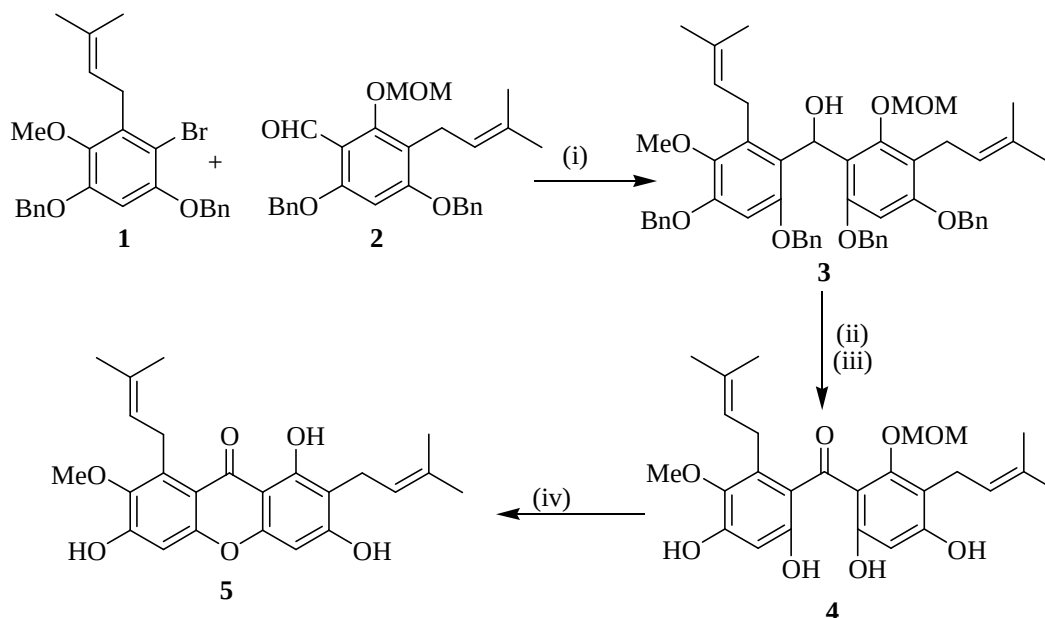
Fig. (3). Preferred positions for prenylation.

3. SYNTHETIC METHODS

The methodologies to obtain synthetic prenylated xanthenes and their respective cyclic derivatives are based on different strategies of molecular modification, such as molecular extension through prenylation of simple and suitable xanthonic building blocks, as well as by molecular rigidification through Claisen rearrangement and /or cyclization of prenylated precursors. These molecular modifications were achieved by the application of several classical and non-classical methodologies, which involves microwave-assisted organic synthesis (MAOS) and heterogeneous catalysis, using Montmorillonite K10 clay as catalyst.

4.1. Prenylation of building blocks: The use of $\text{PPh}_3/\text{CCl}_4$ to build prenylated xanthone scaffold was the key cyclization reaction and constituted a method for the total synthesis of

the naturally occurring α -mangostin (**5**) (Scheme 1) [13]. The cyclization of benzophenone **4**, obtained *via* the parent alcohol **3** by a coupling reaction between the benzaldehyde **2** and an anion generated from **1**, furnished the natural xanthone **5**.

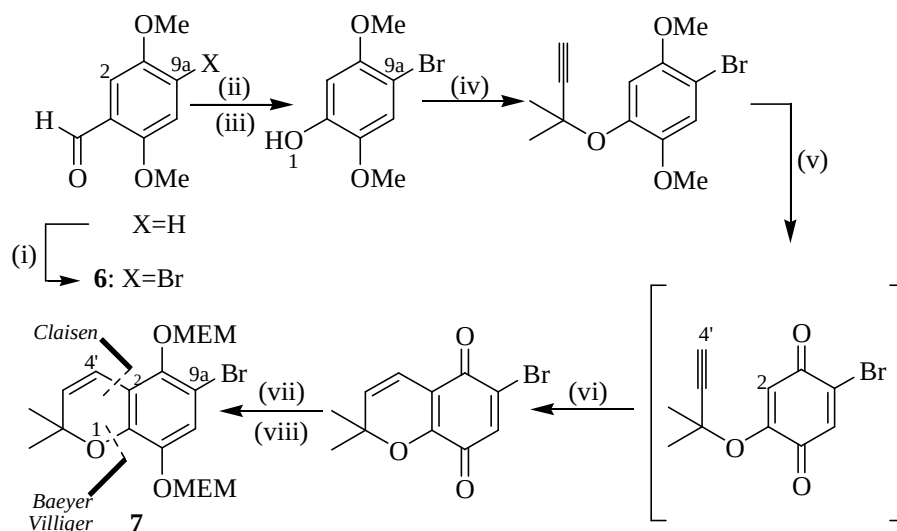


Scheme 1. (i): *s*BuLi, THF, -78°C, 49%; (ii) IBX, toluene/DMSO (1/1), rt, 76%; (iii) 10% Pd/C, HCO₂NH₄, acetone, rt, 63%; (iv) PPh₃, CCl₄, THF, rt, then silica gel, 43%.

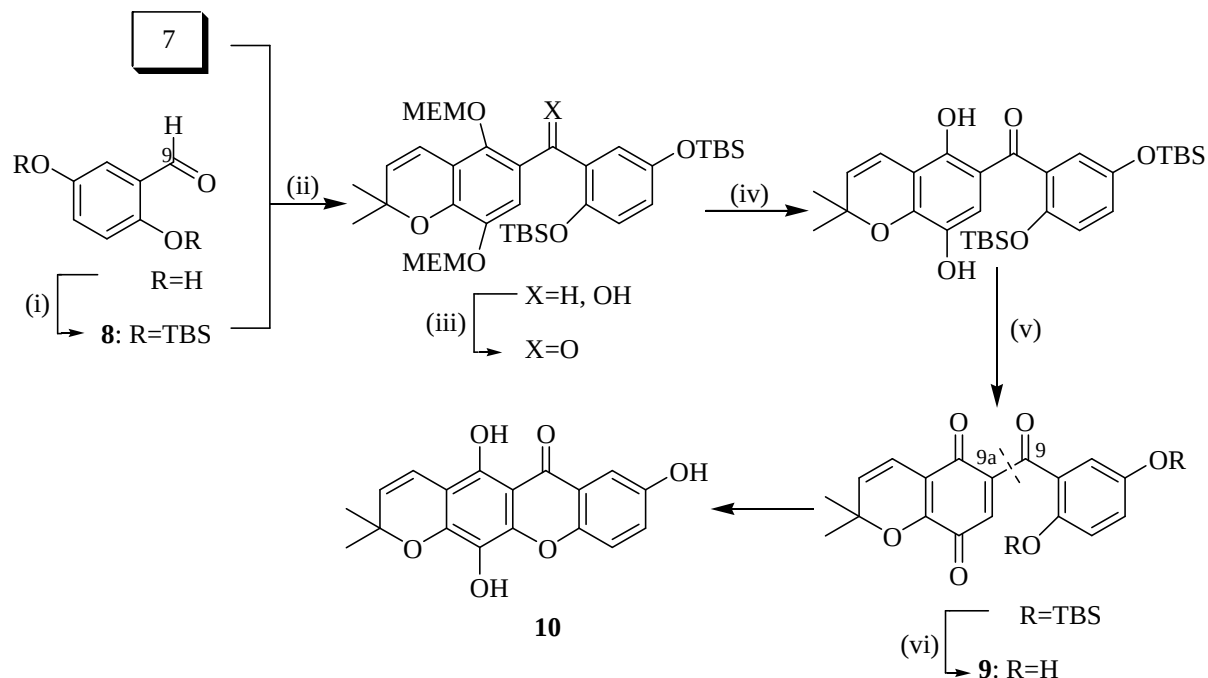
Deprenyl and benzophenone-type congeners of α -mangostin have been synthesized later by the same method [14] to investigate the structure-activity relationship (SAR) for some biological activities.

The total synthesis of atroviridin (**10**), a tetracyclic polyhydroxylated xanthone isolated from the stem bark of *Garcinia atroviridis*, based on biosynthetic pathways is reported by *Tisdale et al.* [15]. In biosynthetic point of view, atroviridin was thought to arise from benzophenone-like intermediate **9** through an intramolecular conjugate addition. Moreover, disconnection across the C9-C9a bond (xanthone numbering) suggests a synthetic route towards **9** based on coupling of aldehyde **8** with aryl bromide **7**. The latter compound was envisioned to arise from protected hydroquinone **6** by a sequence of steps including a Baeyer-Villiger oxidation

(introduction of O1 atom) and Claisen cyclization (construction of C2-C4' bond). Reduction of this plan to the synthesis of **10** is shown in Schemes 2 and 3.

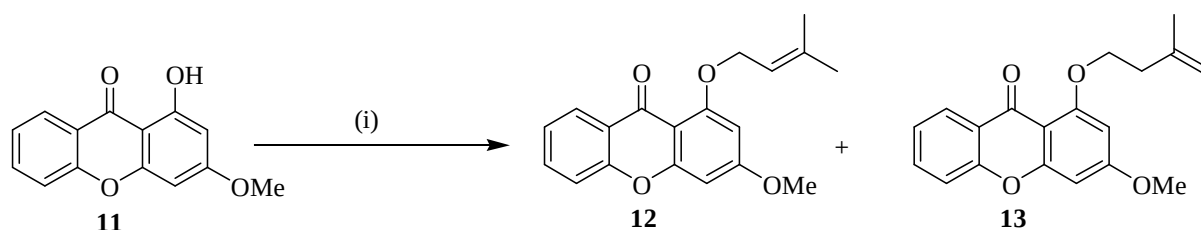


Scheme 2. (i) 1.1equiv. Br₂, AcOH, 4h, 25°C, 45%; (ii) 1.3 equiv. *m*-CPBA, CH₂Cl₂, 4h, 25°C; (iii) 10% NaOH (aq.) in MeOH, 1h, 25°C, 99% (over two steps); (iv) 1.2 equiv. 1,1-dimethylprop-2-ynyl methyl carbonate, 1.3 equiv. DBU, 0.03 mol% CuCl₂, CH₃CN, 6h, 0°C, 84%; (v) 2.5 equiv. CAN, 40% H₂O in CH₃CN, 0.5h, 25°C; (vi) PhCH₃, 0.5h, 40°C, 77% overall; (vii) 2.2 equiv. NaBH₄, 22 equiv. AcOH, THF, 0.5h, 25°C; (viii) 2.5 equiv. MEMCl, 2.8 equiv. DIPEA, CH₂Cl₂, 2h, 0°C, 73% (over two steps).

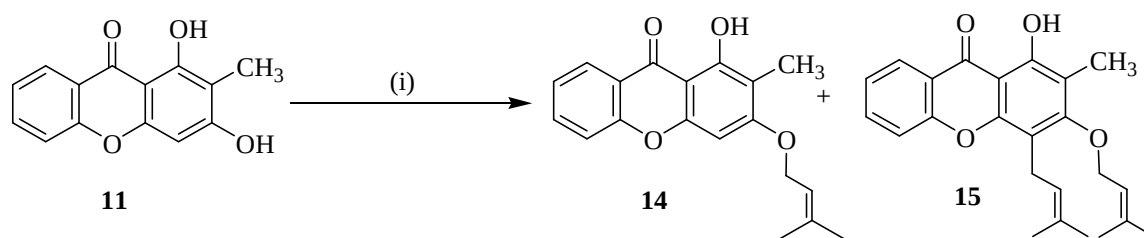


Scheme 3. (i) 2.2 equiv. TBSCl, 2.5 equiv. imid, CH₂Cl₂, 4h, 25°C, 62%; (ii) 1.3 equiv. *n*-BuLi, Et₂O, 1h, -78 to 0°C, 52%; (iii) 1.5 equiv. Dess-Martin periodinane, CH₂Cl₂, 1h, 25°C, 66%; (iv) 5.0 equiv. ZnBr₂, CH₂Cl₂, 4h, 25°C, 70%; (v) 2.5 equiv. IBX, 5% DMF in CHCl₃, 4h, 25°C, 31%; (vi) 2.2 equiv. TBAF, THF, 1h, 25°C, 40%.

4.2. By Molecular Modification on Xanthenes: Direct Prenylation: This synthetic approach used to synthesize prenylated xanthenes was by nucleophilic substitution of xanthonic building blocks (**11**), with prenyl bromide in alkaline medium, usually K_2CO_3 [9-10, 16]. This method normally affords prenyloxy xanthenes (**12**, **13**) (Scheme 4). However, in some cases, diprenylated derivatives (**15**) with one prenyl group on the carbon adjacent to the prenyloxy substituent were also obtained (Scheme 5) [16].

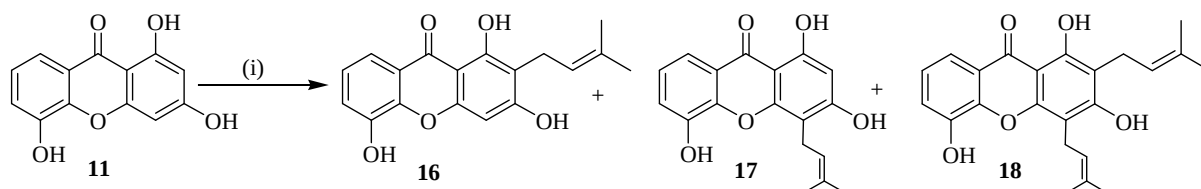


Scheme 4. (i) Prenyl bromide, K_2CO_3 , DMF, reflux, 48h (**12**, 60%; **13**, 30%).



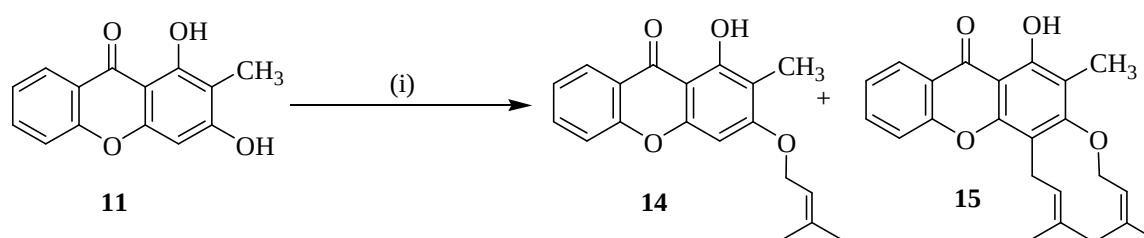
Scheme 5. (i) Prenyl bromide, K_2CO_3 , Acetone, reflux, 8h (**14**, 48%; **15**, 3%).

On the other hand, C-prenylation could occur when the reaction is performed in aqueous potassium hydroxide solution giving xanthenes **16-18** (Scheme 6) [11,17].



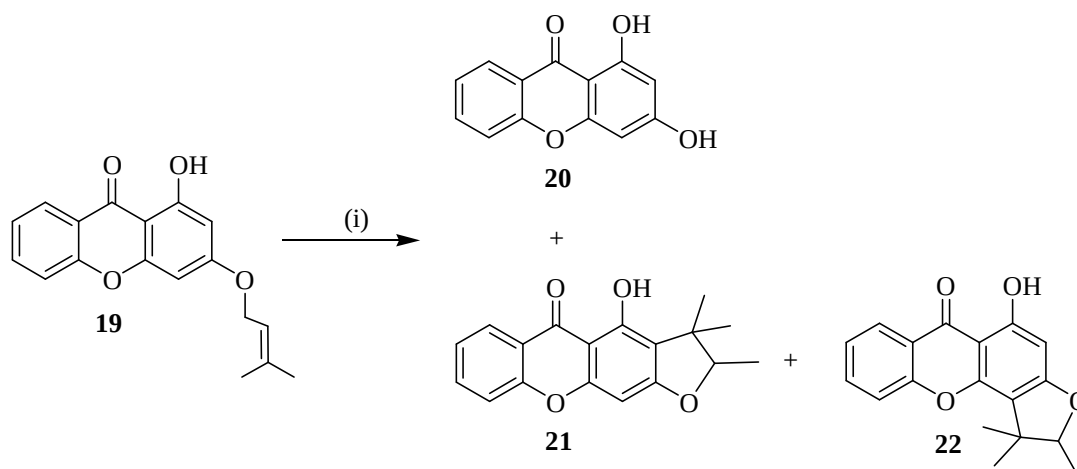
Scheme 6. (i): Prenyl bromide, aq. KOH 10%, rt, overnight (**16**, 11%; **17**, 13%; **18**, 10%).

In order to optimize the synthetic process to obtain biologically active prenylated xanthenes, MAOS has been recently used [18]. MAOS is a methodology in growth, which has been demonstrated not only to dramatically accelerate many organic reactions, typically from days or hours to minutes or even seconds, but also to improve yields and selectivity. Therefore, *Castanheiro et al.* have synthesized the prenylated xanthenes (**14-15**), previously obtained by the reaction of **11** with prenyl bromide in alkaline medium [16], by microwave (MW) irradiation, with increased yields and in a remarkable shorter reaction time when compared to the conventional heating in the classical synthesis (Scheme 7) [18].



Scheme 7. (i) Prenyl bromide, K₂CO₃, Acetone, MW, 200W, 3×20min, 59°C (**14**, 83%; **15**, 5%).

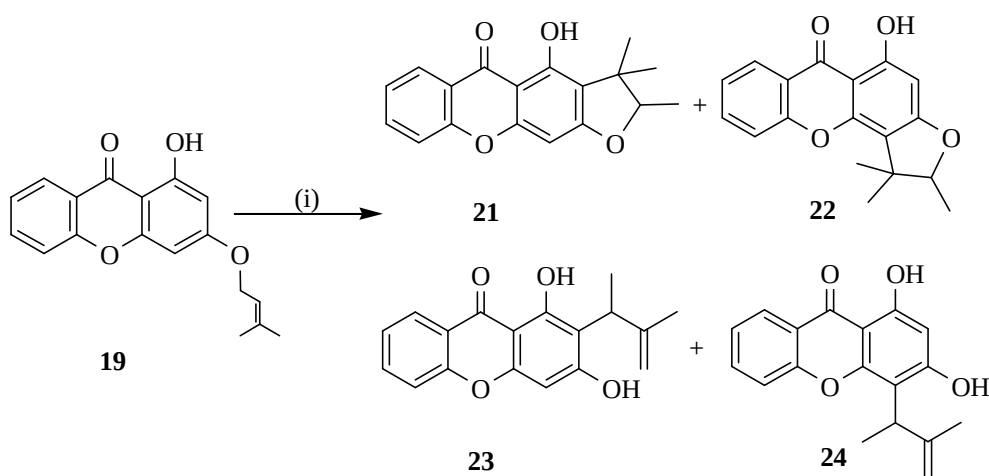
4.3. By Claisen rearrangement of Prenylated Xanthenes: Some prenylated xanthenes such as 1-hydroxy-3-(3-methylbut-2-enyloxy)xanthone (**19**) were subsequently subjected to Claisen rearrangement by heating directly either *in vacuum* at 200-210°C or with quinoline at 230-240°C, in order to obtain rearranged prenyl xanthenes and/or cyclic derivatives.



Scheme 8. (i): Vacuum, 200-210°C (**20**, 32%; **21**, 18%; **22**, 9%).

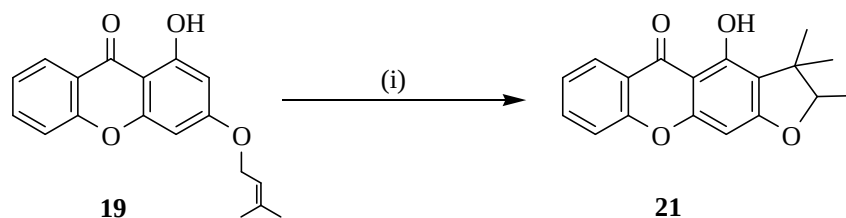
In the first process, 3 products were formed and were initially separated by an alkaline extraction. The alkaline-soluble part gave 1,3-dihydroxyxanthone (**20**) while the insoluble fraction, after chromatographic separation, gave two isomeric products with a 4,4,5-trimethyl-4,5-dihydrofuran-ring condensed in either linear (**21**) or angular (**22**) ways (Scheme 8). The formation of these dihydrofuran derivatives can be explained by the occurrence of a normal Claisen rearrangement in both the available *ortho* positions of the xanthone scaffold to give (1,1-dimethylallyl) derivatives followed by spontaneous cyclization involving the 3-hydroxy group [19].

The dihydrofuranoxanthones **21** and **22** were also obtained when 1-hydroxy-3-(3-methylbut-2-enyloxy)xanthone (**19**) was subjected to Claisen rearrangement in *N,N*-diethylaniline (*N,N*-DEA) by MW irradiation, but with shorter reaction times [18]. Interestingly, when *N,N*-DEA was used as solvent, both linear (**21**) and angular (**22**) dihydrofuranoxanthones were obtained, along with two rearranged by-products (**23-24**) (Scheme 9).



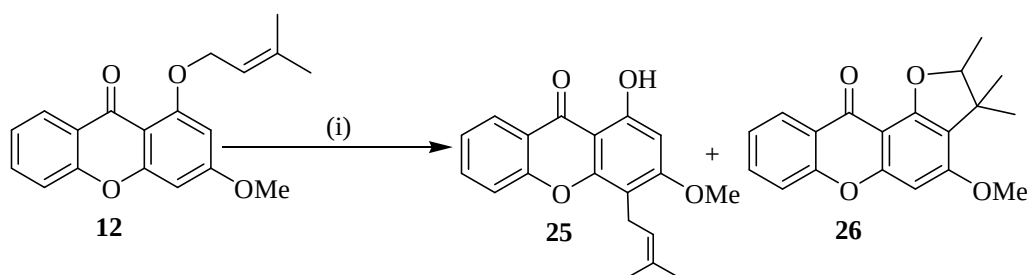
Scheme 9. (i): *N,N*-DEA, MW, 750W, 3×15min, 225°C (**21**, 7%; **22**, 6%; **23**, 5%; **24**, 5%).

However if the reaction was performed in *N*-methyl-2-pyrrolidone (NMP), Claisen rearrangement of monoprenylated xanthone **19** gave only the linear dihydrofuranoxanthone **21** (Scheme 10) [18].



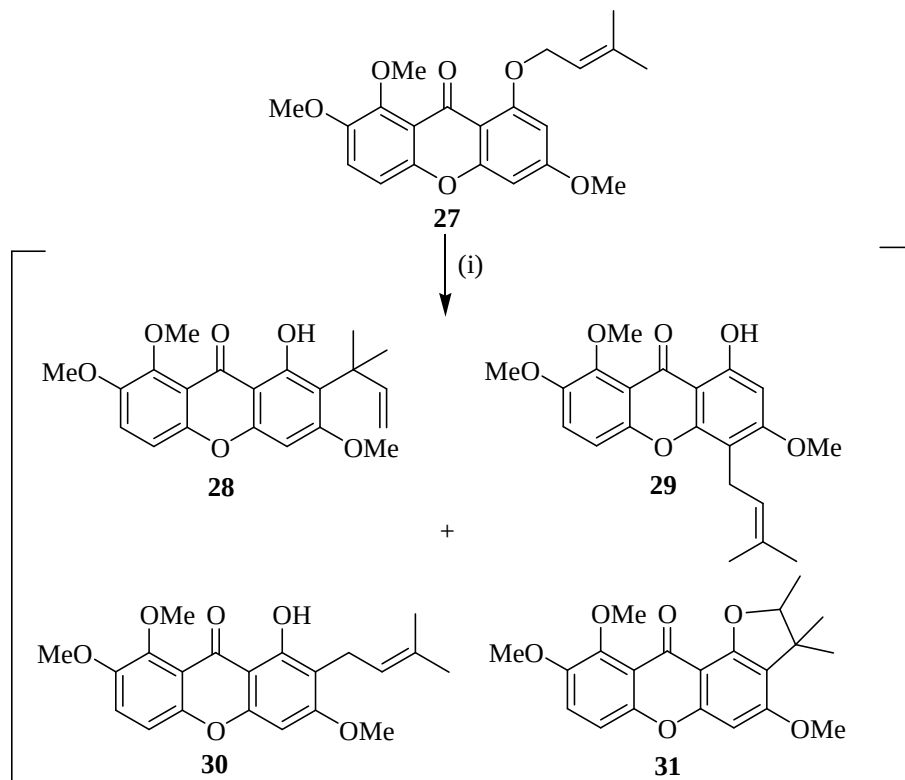
Scheme 10. (i): NMP, MW, 2×30min, 202°C (**21**, 20%).

Claisen rearrangement was also performed in *N,N*-dimethylaniline (*N,N*-DMA) [10]. One example was the Claisen rearrangement of 3-methoxy-1-(3-methylbut-2-enyloxy)xanthone (**12**) which gave a mixture of 1-hydroxy-3-methoxy-4-(3-methylbut-2-enyl) xanthone (**25**) and the furanoxanthone (**26**), along with a small amount of starting material (**12**) (Scheme 11). While xanthone **25** was a result of a *para* Claisen rearrangement of xanthone **12**, dihydrofuranoxanthone **26** was obtained from an *ortho* Claisen rearrangement, followed by a spontaneous cyclization of 1,1-dimethylallyl group with 1-hydroxy group.

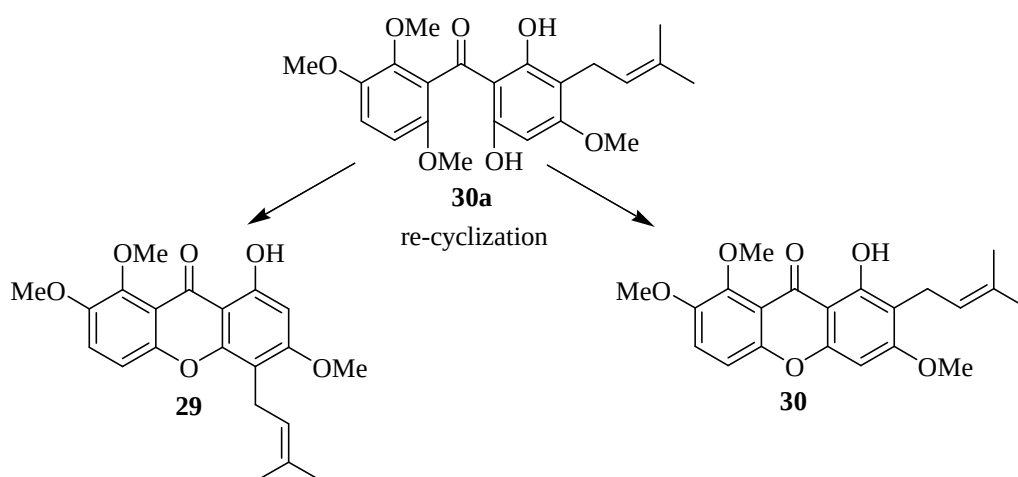


Scheme 11. (i): *N,N*-DMA, 200°C, 8h (**25**, 60%; **26**, 30%).

Claisen rearrangement can also be performed in *N,N*-DEA [9], as was for 3,7,8-trimethoxy-1-(3-methylbut-2-enyloxy)xanthone (**27**), which gave four isomeric products (**28-31**) (Scheme 12a).



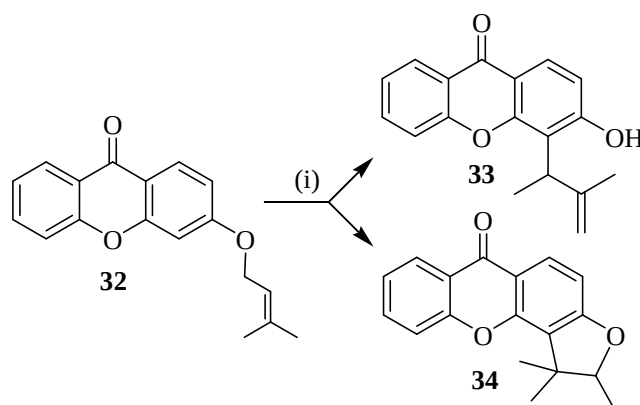
Scheme 12a. (i): *N,N*-DEA, N_2 , reflux, 4h (**28**, 18%; **29**, 8%; **30**, 9%; **31**, 2%).



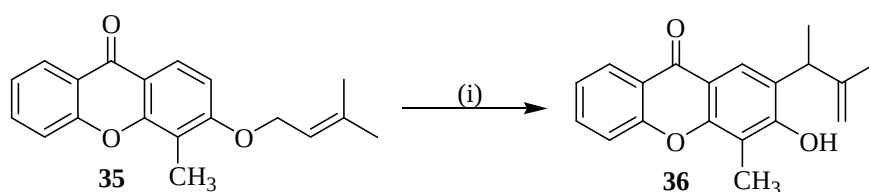
Scheme 12b. Re-cyclization of **30a** to produce a mixture of **29** and **30**.

Formation of compounds **28** and **29** can be explained by the classical Claisen rearrangement whereas compound **31** was a result of the cyclization of prenyl group in xanthone **28**. The formation of compound **30** from **27** could only be explained by a ring opening in **30** to give a benzophenone intermediate (**30a**), which by a subsequent re-cyclization produced a mixture of **29** and **30** (Scheme 12b).

Patel & Trivedi [20] have reported abnormal Claisen rearrangements of 3-prenyloxanthone (**32**) and 3-prenyloxy-4-methylxanthone (**35**). Thus, refluxing **32** in *N,N*-DMA gave 4-(1,2-dimethylpropenyl)-3-hydroxyxanthone (**33**) and 1,1,2-trimethyl-1,2-dihydro-6*H*-furo[3,4-*b*]xanthone (**34**) (Scheme 13) whereas **35** gave only 2-(1,2-dimethylpropenyl)-3-hydroxy-4-methylxanthone (**36**) (Scheme 14). It can be inferred in this case that the methyl group on C4 influences by steric and electronic ways the course of the reaction.



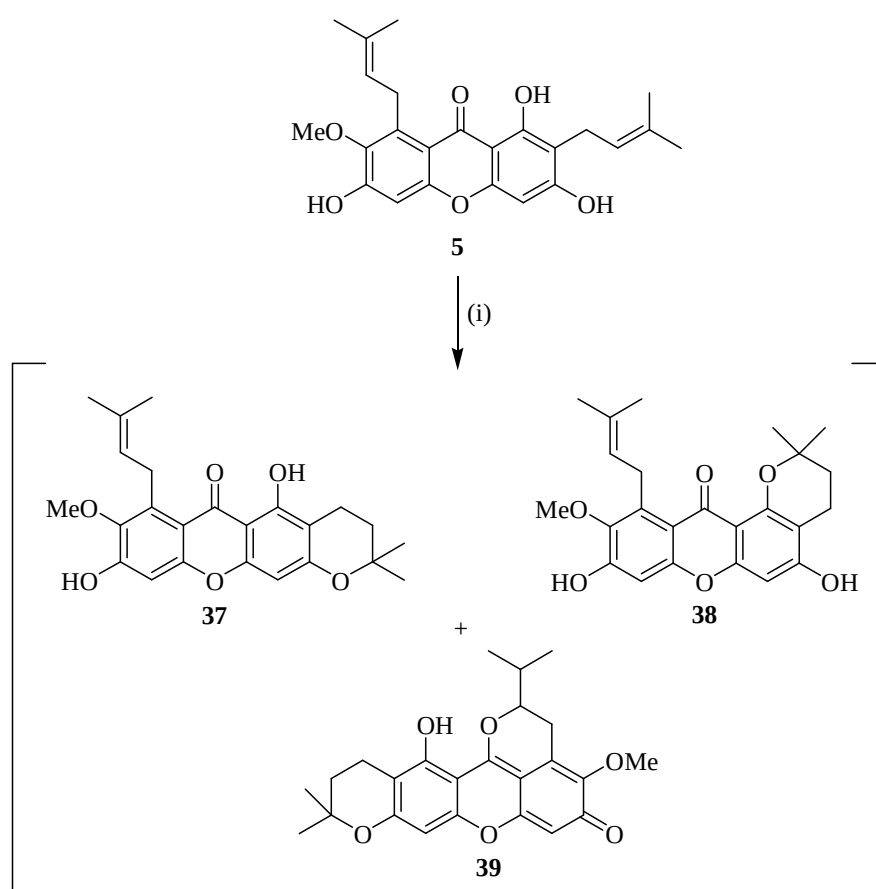
Scheme 13. (i): *N,N*-DMA, reflux, 4h.



Scheme 14. (i): *N,N*-DMA, reflux, 4h.

Claisen rearrangement of **32** has also been carried out in a mixture of dimethylaniline and butyric anhydride, giving **33**, **34** and 3-hydroxyxanthone. However, when the reaction was performed in butyric anhydride, **33** and 3-hydroxyxanthone were obtained. On the other hand, no migration has been observed in decalin (2h). Surprisingly, when **32** was refluxed in decalin for 6h or heated under vacuum, 3-hydroxyxanthone was formed [20].

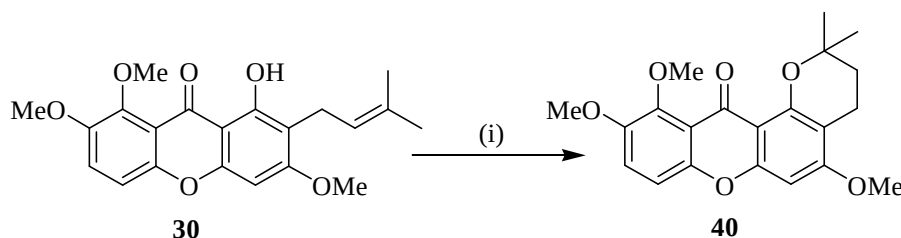
4.4. Pyran Derivatives of Prenylated Xanthenes: Cyclization of the naturally occurring α -mangostin (**5**) with *p*-toluenesulfonic acid in benzene [21] yielded three products comprising the two known natural compounds, 3-isomangostin (**37**), 1-isomangostin (**38**) as well as an unexpected bicyclomangostin (**39**) (Scheme 15).



Scheme 15. (i): *p*-toluenesulfonic acid, benzene, reflux, 1h (**37**, 52%; **38**, 8%; **39**, 21%).

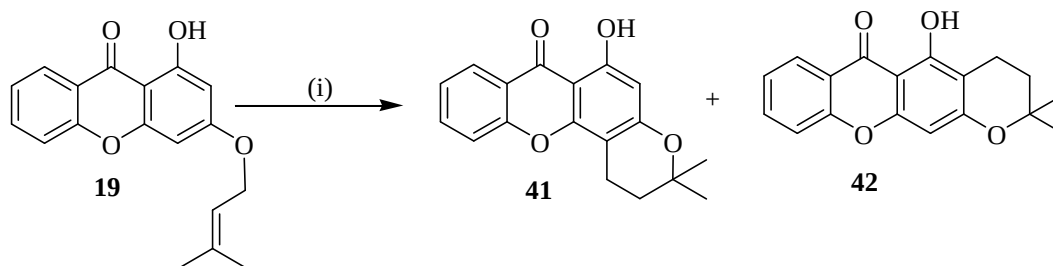
Cyclization was first induced with *p*-toluenesulfonic acid to give either 3-isomangostin (**37**) or 1-isomangostin (**38**), with the former being the main product; further cyclization of **37** can occur affording **39**. This event could be confirmed by an experiment making the compound **37** to react with *p*-toluenesulfonic acid to give bicyclomangostin **39**, as the only product in good yield (80%) [21].

The cyclization can also be performed in formic acid [9]. Thus refluxing xanthone **30** in formic acid during one hour afforded the angular dihydropyranoxanthone **40** (Scheme 16).



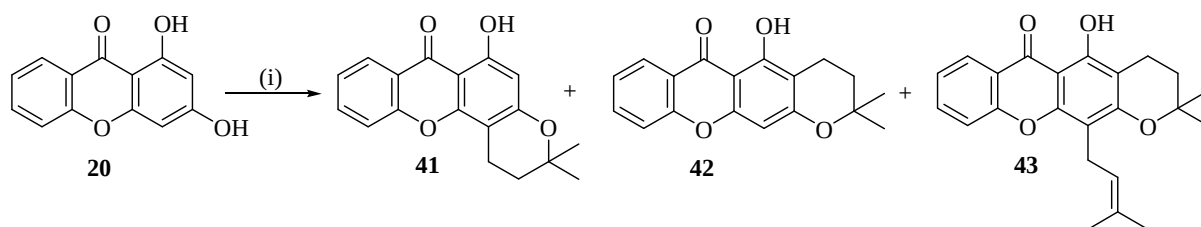
Scheme 16. (i) HCO₂H, reflux, 1h.

On the other hand, when xanthone **19** was heated with a catalytic amount of zinc chloride in dry xylene, a mixture of angular and linear dihydropyranoxanthones **41** and **42** was obtained (Scheme 17), thus constituting another method for the synthesis of cyclic xanthonic derivatives [10, 16].



Scheme 17. (i) ZnCl₂ anhydrous, dry xylene, reflux, 12h (**41**, 4%; **42**, 3%).

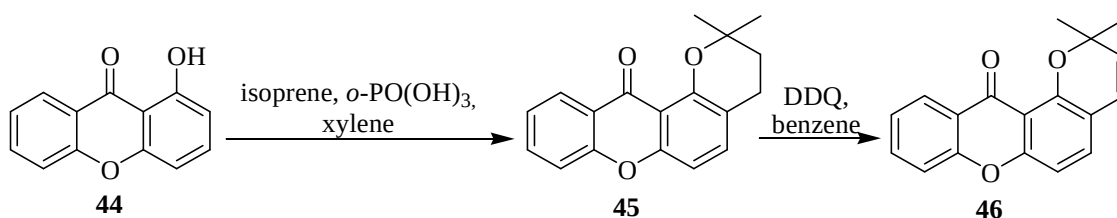
An attempt to improve the yields and selectivity of dihydropyranoxanthenes has led to the application of synthetic methods using heterogeneous catalysis and the combination of heterogeneous catalysis with MW irradiation. Recently, much attention has been paid to clays, which can act as solid catalysts for a wide range of organic reactions. A subgroup of clays, known as Montmorillonite, is particularly useful as a catalyst. With this clay, the reaction proceeds not only under mild conditions but also with selectivity, good yields and short reaction times. As this catalyst can be easily separated from the reaction mixture and can be regenerated, the purification procedures are usually simple [22-23]. Furthermore, the coupling of MW irradiation with the use of inorganic solid supports such as Montmorillonite K10 clay, either with solvent or under solvent-free conditions, can also provide a chemical process with inherent advantages such as enhanced reaction rates, high yields, ease of manipulation and selectivity [24]. Consequently, through a one-pot Montmorillonite K₁₀ clay-catalyzed condensation of 1,3-dihydroxyxanthone (**20**) with prenyl bromide at room temperature (Method A) or at 100°C (Method B) under conventional thermal heating, or with MW irradiation (Method C), compounds **41** and **42** (Scheme 18) were obtained, along with an additional diprenylated compound (**43**) that seemed to be formed when the condensation was performed in the presence of Montmorillonite K10 clay [18].



Scheme 18. (i) Method A: K10 Clay (20 eq by weight), CHCl₃, prenyl bromide, stirring, rt; Method B: K10 Clay (20 eq by weight) (dry or commercial), CHCl₃, prenyl bromide, stirring, 100°C; Method C: K10 Clay (20 eq by weight), prenyl bromide, stirring, MW, with or without solvent.

The combination of Montmorillonite K10 clay-catalysis with MW irradiation was found to be the method of choice to prepare dihydropyranoxanthenes from suitable hydroxyxanthenes, since it dramatically increased the products yields and shortened the reaction time [18].

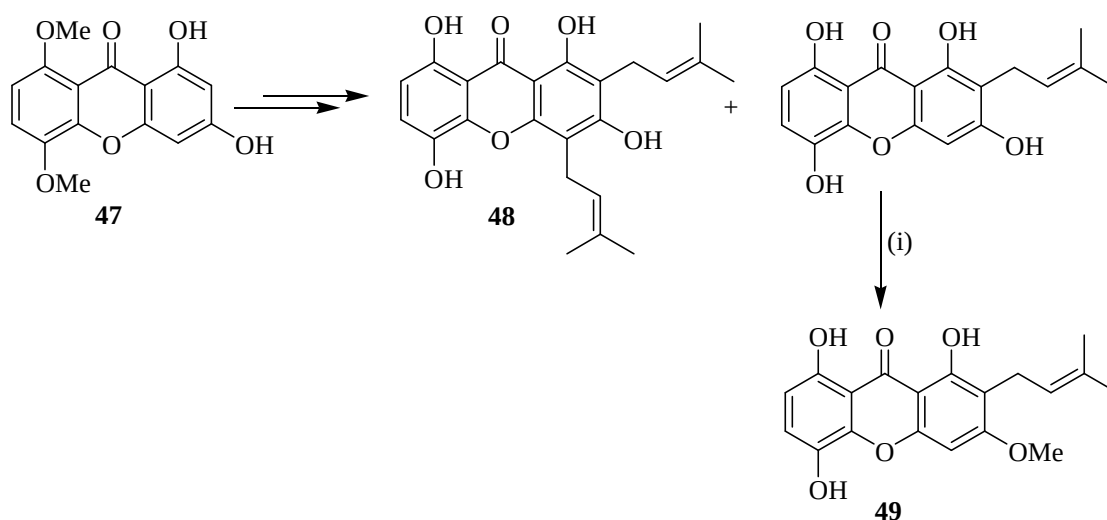
Another attempt to synthesize dihydropyranoxanthenes was described by *Ahluwalia et al* [25], which involves the condensation of hydroxyxanthenes with isoprene in the presence of orthophosphoric acid. Thus, the condensation of 1-hydroxyxanthone (**44**) with isoprene in orthophosphoric acid gave 3,4-dihydro-2,2-dimethyl-2*H*,12*H*-pyrano[2,3-*a*]xanthen-12-one (**45**) (yield 70%) as the only product. Compound **45**, on reaction with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in refluxing benzene, gave the corresponding pyranoxanthone, 2,2-dimethyl-2*H*,12*H*-pyrano[2,3-*a*]xanthen-12-one (**46**) with 80% of yield (Scheme 19). This report also described the synthesis of some other dihydropyranoxanthenes, as well as their dehydrogenation to the corresponding pyranoxanthenes.



Scheme 19.

4.5. Synthesis of Naturally Occurring Prenylated Xanthenes - different approaches and methodologies: *Bennett et al.* have reported the synthesis of gartanin (**48**) and 1,5,8-trihydroxy-3-methoxy-2-(3-methylbut-2-enyl)xanthone (**49**) [26], previously isolated from *Garcinia mangostana* [27]. Though a direct approach to the synthesis of **48** and **49** would be the prenylation of 1,3,5,8-tetrahydroxyxanthone. As this xanthone was obtained in poor yield, a more viable starting material was 1,3-dihydroxy-5,8-dimethoxyxanthone (**47**) obtained by

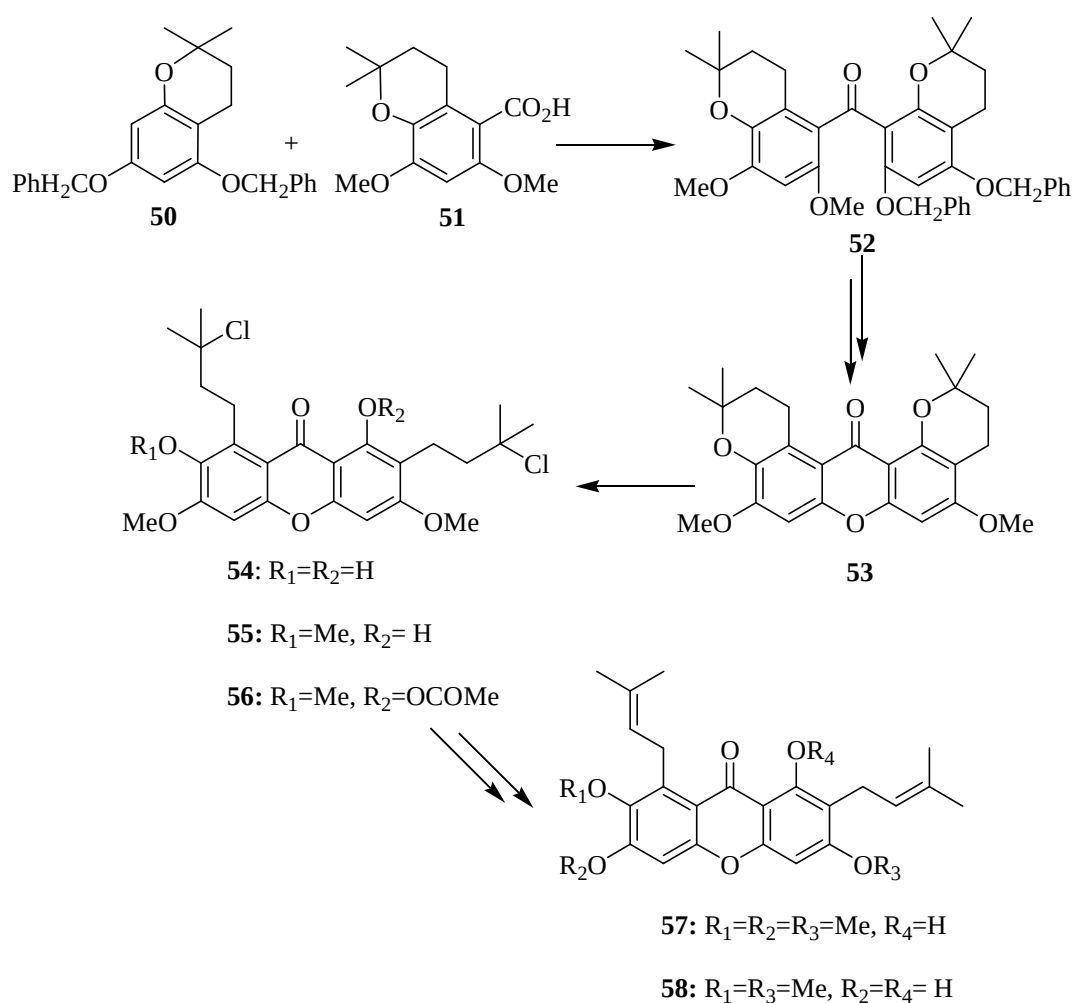
Grover, Shah and Shah method. Prenylation of **47** with prenyl bromide in the presence of a solution of NaOMe and under N₂, followed by demethylation of the products with aqueous morpholine under N₂, produced the desired tetrahydroxy precursor of **49** as well as gartanin (**48**) (Scheme 20).



Scheme 20. Me₂SO₄, K₂CO₃, Me₂CO, reflux.

Hiok-Huang Lee also described the synthesis of naturally occurring xanthenes namely dimethylmangostin (**57**) and β -mangostin (**58**) by an ingenious method with unusual starting building blocks [28]. Therefore, condensation of 5,7-bisbenzyloxy-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran (**50**) with 6,8-dimethoxy-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-5-carboxylic acid (**51**) in the presence of trifluoroacetic anhydride at room temperature gave 3,4-dihydro-6,8-dimethoxy-2,2-dimethyl-2H-1-benzopyran-5-yl ketone (**52**), which was converted, in three steps, into dimethyl-1-isonormangostin (**53**). Reaction of **53** with concentrated boron trichloride solution resulted in the cleavage of the two pyran rings to give 1,7-bis-(3-chloro-3-methylbutyl)-2,8-dihydroxy-3,6-dimethoxyxanthen-9-one (**54**). Selective methylation of **54**, with iodomethane in refluxing acetone in the presence of anhydrous potassium carbonate, afforded the 1,7-bis-(3-chloro-3-methylbutyl)-8-hydroxy-2,3,6-

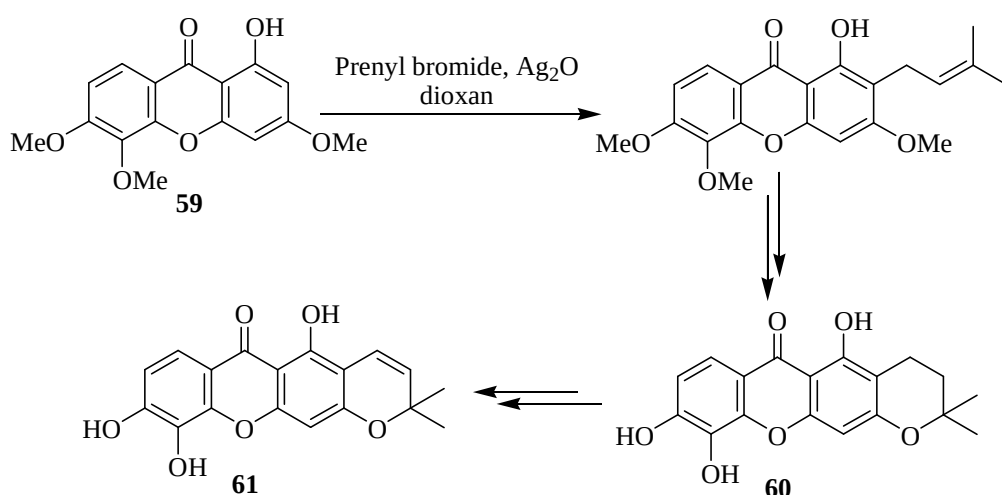
trimethoxyxanthen-9-one (**55**). Dehydrochlorination of the methoxycarbonyloxy derivative **56**, obtained from **55**, with lithium chloride in dimethylformamide gave a mixture from which dimethylmangostin (**57**) and 1,7-bis-(3-methylbut-3-enyl)-8-hydroxy-2,3,6-trimethoxyxanthen-9-one were isolated, by preparative high pressure liquid chromatography. In an attempt to improve the yield of dimethylmangostin (**57**), compound **55** was treated with potassium *tert*-butoxide in dimethyl sulphoxide to give a mixture from which β -mangostin (**58**) was obtained, by high pressure liquid chromatography (Scheme 21).



Scheme 21.

An unambiguous synthesis of jacareubin (**61**) has been achieved by following a plausible biogenetic route [29]. Thus, introduction of a 3,3-dimethylallyl side-chain into C-2 of 1-

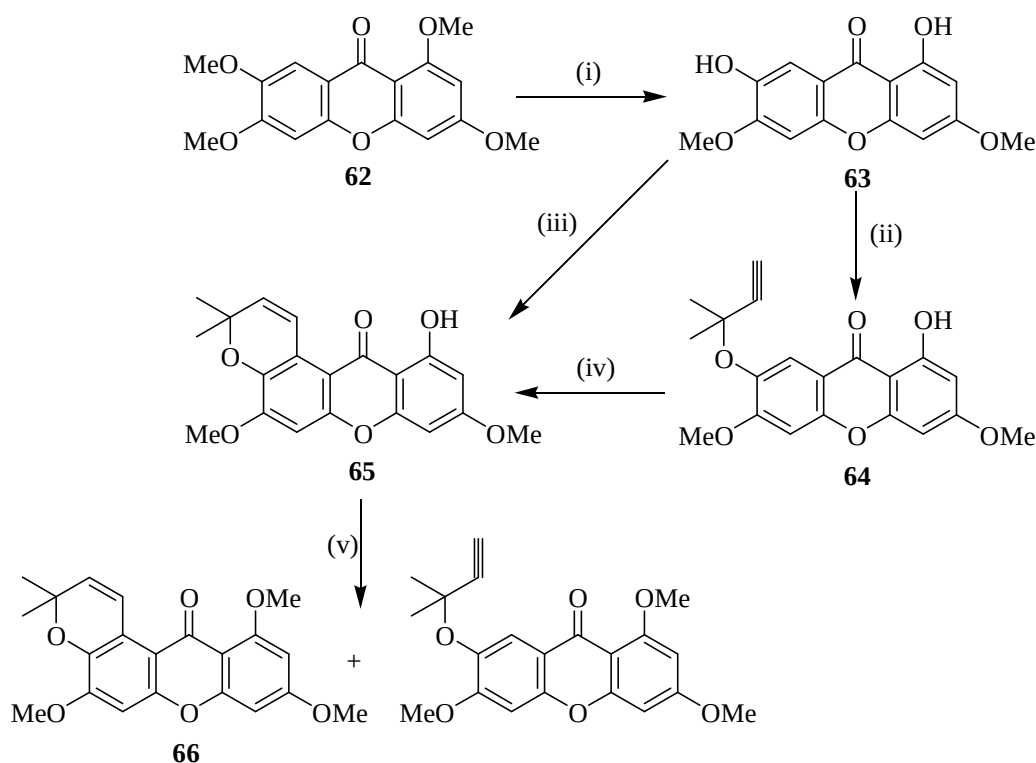
hydroxy-3,5,6-trimethoxyxanthone (**59**) was carried out in dioxan at room temperature in the presence of silver oxide, followed by methylation and treatment with hydroiodic acid, to give dihydrojacareubin (**60**) which was dehydrogenated, by allylic bromination of the triacetyl derivative of dihydrojacareubin with *N*-bromosuccinimide, followed by dehydrobromination and hydrolysis with pyridine and ethanolic potassium hydroxide to yield jacareubin (**61**) (Scheme 22).



Scheme 22.

Cotterill and Scheinmann have performed structural and synthetic studies on the naturally occurring pyranoxanthone, toxyloxanthone B [30]. The structure of this pyranoxanthone was confirmed by the synthesis of its trimethyl ether and by direct comparison with an authentic sample. The total synthesis of toxyloxanthone B trimethyl ether was achieved from 1,3,6,7-tetramethoxyxanthone (**62**), obtained by cyclization in aqueous sodium hydroxide solution of both 2-hydroxy-2',4,4',5,6'-pentamethoxybenzophenone and 2-hydroxy-2',4,4',5',6-pentamethoxybenzophenone, which underwent selective demethylation with hydrogen bromide in glacial acetic acid to give 1,7-dihydroxy-3,6-dimethoxyxanthone (**63**). By treating **63** with 3-bromo-3-methylbut-1-yne and potassium carbonate in boiling acetone, the intermediate 7-(1,1-dimethylprop-2-ynyl) ether (**64**) was then obtained which underwent

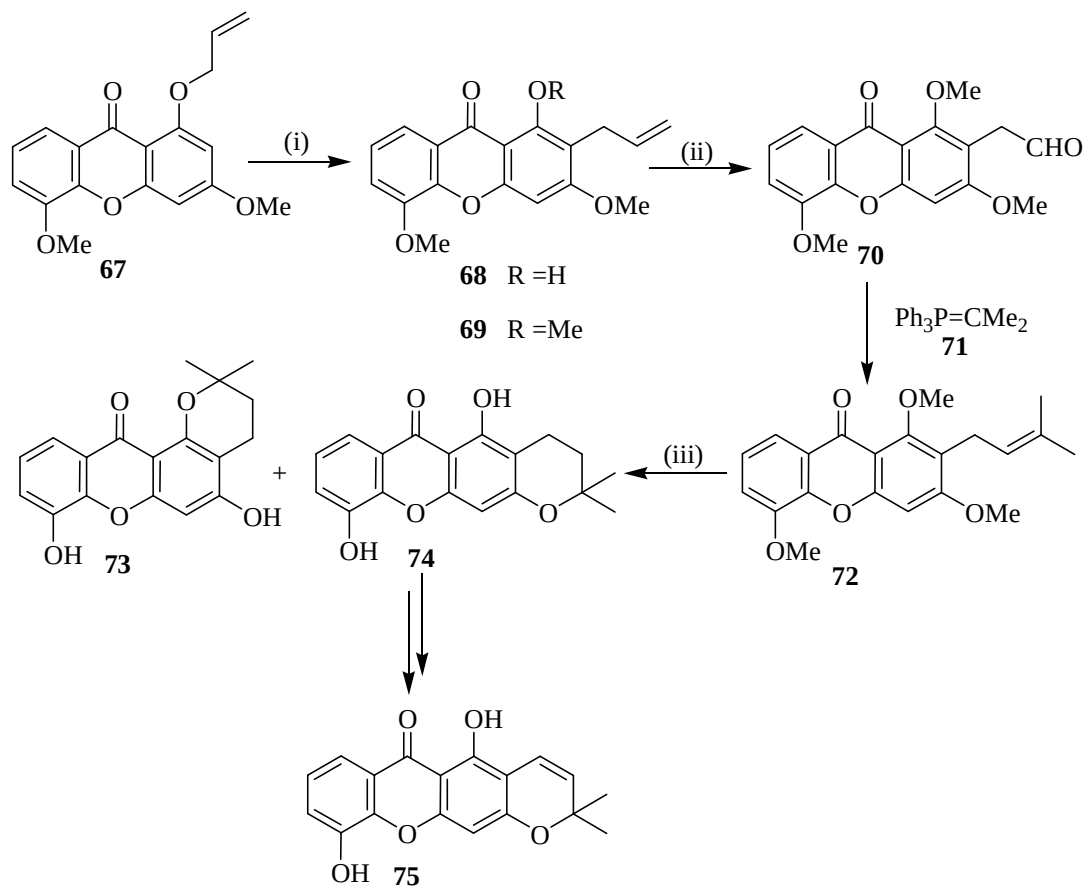
cyclization under the conditions of the reaction to afford 11-hydroxy-5,9-dimethoxy-3,3-dimethylpyrano[3,2-a]xanthone (**65**). To complete the synthesis of toxylloxanthone B trimethyl ether (**66**) the free hydroxyl group of **65** was then methylated (Scheme 23).



Scheme 23. (i) HBr, AcOH; (ii) $\text{ClCMe}_2\text{C}\equiv\text{CH}$, K_2CO_3 , Me_2CO , 18°C ; (iii) as II but reflux in $\text{H}_2\text{O}-\text{Me}_2\text{CO}$; (iv) MeOH , 60°C ; (v) Me_2SO_4 , K_2CO_3 , Me_2CO , 54°C .

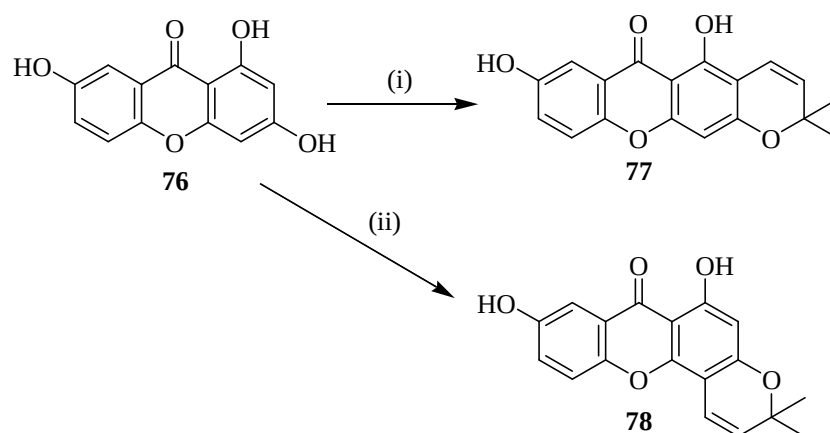
Locksley et al have reported [31] the synthesis of naturally occurring 6-deoxyjacareubin (**75**) and the related 3,3- and 1,1-dimethylxanthenes by using some methods previously described in this review. One of them was the classic prenylation with prenyl bromide and potassium carbonate in boiling acetone. The prenyloxy derivatives were submitted to a Claisen rearrangement in *N,N*-DMA but furanoxanthenes were obtained instead of 1,1-dimethylallyl derivatives as occurred previously. By this way, a method for introduction of a 3-methylbut-2-enyl side chain in the C-2 position of xanthone scaffold was developed. This was based on the preparation of 2-allyl-1-hydroxy-3,5-dimethoxyxanthone (**68**), from a Claisen rearrangement of 1-allyloxy-3,5-dimethoxyxanthone (**67**) and further modification of the allyl

side chain. Ozonolysis of the trimethyl ether (**69**) gave 1,3,5-trimethoxy-2-(2-oxoethyl)xanthone (**70**). A Wittig reaction of the product **70** with phosphorane (**71**), gave 1,3,5-trimethoxy-2-(3-methylbut-2-enyl)xanthone (**72**) with a 3-methylbut-2-enyl side chain at C-2. Treatment of xanthone **72** with hydriodic acid in the presence of hypophosphorous and acetic acids gave a mixture of angular (**73**) and linear (**74**) dihydropyranoxanthones by successive demethylation and cyclization reactions. The linear isomer, dihydro-6-deoxyjacareubin (**74**), was converted into 6-deoxyjacareubin (**75**) by the method, previously described in this review, that was successful in the total synthesis of jacareubin (**61**) [29]. Thus by allylic bromination of the diacetate of **74**, with *N*-bromosuccinimide, followed by dehydrobromination and hydrolysis, gave a mixture containing 6-deoxyjacareubin (**75**) and a bromo-compound. After purification and isolation of **75**, the remaining bromo-compound was converted into 6-deoxyjacareubin (**75**) by treatment with zinc and acetic acid (Scheme 24).



Scheme 24. (i) PhNMe_2 , reflux 4h; (ii) NaClO_3^- , OsO_4 , NaIO_4 ; (iii) HI , H_3PO_2 , AcOH .

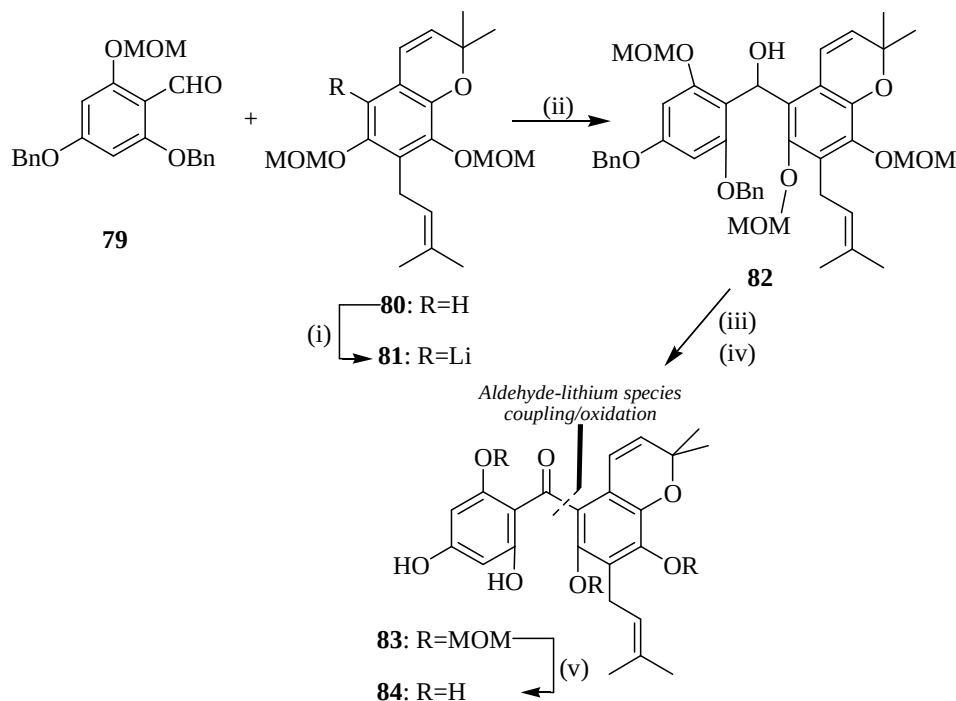
A simple and efficient synthesis of osajaxanthone (**77**) and nigrolineaxanthone F (**78**), previously isolated from *Calophyllum enervosum* [32] and *Garcinia nigrolineata* [33], respectively, has been reported by Mondal *et al* [34]. This method was based on the regioselective coupling reaction of 1,3,7-trihydroxyxanthone (**76**) with prenal in the presence of calcium hydroxide at room temperature and/or under thermal conditions at 140-150°C to exclusively obtain the natural products osajaxanthone (**77**) and nigrolineaxanthone F (**78**) in high yields (Scheme 25).



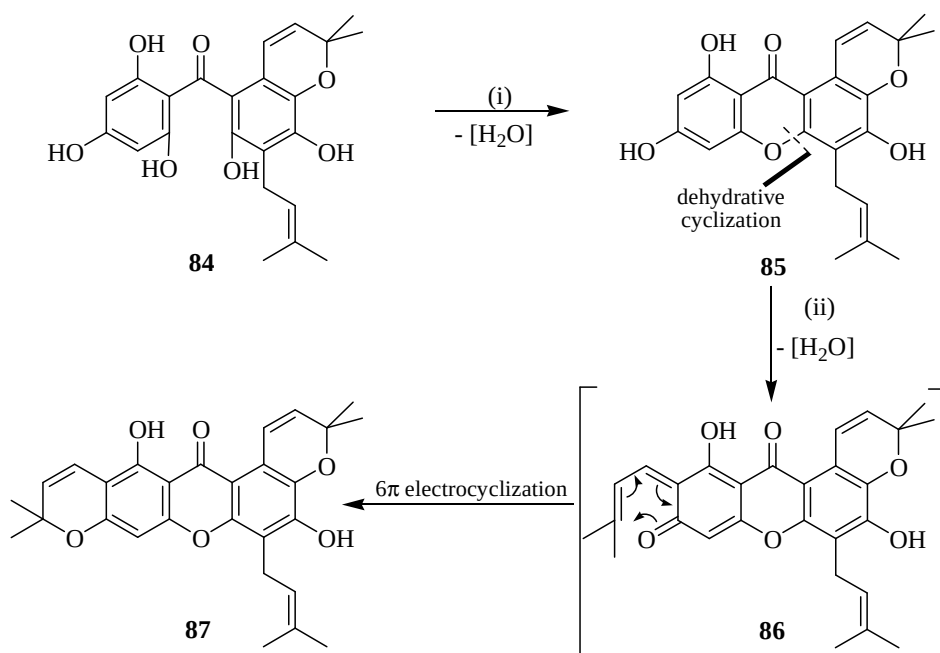
Scheme 25. (i) prenal/crotonaldehyde/citral (5.0 equiv), $\text{Ca}(\text{OH})_2$ (2.0 equiv), methanol, rt, 36h (**77**, 75%); (ii) prenal/crotonaldehyde/citral (10.0 equiv), 140-150°C, 6h (**78**, 98%).

Joe and Nicolaou have reported the synthesis of tovophyllin B (**87**), previously isolated from *Tovomita macrophylla* [35]. Scheme 26 summarizes the synthesis of the intermediate bisaryl ketone (**84**). This compound was obtained through a lithium-mediated coupling between the bis-benzyl-MOM protected benzaldehyde derivative **79** and the lithiated species **81**, achieved from the prenylated chromene **80**, to give the coupling product **82**. This step was followed by the oxidation of hydroxyl group and selective removal of benzyl groups of compound **82** to form the corresponding diphenol **83**, from which the MOM groups were removed, leading to the desired tricyclic precursor **84**. The final steps of the synthesis of tovophyllin B (**87**) are shown in scheme 27. Accordingly, cycloetherification of **84** under the influence of silica gel furnished, by dehydration, xanthone **85**. The missing 2,2-dimethylchromene ring of the

growing molecule was achieved through a cascade sequence involving CaO-induced aldol type reaction of xanthone **85** with prenal (**85'**) and a dehydration process to give the transient intermediate **86**, which after a 6π electrocyclization, afforded the target molecule **87**.



Scheme 26. (i) *n*BuLi (1.5 equiv), THF, 25°C, 15min; (ii) **79** (1.5 equiv), THF, -78°C, 15h, 58%; (iii) DMP (1.4 equiv), NaHCO₃ (5.0 equiv), CH₂Cl₂, 25°C, 2h, 80%; (iv) 10% Pd/C (0.34 equiv), Et₃N (1.0 equiv), HCO₂H (32 equiv), acetone, 25°C, 1.5h, 89%; (v) CSA (5.0 equiv), MeOH, 25°C, 8h.



Scheme 27. (i) Impregnation on silica gel plate (1.5h), then elution with EtOAc, 65%; (ii) CaO (7.5 equiv), prenal (**85'**) (15 equiv), MeOH, 25°C, 16h, 55%.

4. BIOLOGICAL ACTIVITIES:

Prenylated xanthenes, especially from natural sources have been shown to exhibit a wide range of interesting biological and pharmacological activities [7-8]. Consequently, we have reported an updated data on the biological activities of naturally occurring prenylated xanthenes and related them with the targets involved [8]. The activities reported included antimicrobial, like antibacterial, antifungal, antimalarial and antiretroviral, neurological disorders, antiplatelet, anti-inflammatory, antioxidant and antitumor. Among these, the *in vitro* growth inhibitory activity against tumor cell lines was noteworthy, since these compounds were shown to exert their effect on a broad range of different tumor cell lines.

Among the prenylated xanthenes described in this review only a small fraction has been tested for their biological activities. However, some other activities such as antitumor activity, inhibition of protein kinases, inhibition of P-glycoprotein and acidic sphingomyelinase have been reported for some synthetic prenylated xanthenes (Table 1).

The synthetic prenylated derivatives **22**, **42**, **104**, **107** and **116** were evaluated for their antitumor activity against MCF-7 cell line. Compounds **104**, **107** and **116** were found to be selective and potent growth inhibitors against this cell line while the others were only moderate inhibitors. Considering the structural feature of these active compounds, it appears that the presence of the prenyl group on C-2 of the xanthonic scaffold is important for the antitumor activity. It was also observed that the presence of an extra dihydropyran or dihydrofuran ring could be important for an effect in compounds **22**, **42** and **116**. Similarly diprenylated xanthone **15** could be a new η -isoform-specific PKC inhibitor.

Prenylated xanthenes **28-30** were found to be potential P-glycoprotein inhibitors. This effect was attributed to their binding affinity for the P-glycoprotein C-terminal cytosolic domain. It was shown that prenylation at either C-2 (xanthenes **28** and **30**) or C-4 (xanthone **29**) of ring A of the xanthonic scaffold could increase their binding affinity. In contrast, the gain in

affinity was not observed when prenylation occurred on the hydroxyl group on C-1, either as prenyloxy side chain (as in xanthone **27**) or as a cyclic form with C-2 (as in xanthone **31**). Consequently, decreasing polarity, due to prenylation, was found to enhance the binding affinity for the P-glycoprotein, however, a free hydroxyl group next to the carbonyl was required for efficient activity.

Table 1. Synthetic prenylated xanthenes obtained in 1963-2009.

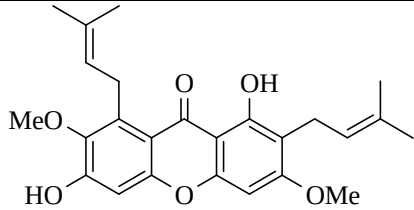
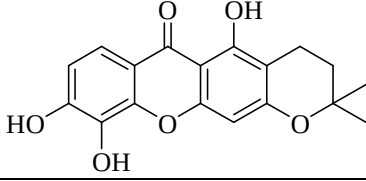
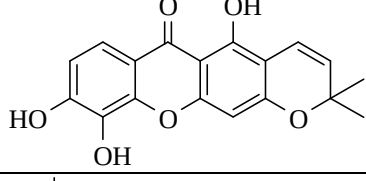
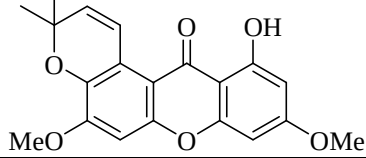
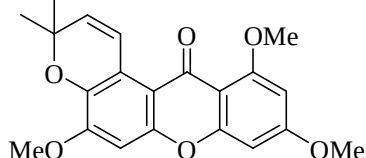
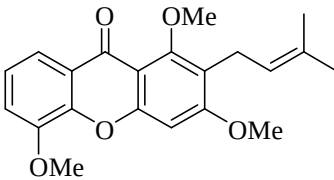
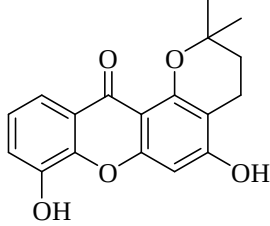
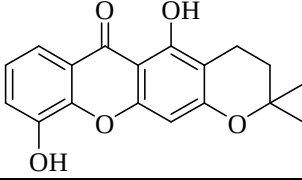
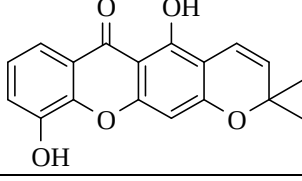
Nº	Name of the Compounds	Structure	Origin	Activities	Ref
5	α -Mangostin		Synthesis and Natural	Antitumor, antioxidant, antimicrobial, antibacterial, antifungal and antimalarial activity; Inhibitor of acidic sphingomyelinase; Inhibitory effect against topoisomerase II; Inhibitory activity on EBV-early antigen activation; Inhibition of protein kinases; Inhibitory activity on HIV protease	8, 13, 37
10	Atroviridin		Synthesis and Natural		15
12	3-Methoxy-1-(3-methylbut-2-enyloxy)-9H-xanthen-9-one		Synthesis		10
13	3-Methoxy-1-(3-methylbut-3-enyloxy)-9H-xanthen-9-one		Synthesis		10
14	1-Hydroxy-2-methyl-3-(3-methylbut-2-enyloxy)-9H-xanthen-9-one		Synthesis		16, 18
15	1-Hydroxy-2-methyl-4-(3-methylbut-2-enyl)-3-(3-methylbut-2-enyloxy)-9H-xanthen-9-one		Synthesis	η -isoform-specific PKC inhibitor	16, 18

16	1,3,5-Trihydroxy-2-(3-methylbut-2-enyl)-9 <i>H</i> -xanthen-9-one		Synthesis and Natural	Antimalarial activity against chloroquino-resistant strains of <i>Plasmodium falciparum</i>	11, 17, 36
17	1,3,5-Trihydroxy-4-(3-methylbut-2-enyl)-9 <i>H</i> -xanthen-9-one		Synthesis and Natural	Antimalarial activity against chloroquino-resistant strains of <i>Plasmodium falciparum</i>	11, 17
18	1,3,5-Trihydroxy-2,4-bis-(3-methylbut-2-enyl)-9 <i>H</i> -xanthen-9-one		Synthesis and Natural	Antimalarial activity against chloroquino-resistant strains of <i>Plasmodium falciparum</i> .	11, 17, 36
19	1-Hydroxy-3-(3-methylbut-2-enyloxy)-9 <i>H</i> -xanthen-9-one		Synthesis		10, 16, 18, 19
21	4-Hydroxy-2,3,3-trimethyl-2,3-dihydrofuro[3,2- <i>b</i>]xanthen-5-one		Synthesis		10, 18, 19
22	5-Hydroxy-1,1,2-trimethyl-1,2-dihydrofuro[2,3- <i>c</i>]xanthen-6-one		Synthesis	Moderate antitumor activity against MCF-7 cell line	18, 19
23	1,3-Dihydroxy-2-(3-methylbut-3-en-2-yl)-9 <i>H</i> -xanthen-9-one		Synthesis		18
24	1,3-Dihydroxy-4-(3-methylbut-3-en-2-yl)-9 <i>H</i> -xanthen-9-one		Synthesis		18
25	1-Hydroxy-3-methoxy-4-(3-methylbut-2-enyl)-9 <i>H</i> -xanthen-9-one		Synthesis		10

26	4-Methoxy-2,3,3-trimethyl-2,3-dihydrofuro[2,3- <i>a</i>]xanthen-11-one		Synthesis		10
27	3,7,8-Trimethoxy-1-(3-methylbut-2-enyloxy)-9 <i>H</i> -xanthen-9-one		Synthesis		9
28	1-Hydroxy-3,7,8-trimethoxy-2-(1,1-dimethylallyl)-9 <i>H</i> -xanthen-9-one		Synthesis	Potential P-Glycoprotein inhibitors	9
29	1-Hydroxy-3,7,8-trimethoxy-4-(3,3-dimethylallyl)-9 <i>H</i> -xanthen-9-one		Synthesis	Potential P-Glycoprotein inhibitors	9
30	1-Hydroxy-3,7,8-trimethoxy-2-(3,3-dimethylallyl)-9 <i>H</i> -xanthen-9-one		Synthesis	Potential P-Glycoprotein inhibitors	9
31	4,9,10-Trimethoxy-2,3,3-trimethyl-2,3-dihydrofuro[2,3- <i>a</i>]xanthen-11-one		Synthesis		9
32	3-(3-Methylbut-2-enyloxy)-9 <i>H</i> -xanthen-9-one		Synthesis		18, 20
33	3-Hydroxy-4-(3-methylbut-3-en-2-yl)-9 <i>H</i> -xanthen-9-one		Synthesis		20
34	1,1,2-Trimethyl-1,2-dihydrofuro[2,3- <i>c</i>]xanthen-6-one		Synthesis		20
35	4-Methyl-3-(3-methylbut-2-enyloxy)-9 <i>H</i> -xanthen-9-one		Synthesis		20

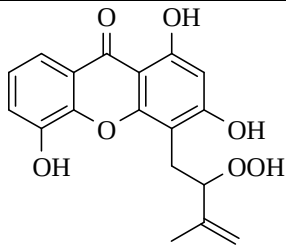
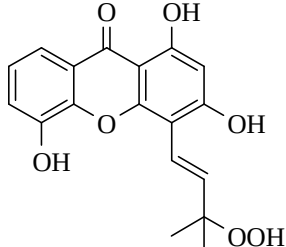
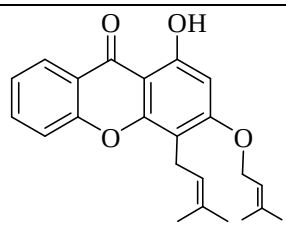
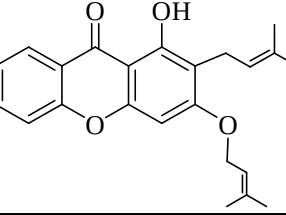
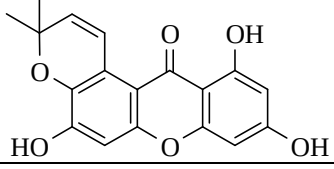
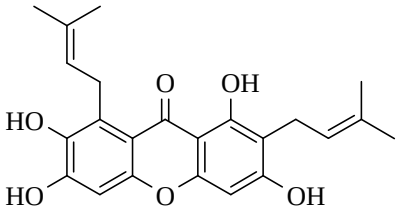
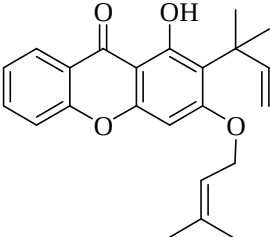
36	3-Hydroxy-4-methyl-2-(3-methylbut-3-en-2-yl)-9H-xanthen-9-one		Synthesis		20
37	3-Isomangostin		Synthesis and Natural		21
38	1-Isomangostin		Synthesis and Natural		21
39	Bicyclomangostin		Synthesis		21
40	5,10,11-Trimethoxy-2,2-dimethyl-3,4-dihydropyrano[2,3-a]xanthen-12(2H)-one		Synthesis		9
41	6-Hydroxy-3,3-dimethyl-2,3-dihydropyrano [2,3-c]xanthen-7(1H)-one		Synthesis		10, 16, 18
42	5-Hydroxy-2,2-dimethyl-3,4-dihydropyrano [3,2-b]xanthen-6(2H)-one		Synthesis	Moderate antitumor activity against MCF-7 cell line	10, 16, 18
43	5-Hydroxy-2,2-dimethyl-12-(3-methylbut-2-enyl)-3,4-dihydropyrano[3,2-b]xanthen-6(2H)-one		Synthesis		10, 18
45	2,2-Dimethyl-3,4-dihydropyrano[2,3-a]xanthen-12(2H)-one		Synthesis		25

46	2,2-Dimethylpyrano[2,3- <i>a</i>]xanthen-12(2 <i>H</i>)-one		Synthesis		25
48	Gartanin		Synthesis and Natural	Antitumor, antifungal and antioxidant activity	26, 27
49	11,5,8-Trihydroxy-3-methoxy-2-(3-methylbut-2-enyl)-9 <i>H</i> -xanthen-9-one		Synthesis and Natural		26, 27
53	Dimethyl-1-isonormangostin		Synthesis and Natural		28
54	1,7-Bis(3-chloro-3-methylbutyl)-2,8-dihydroxy-3,6-dimethoxy-9 <i>H</i> -xanthen-9-one		Synthesis		28
55	3',3"-Dichloro tetrahydrodimethylmangostin (1,7-bis(3-chloro-3-methylbutyl)-8-hydroxy-2,3,6-trimethoxy-9 <i>H</i> -xanthen-9-one)		Synthesis		28
56	1,7-Bis-(3-chloro-3-methylbutyl)- 2,3,6-trimethoxy-8-methoxycarbonyloxy-9 <i>H</i> -xanthen-9-one		Synthesis		28
57	Dimethylmangostin		Synthesis and Natural		28, 37

58	β -Mangostin		Synthesis and Natural	Antitumor, antimicrobial, antibacterial and antimalarial activity; Inhibitory activity on EBV- early antigen activation	28, 37
60	Dihydrojacareubin		Synthesis		29
61	Jacareubin		Synthesis and Natural	Antibacterial, trypanocidal and antifungal activity	29
65	11-Hydroxy-5,9-dimethoxy-3,3-dimethylpyrano[3,2-a]xanthen-12(3H)-one		Synthesis		30
66	Toxyloxanthone B trimethyl ether		Synthesis		30
72	1,3,5-Trimethoxy-2-(3-methylbut-2-enyl)-9H-xanthen-9-one		Synthesis		31
73	5,8-Dihydroxy-2,2-dimethyl-3,4-dihydropyrano[2,3-a]xanthen-12(2H)-one		Synthesis		31
74	Dihydro-6-deoxyjacareubin		Synthesis		31
75	6-Deoxyjacareubin		Synthesis and Natural	Trypanocidal and antibacterial activity; Inhibition of PAF receptor binding; Inhibition of dog gastric H ⁺ , K ⁺ -ATPase activity	31

77	Osajaxanthone		Synthesis and Natural		32, 34
78	Nigrolineaxanthone F		Synthesis and Natural		33, 34
85	5,9,11-Trihydroxy-3,3-dimethyl-6-(3-methylbut-2-enyl)pyrano[3,2-a]xanthen-12(3H)-one		Synthesis		35
87	Tovophyllin B		Synthesis and Natural	Antimicrobial activity	35
88	1,3,5,8-Tetrahydroxy-2-(3-methylbut-2-enyl)-9H-xanthen-9-one		Synthesis		26
89	1,3,7,8-Tetrahydroxy-2-(3-methylbut-2-enyl)-9H-xanthen-9-one		Synthesis		26
90	1,3,8-Trihydroxy-5-methoxy-2-(3-methylbut-2-enyl)-9H-xanthen-9-one		Synthesis		26
91	1,3,8-Trihydroxy-7-methoxy-2-(3-methylbut-2-enyl)-9H-xanthen-9-one		Synthesis		26
92	1,3,6-Trihydroxy-7-methoxy-2-(3-methylbut-2-enyl)-9H-xanthen-9-one		Synthesis	Inhibitor of acidic sphingomyelinase	14

93	1,3,6-Trihydroxy-7-methoxy-8-(3-methylbut-2-enyl)-9H-xanthen-9-one		Synthesis and Natural	Inhibitor of acidic sphingomyelinase	14
94	1-Hydroxy-3,5,8-trimethoxy-2-(3-methylbut-2-enyl)-9H-xanthen-9-one		Synthesis		26
95	1-Hydroxy-3,5,8-trimethoxy-4-(3-methylbut-2-enyl)-9H-xanthen-9-one		Synthesis		26
96	1,3,5,8-Tetramethoxy-2-(3-methylbut-2-enyl)-9H-xanthen-9-one		Synthesis		26
97	1,3,7,8-Tetramethoxy-2-(3-methylbut-2-enyl)-9H-xanthen-9-one		Synthesis		26
98	Caledol (1,3,5-trihydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-9H-xanthen-9-one)		Synthesis and Natural	Antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i>	11, 17, 36
99	Dicaledol (1,3,5-trihydroxy-2,4-bis(2-hydroxy-3-methylbut-3-enyl)-9H-xanthen-9-one)		Synthesis and Natural	Antifungal activity against <i>Aspergillus fumigatus</i>	11, 17, 36
100	1,3,5-Trihydroxy-4-(2-hydroxy-3-methylbut-3-enyl)-9H-xanthen-9-one		Synthesis		11, 36

101	1,3,5-Trihydroxy-4-(2-hydroperoxy-3-methylbut-3-enyl)-9H-xanthen-9-one		Synthesis		11
102	1,3,5-Trihydroxy-4-(3-hydroperoxy-3-methylbut-1-enyl)-9H-xanthen-9-one		Synthesis		11
103	1-Hydroxy-4-(3-methylbut-2-enyl)-3-(3-methylbut-2-enyloxy)-9H-xanthen-9-one		Synthesis		16, 18
104	1-Hydroxy-2-(3-methylbut-2-enyl)-3-(3-methylbut-2-enyloxy)-9H-xanthen-9-one		Synthesis	Potent antitumor activity against MCF-7 cell line	16, 18
105	Toxyloxanthone B		Synthesis and Natural		30
106	γ -Mangostin		Synthesis and Natural	Antitumor, antioxidant, antimicrobial and antifungal activity; Inhibition of cyclooxygenase and prostaglandin E2; Inhibitory effect against topoisomerase II; Inhibition of k _B kinase activity and decrease lipopolysaccharide-induced cyclooxygenase-2 gene expression in C6 rat glioma cells; Inhibition of protein kinases; Inhibitory activity on HIV protease; 5-hydroxy tryptamine 2A receptor antagonist in the central nervous system	8, 37
107	1-Hydroxy-3-(3-methylbut-2-enyloxy)-2-(2-methylbut-3-en-2-yl)-9H-xanthen-9-one		Synthesis	Potent antitumor activity against MCF-7 cell line	16, 18

108	1,3,8-Trihydroxy-5-methoxy-2,4-bis(3-methylbut-2-enyl)-9H-xanthen-9-one		Synthesis		26
109	1-Hydroxy-3,5,8-trimethoxy-2,4-bis(3-methylbut-2-enyl)-9H-xanthen-9-one		Synthesis		26
110	2,2-Dimethyl-5-(3-methylbut-2-enyloxy)-3,4-dihydropyrano[3,2-b]xanthen-6(2H)-one		Synthesis		10
111	2,2,3,11-Tetramethyl-2,3-dihydrofuro[3,2-b]xanthen-5-one		Synthesis		20
112	5-Hydroxy-1,1,2,4-tetramethyl-1,2-dihydrofuro[2,3-c]xanthen-6-one		Synthesis		18
113	2,2-Dimethyl-3,4-dihydropyrano[3,2-b]xanthen-6(2H)-one		Synthesis		18
114	3,3-Dimethyl-2,3-dihydropyrano[2,3-c]xanthen-7(1H)-one		Synthesis		18
115	2,2-Dimethyl-6-oxo-2,3,4,6-tetrahydropyrano[3,2-b]xanthen-5-yl acetate		Synthesis		10
116	6-Hydroxy-3,3,5-trimethyl-2,3-dihydropyrano[2,3-c]xanthen-7(1H)-one		Synthesis	Antitumor activity against MCF-7 cell line	16; 18

117	5-Hydroxy-2,2-dimethylpyrano[3,2- <i>b</i>]xanthen-6-one		Synthesis		10
118	6-Hydroxy-3,3-dimethylpyrano[2,3- <i>c</i>]xanthen-7(3 <i>H</i>)-one		Synthesis		38, 39, 40
119	6-Deoxyisojacareubin (6,11-dihydroxy-3,3-dimethylpyrano[2,3- <i>c</i>]xanthen-7(3 <i>H</i>)-one)		Synthesis and Natural	Antimalarial activity against chloroquine-resistant strains of <i>Plasmodium falciparum</i>	11, 36
120	2,2-Dimethyl-5-(3-methylbut-2-enyloxy)pyrano[3,2- <i>b</i>]xanthen-6(2 <i>H</i>)-one		Synthesis		10
121	5-Hydroxy-2,2-dimethyl-12-(3-methylbut-2-enyl)pyrano[3,2- <i>b</i>]xanthen-6(2 <i>H</i>)-one		Synthesis		10
122	6,11-Dihydroxy-5-(2-hydroxy-3-methylbut-3-enyl)-3,3-dimethylpyrano[2,3- <i>c</i>]xanthen-7(3 <i>H</i>)-one		Synthesis and Natural		11, 17, 36
123	Bicyclomangostin 13-methyl ether		Synthesis		21
124	Isobicyclomangostin-5-methyl ether		Synthesis		21
125	Dimethylbicyclomangostin methyl sulfate		Synthesis		21

Prenylated xanthenes **92** and **93** were found to exhibit an inhibitory activity against sphingomyelinase (SMase). It was demonstrated that compound **93**, carrying no prenyl group on the ring A of the xanthonic scaffold, possessed strong inhibitory effect against both acidic (ASMase) and neutral (NSMase) sphingomyelinases but no selective inhibition between both SMase. On the contrary, xanthone **92**, whose prenyl group is on ring A, was found to exhibit activity against only the ASMase and consequently showing selective inhibition against this form.

As already described, the well known naturally occurring prenylated xanthenes **5**, **48**, **58**, **61**, **106** and **75**, exhibited a wide range of biological activities such as antitumor, antioxidant, antibacterial and antifungal, among others (see **Table 1**).

CONCLUSIONS: This review provides an update of the current methods for the synthesis of prenylated xanthenes. Many of these strategies are based on molecular modifications of natural compounds in order to improve their physical-chemical properties and biological activities.

More recent methodologies of synthesis of prenylated xanthenes, such as Microwave Assisted Organic Synthesis (MAOS) and application of heterogeneous catalysis have proved to be very efficient and environmentally friendly. Besides that, these processes can give a very interesting contribution in order to obtain molecular diversity, which can help to rationalize the structure-activity relationship for this family of compounds.

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ABBREVIATIONS

MAOS – Microwave-assisted organic synthesis

SAR – Structure-activity relationship

MW – Microwave

N,N-DEA – *N,N*-Diethylaniline

N,N-DMA – *N,N*-Dimethylaniline

NMP – *N*-Methyl-2-pyrrolidone

DDQ – 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone

MCF-7 – Breast adenocarcinoma cell line

EBV – Epstein-Barr virus

HIV – Human immunodeficiency virus

PKC – Protein Kinase C

PAF – Platelet Activating Factor

REFERENCES

- [1] Peres, V.; Nagem, T.J. Trioxygenated Naturally Occurring Xanthenes. *Phytochemistry*, **1997**, *44*, 191-214.
- [2] Peres, V.; Nagem, T.J. Naturally Occurring Penta-oxygenated, Hexa-oxygenated and Dimeric Xanthenes: A Literature Survey. *Quím. Nova*, **1997**, *20*, 388-397.
- [3] Peres, V.; Nagem, T.J.; de Oliveira, F.F. Tetra-oxygenated naturally occurring xanthenes. *Phytochemistry*, **2000**, *55*, 683-710.
- [4] Vieira, L. M. M.; Kijjoo, A. Naturally-Occurring Xanthenes: Recent Developments. *Curr. Med. Chem.*, **2005**, *12*, 2413-2446.
- [5] Bennett, G.J.; Lee, H.-H. Xanthenes from Guttiferae. *Phytochemistry*, **1989**, *28*(4), 967-998.
- [6] Sultanbawa, M. U. S. Xanthenoids of Tropical Plants. *Tetrahedron*, **1980**, *36*, 1465-1506.
- [7] Pinto, M.M.M.; Sousa, M.E.; Nascimento, M.S.J. Xanthone Derivatives: New Insights in Biological Activities. *Curr. Med. Chem.*, **2005**, *12*, 2517-2538.
- [8] Pinto, M.; Castanheiro, R.; Natural Prenylated Xanthenes: Chemistry and Biological Activities. In *Natural Products: Chemistry, Biochemistry and Pharmacology*. Brahmachari, G. Ed., Narosa Publishing House PVT. LTD., New Delhi, India, ISBN: 978-81-7319-886-1, **2009**, Chap. 17, pp. 520-676.
- [9] Tchamo, D. N.; Dijoux-Franca, M.G.; Mariotte, A. M.; Tsamo, E.; Daskiewicz, J. B.; Bayet, C.; Barron, D.; Conseil G.; Di Pietro, A. Prenylated Xanthenes as Potential P-Glycoprotein Modulators. *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 1343-1345.
- [10] Subba Rao, G. S. R.; Raghavan, S. Synthetic studies on morellin. Part 4: Synthesis of 2,2-dimethyl-12-[3-methylbut-2-enyl]-2H,6H-pyrano[3,2-b]xanthen-6-one. *J. Indian Inst. Sci.*, **2001**, *81*, 393-401.
- [11] Helesbeux, J. J.; Duval, O.; Dartiguelongue, C.; Séraphin, D.; Oger, J. M.; Richomme, P. Synthesis of 2-hydroxy-3-methylbut-3-enyl substituted coumarins and xanthenes as natural products. Application of the Schenck ene reaction of singlet oxygen with ortho-prenylphenol precursors. *Tetrahedron*, **2004**, *60*, 2293-2300.
- [12] Sousa, M. E.; Pinto, M. M. M. Synthesis of Xanthenes: An Overview. *Curr. Med. Chem.*, **2005**, *12*, 2447-2479.
- [13] Iikubo, K.; Ishikawa, Y.; Ando, N.; Umezawa, K.; Nishiyama, S. The first direct synthesis of α -mangostin, a potent inhibitor of the acidic sphingomyelinase. *Tetrahedron Lett.*, **2002**, *43*, 291-293.
- [14] Hamada, M.; Iikubo, K.; Ishikawa, Y.; Ikeda, A.; Umezawa, K.; Nishiyama, S. Biological Activities of α -Mangostin Derivatives against Acidic Sphingomyelinase. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 3151-3153.

- [15]Tisdale, E. J.; Kochman, D. A.; Theodorakis, E. A. Total synthesis of atroviridin. *Tetrahedron Lett.*, **2003**, 44, 3281-3284.
- [16]Castanheiro, R. A. P., Pinto, M. M. M., Silva, A. M. S., Cravo, S. M. M., Gales, L., Damas, A. M., Nazareth, N., Nascimento, M. S. J., Eaton, G. Dihydroxyxanthenes prenylated derivatives: Synthesis, structure elucidation, and growth inhibitory activity on human tumor cell lines with improvement of selectivity for MCF-7. *Bioorg. Med. Chem.*, **2007**,15, 6080-6088.
- [17]Oger, J.-M.; Morel, C.; Helesbeux, J.-J.; Litaudon, M.; Séraphin, D.; Dartiguelongue, C.; Larcher, G.; Richomme, P.; Duval, O. First 2-Hydroxy-3-Methylbut-3-Enyl Substituted Xanthenes Isolated from Plants: Structure Elucidation, Synthesis and Antifungal Activity. *Nat. Prod. Res.*, **2003**, 17, 195-199.
- [18]Castanheiro, R. A. P.; Pinto, M. M. M.; Cravo, S. M. M.; Pinto, D. C. G. A.; Silva, A. M. S.; Kijjoa, A. Improved methodologies for synthesis of prenylated xanthenes by microwave irradiation and combination of heterogeneous catalysis (K10 clay) with microwave irradiation. *Tetrahedron*, **2009**, 65, 3848-3857.
- [19]Jain, A. C.; Anand, S. M. Claisen Rearrangement of 1-Hydroxy-3-(3-methylbut-2-enyloxy)xanthenes. *J. Chem. Soc. Perkin Trans. 1*, **1974**, 329-333.
- [20]Patel, G. N.; Trivedi, K. N. Abnormal Claisen Rearrangement of 3-Prenyloxyxanthone and 3-Prenyloxy-4-methylxanthone. *J. Indian Chem. Soc.*, **1988**, 65, 192-193.
- [21]Mahabusarakam, W.; Pakawatchai, C.; Wiriyaichitra, P.; Taylor, W. C.; Skelton, B. W.; White, A. H. Bicyclomangostin: a New Acid-Catalysed Cyclization Product from Mangostin. *Aust. J. Chem.*, **1998**, 51, 249-254.
- [22]Nagendrappa, G. Organic Synthesis using Clay Catalysts. *Resonance*, **2002**, 64-77.
- [23]Dintzner, M.R.; McClelland, K.M.; Morse, K.M.; Akroush, M.H. Montmorillonite Clays in Organic Synthesis: A One-Pot Conversion of Phenols to 2,2-Dimethylbenzopyrans. *Synlett*, **2004**, 11, 2028-2030.
- [24]Mortoni, A. ; Martinelli, M.; Piarulli, U.; Regalia, N.; Gagliardi, S. Microwave-assisted solvent-free synthesis of a quinoline-3,4-dicarboximide library on inorganic solid supports. *Tetrahedron Lett.*, **2004**, 45, 6623-6627.
- [25]Ahluwalia, V. K.; Jolly, R. S.; Tehim, A. K. A Convenient Synthesis of Dihydropyranoxanthenes. *J. Chem. Soc. Perkin Trans. 1*, **1983**, 1229-1233.
- [26]Bennett, G. J.; Lee, H. H.; Lee, L. P. Synthesis of Minor Xanthenes from *Garcinia Mangostana*. *J. Nat. Prod.*, **1990**, 53(6), 1463-1470.

- [27] Govindachari, T. R.; Kalyanaraman, P. S.; Muthukumaraswamy, N.; Pai, B. R. Xanthonenes of *Garcinia mangostana* Linn. *Tetrahedron*, **1971**, 27(16), 3919-3926.
- [28] Lee, H.-H. Synthesis of the Mangostins. *J. Chem. Soc. Perkin Trans. 1*, **1981**, 3205-3213.
- [29] Jefferson, A.; Scheinmann, F. Studies in the Xanthone Series. Part VIII. An Unambiguous Synthesis of Jacareubin. *J. Chem. Soc. (C)*, **1966**, 175-178.
- [30] Cotterill, P. J.; Scheinmann, F. Studies in the Xanthone Series. Part 13. Structural and Synthetic Studies on Toxyloxanthone B. *J. Chem. Soc. Perkin Trans. 1*, **1980**, 2353-2357.
- [31] Locksley, H. D.; Quillinan, A. J.; Scheinmann, F. Extractives from Guttiferae. Part XXIII. An Unambiguous Synthesis of 6-Deoxyjacareubin and Related 3,3- and 1,1-Dimethylallyl and Annulated Xanthonenes. *J. Chem. Soc. (C)*, **1971**, 3804-3818.
- [32] Taher, M.; Idris, M. S.; Ahmad, F.; Arbain, D. A polyisoprenylated ketone from *Calophyllum nervosum*. *Phytochemistry*, **2005**, 66, 723-726.
- [33] Rukachaisirikul, V.; Ritthiwigrom, T.; Pinsa, A.; Sawangchote, P.; Taylor, W.C. Xanthonenes from the stem bark of *Garcinia nigrolineata*. *Phytochemistry*, **2003**, 64, 1149-1156.
- [34] Mondal, M.; Puranik, V.G.; Argade, N.P. Facile Synthesis of 1,3,7-Trihydroxyxanthone and Its Regioselective Coupling Reactions with Prenal: Simple and Efficient Access to Osajaxanthone and Nigrolineaxanthone F. *J. Org. Chem.*, **2006**, 71, 4992-4995.
- [35] Jeso, V.; Nicolaou, K. C.; Total synthesis of tovophyllin B. *Tetrahedron Lett.*, **2009**, 50, 1161-1163.
- [36] Hay, A.-E.; Hélesbeux, J.-J.; Duval, O.; Labaïed, M.; Grellier, P.; Richomme, P. Antimalarial xanthonenes from *Calophyllum caledonicum* and *Garcinia vieillardii*. *Life Sci.*, **2004**, 75, 3077-3085.
- [37] Jefferson, A.; Quillinan, A. J.; Scheinmann, F.; Sim, K. Y. Studies in the Xanthone Series. *Aust. J. Chem.*, **1970**, 23, 2539-2543.
- [38] Kolokythas, G.; Kostakis, I. K.; Pouli, N.; Marakos, P.; Kousidou, O. Ch.; Tzanakakis, G. N.; Karamanos, N. K. Design and synthesis of new pyranoxanthenones bearing a nitro group or an aminosubstituted side chain on the pyran ring. Evaluation of their growth inhibitory activity in breast cancer cells. *Eur. J. Med. Chem.*, **2007**, 42(3), 307-319.
- [39] Kostakis, I. K.; Magiatis, P.; Pouli, N.; Marakos, P.; Skaltsounis, A.-L.; Pratsinis, H.; Leonce, S.; Pierre, A. Design, Synthesis, and Antiproliferative Activity of Some New Pyrazole-Fused Amino Derivatives of the Pyranoxanthenone, Pyranothioxanthenone, and Pyranoacridone Ring Systems: A New Class of Cytotoxic Agents. *J. Med. Chem.*, **2002**, 45(12), 2599-2609.

- [40] Kostakis, I.; Ghirtis, K.; Pouli, N.; Marakos, P.; Skaltsounis, A.-L.; Leonce, S.; Caignard, D. H.; Atassi, G. Synthesis and cytotoxic activity of 2-dialkylaminoethylamino substituted xanthenone and thioxanthenone derivatives. *Il Farmaco*, **2000**, 55, 455-460.

ANEXO IV

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Dihydroxyxanthenes prenylated derivatives: Synthesis, structure elucidation, and growth inhibitory activity on human tumor cell lines with improvement of selectivity for MCF-7

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Abstract—The synthesis, structure elucidation, and antitumor activity of 11 xanthenes are reported, being the compounds **3**, **4**, **6–8**, and **9** described for the first time. Xanthenes **1** and **2** were used as building blocks to obtain the prenylated derivatives **3–8**. Prenylation was carried out using prenyl bromide in alkaline medium. Dihydropyrano-xanthenes **9–11** were obtained from compounds **4** and **5** by an oxidative ring closure. The structure of the compounds was established by IR, UV, MS, and NMR (¹H, ¹³C, COSY, HSQC, and HMBC) techniques and for compounds **4**, **6**, and **11** the structure was confirmed by X-ray crystallographic analysis. The effect of the 11 xanthenes on the in vitro growth of four human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), SF-268 (central nervous system cancer), and UACC-62 (melanoma) is also described.
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1. Introduction

Xanthonic compounds show interesting biological activities associated with their tricyclic scaffold depending on the nature and/or position of the different substituents.¹

A relationship between activity and the presence of prenyl groups in key-positions on the xanthone nucleus was associated with some biological activities, such as inhibition of human lymphocyte proliferation,² PKC modulation,³ antitumor,⁴ and anti-inflammatory.⁵

The influence of these groups is dual, considering the influence on physicochemical properties, namely lipo-

philicity, and on three-dimensional properties affecting steric effects on interaction with the biological targets.

Recently, we have investigated the effect of several hydroxy and methoxyxanthenes on the in vitro growth of human tumor cell lines.⁶ Among 27 xanthenes tested 1,3-dihydroxy-2-methylxanthone (**1**) was found to have the best growth inhibitory activity against the three cell lines tested, namely MCF-7 (breast cancer), TK-10 (renal cancer), and UACC-62 (melanoma). Simple dihydroxyxanthone derivatives also showed some interesting tumor growth inhibitory activity.⁶

In order to modulate and improve the antitumor activity of these compounds, we have synthesized new prenylated derivatives, using as building blocks 1,3-dihydroxy-2-methylxanthone (**1**) and the *nor*-derivative 1,3-dihydroxyxanthone (**2**) (Fig. 1) and their activity was evaluated (Table 1).

Keywords: Xanthenes; Prenylation; Antitumor activity; X-ray crystallography; NMR spectroscopy.

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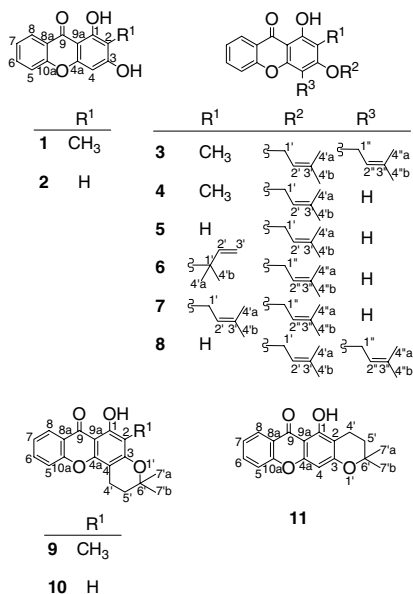


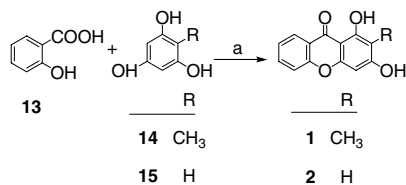
Figure 1. Structures of building blocks **1** and **2** and prenylated derivatives **3–11** (the numbering used concerns the NMR discussion).

Table 1. Effects of xanthenes **1** and **2** and xanthone derivatives **3–11** on the growth of human tumor cell lines

Compound	GI ₅₀ (μM)			
	MCF-7	NCI-H460	SF-268	UACC-62
1	21.9 ± 0.4	20.6 ± 0.9	33.4 ± 0.2	20.0 ± 0.5
2	50.8 ± 2.2	37.9 ± 2.9	61.4 ± 5.2	38.0 ± 1.6
3	>130	>130	>130	>130
4	>160	>160	>160	>160
5	>160	>160	>160	>160
6	6.0 ± 0.7	>130	>130	>130
7	9.1 ± 1.5	>130	>130	>130
8	112.5 ± 10.1	>130	>130	>130
9	18.4 ± 1.9	>160	>160	ND
10	>160	>160	>160	ND
11	88.6 ± 12.9	>160	>160	ND

Results expressed as GI₅₀, concentrations of compound that cause 50% inhibition of tumor cell lines growth, are means ± SEM of 3–8 independent experiments performed in duplicate. Doxorubicin was used as positive control, GI₅₀: MCF-7 = 42.8 ± 8.2 nM; NCI-H460 = 94.0 ± 8.7 nM; SF-268 = 93.0 ± 7.0 nM; UACC-62 = 94.0 ± 9.4 nM. ND, not done.

We report the synthesis of the xanthonic building blocks **1** and **2** (Scheme 1) as well as of nine prenylated derivatives **3–11** (Fig. 1). The synthetic approach used to



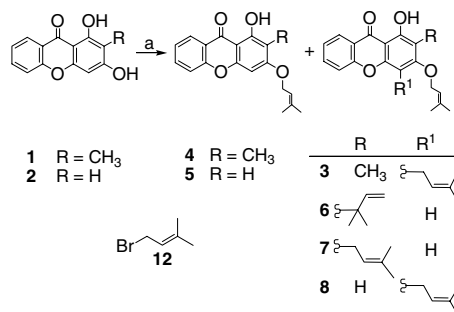
Scheme 1. Reagents and condition: (a) ZnCl₂, POCl₃, 70 °C, 3 h.

synthesize the prenylated xanthenes **3–8** was by nucleophilic substitution on the xanthonic building blocks **1** and **2**, with prenyl bromide (**12**) in alkaline medium⁷ (Scheme 2). The cyclic derivatives **9** and **10–11** were obtained from the prenylated xanthenes **4** and **5**, respectively, by refluxing with a catalytic amount of zinc chloride in dry xylene⁷ (Scheme 3).

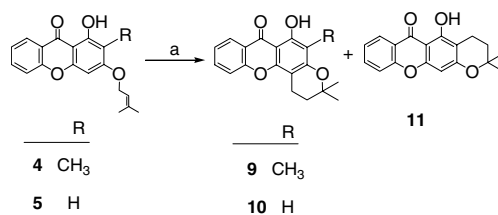
The xanthonic building blocks **1** and **2** were evaluated together with the prenylated derivatives **3–11** (Table 1), for their capacity to inhibit the in vitro growth of four human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), SF-268 (central nervous system cancer), and UACC-62 (melanoma).

Considering the *O*-prenylderivatives **3** and **4** from the xanthone **1** (Fig. 1) the antitumor activity for cellular lines tested was not improved (Table 1). However the corresponding cyclic derivative **9**, showed specificity for MCF-7 cell line.

Starting with xanthone **2** the compounds **5–8** were obtained and it could be found that compounds **6** and **7** showed a selective and highly potent growth inhibitory activity against the MCF-7 cell line. Considering the cyclic derivatives **10** and **11**, an enhancement on compound **10** activity was not observed, when compared to their precursor **5** (Fig. 1 and Table 1).



Scheme 2. Reagents and condition: (a) Prenyl bromide (**12**), K₂CO₃, Acetone, Reflux, 8 h.



Scheme 3. Reagents and condition: (a) ZnCl₂, *o*-xylene, 200 °C, 21 h.

2. Results and discussion

2.1. Synthesis of xanthone prenylated derivatives

Xanthenes **1** and **2** were obtained by the Grover, Shah, and Shah method.^{7–9} 1,3-dihydroxyxanthenes (**1** and **2**) have been obtained by condensation of salicylic acid (**13**) and phloroglucinol derivatives (**14** and **15**)⁹ (Scheme 1).

The prenylated derivatives **3–8** were obtained by the reaction of xanthenes **1** or **2** and prenyl bromide in alkaline medium.⁷ Xanthone **1** gave two prenylated derivatives **3** and **4**, and xanthone **2** afforded the prenylated derivatives **5–8**, being the compounds **3**, **4**, and **6–8** described for the first time (Scheme 2). The cyclic derivatives **9–11** were obtained by refluxing the prenylated xanthenes **4** or **5** with a catalytic amount of zinc chloride, in dry xylene.⁷ The prenylated xanthone **4** gave the novel cyclic derivative **9** (described for the first time) while the prenylated xanthone **5** afforded the derivatives **10** and **11** (Scheme 3).

2.2. Structural elucidation of prenylated xanthenes

For compounds **1** and **2** all the data are according to the literature.^{7,8,10} The structure elucidation of compounds **3–11** was established on the basis of UV, IR, MS, and NMR techniques. The ¹H NMR and ¹³C NMR data of prenylated xanthenes are reported in Tables 2 and 3, respectively.

The ¹H NMR spectra of all prenylated xanthenes had in common the signals of hydrogen-bonded hydroxyl group δ_{H} 12.64–13.67 ppm (OH-1) and four aromatic protons corresponding to the phenyl ring. The ¹H NMR spectra of prenylated xanthenes **3**, **4**, and **9** contained a signal due to a methyl group at δ_{H} 2.09–2.24 ppm. The ¹H NMR spectra of xanthenes **4** and **5** showed signals that evidence one 3,3-dimethylallyl (prenyl) group, while the spectra of xanthenes **3**, **6–8** showed signals concerning the presence of two prenyl groups. The spectra of xanthenes **9**, **10**, and **11** showed the presence of a fused dihydropyran ring considering two triplets due to the two methylene protons and the signal for the protons of two methyl groups appearing as a singlet. The ¹³C NMR spectra revealed signals for one carbonyl group (compounds **3–11**), two aromatic rings (**3–11**), one of them containing a methyl carbon in the case of compounds **3**, **4**, and **9**, two oxygenated carbons (**3–11**), one (**4**, **5**) or two (**3**, **6–8**) prenyl groups, and a 2,3-dihydropyran ring (**9**, **10**) or a 3,4-dihydropyran ring (**11**). The position of the substituents on the xanthone skeleton was determined on the basis of HSQC and HMBC spectral analysis (Fig. 2).

In HMBC spectra of all prenylated xanthenes, the hydrogen-bonded hydroxyl group (OH-1) correlated with C-1 and C-9a, allowing the assignment of these two carbon resonances. In the same way H-1' and H-1'' of prenyl group, in compounds **3–5**, **8**, and **6**, **7**, respectively, correlated with C-3 of xanthone ring indi-

cating that all the prenylated xanthenes had a 3,3-dimethylallyloxy group at C-3.

For diprenylated xanthenes, it was observed that the H-1'' of the other prenyl group correlated with C-4 and C-4a in compounds **3** and **8**, and the H-1' correlated with C-2 in compound **7**. The presence of the 1,1-dimethylallyl group in xanthone **6** was assigned by their C-1' quaternary carbon and by the two double doublets corresponding to 2 $\times$ H-3' ($J = 17.5$, 10.6 and 17.5, 1.3 Hz).

In the case of dihydropyranoxanthenes, it was observed that H-4' of the pyran ring of xanthenes **9** and **10** correlated with C-3, C-4, C-4a, C-5', and C-6' indicating the presence of a 3,4-dihydropyran ring, on the other hand the H-4' of the pyran ring of xanthone **11** correlated with C-1, C-2, C-3, C-5', and C-6' indicating the presence of a 2,3-dihydropyran ring.

The structure of compounds **4**, **6**, and **11** was also determined by X-ray crystallography. A perspective view of the crystal structures, obtained using ORTEP¹¹ and showing the atomic numbering, is presented in Figure 3.

Like in most of the crystal structures reported until now,¹² the xanthone basic skeletons of **4**, **6**, and **11** are essentially planar and the central pyranoid rings of the three compounds have a partial aromatic character. The C4a–O10–C10a angles are 119.43(11)° (**4**), 119.12(18)° (**6**), and 119.64(13)° (**11**); the C4a–O10 bond lengths are 1.3630(16) Å (**4**), 1.366(3) Å (**6**), and 1.375(2) Å (**11**), and the C10a–O10 bond lengths are 1.3612(16) Å (**4**), 1.363(3) Å (**6**) and 1.373(2) Å (**11**), which are values slightly lower than those observed for diaryl ethers C_{ar}–O–C_{ar}: 1.384(14) Å,¹³ suggesting that the p_z electrons of O-10, C-4a, and C-10a are used in conjugation in the central ring.

It was already reported that in hydroxylated or methoxylated xanthenes a coplanar conformation with respect to the xanthone skeleton is usually adopted.^{14,15} Moreover, when the –OH group is bound to C-1 or C-8, as it happens in **4**, **6**, and **11**, a hydrogen bond to O-11 is always established.¹²

The bond lengths and angles of the prenyl group of **4** and **6** are comparable with those found in the crystal structure of *Emericellin*.¹⁶ Compound **11** comprises four six-membered rings with a dihydropyran ring linearly fused to the xanthone skeleton. Three crystal structures of xanthenes with a similar four-ring system arrangement were already elucidated: 1-hydroxy-6,7-dimethoxy-8-(3-methylbut-2-enyl)-6',6'-dimethylpyrano(2',3':3,2)xanthone,¹⁷ *Dulxanthone E*,¹⁸ and 6-*Deoxyjacareubin*.¹⁹ In all three crystal structures now available, the xanthone skeleton is almost flat and the dihydropyran ring assumes a half-chair conformation.

2.3. Biological studies

The effects of the prenylated xanthenes **3–11** and of the two xanthonic building blocks, **1** and **2** on the growth of

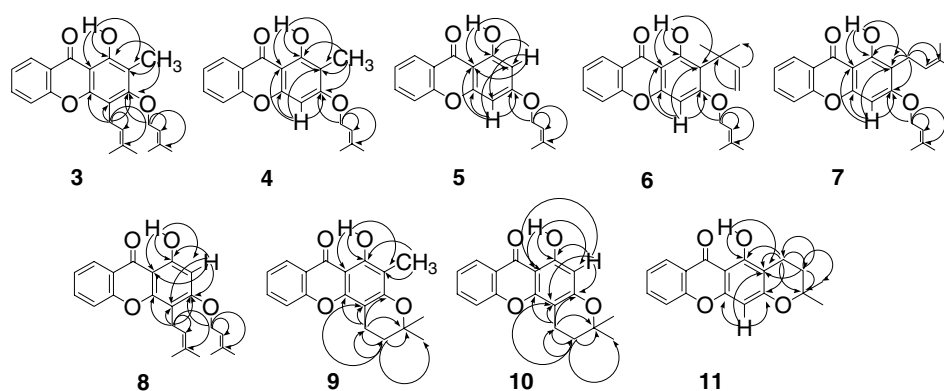
Table 2. ¹H NMR chemical shifts of prenylated xanthenes 3–11^a

	3	4	5	6	7	8
H-1	12.98 [OH, s]	12.91 [OH, s]	12.85 [OH, s]	13.67 [OH, s]	12.92 [OH, s]	12.97 [OH, s]
H-2	—	—	6.34 (d, <i>J</i> = 2.2)	—	—	6.39 (s)
H-4	—	6.39 (s)	6.42 (d, <i>J</i> = 2.2)	6.42 (s)	6.44 (s)	—
H-5	7.47 (d, <i>J</i> = 8.4)	7.38 (d, <i>J</i> = 8.4)	7.41 (d, <i>J</i> = 8.3)	7.40 (d, <i>J</i> = 8.6)	7.42 (d, <i>J</i> = 8.4)	7.46 (d, <i>J</i> = 8.2)
H-6	7.72 (ddd, <i>J</i> = 8.4, 7.4, 1.6)	7.67 (ddd, <i>J</i> = 8.4, 7.2, 1.6)	7.69 (ddd, <i>J</i> = 8.3, 7.2, 1.6)	7.69 (ddd, <i>J</i> = 8.6, 7.0, 1.6)	7.69 (ddd, <i>J</i> = 8.4, 7.0, 1.6)	7.71 (ddd, <i>J</i> = 8.2, 7.1, 1.6)
H-7	7.37 (t, <i>J</i> = 7.8, 7.4)	7.32 (d, <i>J</i> = 7.2)	7.36 (t, <i>J</i> = 7.9, 7.2)	7.36 (t, <i>J</i> = 8.1, 7.0)	7.36 (t, <i>J</i> = 8.0, 7.0)	7.36 (t, <i>J</i> = 8.0, 7.1)
H-8	8.26 (dd, <i>J</i> = 7.8, 1.6)	8.22 (dd, <i>J</i> = 7.9, 1.6)	8.23 (dd, <i>J</i> = 7.9, 1.6)	8.26 (dd, <i>J</i> = 8.1, 1.6)	8.26 (dd, <i>J</i> = 8.0, 1.6)	8.24 (dd, <i>J</i> = 8.0, 1.6)
H-10	2.24 (s)	2.09 (s)	—	—	—	—
H-1'	4.41 (d, <i>J</i> = 7.1)	4.61 (d, <i>J</i> = 6.5)	4.59 (d, <i>J</i> = 6.7)	6.32 (dd, <i>J</i> = 17.4, 10.6)	3.38 (d, <i>J</i> = 7.2)	4.63 (d, <i>J</i> = 6.6)
H-2'	5.61 (t, <i>J</i> = 7.1)	5.51 (t, <i>J</i> = 6.5)	5.50 (t, <i>J</i> = 6.7)	4.88 (dd, <i>J</i> = 17.4, 1.2)	5.25 (t, <i>J</i> = 7.2)	5.49 (t, <i>J</i> = 6.6)
H-3'	—	—	—	4.81 (dd, <i>J</i> = 10.6, 1.2)	—	—
H-4'	1.82, 1.72 (2s)	1.82, 1.78 (2s)	1.82, 1.77 (2s)	1.61, 1.59 (2s)	1.79, 1.68 (2s)	1.81, 1.76 (2s)
H-1''	3.57 (d, <i>J</i> = 6.9)	—	—	4.58 (d, <i>J</i> = 6.5)	4.63 (d, <i>J</i> = 6.6)	3.50 (d, <i>J</i> = 7.0)
H-2''	5.24 (t, <i>J</i> = 6.9)	—	—	5.49 (t, <i>J</i> = 6.5)	5.51 (t, <i>J</i> = 6.6)	5.23 (t, <i>J</i> = 7.0)
H-4''	1.89, 1.69 (2s)	—	—	1.81, 1.76 (2s)	1.82, 1.78 (2s)	1.87, 1.68 (2s)
10						
H-1	—	12.88 [OH, s]	—	12.64 [OH, s]	—	13.22 [OH, s]
H-2	—	—	—	6.26 (s)	—	—
H-4	—	—	—	—	—	6.35 (s)
H-5	7.44 (dd, <i>J</i> = 8.4, 0.9)	7.44 (dd, <i>J</i> = 8.4, 0.9)	—	7.47 (d, <i>J</i> = 8.4)	7.42 (d, <i>J</i> = 8.4)	7.42 (d, <i>J</i> = 8.4)
H-6	7.68 (ddd, <i>J</i> = 8.4, 7.1, 1.6)	7.68 (ddd, <i>J</i> = 8.4, 7.1, 1.6)	—	7.71 (ddd, <i>J</i> = 8.4, 7.2, 1.6)	7.69 (ddd, <i>J</i> = 8.4, 7.1, 1.6)	7.69 (ddd, <i>J</i> = 8.4, 7.1, 1.6)
H-7	7.35 (t, <i>J</i> = 7.9, 7.1, 0.9)	7.35 (t, <i>J</i> = 7.9, 7.1, 0.9)	—	7.35 (t, <i>J</i> = 8.0, 7.2)	7.35 (t, <i>J</i> = 8.0, 7.1)	7.35 (t, <i>J</i> = 8.0, 7.1)
H-8	8.25 (dd, <i>J</i> = 7.9, 1.6)	8.25 (dd, <i>J</i> = 7.9, 1.6)	—	8.26 (dd, <i>J</i> = 8.0, 1.6)	8.24 (dd, <i>J</i> = 8.0, 1.6)	8.24 (dd, <i>J</i> = 8.0, 1.6)
H-10	2.09 (s)	2.09 (s)	—	—	—	—
H-4'	2.89 (t, <i>J</i> = 6.8)	2.89 (t, <i>J</i> = 6.8)	—	2.88 (t, <i>J</i> = 6.8)	2.74 (t, <i>J</i> = 6.8)	2.74 (t, <i>J</i> = 6.8)
H-5'	1.88 (t, <i>J</i> = 6.8)	1.88 (t, <i>J</i> = 6.8)	—	1.89 (t, <i>J</i> = 6.8)	1.86 (t, <i>J</i> = 6.8)	1.86 (t, <i>J</i> = 6.8)
H-7'	1.40 (br s)	1.40 (br s)	—	1.40 (br s)	1.39 (br s)	1.39 (br s)
11						

^a Values in ppm (δ_H). Measured in CDCl₃, at 300.13 MHz. *J* values (Hz) are shown in parentheses.

Table 3. ^{13}C NMR chemical shifts of prenylated xanthenes 3–11^a

	3	4	5	6	7	8	9	10	11
C-1	158.9	159.6	163.4	161.9	159.6	161.8	157.9	160.9	160.6
C-2	113.4	108.1	97.6	117.0	112.1	95.1	107.5	99.4	104.1
C-3	162.9	164.0	166.0	165.3	163.8	163.6	159.7	161.7	161.8
C-4	113.2	90.3	93.4	91.3	90.7	108.1	99.0	99.8	95.0
C-5	117.7	117.4	117.5	118.8	117.4	117.6	117.4	117.5	117.6
C-6	135.0	134.6	134.9	134.6	134.6	134.9	134.4	134.7	134.8
C-7	123.7	123.7	123.9	123.8	123.8	123.7	123.7	124.0	123.6
C-8	125.9	125.8	125.8	126.0	125.9	125.8	125.8	125.9	125.8
C-9	181.8	180.6	180.7	181.0	180.7	181.2	180.7	180.8	180.8
C-10	8.8	7.3	—	—	—	—	7.2	—	—
C-4a	152.8	155.8	157.6	156.1	156.1	154.1	152.5	154.7	155.6
C-10a	156.1	155.8	156.0	155.6	155.9	156.2	155.8	155.9	156.1
C-8a	120.4	120.7	120.6	120.7	120.8	120.4	120.7	120.7	120.6
C-9a	105.8	103.4	103.8	103.9	103.8	103.4	103.0	103.7	^b
C-1'	70.7	65.6	65.4	41.1	21.4	65.7	—	—	—
C-2'	119.8	118.9	118.5	150.6	122.1	119.0	—	—	—
C-3'	138.5	138.4	139.4	106.8	131.7	138.6	—	—	—
C-4'	25.9; 18.1	25.8; 18.3	25.8; 18.3	29.7; 29.0	25.8; 17.8	25.8; 18.3	16.4	16.2	16.0
C-5'	—	—	—	—	—	—	31.7	31.8	31.8
C-6'	—	—	—	—	—	—	76.0	76.2	76.3
C-7'	—	—	—	—	—	—	26.8	26.7	26.8
C-1''	22.8	—	—	65.7	65.6	21.7	—	—	—
C-2''	122.8	—	—	118.8	119.0	122.2	—	—	—
C-3''	131.7	—	—	138.1	138.5	131.5	—	—	—
C-4''	25.7; 18.0	—	—	25.7; 18.3	25.8; 18.3	25.8; 17.9	—	—	—

^a Values in ppm (δ_{C}). Measured in CDCl_3 , at 75.47 MHz.^b Not observed.**Figure 2.** Main connectivities found in the HMBC of prenylated xanthenes 3–11.

four human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), SF-268 (central nervous system cancer), and UACC-62 (melanoma), given in concentrations that were able to cause 50% of cell growth inhibition (GI_{50}), are summarized in Table 1.

Though the number of compounds is small, some trends in structure-activity relationship are apparent. Considering compounds 1, 6, and 7 it seems to be important the existence of an alkyl group at C-2 for the antitumor activity. The size of this alkyl group is also important, since the prenyl groups are associated with more selective compounds. This kind of selectivity

for MCF-7 cell line was not previously described for prenylated xanthenes and probably can be related with a molecular mechanism concerning interaction with estrogen receptors present in this estrogen receptor positive (ER+) breast cell line.

Comparing the growth inhibitory effects on MCF-7 cell line of compounds 9–11, and their precursors 4 and 5, it can be concluded that the extra pyran ring led to the appearance of an effect in compounds 9 and 11, but not in compound 10.

It is also interesting to point out that the higher activity of compound 9 for MCF-7 corresponds to

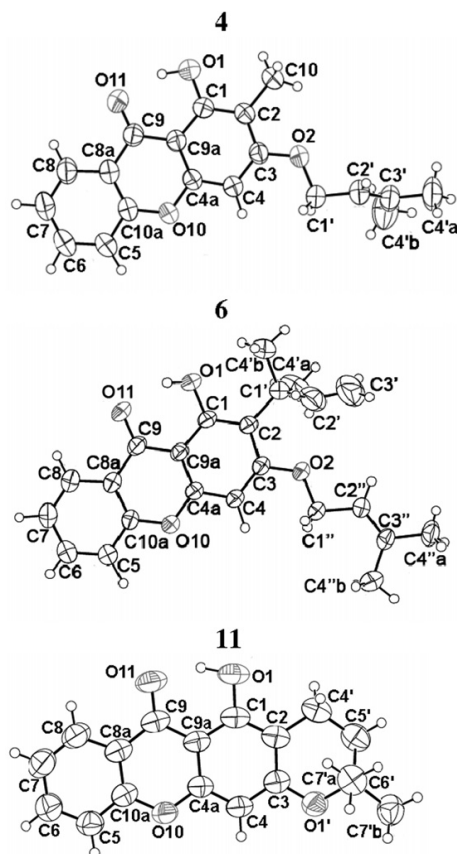


Figure 3. View of the molecular structure of compounds **4**, **6**, and **11** showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms are represented by circles of arbitrary radii.

a global angular structure with a methyl group at C-2, while the compound **10**, although with an angular structure but without substituent at C-2, shows no activity.

3. Conclusions

By a classic method of prenylation six new prenylated xanthenes were obtained, **3–4** and **6–9**. Long-range C, H correlations led to an unambiguous establishment of the structures of different compounds and a detailed structural analysis for three of them (**4**, **6**, and **11**) was obtained by X-ray crystallography.

With the molecular modification concerning prenylation of xanthenes the improvement of bioactivity was achieved leading to compounds **6**, **7**, and **9** with a selective and potent growth inhibitory activity against the breast cancer MCF-7 cell line, if compared with their parent compounds **1** and **2**, while the growth inhibitory activity against the other cell lines was lost.

4. Experimental

4.1. General methods

Purifications of compounds were performed by flash chromatography using Merck silica gel 60 (0.040–0.063 mm) and preparative thin layer chromatography (TLC) using Merck silica gel 60 (GF₂₅₄) plates. Melting points were obtained in a Köfler microscope and are uncorrected. IR spectra were measured on an ATI Mattson Genesis series FTIR (software: WinFirst v.2.10) spectrophotometer in KBr microplates (cm^{−1}). UV spectra were taken in ethanol²⁰ and were recorded on a Varian CARY 100 spectrophotometer; λ_{max} in nm (software: Cary Win UV, v. 3.0). ¹H and ¹³C NMR spectra were taken in CDCl₃ or DMSO-*d*₆ at room temperature, on Bruker Avance 300 instrument (300.13 MHz for ¹H and 75.47 MHz for ¹³C). Chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane (TMS) as an internal reference; ¹³C NMR assignments were made by 2D HSQC and HMBC experiments (long-range C, H coupling constants were optimized to 7 and 1 Hz). EIMS spectra were recorded as EI (electronic impact) mode on a VG Autospec Q spectrometer (*m/z*) and HRMS mass spectra were measured on a Kratos Concept III 2 Sector Mass Spectrometer, recorded as FAB (Fast Atom Bombardment) or EI (electronic impact) mode. Prenyl bromide was purchased from Sigma Aldrich. The following materials were synthesized and purified by the described procedures.

4.2. Synthesis of the building blocks 1,3-dihydroxy-2-methylxanthone (**1**) and 1,3-dihydroxyxanthone (**2**)

The compounds were obtained, 32% and 53% respectively, and characterized according to the described procedures.^{7–10}

4.3. Prenylation of 1,3-dihydroxy-2-methylxanthone (**1**)

A mixture of 1,3-dihydroxy-2-methylxanthone (**1**) (0.50 g; 2.06 mmol), prenyl bromide (0.66 g; 4.43 mmol), and anhydrous K₂CO₃ (0.69 g; 4.99 mmol) in anhydrous acetone (90 mL) was refluxed at 65 °C for 8 h. After cooling, the solid was filtered and the solvent removed under reduced pressure and afforded the crude product. This crude product was purified by flash chromatography (SiO₂; hexane/AcOEt, 99:1) yielding successively **3**, a mixture of **3** + **4**, and **4**. The isolation of the components of the mixture was then carried out by preparative TLC (SiO₂; hexane/AcOEt, 95:5). Prenylated xanthenes **3** and **4** were crystallized from EtOH.

4.3.1. 1-Hydroxy-2-methyl-4-(3-methylbut-2-enyl)-3-(3-methylbut-2-enyloxy)xanthone (3**).** Three percent as yellow crystals, mp 173–175 °C (EtOH); UV (EtOH) λ_{max} (ϵ): 374, 304, 259, 234, 214 (14,735; 46,212; 78,674; 84,659; 82,462); (EtOH + NaOH): 417, 308, 274, 233 (18,939; 50,947; 57,045; 88,295); (EtOH + AlCl₃): 368, 306, 261, 234, 215 (16,894; 47,841; 72,727; 87,614; 84,053); (EtOH + AlCl₃ + HCl): 368, 309, 263, 234, 213 (11,553; 39,583; 55,303; 75,038; 75,152); (EtOH + NaOAc): unchanged; IR (KBr) ν_{max} : 3446,

3230, 2962, 2926, 2856, 1645, 1610, 1570, 1522, 1473, 1433, 1132, 1101, 816, 758; ^1H NMR data, see Table 2; ^{13}C NMR data, see Table 3; EIMS: 378(49, M^+), 310(100), 295(85), 267(34), 255(63), 242(63), 225(15), 121(15), 77(13), 69(72); Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{O}_4$: 379.4776; found: 379.1909 or FABHRMS: 379.1909 ($[\text{M}+\text{H}]^+$, $\text{C}_{24}\text{H}_{27}\text{O}_4^+$; calcd 379.4776).

4.3.2. 1-Hydroxy-2-methyl-3-(3-methylbut-2-enyloxy)xanthone (4). Forty-eight percent as yellow solid, mp 140–142 °C (EtOH); UV (EtOH) λ_{max} (ϵ): 310, 239, 217 (40,590; 63,323; 62,640); (EtOH + NaOH): 395, 301, 277, 213 (6615; 22,081; 23,882; 103,385); (EtOH + AlCl_3): 334, 263, 238, 222 (56,056; 48,106; 62,733; 71,149); (EtOH + AlCl_3 + HCl): 329, 262, 237, 221 (50,559; 37,826; 55,373; 67,547); (EtOH + NaOAc): unchanged; IR (KBr) ν_{max} : 3086, 3043, 2960, 2927, 2856, 1645, 1608, 1570, 1514, 1313, 1290, 1228, 1205, 1132, 1099, 818, 775, 754; ^1H NMR data, see Table 2; ^{13}C NMR data, see Table 3; EIMS: 310(30, M^+), 242(100), 213(17), 69(30); Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{O}_4$: 311.3586; found: 311.1284 or FABHRMS: 311.1284 ($[\text{M}+\text{H}]^+$, $\text{C}_{19}\text{H}_{19}\text{O}_4^+$; calcd 311.3586).

4.4. Prenylation of 1,3-dihydroxyxanthone (2)

A mixture of 1,3-dihydroxyxanthone (**2**) (0.50 g; 2.19 mmol), prenyl bromide (0.67 g; 4.50 mmol), and anhydrous K_2CO_3 (0.60 g; 4.34 mmol) in acetone (90 mL) was refluxed at 65 °C for 8 h. After cooling, the solid was filtered and the solvent removed under reduced pressure affording the crude product. This crude product was purified by flash chromatography (SiO_2 ; CH_2Cl_2 /petroleum ether/Et₂O, 5:90:5) yielding successively **6**, a mixture of **6** + **7**, a mixture of **8** + **5**, and **5**. The isolation of the components of the mixture **6** + **7** was carried out by preparative TLC (SiO_2 ; CH_2Cl_2 /petroleum ether/Et₂O, 5:90:5) and for mixture **8** + **5** by preparative TLC (SiO_2 ; hexane/AcOEt, 8:2). Prenylated xanthenes **5–8** were crystallized from CH_2Cl_2 /petroleum ether (60–80).

4.4.1. 1-Hydroxy-3-(3-methylbut-2-enyloxy)xanthone (5). Twenty-five percent as yellow thick needles, mp 137–139 °C (CH_2Cl_2 /petroleum ether (60–80)); UV (EtOH) λ_{max} (ϵ): 347, 305, 254, 236 (12,374; 41,128; 58,932; 66,736); (EtOH + NaOH): 385, 308, 294, 269, 221 (18,487; 31,662; 33,086; 53,175; 95,727); (EtOH + AlCl_3): 376, 328, 266, 224 (13,946; 53,116; 60,623; 57,507); (EtOH + AlCl_3 + HCl): 383, 323, 264, 224 (11,484; 42,374; 49,763; 47,893); (EtOH + NaOAc): unchanged; IR (KBr) ν_{max} : 3427, 2964, 2924, 2856, 1656, 1606, 1566, 1462, 1429, 1296, 1213, 1155, 1072, 820, 787, 750; ^1H NMR data, see Table 2; ^{13}C NMR data, see Table 3; EIMS: 296(42, M^+), 228(100), 199(16), 69(38); Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{O}_4$: 297.3316; found: 297.1127 or FABHRMS: 297.1127 ($[\text{M}+\text{H}]^+$, $\text{C}_{18}\text{H}_{17}\text{O}_4^+$; calcd 297.3316).

4.4.2. 1-Hydroxy-3-(3-methylbut-2-enyloxy)-2-(1,1-dimethylprop-2-enyl)xanthone (6). Five percent as yellow crystals, mp 102–104 °C (CH_2Cl_2 /petroleum ether (60–80)); UV (EtOH) λ_{max} (ϵ): 312, 240, 219 (32,299;

55,036; 56,022); (EtOH + NaOH): 408, 303, 283, 218 (7372; 32,774; 29,380; 87,628); (EtOH + AlCl_3): 318, 240, 223, 204 (37,737; 65,000; 62,555; 48,759); (EtOH + AlCl_3 + HCl): 323, 239, 222, 203 (32,701; 52,956; 52,226; 48,723); (EtOH + NaOAc): unchanged; IR (KBr) ν_{max} : 3433, 2958, 2922, 2850, 1633, 1595, 1558, 1450, 1282, 1144, 1084, 847; ^1H NMR data, see Table 2; ^{13}C NMR data, see Table 3; EIMS: 364(60, M^+), 295(80), 281(100), 267(41), 253(52), 241(56), 121(16), 69(52); Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{O}_4$: 365.4506; found: 365.1753 or FABHRMS: 365.1753 ($[\text{M}+\text{H}]^+$, $\text{C}_{23}\text{H}_{25}\text{O}_4^+$; calcd 365.4506).

4.4.3. 1-Hydroxy-2-(3-methylbut-2-enyl)-3-(3-methylbut-2-enyloxy)xanthone (7). Two percent as yellow solid, mp 112–114 °C (CH_2Cl_2 /petroleum ether (60–80)); UV (EtOH) λ_{max} (ϵ): 309, 241, 219 (60,584; 91,350; 86,168); (EtOH + NaOH): 400, 300, 279, 226 (16,752; 57,810; 62,153; 90,474); (EtOH + AlCl_3): 333, 263, 239, 223 (67,628; 73,686; 83,869; 89,234); (EtOH + AlCl_3 + HCl): 328, 263, 238, 222 (59,708; 59,526; 72,591; 85,255); (EtOH + NaOAc): unchanged; IR (KBr) ν_{max} : 3435, 2964, 2922, 2858, 1643, 1608, 1558, 1464, 1306, 1217, 1120, 1082, 1030, 955; ^1H NMR data, see Table 2; ^{13}C NMR data, see Table 3; EIMS: 364(50, M^+), 309(19), 295(73), 281(36), 253(65), 241(100), 228(15), 69(33); Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{O}_4$: 365.4506; found: 365.1754 or FABHRMS: 365.1754 ($[\text{M}+\text{H}]^+$, $\text{C}_{23}\text{H}_{25}\text{O}_4^+$; calcd 365.4506).

4.4.4. 1-Hydroxy-4-(3-methylbut-2-enyl)-3-(3-methylbut-2-enyloxy)xanthone (8). Three percent as yellow thin needles, mp 132–134 °C (CH_2Cl_2 /petroleum ether (60–80)); UV (EtOH) λ_{max} (ϵ): 364, 310, 260, 235 (7336; 22,956; 47,080; 47,628); (EtOH + NaOH): 398, 294, 272, 220 (12,664; 27,956; 37,847; 98,358); (EtOH + AlCl_3): 364, 326, 273, 233 (13,577; 35,109; 45,949; 51,971); (EtOH + AlCl_3 + HCl): 368, 325, 272, 234 (9964; 27,263; 36,971; 41,058); (EtOH + NaOAc): unchanged; IR (KBr) ν_{max} : 3469, 2956, 2922, 2854, 1655, 1604, 1570, 1468, 1423, 1369, 1292, 1232, 1080, 810, 783, 756; ^1H NMR data, see Table 2; ^{13}C NMR data, see Table 3; EIMS: 364(43, M^+), 296(65), 281(100), 253(30), 241(47), 228(52), 121(12), 77(11), 69(53); Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{O}_4$: 365.4506; found: 365.1753 or FABHRMS: 365.1753 ($[\text{M}+\text{H}]^+$, $\text{C}_{23}\text{H}_{25}\text{O}_4^+$; calcd 365.4506).

4.5. Synthesis of dihydropyranoxanthone 9 from 4

To a solution of the xanthone (**4**) (0.10 g; 0.32 mmol) in dry *o*-xylene (1 mL), anhydrous ZnCl_2 (3.00 mg; 0.02 mmol) was added and heated at 200 °C for 21 h. The reaction mixture was cooled and purified by flash chromatography (SiO_2 ; hexane/AcOEt, 99.5:0.5) and by preparative TLC (SiO_2 ; hexane/AcOEt, 8:2). Prenylated xanthone **9** was crystallized from EtOH.

4.5.1. 1-Hydroxy-2,6',6'-trimethyl-4',5'-dihydropyrano(2',3':3,4)xanthone (9). Twenty-two percent as yellow solid, mp 188–190 °C (EtOH); UV (EtOH) λ_{max} (ϵ): 316, 257, 239, 216 (36,366; 43,385; 64,503; 57,205); (EtOH + NaOH): 405, 301, 282, 220 (9348; 39,876;

37,174; 105,590); (EtOH + AlCl₃): 338, 265, 239, 222 (41,584; 43,106; 59,348; 75,280); (EtOH + AlCl₃ + HCl): 423, 333, 278, 263, 239, 221 (6553; 41,677; 37,981; 35,342; 53,230; 71,863); (EtOH + NaOAc): unchanged; IR (KBr) ν_{max} : 2970, 2925, 2854, 1653, 1612, 1570, 1475, 1437, 1332, 1267, 1153, 1107, 812, 787, 754; ¹H NMR data, see Table 2; ¹³C NMR data, see Table 3; EIMS: 310(89, M⁺), 295(29), 255(100), 242(18), 225(26), 197(16), 121(9), 77(7); Anal. Calcd for C₁₉H₁₈O₄: 310.3506; found: 310.1205 or EIHRMS: 310.1205 (M⁺, C₁₉H₁₈O₄⁺; calcd 310.3506).

4.6. Synthesis of dihydropyranoanthrones **10** and **11** from **5**

To a solution of the xanthone (**5**) (0.09 g; 0.30 mmol) in dry *o*-xylene (1 mL), anhydrous ZnCl₂ (0.003 g; 0.02 mmol) was added and heated at 200 °C for 20 h 30 min. The reaction mixture was cooled and purified by a mini-column chromatography (SiO₂; hexane, AcOEt, and Me₂CO) and by preparative TLC (SiO₂; hexane/AcOEt, 95:5). Prenylated xanthenes **10** and **11** were crystallized from CH₂Cl₂/petroleum ether (60–80).

4.6.1. 1-Hydroxy-6',6'-dimethyl-4',5'-dihydropyrano(2',3':3,4)xanthone (10). Four percent as yellow solid, mp 187–190 °C (CH₂Cl₂/petroleum ether (60–80)); UV (EtOH) λ_{max} (ϵ): 310, 259, 238, 212 (12,018; 18,249; 23,798; 20,059); (EtOH + NaOH): 390, 274, 225 (6558; 22,967; 69,525); (EtOH + AlCl₃): 363, 324, 263, 240, 204 (17,122; 24,718; 27,122; 40,593; 28,991); (EtOH + AlCl₃ + HCl): 363, 322, 239, 203 (13,264; 20,653; 33,591; 30,504); (EtOH + NaOAc): unchanged; IR (KBr) ν_{max} : 3427, 2968, 2924, 2854, 1662, 1606, 1571, 1471, 1429, 1329, 1290, 1232, 1157, 1116, 1078, 817, 752; ¹H NMR data, see Table 2; ¹³C NMR data, see Table 3; EIMS: 296(68, M⁺), 281(31), 241(100), 228(18), 212(20), 149(17), 83(16), 71(21), 57(35); Anal. Calcd for C₁₈H₁₆O₄: 296.3236; found: 296.1049 or EIHRMS: 296.1049 (M⁺, C₁₈H₁₆O₄⁺; calcd 296.3236).

4.6.2. 1-Hydroxy-6',6'-dimethyl-4',5'-dihydropyrano(2',3':3,2)xanthone (11). Three percent as yellow solid, mp 147–148 °C (CH₂Cl₂/petroleum ether (60–80)); UV (EtOH) λ_{max} (ϵ): 313, 256, 237, 218 (24,985; 35,104; 46,706; 37,834); (EtOH + NaOH): 396, 274, 223 (8487; 29,110; 69,050); (EtOH + AlCl₃): 329, 263, 239, 222, 205 (36,202; 43,531; 54,421; 49,199; 37,448); (EtOH + AlCl₃ + HCl): 325, 262, 239, 222, 204 (29,347; 34,065; 43,591; 38,843; 36,469); (EtOH + NaOAc): unchanged; IR (KBr) ν_{max} : 3471, 2972, 2924, 2856, 1647, 1606, 1570, 1450, 1300, 1263, 1219, 1134, 1080, 823, 754; ¹H NMR data, see Table 2; ¹³C NMR data, see Table 3; EIMS: 296(67, M⁺), 281(20), 253(32), 241(100), 228(11), 212(14), 149(16), 121(13), 71(20), 57(33); Anal. Calcd for C₁₈H₁₆O₄: 296.3236; found: 296.1048 or EIHRMS: 296.1048 (M⁺, C₁₈H₁₆O₄⁺; calcd 296.3236).

4.7. X-ray crystallography

Suitable crystals of **4**, **6**, and **11** were obtained by slow evaporation of solutions of the compounds in ethanol.

The crystals were mounted on glass fibers and diffraction data were collected at 293 K with a Stoe IPDS plate equipped with Mo-K α radiation (λ = 0.71073 Å). The structures of **4**, **6**, and **11** were solved by direct methods using SHELXS²¹ and refined using SHELXL²² program. All non-H-atoms were refined anisotropically. The H-4'a and H-4'b of **4**, the H-3', H-4'a, H-4'a, and H-4'b of **6**, and all hydrogen atoms of **11** were positioned with idealized geometry and their coordinates were only altered in accordance with the refinement of their parent C or O atoms. The rest of the hydrogen atoms of **4** and **6** were refined freely with isotropic displacement parameters.

CCDC-649346 (**4**), -649347 (**6**), and -649348 (**11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

4.8. Tumor cell growth assay

Stock solutions of compounds were prepared in DMSO (Sigma Chemical Co.) and stored at –20 °C. The frozen samples were freshly diluted with culture medium just prior to the assays. Final concentrations of DMSO ($\leq 25\%$) did not interfere with the biological activity tested.

The effects of compounds on the growth of the human tumor cell lines were evaluated according to the procedure adopted by the National Cancer Institute (NCI, USA) in the in vitro anticancer drug discovery screen which uses the protein-binding dye sulforhodamine B (Sigma Chemical Co.) to assess cell growth.^{23,24} Four human tumor cell lines were used, namely MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), SF-268 (CNS cancer), and UACC-62 (melanoma). Cells were routinely maintained as adherent cell cultures in RPMI-1640 medium (Gibco-BRL) supplemented with 5% heat-inactivated fetal bovine serum (Gibco-BRL), 2 mM glutamine (Sigma Chemical Co.), and 50 $\mu\text{g/mL}$ of gentamicin (Sigma Chemical Co.) at 37 °C in a humidified atmosphere containing 5% CO₂. The optimal plating density of each cell line, that ensures exponential growth throughout all the experimental period, was the same as originally published²³ and was, respectively, 1.5×10^5 cells/mL for MCF-7 and SF-268, 1.0×10^5 cells/mL for UACC-62 and 7.5×10^4 cells/mL to NCI-H460. Cells in 96-well plates were allowed to attach overnight and then exposed for 48 h to five concentrations of compounds. Following this incubation period the adherent cells were fixed in situ, washed, and dyed with SRB. The bound stain was solubilized and the absorbance was measured at 492 nm in a plate reader (EAR 400, STL-Lab Instruments). For each compound tested a dose-response curve was generated and the growth inhibition of 50% (GI₅₀), corresponding to the concentration of compound that inhibits 50% of the net cell growth, was determined as described.²³ Doxorubicin (Sigma Chemical Co.), used as a positive control, was tested

in the same manner. Final concentrations of DMSO did not interfere with the growth of cells.

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References and notes

- Pinto, M. M. M.; Sousa, M. E.; Nascimento, M. S. J. *Curr. Med. Chem.* **2005**, *12*, 2517.
- Gonzalez, M. J.; Nascimento, M. S. J.; Cidade, H. M.; Pinto, M. M. M.; Kijjioa, A.; Anantachoke, C.; Silva, A. M. S.; Herz, W. *Planta Med.* **1999**, *65*, 368.
- (a) Lu, Z. X.; Hasmeda, M.; Mahabusarakam, W.; Ternai, B.; Ternai, P. C.; Polya, G. M. *Chem.-Biol. Interact.* **1998**, *114*, 121; (b) Jinsart, W.; Ternai, B.; Buddhasukh, D.; Polya, G. M. *Phytochemistry* **1992**, *31*, 3711.
- Ho, C.-K.; Huang, Y.-L.; Chen, C.-C. *Planta Med.* **2002**, *68*, 975.
- Nakatani, K.; Nakahata, N.; Arakawa, T.; Yasuda, H.; Ohizumi, Y. *Biochem. Pharmacol.* **2002**, *63*, 73.
- Pedro, M.; Cerqueira, F.; Sousa, M. E.; Nascimento, M. S. J.; Pinto, M. *Bioorg. Med. Chem.* **2002**, *10*, 3725.
- Subba Rao, G. S. R.; Raghavan, S. *J. Indian Inst. Sci.* **2001**, *81*, 393.
- Pinto, M. M.; Polónia, J. *Helv. Chim. Acta* **1974**, *57*, 2613.
- Grover, P. K.; Shah, G. D.; Shah, R. C. *J. Chem. Soc.* **1995**, 3982.
- Fernandes, E. G. R.; Silva, A. M. S.; Cavaleiro, J. A. S.; Silva, F. M.; Borges, M. F. M.; Pinto, M. M. *Magn. Reson. Chem.* **1998**, *36*, 305.
- Farrugia, L. J. *J. Appl. Cryst.* **1997**, *30*, 565.
- Gales, L.; Damas, A. M. *Curr. Med. Chem.* **2005**, *12*, 2499.
- Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc. Perkin Trans., 2* **1987**, *12*, S1.
- Gales, L.; Sousa, M. E.; Pinto, M. M. M.; Kijjioa, A.; Damas, A. M. *Acta Cryst.* **2001**, *C57*, 1319.
- Gales, L.; Sousa, M. E.; Pinto, M. M. M.; Damas, A. M. *Acta Cryst.* **2005**, *E61*, o2213.
- Fukuyama, K.; Tsukihara, T.; Kishida, S.; Katsube, Y.; Ishida, M.; Hamasaki, T.; Hatsuda, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2947.
- Ravikumar, K.; Rajan, S. S. *Acta Cryst.* **1987**, *C43*, 553.
- Kosela, S.; Hu, L.; Yip, S.; Rachmatia, T.; Sukri, T.; Daulay, T. S.; Tan, G.; Vittal, J. J.; Sim, K. *Phytochemistry* **1999**, *52*, 1375.
- Doriguetto, A. C.; Santos, M. H.; Ellena, J. A.; Nagem, T. J. *Acta Cryst.* **2001**, *C57*, 1095.
- Mesquita, A.; Corrêa, D.; Gottlieb, O.; Magalhães, M. *Anal. Chim. Acta* **1968**, *42*, 311.
- Sheldrick, G. M. *Acta Cryst.* **1990**, *A46*, 467.
- Sheldrick, G. M. In *SHELXL97*, University of Göttingen: Germany, 1997.
- Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigrowolf, A.; Graygoodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. *J. Natl. Cancer Inst.* **1991**, *83*, 757.
- Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokessch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1107.

ANEXO V

Antitumor xanthone derivatives: prenylation as a key approach to improve activity

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Abstract

The synthesis, structure elucidation and antitumor activity of three new prenylated xanthenes **6**, **10** and **11**, as well as the previously described pyranoxanthenes **7-8**, are described. Pyranoxanthenes **6-8** were obtained by dehydrogenation of dihydropyranoxanthenes **3-5**, with DDQ in dry dioxane. Prenylated xanthone **10** was obtained by prenylation of 1-hydroxyxanthone (**9**), with prenyl bromide in alkaline medium, whereas prenylated xanthone **11** was obtained by condensation of xanthone **9** with isoprene in the presence of orthophosphoric acid. The structures of compounds **6-8**, **10** and **11** were established by IR, UV, HRMS and NMR (^1H , ^{13}C , HSQC and HMBC) techniques. The effect of pyranoxanthenes **6-8** and prenylated xanthenes **10** and **11** on the *in vitro* growth of human tumor cell lines MCF-7 (breast adenocarcinoma) and NCI-H460 (non-small cell lung cancer) is also reported.

1. Introduction. – Many naturally occurring xanthenes and their prenylated derivative are found to exhibit significant biological and pharmacological activities, such as antibacterial, antifungal and antitumor and it was presumed that the prenyl groups can be associated with an improvement of potency and selectivity for some of these properties [1][2]. As a large number of biologically active xanthonic derivatives with pyran and dihydropyran rings are commonly found in nature, we were interested in obtaining this type of compounds to evaluate for their antitumor activity. For this purpose, molecular modifications of the hit compounds, 1,3-dihydroxy-2-methylxanthone (**1**) and 1,3-dihydroxyxanthone (**2**) (*Figure 1*) have been carried out in order to improve potency and/or selectivity towards the tumour cells [3]. Prenylation of xanthenes **1** and **2** with prenyl bromide followed by cyclisation of the respective monoprenylated products, furnished dihydropyranoxanthenes **3-5** [3] (*Figure 1, Scheme 1*). Dihydropyranoxanthenes **3-5** were also evaluated for their effects on the *in vitro* growth of some human tumour cell lines. In contrast to their building blocks (**1** and **2**), dihydropyranoxanthenes **3** and **5** were found to be more selective, showing their growth inhibitory effects against only the breast cancer MCF-7 cell line [3] (*Table 1*).

Insert Figure 1.

Insert Table 1.

Insert Scheme 1.

The fact that naturally occurring pyranoxanthenes are more biologically active than dihydropyranoxanthenes, has led us to resort the rigidification strategy to improve the antitumor activity of the xanthone derivatives. As a result, the first approach to improve potency and/or selectivity towards MCF-cells was the introduction of a rigid moiety to the molecule. Thus, insaturation strategy was applied to the dihydropyran ring of dihydropyranoxanthenes **3-5** to give pyranoxanthenes **6-8**, respectively (*Figure 1, Schemes 2a and 2b*).

Insert Scheme 2a

Insert Scheme 2b

The second approach is to introduce the prenyl side chain to the xanthonic nucleus using C-prenylation strategy. Thus, two C-prenylated derivatives, **10** and **11** were synthesized by prenylation of xanthone **9** (*Figure 1*). Prenylation of xanthone **9** with prenyl bromide and anhydrous potassium carbonate in dry DMF furnished compound **10** (*Scheme 3*).

However, when isoprene in 85% phosphoric acid was used, compound **11** was obtained (*Scheme 3*).

Insert Scheme 3

The prenylated xanthonic derivatives **6-8**, **10** and **11**, were then evaluated for their capacity to inhibit the *in vitro* growth of MCF-7 (breast adenocarcinoma) and

NCI-H460 (non-small cell lung cancer) cells, and their effects were compared with those of their building blocks [3][4] (*Table 1*).

2. Results and Discussion. – Synthesis of prenylated derivatives.

Pyranoxanthenes **6-8** were obtained by dehydrogenation of the respective dihydropyranoxanthenes **3-5**, with DDQ in refluxing dry dioxane [5]. While dihydropyranoxanthone **3** gave pyranoxanthone **6**, dihydropyranoxanthone **4** afforded pyranoxanthone **7** (*Scheme 2a*) and dihydropyranoxanthone **5** gave pyranoxanthone **8** (*Scheme 2b*).

Insert Table 2.

From the results in *Table 2*, it can be inferred that dehydrogenation of dihydropyranoxanthenes **3-5**, with DDQ in refluxing dry dioxane, gave pyranoxanthenes **6-8** in 25-67% yields. From these, pyranoxanthone **6**, containing a methyl group at C(2) was formed with the highest yield. It can be also observed that the angular pyranoxanthone **7** was obtained in higher yield than the linear pyranoxanthone **8**.

Prenylation of 1-hydroxyxanthone (**9**), either with prenyl bromide or isoprene, gave the 1,1-dimethylallyl (**10**) or 3,3-dimethylallyl (**11**) derivatives, respectively, in low yields and long reaction times. Xanthone **10** was obtained by the reaction of 1-hydroxyxanthone (**9**) with prenyl bromide, in alkaline medium and refluxing *N,N*-dimethylformamide [6] (DMF) (*Scheme 3*). With this method, prenylation occurs at 1-OH group; however, at the described reaction conditions an *ortho* Claisen

rearrangement of prenyl group to C(2) position of xanthone scaffold had occurred giving the 1,1-dimethylallyl derivative **10**. The prenylated derivative **11** was obtained by condensation of 1-hydroxyxanthone (**9**) with isoprene, in the presence of catalytic amounts of orthophosphoric acid [7] (*Scheme 4*). The acid-catalysed condensation of isoprene with the phenol moiety of the xanthonic scaffold may be regarded as the chemical equivalent of the proposed biogenetic pathways [7].

Structural elucidation of the prenylated xanthones. The structures of compounds **6-8** and **10, 11** were established by IR, UV, HRMS and NMR (^1H , ^{13}C , HSQC and HMBC) techniques, while the spectroscopic data of compounds **1-5** and **9** are according those reported in the literature [3][8-11]. Although the spectroscopic data of pyranoxanthonenes **7** and **8** have been previously described [12][13], here we provide an update and complete structure elucidation of these compounds. The EI-HR-MS of compound **6** gave the accurate molecular mass at 308.1049 and the molecular formula $\text{C}_{19}\text{H}_{16}\text{O}_4$, indicating that there were two hydrogen atoms less than its dihydropyranoxanthone precursor (**3**). The ^1H -NMR spectrum of compound **6** was very similar to that of compound **3**, except for the two doublets of the olefinic protons at δ_{H} 5.62 ($J=10\text{Hz}$) and δ_{H} 6.86 ($J=10\text{Hz}$), instead of the triplets of the protons of two methylene groups at δ_{H} 1.88t ($J=6.8\text{Hz}$) and δ_{H} 2.89t ($J=6.8\text{Hz}$) of the dihydropyran ring [3]. The protons of the geminal methyl groups of the pyran ring in compound **6** appeared as a singlet at δ_{H} 1.50. The ^{13}C -NMR spectrum of compound **6** was also similar to that of dihydropyranoxanthone **3** [3] except for the substitution of the two methylene carbons at δ_{C} 16.4 and 31.7 with the two olefinic carbon signals at δ_{C} 115.3 and δ_{C} 126.8. In turn, the EI-HR-MS of compound **7** indicated the accurate

molecular mass at 294.0886, corresponding to the molecular formula $C_{18}H_{14}O_4$. The ^1H and ^{13}C -NMR spectra of compound **7** were very similar to those of compound **6**, except for the presence of a singlet of H-C(2) at δ_H 6.28 instead of the singlet of the methyl group at δ_H 2.12. As in compound **6**, the presence of the pyran ring in compound **7** was confirmed by the two singlets of the olefinic protons at δ_H 5.62d ($J=10Hz$) and δ_H 6.85 ($J=10Hz$) in the ^1H spectrum which showed cross peaks with of the olefinic carbons at δ_C 127.2 and δ_C 115.0, respectively in the HSQC spectrum. The EI-HR-MS of compound **8** gave the accurate molecular mass at 294.0898 and the molecular formula $C_{18}H_{14}O_4$. As expected, the ^1H and ^{13}C -NMR spectra of compound **8** were similar to those of its dihydropyranoanthone precursor (**5**) [3], except for the signals of the olefinic protons (δ_H 6.74, $J=10Hz$ and δ_H 5.61, $J=10Hz$) and carbons (δ_C 115.4 and δ_C 127.6). In turn, the EI-HR-MS of compounds **10** and **11** indicated their accurate molecular masses at 280.1099 and 280.1096, respectively, and thus, a molecular formula $C_{18}H_{16}O_3$ for both compounds. This molecular formula confirmed the prenylation of xanthone **9**. In turn, the ^1H -NMR spectra of compounds **10** and **11** showed, besides, the proton signals corresponding to the non substituted aromatic ring of the xanthone nucleus, the signals of another two *ortho* coupled aromatic protons (δ_H 6.88d, $J=8.8Hz$; δ_H 7.64d, $J=8.8Hz$ and δ_H 6.76d, $J=8.4Hz$; δ_H 7.46d, $J=8.4Hz$) and OH(1) (δ_H 13.47s, δ_H 12.56s). The presence of these two *ortho* coupled aromatic protons indicated that the prenylation occurred at C(2). That the side chain of compound **10** was 2-methylbut-3-en-2-yl was confirmed by the signals of the protons of the vinyl group at δ_H 5.07dd ($J=17.0, 1.2Hz$), δ_H 5.02dd ($J=11.0, 1.2Hz$) and δ_H 6.28dd ($J=17.0, 11.0Hz$) and the methyl groups at δ_H 1.55s, respectively. This was corroborated by the correlation between the proton signal at

δ_H 6.28dd ($J=17.0, 11.0\text{Hz}$, H-2') and the carbon signal at δ_C 128.9 (C(2)). On the other hand, the 3-methylbut-2-enyl side chain of compound **11** was established by the presence of the signals of the allylic proton at δ_H 5.33t ($J=7.4\text{Hz}$), the methyl protons at δ_H 1.76 and δ_H 1.81s and the methylene protons at δ_H 3.53d ($J=7.4\text{Hz}$). The HBMC spectrum of compound **11** also showed the correlation between the signal of the methylene protons (δ_H 3.53d) and the signal of C(1) at δ_C 160.0.

Insert Figure 2.

Biological Activity studies. Though the number of compounds is small, some trends in structure-activity relationship can be observed. When the effects of the prenylated xanthenes **6-8** on the growth of MCF-7 cells are compared with those of their respective xanthonic building blocks **3-5**, it was found that the presence of the insaturation in the pyran ring was associated with a loss of inhibitory activity against MCF-7 (Table 1). It can be presumed that the lack of activity of compounds **6** and **8** could be a consequence of the rigidification of the dihydropyran ring. On the other hand, C-prenylation of the inactive xanthone **9** [4] was found to be responsible for the growth inhibitory activity against MCF-7 of the prenylated derivatives **10** and **11** (Table 1). The introduction of the lipophilic prenyl group in C-2 of the xanthonic scaffold could probably be the reason for transforming the inactive xanthone **9** into two active prenylated xanthenes (**10** and **11**). These results have led to the conclusion that this strategy could be an important step to obtain bioactive compounds

3. Conclusions. – Contrary to their dihydropyranoxanthone precursors (**3-5**), the pyranoxanthones (**6-8**) did not exhibit the growth inhibitory effects against the breast adenocarcinoma MCF-7 cells. On the other hand, C-prenylation of the inactive hydroxyxanthone **9**, led to new prenylated derivatives **10** and **11** which exhibited a moderate growth inhibitory activity against the MCF-cells. From these results, we can conclude that introduction of a rigidification does not always improve the biological activity of the compounds. On the other hand, introduction of the prenyl side chain can improve the biological activity of the compound through an increase of lipophilicity of the molecule which could be a key step to improve their activity.

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Experimental Part

1. *General.* Purifications of compounds were performed by flash chromatography using Merck silica gel 60 (0.040-0.063 mm) and preparative thin layer chromatography (TLC) using Merck silica gel 60 (GF₂₅₄) plates. Reactions were monitored by TLC. Melting points were obtained in a Köfler microscope and are uncorrected. IR spectra were measured on an ATI Mattson Genesis series FTIR (software: WinFirst v. 2.10) spectrophotometer in KBr microplates (cm⁻¹). UV

spectra were taken in ethanol [14] and were recorded on a Varian CARY 100 spectrophotometer: λ_{max} in nm (software: Cary Win UV v. 3.0). ^1H and ^{13}C NMR spectra were taken in CDCl_3 at room temperature, on a Bruker Avance 300 instrument. Chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane (TMS) as an internal reference. ^1H NMR spectra were measured at 300.13 MHz and assignment abbreviations are the following: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), and double doublet of doublets (ddd). ^{13}C NMR spectra were measured at 75.47 MHz. ^{13}C NMR assignments were made by 2D HSQC and HMBC experiments (long-range C, H coupling constants were optimized to 7 Hz). HRMS spectra were recorded as EI (electronic impact) mode on a VG Autospec M spectrometer (m/z) at CACTI – University of Vigo. Prenyl bromide, Isoprene and DDQ were purchased from Sigma Aldrich. Compounds **1-5** and **9** were obtained and characterized according to the described procedures [3][8-11]. The following materials were synthesized and purified by the described procedures.

2. *General Procedure for the Synthesis of Pyranoxanthonones 6-8.* To a solution of dihydropyranoxanthonones **3-5** (0.06 mmol) in dry dioxane (10 ml) was added DDQ (0.12 mmol) and the reaction mixture was refluxed (100°C) for 9-18 h. After cooling, the precipitate was filtered off and the filtrate evaporated. The crude product was purified by preparative TLC (SiO_2 ; Hexane/EtOAc 95:5 or light petroleum/ CHCl_3 5:5). Compounds **6**, **7** [12] and **8** [13] were identified by their spectroscopic and analytical data.

*6-hydroxy-3,3,5-trimethylpyrano[2,3-*c*]xanthen-7(3*H*)-one (6)*. The compound was obtained (67%) as yellow solid; m.p. 196-198°C (EtOH); $\lambda_{\max}$ (ϵ): 327, 273, 250 (6821, 25216, 22253); (EtOH + NaOH): 426, 296, 217 (3056, 30278, 95370); (EtOH + AlCl₃): 330, 275, 235 (6481, 24753, 17685); $\nu_{\max}$ (KBr): 3431, 2959, 2917, 1644, 1606, 1564, 1471, 1431, 1320, 1145, 1108, 742 cm⁻¹; ¹H-NMR (300.13 MHz; CDCl₃): δ =13.22 (s, 1H, OH), 8.25 (dd, 1H, *J* = 8.0, 1.6 Hz, H-C(8)), 7.70 (ddd, 1H, *J* = 8.4, 7.1, 1.6 Hz, H-C(6)), 7.44 (d, 1H, *J* = 8.4 Hz, H-C(5)), 7.36 (dd, 1H, *J* = 8.0, 7.1 Hz, H-C(7)), 6.86 (d, 1H, *J* = 10.0 Hz, H-C(4')), 5.62 (d, 1H, *J*=10.0 Hz, H-C(5')), 2.12 (s, 3H, CH₃(2)), 1.50 (s, 3H, CH₃(6')) ppm; ¹³C-NMR (75.47 MHz; CDCl₃): δ =180.8 (C(9)), 160.5 (C(1)), 158.8 (C(3)), 155.8 (C(10a)), 149.8 (C(4a)), 134.7 (C(6)), 126.8 (C(5')), 125.9 (C(8)), 123.8 (C(7)), 120.6 (C(8a)), 117.5 (C(5)), 115.3 (C(4')), 107.8 (C(2)), 103.1 (C(9a)), 100.5 (C(4)), 78.0 (C(6')), 28.4 (CH₃(6')), 7.0 (CH₃(2)) ppm; EI-MS *m/z* (%): 308 (6, M⁺), 293 (100), 267 (4), 149 (5), 137 (4), 121 (4), 109 (5), 95 (6), 81 (11), 69 (12); EI-HR-MS *m/z*: Anal. Calc. for C₁₉H₁₆O₄: 308.1049; found: 308.1049.

*6-hydroxy-3,3-dimethylpyrano[2,3-*c*]xanthen-7(3*H*)-one (7)*. The compound was obtained (41%) as yellow crystals; m.p. 164-168°C (Acetone); $\lambda_{\max}$ (ϵ): 271, 244, 201 (8471, 7588, 5603); (EtOH + NaOH): 293, 216 (9103, 45176); (EtOH + AlCl₃): 335, 285, 228, 201 (2838, 9412, 6941, 6147); $\nu_{\max}$ (KBr): 3432, 2956, 2921, 2853, 1650, 1596, 1465, 1279, 1142, 1102, 1073, 804, 749 cm⁻¹; ¹H-NMR (300.13 MHz; CDCl₃): δ =12.97 (s, 1H, OH), 8.25 (d, 1H, *J* = 7.8 Hz, H-C(8)), 7.72 (dd, 1H, *J* = 8.4, 7.4 Hz, H-C(6)), 7.46 (d, 1H, *J* = 8.4 Hz, H-C(5)), 7.38 (t, 1H, *J* = 7.8, 7.4 Hz, H-C(7)), 6.85 (d, 1H, *J* = 10.0 Hz, H-C(4')), 6.28 (s, 1H, H-C(2)), 5.62 (d, 1H,

$J=10.0$ Hz, H-C(5')), 1.49 (s, 3H, CH₃(6')) ppm; ¹³C-NMR (75.47 MHz; CDCl₃): $\delta=180.9$ (C(9)), 163.2 (C(1)), 161.0 (C(4a)), 155.8 (C(10a)), 151.8 (C(3)), 135.0 (C(6)), 127.2 (C(5')), 125.9 (C(8)), 124.1 (C(7)), 120.6 (C(8a)), 117.6 (C(5)), 115.0 (C(4')), 103.8 (C(9a)), 101.1 (C(4)), 99.4 (C(2)), 78.3 (C(6')), 28.3 (CH₃(6')) ppm; EI-MS m/z (%): 294 (2, M⁺), 279 (22), 183 (74), 181 (78), 171 (60), 169 (66), 163 (100), 149 (20), 145 (25), 117 (40), 115 (37), 104 (30), 103 (46), 91 (35), 90 (50), 89 (53), 77 (26); EI-HR-MS m/z : Anal. Calc. for C₁₈H₁₄O₄: 294.0892; found: 294.0886.

*5-hydroxy-2,2-dimethylpyrano[3,2-*b*]xanthen-6(2*H*)-one (8)*. The compound was obtained (25%) as yellow crystals; m.p. 170-173°C (Acetone); λ_{max} (ϵ): 289, 237, 201 (17059, 14676, 11853); (EtOH + NaOH): 405, 309, 215 (1647, 14471, 88324); (EtOH + AlCl₃): 293, 237, 201 (16471, 14765, 13324); ν_{max} (KBr): 3410, 2963, 2921, 2855, 1646, 1609, 1567, 1453, 1301, 1212, 1139, 1081, 749 cm⁻¹; ¹H-NMR (300.13 MHz; CDCl₃): $\delta=13.17$ (s, 1H, OH), 8.24 (dd, 1H, $J = 8.0, 1.6$ Hz, H-C(8)), 7.70 (ddd, 1H, $J = 8.6, 7.1, 1.6$ Hz, H-C(6)), 7.43 (d, 1H, $J = 8.6$ Hz, H-C(5)), 7.37 (t, 1H, $J = 8.0, 7.1$ Hz, H-C(7)), 6.74 (d, 1H, $J = 10.0$ Hz, H-C(4')), 6.36 (s, 1H, H-C(4)), 5.61 (d, 1H, $J=10.0$ Hz, H-C(5')), 1.49 (s, 3H, CH₃(6')) ppm; ¹³C-NMR (75.47 MHz; CDCl₃): $\delta=180.8$ (C(9)), 160.9 (C(3)), 157.7 (C(1)), 157.1 (C(4a)), 155.9 (C(10a)), 134.9 (C(6)), 127.6 (C(5')), 125.8 (C(8)), 124.0 (C(7)), 120.5 (C(8a)), 117.6 (C(5)), 115.4 (C(4')), 107.1 (C(4)), 104.6 (C(2)), 103.8 (C(9a)), 78.3 (C(6')), 28.4 (CH₃(6')) ppm; EI-MS m/z (%): 294 (9, M⁺), 279 (100), 69 (7); EI-HR-MS m/z : Anal. Calc. for C₁₈H₁₄O₄: 294.0892; found: 294.0898.

3. *Synthesis of Prenylated Xanthone 10 from 9.* A mixture of 1-hydroxyxanthone (**9**) (0.10 g; 0.47 mmol), prenyl bromide (110 μ L; 0.95 mmol) and anhydrous K_2CO_3 (0.22 g, 1.58 mmol) in dry DMF (7 ml), was refluxed at 150°C for 24 h. After cooling, the solid was filtered and the solvent removed under reduced pressure, affording the crude product. This crude product was purified by flash chromatography (SiO_2 ; Hexane/EtOAc 95:5) and by preparative TLC (SiO_2 ; Hexane/ $CHCl_3$ 9:1). Compound **10** was identified by their spectroscopic and analytical data.

1-hydroxy-2-(2-methylbut-3-en-2-yl)-9H-xanthen-9-one (10). The compound was obtained (6%) as yellow crystals; m.p. 99-102°C (Acetone); λ_{max} (ϵ): 281, 258, 230, 203 (2511, 10196, 9453, 6858); (EtOH + NaOH): 426, 309, 216 (1641, 3815, 43184); (EtOH + $AlCl_3$): 259, 231, 206 (7475, 9341, 6466); ν_{max} (KBr): 3432, 2954, 2919, 2858, 1632, 1608, 1462, 1433, 1374, 1285, 1213, 1057, 752 cm^{-1} ; ^1H -NMR (300.13 MHz; $CDCl_3$): δ =13.47 (s, 1H, OH), 8.29 (dd, 1H, J = 8.0, 1.6 Hz, H-C(8)), 7.74 (ddd, 1H, J = 8.7, 7.0, 1.6 Hz, H-C(6)), 7.64 (d, 1H, J = 8.8 Hz, H-C(3)), 7.45 (d, 1H, J = 8.7 Hz, H-C(5)), 7.38 (dd, 1H, J = 8.0, 7.0 Hz, H-C(7)), 6.88 (d, 1H, J = 8.8 Hz, H-C(4)), 6.28 (dd, 1H, J = 17.0, 11.0 Hz, H-C(2')), 5.07 (dd, 1H, J =17.0, 1.2 Hz, H-C(3')), 5.02 (dd, 1H, J =11.0, 1.2 Hz, H-C(3')), 1.55 (2s, 6H, CH_3 (1')) ppm; ^{13}C -NMR (75.47 MHz; $CDCl_3$): δ =182.9 (C(9)), 160.5 (C(1)), 156.1 (C(10a)), 154.8 (C(4a)), 147.0 (C(2')), 135.4 (C(6)), 135.0 (C(3)), 128.9 (C(2)), 126.0 (C(8)), 123.8 (C(7)), 120.5 (C(8a)), 117.7 (C(5)), 110.6 (C(3')), 108.8 (C(9a)), 105.6 (C(4)), 40.3 (C(1')), 26.7 (CH_3 (1')) ppm; EI-MS m/z (%): 280 (20, M^+), 265 (100), 251 (17), 250

(16), 239 (16), 237 (20), 225 (35), 69 (11); EI-HR-MS m/z : Anal. Calc. for $C_{18}H_{16}O_3$: 280.1100; found: 280.1099.

4. *Synthesis of Prenylated Xanthone 11 from 9.* A solution of isoprene (200 μ l; 2.00 mmol) in xylene (1 ml) was added to a stirred mixture of 1-hydroxyxanthone (**9**) (0.20 mg; 0.96 mmol), orthophosphoric acid (85%, 1 ml) and xylene (4 ml), with constant stirring at 31°C during 2 h. The mixture was stirred for a further 28 h and then neutralised with hydrogen carbonate solution (5%). The mixture thus obtained, was extracted with diethyl ether. The extract was washed with water, dried (Na_2SO_4) and distilled. The crude product thus obtained was purified by flash chromatography (SiO_2 ; Hexane/EtOAc 98:2) and preparative TLC (SiO_2 ; EP/Et₂O 9:1). Compound **11** was identified by their spectroscopic and analytical data.

1-hydroxy-2-(3-methylbut-2-enyl)-9H-xanthen-9-one (11). The compound was obtained (4%) as yellow crystals; m.p. 68-71°C (Acetone); λ_{max} (ϵ): 368, 300, 257, 232, 203 (3240, 5526, 23689, 24109, 18794); (EtOH + NaOH): 416, 308, 265, 217 (4600, 9257, 16157, 49130); (EtOH + $AlCl_3$): 445, 316, 275, 231, 205 (3394, 7798, 21837, 26452, 20084); ν_{max} (KBr): 3448, 2963, 2917, 2853, 1642, 1604, 1472, 1369, 1279, 1227, 763 cm^{-1} ; ^1H -NMR (300.13 MHz; $CDCl_3$): δ =12.56 (s, 1H, OH), 8.29 (dd, 1H, J = 8.0, 1.6 Hz, H-C(8)), 7.76 (ddd, 1H, J = 8.4, 7.1, 1.6 Hz, H-C(6)), 7.51 (d, 1H, J = 8.4 Hz, H-C(5)), 7.46 (d, 1H, J = 8.4 Hz, H-C(3)), 7.40 (dd, 1H, J = 8.0, 7.1 Hz, H-C(7)), 6.76 (d, 1H, J = 8.4 Hz, H-C(4)), 5.33 (t, 1H, J = 7.4 Hz, H-C(2')), 3.53 (d, 2H, J =7.4 Hz, H-C(1')), 1.81 and 1.76 (2s, 6H, CH_3 (3')) ppm; ^{13}C -NMR (75.47 MHz; $CDCl_3$): δ =182.6 (C(9)), 160.0 (C(1)), 156.1 (C(10a)), 153.4 (C(4a)),

137.0 (C(3)), 135.4 (C(6)), 133.3 (C(3')), 126.0 (C(8)), 124.0 (C(7)), 121.7 (C(2')), 120.5 (C(8a)), 119.3 (C(2)), 117.9 (C(5)), 110.0 (C(4)), 108.9 (C(9a)), 27.6 (C(1')), 25.8 and 17.9 (CH₃(3')) ppm; EI-MS *m/z* (%): 280 (15, M⁺), 265 (33), 225 (12), 149 (11), 137 (18), 121 (18), 109 (12), 107 (12), 95 (26), 81 (69), 69 (100); EI-HR-MS *m/z*: Anal. Calc. for C₁₈H₁₆O₃: 280.1100; found: 280.1096.

5. *Tumor cell growth assay.* Stock solutions of compounds **6-8**, **10** and **11** and of doxorubicin were prepared in DMSO (Sigma Chemical Co) and stored at -20 °C. The frozen samples were freshly diluted with culture medium just prior the assays. Final concentrations of DMSO (0.25%) did not interfere with the growth of cell lines.

The human tumor cell lines MCF-7 (breast adenocarcinoma) and NCI-H460 (non-small cell lung cancer) were used. Cells growing as monolayer, were routinely maintained in RPMI-1640 medium (Gibco BRL) supplemented with 5% heat-inactivated fetal bovine serum (Gibco BRL), 2 mM glutamine (Sigma Chemical Co.), penicillin 100 U/mL and 100 µg/mL streptomycin (Gibco BRL), at 37°C in an humidified atmosphere containing 5% CO₂. The optimal plating density of each cell line, that ensure exponential growth throughout all the experimental period was respectively 1.5 x 10⁵ cells/ml to MCF-7 and 7.5 x 10⁴ cells/ml for NCI-H460.

The effects of compounds on the growth of the human tumor cell lines were evaluated according to the procedure adopted by the National Cancer Institute (NCI, USA) for the "In vitro Anticancer Drug Discovery Screen" that uses the protein-binding dye sulforhodamine B (SRB) (Sigma Chemical Co.) to assess cell growth [15,16]. Briefly, exponentially growing cells were exposed for 48 h to five serial

concentrations (1:2 or 1:3 dilution) of each compound, starting from a maximum concentration of 150 μ M. Following this exposure period adherent cells were fixed in situ with 50% TCA, washed with distillate water and stained with 0.4% SRB solubilized in 1% acetic acid. The bound stain was solubilized and the absorbance was measured at 492 nm in a microplate reader (Bio-tek Instruments Inc., PowerWave XS, Winooski, U.S.A). For each cell line a dose-response curve was obtained and the growth inhibition of 50% (GI_{50}), corresponding to the concentration of compound that inhibited 50% of the net cell growth, was determined as described elsewhere [15]. Doxorubicin used as a positive control, was tested in the same manner. Moreover the effect of the vehicle solvent (DMSO) on the growth of these cell lines was evaluated in all experiments by exposing untreated control cells to the maximum concentration (0.25%) of DMSO used in each assay.

REFERENCES

- [1] M. Pinto, R. Castanheiro, In *Natural Prenylated Xanthenes: Chemistry and Biological Activities in Natural Products: Chemistry, Biochemistry and Pharmacology*; Ed. G. Brahmachari, Narosa Publishing House PVT. LTD., Nova Deli, India, 2009, chap. 17, p. 520.
- [2] M. M. M. Pinto, M. E. Sousa, M. S. J. Nascimento, *Curr. Med. Chem.* **2005**, *12*, 2517.
- [3] R. A. P. Castanheiro, M. M. M. Pinto, A. M. S. Silva, S. M. M. Cravo, L. Gales, A. M. Damas, M. M. Pedro, N. Nazareth, M. S. J. Nascimento, G. Eaton, *Bioorg. Med. Chem.* **2007**, *15*, 6080.
- [4] M. Pedro, F. Cerqueira, M. E. Sousa, M. S. J. Nascimento, M. Pinto, *Bioorg. Med. Chem.* **2002**, *10*, 3725.
- [5] L.-K. Ho, H.-J. Yu, C.-T. Ho, M.-J. Don, *J. Chin. Chem. Soc.* **2001**, *48*, 77.
- [6] L. Pisco, M. Kordian, K. Peseke, H. Feist, D. Michalik, E. Estrada, J. Carvalho, G. Hamilton, D. Rando, J. Quincoces, *Eur. J. Med. Chem.* **2006**, *41*, 401.
- [7] V. K. Ahluwalia, K. A. Krishnan, R. S. Jolly, *J. Chem. Soc. Perkin Trans. I*, **1982**, 335.
- [8] E. G. R. Fernandes, A. M. S. Silva, J. A. S. Cavaleiro, F. M. Silva, M. F. M. Borges, M. M. Pinto, *Magn. Reson. Chem.* **1998**, *36*, 305.
- [9] M. M. Pinto, J. Polónia, *Helv. Chim. Acta* **1974**, *57*, 2613.
- [10] P. K. Grover, G. D. Shah, R. C. Shah, *J. Chem. Soc.* **1995**, 3982.
- [11] K.S. Pankajamani, T. R. Seshadri, *J. Sci. Ind. Res.* **1954**, *13 B*, 396.
- [12] G. Kolokythas, I. K. Kostakis, N. Pouli, P. Marakos, O. Ch. Kousidou, G. N. Tzanakakis, N. K. Karamanos, *Eur. J. Med. Chem.* **2007**, *42*, 307.

- [13] G. S. R. Subba Rao, S. Raghavan, *J. Indian Inst. Sci.* **2001**, 81, 393.
- [14] A. Mesquita, D. Corrêa, O. Gottlieb, M. Magalhães, *Anal. Chim. Acta* **1968**, 42, 311.
- [15] A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigrowolff, M. Graygoodrich, H. Campbell, J. Mayo, M. Boyd, *J. Natl. Cancer I.* **1991**, 83, 757.
- [16] P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J. T. Warren, H. Bokessch, S. Kenney, M. R. Boyd, *J. Natl. Cancer I.* **1990**, 82, 1107.

Table 1. *Effect of xanthone derivatives 1-11 on the growth of human tumor cell lines*

Compound	GI ₅₀ (μM)		
	MCF-7	NCI-H460	SF-268
1^{a)}	21.9 ± 0.4	20.6 ± 0.9	33.4 ± 0.2
2^{a)}	50.8 ± 2.2	37.9 ± 2.9	61.4 ± 5.2
3^{a)}	18.4 ± 1.9	>160	>160
4^{a)}	>160	>160	>160
5^{a)}	88.6 ± 12.9	>160	>160
6	>150 ^{b)}	>150 ^{b)}	ND
7	>150	>150 ^{b)}	ND
8	>150 ^{b)}	>150 ^{b)}	ND
9^{a)}	>200	ND	ND
10	55 ^{b)}	>150 ^{b)}	ND
11	88 ^{b)}	ND	ND

Results are given in concentrations that were able to cause 50% of cell growth inhibition (GI₅₀) after a continuous exposure of 48h and represent means of ±SEM of 3 independent experiments performed in duplicate and carry out independently. ^{a)} Results published elsewhere [3][4]. ^{b)} Results of one or two experiments performed in duplicate. Doxorubicin was used as positive control, GI₅₀: MCF-7=42.8±8.2 nM; NCI-H460=94.0±8.7 nM; SF-268=93.0±7.0 nM. ND = not determined.

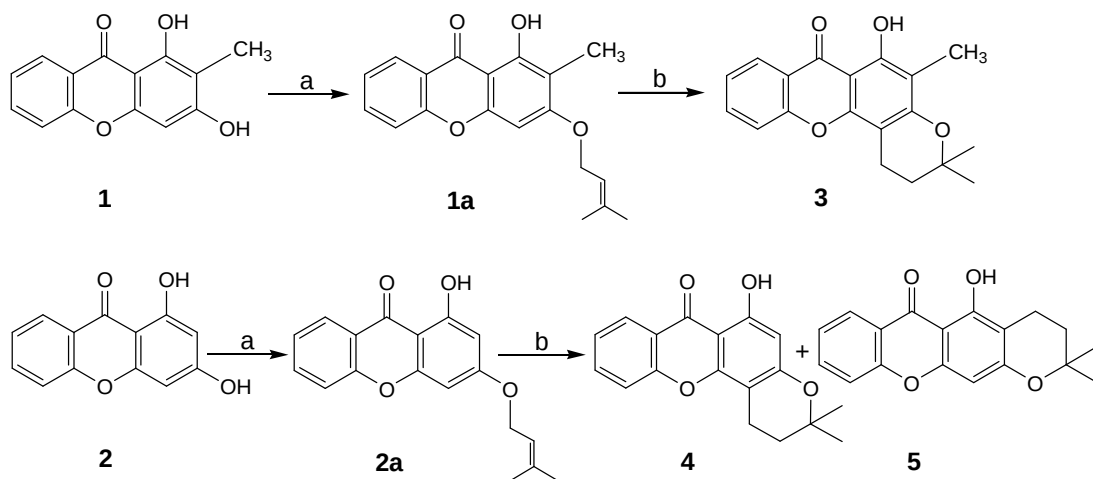
Table 2. Results obtained for the synthesis of prenylated xanthenes **6-8** and **10-11**.

Substrate	Solvent	Reagent	Product	Time (h)	Yield (%)
3			6	9	67
4	Dioxane	DDQ	7	10	41
5			8	18	25
9	DMF	PrBr / K ₂ CO ₃	10	24	6
9	Xylene	Isoprene / H ₃ PO ₄	11	30	4

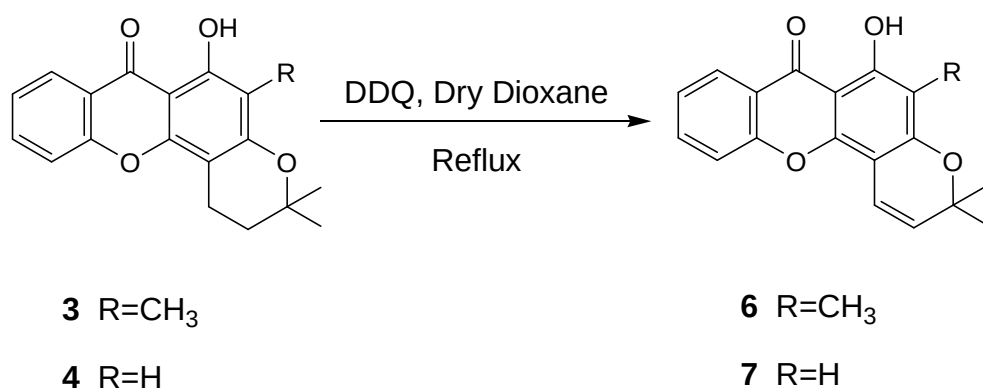
Legends:

- Scheme 1. *Reagents and conditions: (a) Prenyl Bromide, K₂CO₃, Me₂CO, reflux, 8 h; (b) ZnCl₂, o-Xylene, 200°C, 21 h.*
- Scheme 2a.
- Scheme 2b.
- Scheme 3.
- Figure 1. *Structures of building blocks 1-5, 9 and prenylated derivatives 6-8, 10-11 (the numbering used concerns the NMR assignments).*
- Figure 2. *Main connectivities found in the HMBC of prenylated xanthenes 6-8, 10-11.*

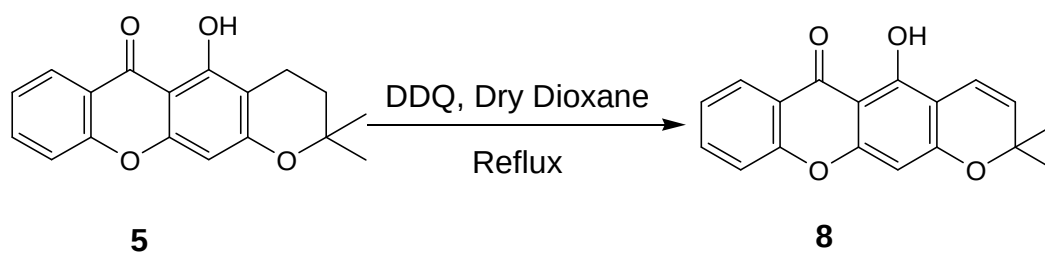
Scheme 1. *Reagents and conditions: (a) Prenyl Bromide, K_2CO_3 , Me_2CO , reflux, 8 h; (b) $ZnCl_2$, *o*-Xylene, 200°C, 21 h.*



Scheme 2a.



Scheme 2b.



Scheme 3.

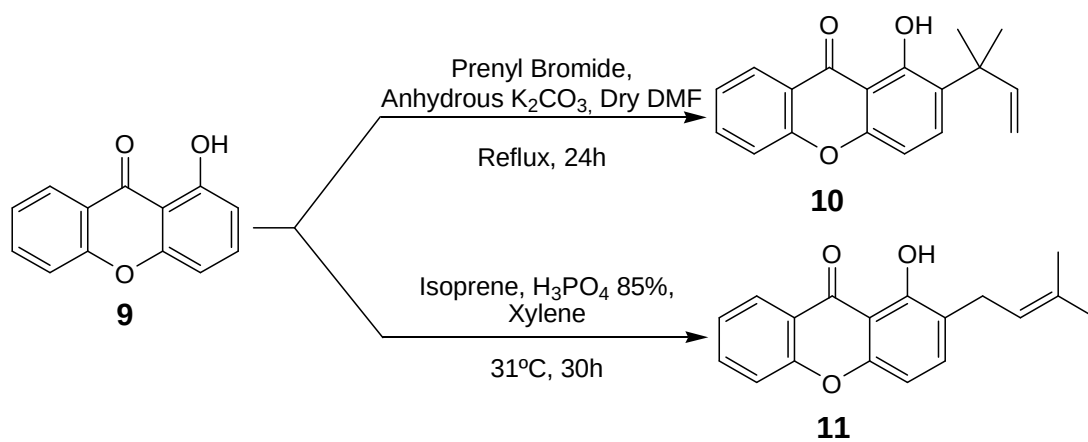


Figure 1. Structures of building blocks **1-5**, **9** and prenylated derivatives **6-8**, **10**, **11** (the numbering used concerns the NMR assignments).

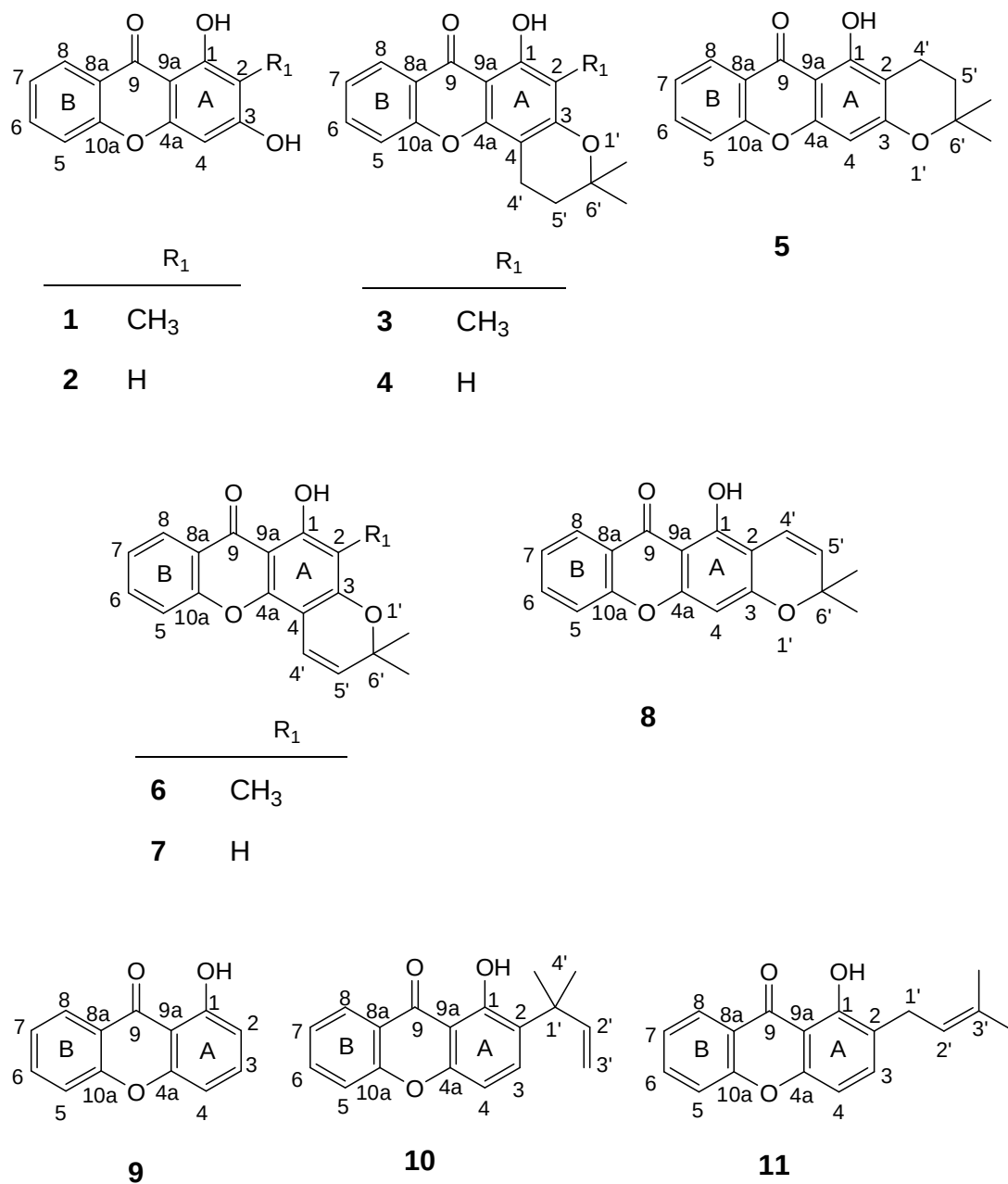
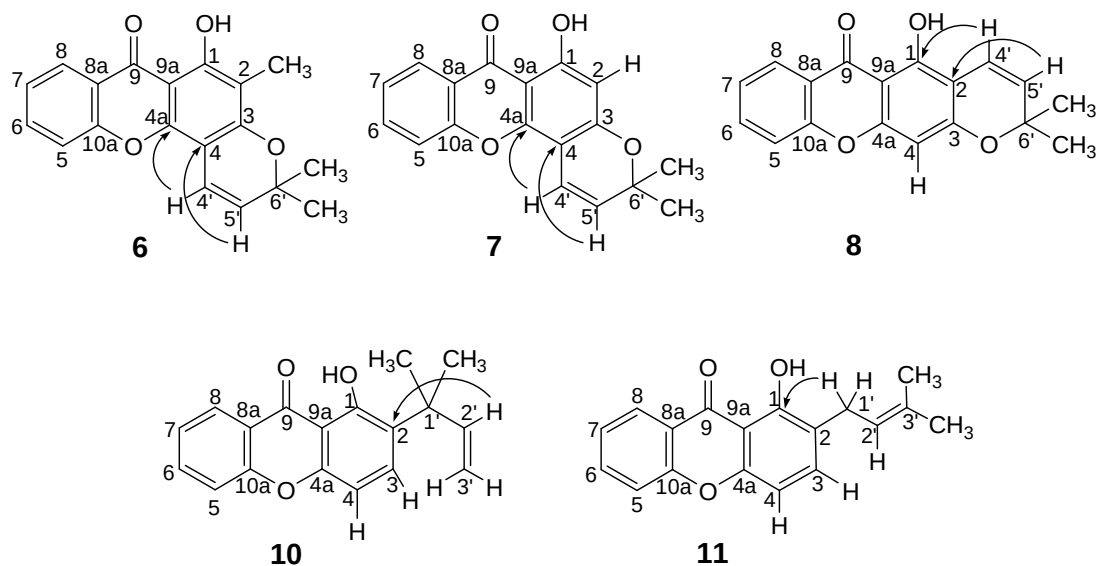
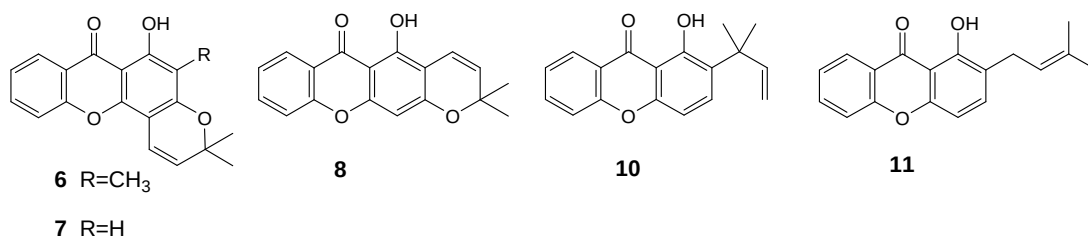


Figure 2. Main connectivities found in the HMBC of prenylated xanthenes **6-8**, **10**, **11**.



Graphical Abstract



ANEXO VI



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Tetrahedron

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Improved methodologies for synthesis of prenylated xanthenes by microwave irradiation and combination of heterogeneous catalysis (K10 clay) with microwave irradiation

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ABSTRACT

Eleven prenylated xanthone derivatives (**4–9**, **11–15**) have been synthesized for the first time by the microwave irradiation method. Prenylation of the xanthone building blocks **1** and **2** with prenyl bromide in alkaline medium, using microwave irradiation, gave the oxyprenylated xanthenes **4** and **6**, as major products in high yields, as well as diprenylated by-products (**5**, **7**, **8**, and **9**) in very low yields. Microwave irradiation of oxyprenylated xanthenes **4** and **6** furnished three new Claisen rearranged products (**11**, **14**, and **15**), as well as the previously described dihydrofuranoxanthenes (**12**, **13**). Furthermore, three new (**19**, **20**, **21**) and three previously described (**16**, **17**, **18**) dihydropyranoxanthenes have also been prepared by a one-pot synthesis from xanthenes **1**, **2**, and **3**, using Montmorillonite K10 clay as a heterogeneous catalyst and a combination of Montmorillonite K10 clay with microwave irradiation in various conditions. The presence of solvent and the type of the clay (commercial or dry) were found to have a strong influence on the product yields. This is the first report of using these methodologies for the synthesis of dihydropyranoxanthone derivatives. The structures of the prenylated xanthenes obtained were established by IR, UV, HRMS, and NMR (¹H, ¹³C, HSQC, and HMBC) techniques.

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1. Introduction

Prenylated xanthenes, including furan and pyran derivatives, have been reported to mediate several interesting biological activities, concerning a large variety of targets with therapeutic value.^{1,2} Although the oxygenation pattern of these derivatives can play an important role in their biological activity, the presence of the prenyl side chains seems also to be associated with the enhanced interaction with biological membranes and with target proteins when compared with their non-prenylated analogs.³ For this reason, we have synthesized a series of prenylated xanthone derivatives to evaluate their effect on the in vitro growth of some human cancer cell lines. The synthesis of the prenylated xanthone derivatives is normally carried out by introduction of the prenyl side chain to the hydroxyxanthone nucleus, in a vigorous condition. In addition, the reactions usually involved toxic reagents.^{4,5}

Consequently, these processes are considered to be not only very demanding but also environmentally unfriendly. Taking this into account, we have looked for an alternative to obtain prenylated xanthenes.

One of the considered methods was the microwave-assisted organic synthesis (MAOS), which has been demonstrated not only to dramatically accelerate many organic reactions, but also to improve yields and selectivity.^{6,7} With this technique, many reaction parameters such as reaction temperature and time, variations in solvents, additives, and catalysts can be evaluated to optimize the desired chemistry.⁸ As a result, pharmaceutical industry is starting to incorporate microwave (MW) methodologies in processes of discovery of pharmacologically active small-molecules.⁸ On the other hand, much attention has been paid to clays, which can act as solid catalysts for a wide range of organic reactions and a subgroup of clays, Montmorillonite, is particularly useful. With this clay, the reaction proceeds not only under mild conditions but also with selectivity, good yields, and short reaction times. As this catalyst can be easily separated from the reaction mixture and can be regenerated, the purification procedures are usually simple.^{9,10}

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Furthermore, the coupling of MW irradiation with the use of inorganic solid supports such as Montmorillonite K10 clay, either with solvent or under solvent-free conditions, can also provide a chemical process with inherent advantages such as enhanced reaction rates, high yields, ease of manipulation, and selectivity.¹¹

Here we report the microwave-assisted synthesis of two oxy-prenylated xanthenes (**4** and **6**), along with four diprenylated by-products (**5**, **7–9**) from the simple hydroxylated xanthenes (**1** and **2**) and prenyl bromide, as well as the synthesis of dihydro-furanoxanthenes (**11–13**) and two new rearranged prenylxanthenes (**14**, **15**) from the oxy-prenylated xanthenes **4** and **6** (Fig. 1). MW method was found to dramatically increase the yields of the two major oxy-prenylated xanthenes (**4**, **6**), while the yields of the diprenylated by-products were not improved. Furthermore, a one-pot synthesis of dihydropyranoxanthenes (**16–21**) from the hydroxylated xanthenes (**1–3**) using the Montmorillonite K10 clay

with different conditions was also described. A combination of MW and Montmorillonite K10 clay with solvent was found to be the method of choice to prepare dihydropyranoxanthenes since it dramatically increased the yields of products as well as shortening the reaction time (Fig. 1).

2. Results and discussion

2.1. Synthesis of prenylated xanthenes

Oxy-prenylated xanthenes are not only an emerging group of biologically interesting natural products³ but also important building blocks for the synthesis of furano- and pyranoxanthone derivatives.¹² Consequently, we have previously described the synthesis of oxy-prenylated xanthenes by prenylation of xanthenes **1**, **2**, and **3** with prenyl bromide and K₂CO₃ in acetone⁵ (Scheme 1).

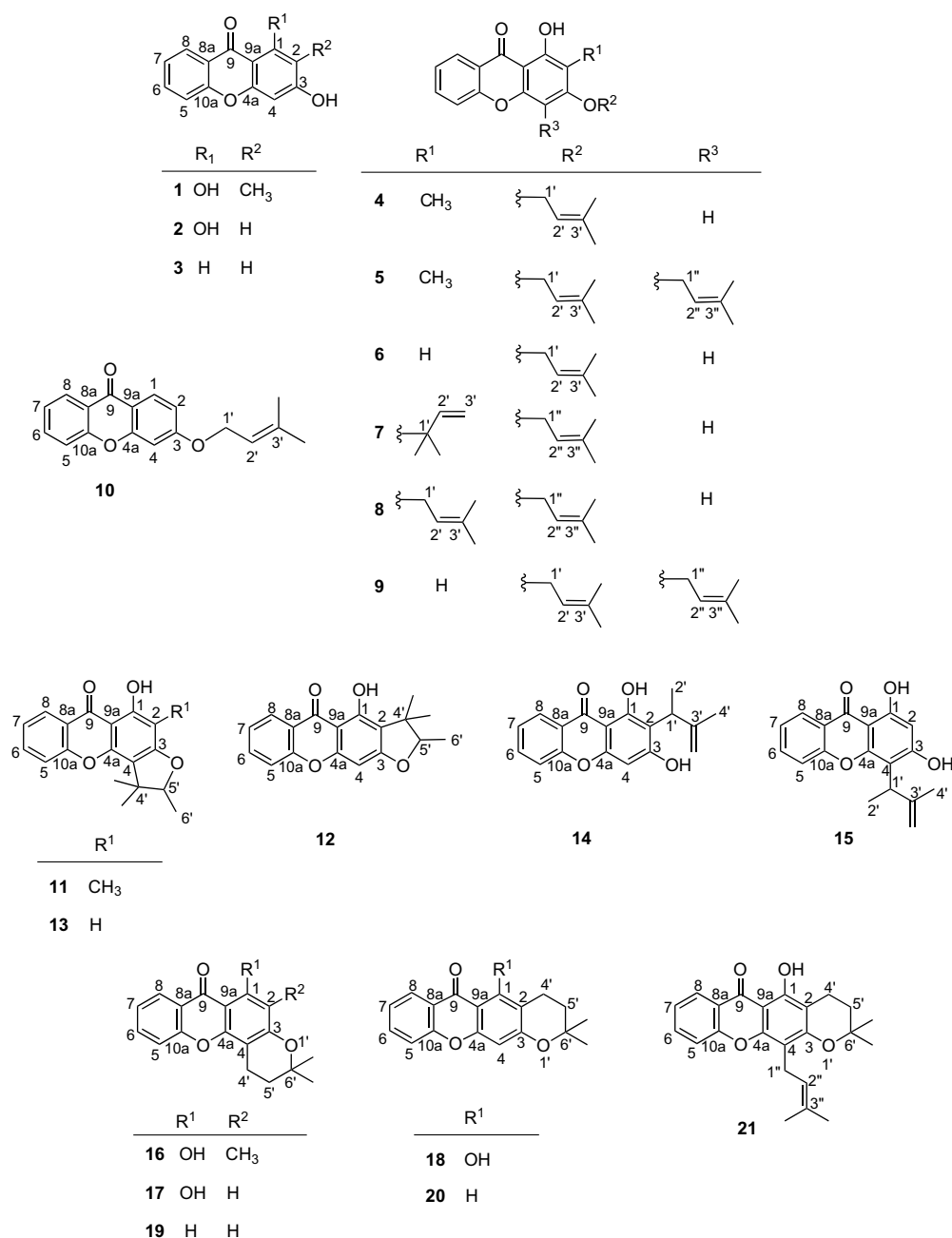
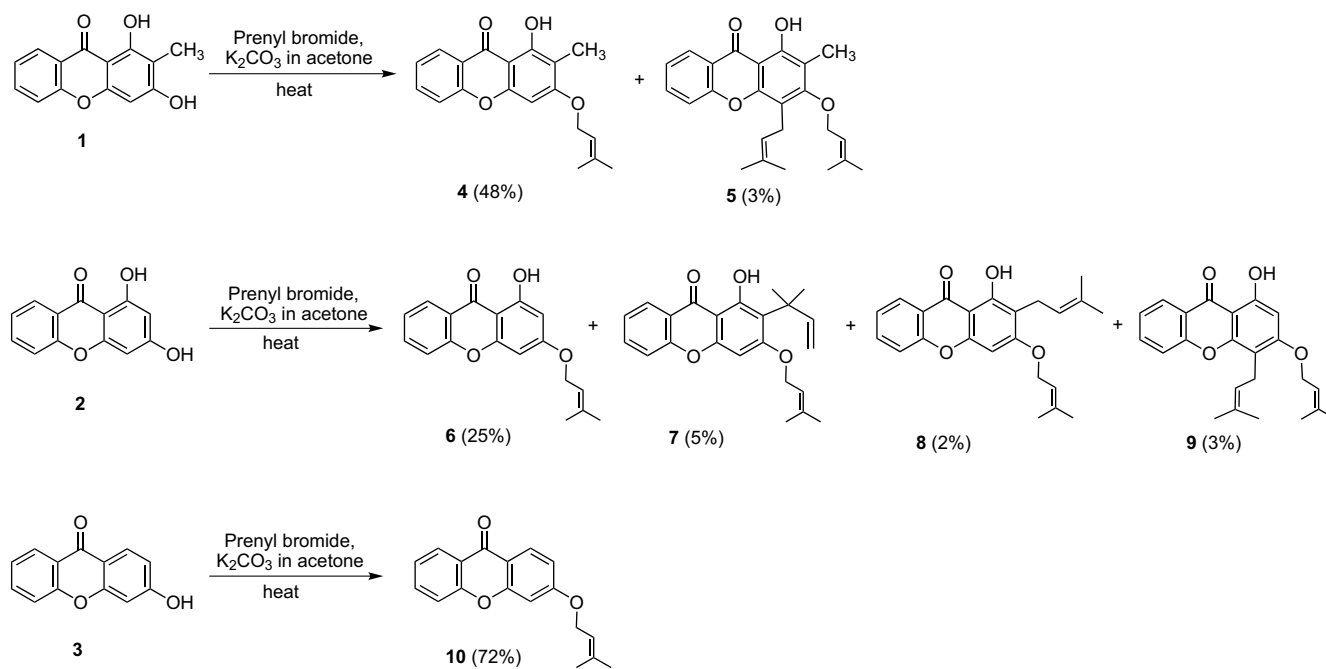


Figure 1. Structures of building blocks **1–3** and of prenylated derivatives **4–21** (the numbering used concerns the NMR assignments).

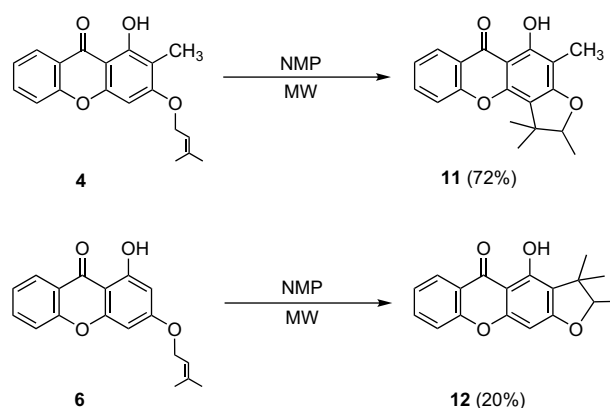


Scheme 1.

Using this method of prenylation, xanthone **1** gave the oxy-prenylated xanthone **4** as a major product in 48% yield and a diprenylated by-product **5** (3%). However, xanthone **2** gave only 25% yield of the oxy-prenylated xanthone **6** and three diprenylated by-products **7** (5%), **8** (2%), and **9** (3%). On the contrary, xanthone **3** gave 72% yield of the oxy-prenylated xanthone **10**.

In order to improve the yields of the oxy-prenylated xanthenes **4** and **6**, we used the MW irradiation instead of conventional heating. With this method, the yields of oxy-prenylated xanthenes **4** and **6** were increased, respectively, to 83% and 53%. However, the yields of the diprenylated xanthone by-products **5**, **7–9** did not change significantly (Table 1). Furthermore, the reaction time was reduced from 8 h in the conventional heating to only 1 h in the MW method.

The oxy-prenylated xanthenes **4** and **6** were then used as precursors for the synthesis of the dihydrofuranoxanthenes **11** and **12**, by MW irradiation. When *N*-methylpyrrolidone (NMP) was used as a solvent, xanthone **4** gave the angular dihydrofuranoxanthone **11** in 72% yield while xanthone **6** gave only 20% yield of the linear dihydrofuranoxanthone **12** (Scheme 2).



Scheme 2.

Table 1

Comparison of results obtained in the prenylation reaction of hydroxyxanthenes **1**, **2** under MW and classical heating conditions

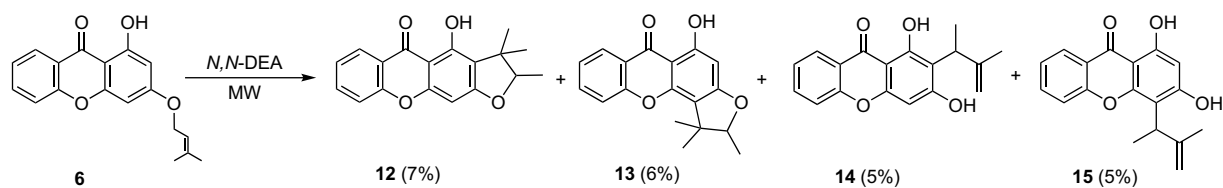
	Classical	MW
4 R=CH ₃ , R ₁ =H	48	83
5 R=CH ₃ , R ₁ =-CH ₂ -CH=C(CH ₃) ₂	3	5
6 R=H, R ₁ =H	25	53
7 R=-C(CH ₃) ₂ -CH=CH ₂ , R ₁ =H	5	1
8 R=-CH ₂ -CH=C(CH ₃) ₂ , R ₁ =H	2	1
9 R=H, R ₁ =-CH ₂ -CH=C(CH ₃) ₂	3	2

However, when the reaction was performed in *N,N*-diethylaniline (*N,N*-DEA), both linear (**12**) and angular (**13**) dihydrofuranoxanthenes were obtained, from the oxy-prenylated xanthone **6**, together with the two new rearranged products **14** and **15** (Scheme 3).

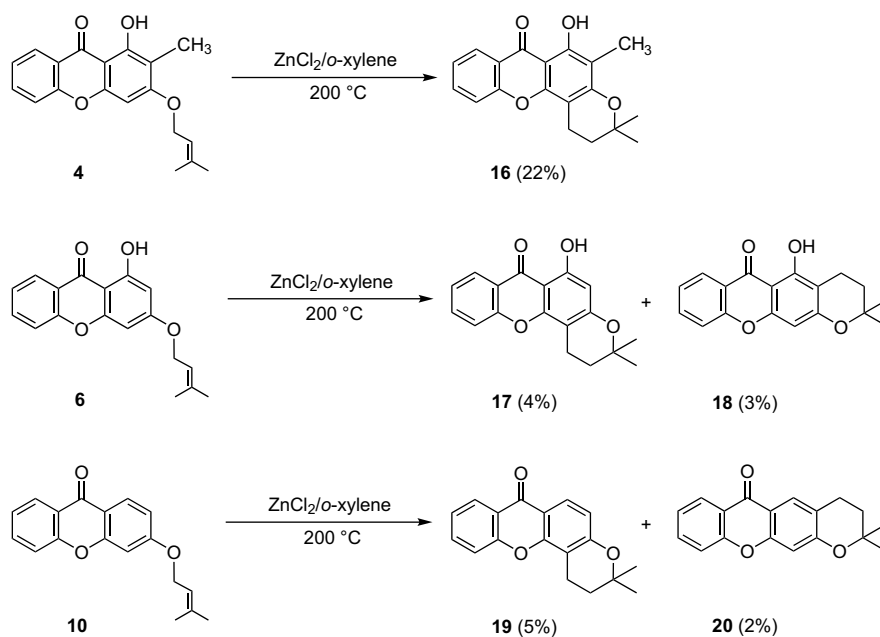
The dihydrofuranoxanthenes **12** (17.5%) and **13** (8.8%) have been previously prepared by heating xanthone **6** in vacuum at 200 °C for 2 h.¹²

Recently, we have also used the oxy-prenylated xanthenes **4** and **6** as precursors for the synthesis of dihydropyranoxanthenes. By heating these xanthenes with ZnCl₂ in *o*-xylene at 200 °C for 21 h, xanthone **4** gave the angular dihydropyranoxanthone **16** in 22% yield, while xanthone **6** furnished both angular and linear dihydropyranoxanthenes **17** and **18** in low yields.⁵ By using the same reaction conditions, we have obtained dihydropyranoxanthenes **19** and **20** from xanthone **10**, also in very low yields (Scheme 4).¹³

In order to improve the yields, we have designed a one-pot synthesis of these dihydropyranoxanthenes by using Montmorillonite K10 clay to catalyze direct condensation of the xanthenes **1**, **2**, and **3**, with prenyl bromide (Scheme 5) in different conditions, either at room temperature (Method A) or at 100 °C under conventional thermal heating (Method B) or with MW irradiation (Method C). As



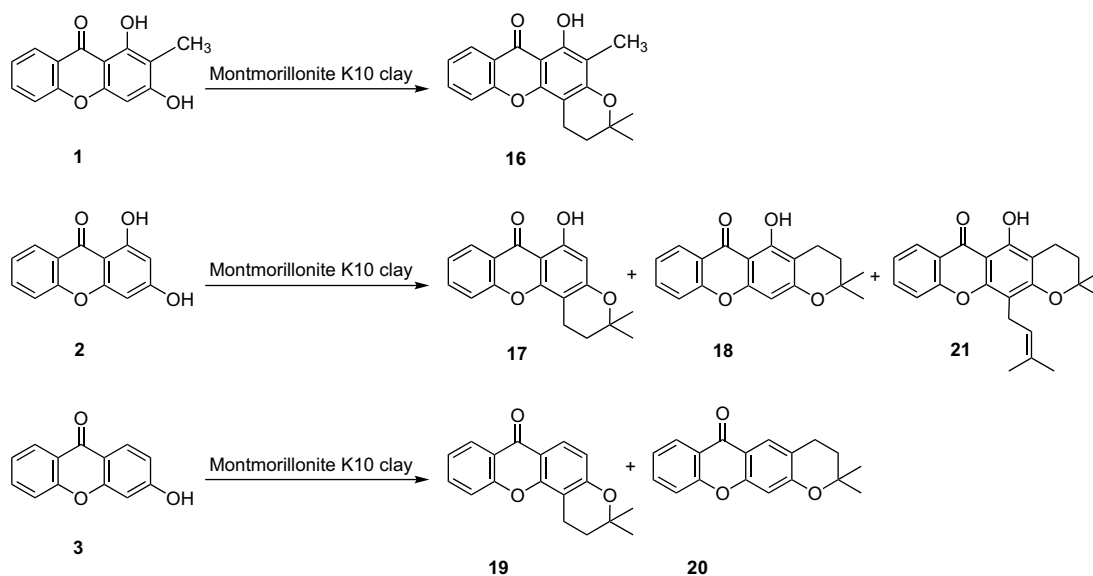
Scheme 3.



Scheme 4.

expected, xanthone **1** gave only the angular dihydropyrano-xanthone **16**, while xanthone **3** gave dihydropyrano-xanthenes **19** and **20**. However, xanthone **2** gave, besides dihydropyrano-xanthenes **17** and **18**, the prenylated dihydropyrano-xanthone **21**.

The yields of these dihydropyrano-xanthenes obtained by using Montmorillonite K10 clay in different conditions and those obtained by a classical synthesis through oxyprenylated xanthenes intermediates are found in Table 2.



Scheme 5.

It can be observed from Table 2 that, the yield of the dihydro-pyranoxanthone **16** was increased, when Montmorillonite K10 clay was used as catalyst in all three methods. When the reaction is performed at room temperature with the commercial Montmorillonite K10 clay, the yield was increased about five folds when compared to that obtained by classical synthesis (51% vs 10.5%). However, the disadvantage of this method is its long reaction time (5 days). The yields of xanthenes **17**, **18**, and **21** were found to be slightly improved but continued to be insignificant while those of xanthenes **19** and **20** were found to decrease. When the Montmorillonite K10 clay was used in combination with conventional heating at 100 °C (Method B), xanthone **16** was obtained in 63% yield with a remarkably shorter reaction time (60 min). Interestingly, the yields of xanthenes **17**, **18**, and **21** were also improved significantly when compared to those obtained by classical synthesis. However, when the commercial clay was replaced by dry clay, the yield of the linear dihydrofuranoxanthone **18** was increased from 12% to 18%. MW irradiation was also used instead of conventional heating and it can be carried out with or without solvent. The advantage of MW irradiation over conventional heating is its shorter reaction time (20 min). However, when this method is performed without solvent, the yield of xanthone **16** was only 53% while the yield of the xanthenes **17**, **18**, and **21** were less than 2%. Surprisingly, when the solvent was used, the yields of all xanthenes were dramatically increased, being 86% for xanthone **16**. Interestingly, when dry clay was used instead of the commercial clay, the yield of xanthone **18** was increased from 14% to 20%.

2.2. Structure elucidation of prenylated xanthenes

The structure of the new prenylated xanthenes **11**, **14**, **15**, and **19–21** were established by IR, UV, HRMS, and NMR techniques. The spectroscopic data of compound **1–10**, **12**, **13**, **16–18** are in agreement with those found in the literature.^{5,12,14,15} The previously

unreported ¹³C NMR of compounds **12** and **13** are also included in Table 4.

The ¹H and ¹³C NMR spectra of the prenylated xanthenes **11–15** and **19–21** (Tables 3 and 4, respectively) showed that all of them have retained a non-substituted aromatic ring of their xanthone precursors. Like the xanthenes precursors, only the ¹H NMR spectra of the xanthenes **11–15** and **21** showed a proton signal of the hydrogen bonded hydroxyl group at ca. 13 ppm (OH-1). The ¹H and ¹³C NMR spectra of xanthenes **11**, **12**, and **13** showed some common features: the presence of a 4',4',5'-trimethyldihydrofuran fused ring, which was evidenced by the two singlets of geminal methyl groups (δ_{H} ca. 1.3 and 1.5) on the quaternary carbon (δ_{C} ca. 43) and a doublet of another methyl group (δ_{H} 1.4, $J \sim 7$ Hz) on the oxy-methine carbon (δ_{C} ca. 90). The EIHRMS gave an accurate molecular mass of 310.1215 and a molecular formula of C₁₉H₁₈O₄ for xanthone **11**. As xanthone **11** was obtained by cyclization of the oxyprenylated xanthone **4**, the proton and carbon chemical shifts of the methyl group on C-2 (δ_{H} 2.12 s; δ_{C} 7.4) of xanthone **11** were similar to those of the methyl group of xanthone **4**. That the 4',4',5'-trimethyldihydrofuran fused ring was on C-3 and C-4 of the xanthone nucleus was supported by the correlations observed between the proton signals of the geminal methyl groups (δ_{H} 1.30 s and 1.58 s) and the carbon signal of C-4 (δ_{C} 111.8) in the HMBC spectrum (Fig. 2). In turn, the EIHRMS gave the molecular formula of C₁₈H₁₆O₄ for both xanthenes **12** and **13**. The ¹H NMR spectra of these xanthenes were similar to that of xanthone **11** except for the singlet of the aromatic proton at δ_{H} 6.35 s for xanthone **12** and at δ_{H} 6.33 s for xanthone **13** instead of the signal of the protons of the methyl group on C-2. The fact that xanthone **12** was a linear dihydrofuranoxanthone was substantiated by the correlations between the proton signals of the geminal methyl groups (δ_{H} 1.27 s and 1.51 s) and the carbon signal of C-2 (δ_{C} 116.8) in the HMBC spectrum. In the same way, the structure of xanthone **13** was established as an angular dihydrofuranoxanthone.

Table 2
Results obtained with different methods for synthesis of compounds **16–21**

Method	K10 clay	Reaction time	Final temp (°C)	Substrate	Product	Yield (%)	
						With K10 clay	Conventional heating ^a
A: K10 clay	Commercial	5 days	rt	1	16	51	10.5
					17	3	1
					18	9	0.5
				3	21	<2	—
					19	<2	3.6
					20	<2	1.4
B: K10 clay with conventional heating	Commercial	60 min	100	1	16	63	10.5
					17	7	1
					18	12	0.5
				2	21	6	—
					16	63	10.5
	Dry	60 min	100	1	17	8	1
					18	18	0.5
				2	21	7	—
					16	63	10.5
C: K10 clay with MW (without solvent)	Commercial	20 min	110	1	16	53	10.5
					17	<2	1
					18	<2	0.5
			150	3	21	<2	—
					19	9	3.6
					20	3	1.4
			132	2	16	86	10.5
					17	10	1
					18	14	0.5
C: K10 clay with MW (with solvent)	Commercial	20 min	105	1	21	4	—
					19	25	3.6
					20	9	1.4
			113	2	17	10	1
					18	20	0.5
					21	5	—
			115	3	16	86	10.5
					17	10	1
					18	20	0.5
C: K10 clay with MW (with solvent)	Dry	20 min	110	2	17	10	1
					18	20	0.5
					21	5	—

^a Yield of the products relative to the precursor xanthenes **1**, **2**, and **3**.

Table 3
¹H NMR chemical shifts of prenylated xanthenes **11–15** and **19–21**^a

	11^b	12^b	13^c	14^b	15^b	19^b	20^b	21^b
H-1	13.36 [OH, s]	13.06 [OH, s]	13.09 [OH, s]	13.44 [OH, s]	12.89 [OH, s]	8.11 (d, <i>J</i> =8.9)	8.07 (s)	13.07 [OH, s]
H-2	—	—	6.33 (s)	—	6.30 (s)	6.83 (d, <i>J</i> =8.9)	—	—
H-3	—	—	—	7.06 [OH, br s]	7.04 [OH, br s]	—	—	—
H-4	—	6.35 (s)	—	6.38 (s)	—	—	6.82 (s)	—
H-5	7.42 (d, <i>J</i> =8.4)	7.42 (d, <i>J</i> =8.5)	7.43 (d, <i>J</i> =8.4)	7.42 (d, <i>J</i> =8.5)	7.48 (d, <i>J</i> =8.5)	7.49 (d, <i>J</i> =8.4)	7.45 (d, <i>J</i> =8.4)	7.44 (d, <i>J</i> =8.4)
H-6	7.69 (ddd, <i>J</i> =8.4, 7.1, 1.6)	7.70 (ddd, <i>J</i> =8.5, 7.2, 1.7)	7.70 (ddd, <i>J</i> =8.4, 7.0, 1.6)	7.71 (ddd, <i>J</i> =8.5, 7.1, 1.6)	7.73 (ddd, <i>J</i> =8.5, 7.1, 1.6)	7.68 (ddd, <i>J</i> =8.4, 7.0, 1.7)	7.69 (ddd, <i>J</i> =8.4, 7.0, 1.7)	7.69 (ddd, <i>J</i> =8.4, 7.1, 1.6)
H-7	7.36 (dd, <i>J</i> =8.1, 7.1)	7.37 (dd, <i>J</i> =8.0, 7.2)	7.37 (dd, <i>J</i> =8.0, 7.0)	7.37 (dd, <i>J</i> =8.0, 7.1)	7.40 (dd, <i>J</i> =8.0, 7.1)	7.37 (t, <i>J</i> =8.0, 7.0)	7.34 (t, <i>J</i> =8.0, 7.0)	7.34 (t, <i>J</i> =8.0, 7.1)
H-8	8.26 (dd, <i>J</i> =8.1, 1.6)	8.24 (dd, <i>J</i> =8.0, 1.7)	8.24 (dd, <i>J</i> =8.0, 1.6)	8.26 (dd, <i>J</i> =8.0, 1.6)	8.27 (dd, <i>J</i> =8.0, 1.6)	8.33 (dd, <i>J</i> =8.0, 1.6)	8.32 (dd, <i>J</i> =8.0, 1.7)	8.24 (dd, <i>J</i> =8.0, 1.6)
2-CH ₃	2.12 (s)	—	—	—	—	—	—	—
H-1'	—	—	—	4.13 (q, <i>J</i> =7.0)	4.24 (q, <i>J</i> =6.9)	—	—	—
H-2'	—	—	—	1.43 (d, <i>J</i> =7.0)	1.49 (d, <i>J</i> =6.9)	—	—	—
3'-CH ₃	—	—	—	1.79 (s)	1.79 (s)	—	—	—
H-4'	—	—	—	—	—	3.01 (t, <i>J</i> =6.8)	2.93 (t, <i>J</i> =6.8)	2.75 (t, <i>J</i> =6.9)
H-5'	4.53 (q, <i>J</i> =6.6)	4.53 (q, <i>J</i> =6.6)	3.29 (q, <i>J</i> =7.2)	5.31, 5.25 (2 s)	5.32, 5.26 (2 s)	1.92 (t, <i>J</i> =6.8)	1.89 (t, <i>J</i> =6.8)	1.86 (t, <i>J</i> =6.9)
H-6'	1.44 (d, <i>J</i> =6.6)	1.41 (d, <i>J</i> =6.6)	1.32 (d, <i>J</i> =7.2)	—	—	—	—	—
4'-CH ₃	1.58, 1.30 (2 s)	1.51, 1.27 (2 s)	1.46, 1.44 (2 s)	—	—	—	—	—
6'-CH ₃	—	—	—	—	—	1.41 (s)	1.40 (s)	1.39 (s)
H-1''	—	—	—	—	—	—	—	3.48 (d, <i>J</i> =7.4)
H-2''	—	—	—	—	—	—	—	5.24 (t, <i>J</i> =7.4)
3''-CH ₃	—	—	—	—	—	—	—	1.67 (s)

^a Values in parts per million (δ_H).^b Measured in CDCl₃ at 300.13 MHz.^c Measured in CDCl₃ at 500.13 MHz. *J* values (Hz) are shown in parenthesis. Assignments were confirmed by HSQC and HMBC experiments.**Table 4**¹³C NMR chemical shifts of prenylated xanthenes **11–15** and **19–21**^a

	11^b	12^b	13^c	14^b	15^b	19^b	20^b	21^b
C-1	161.4	158.7	158.1	160.8	161.9	125.4	126.6	158.4
C-2	102.9	116.8	89.6	111.3	99.5	114.9	119.0	103.7
C-3	164.9	166.2	166.0	163.6	163.3	159.6	160.4	159.3
C-4	111.8	89.5	113.3	95.0	107.2	114.8	104.1	167.1
C-5	117.3	117.5	117.5	117.5	117.5	117.6	117.7	117.5
C-6	134.5	134.6	134.6	134.9	134.9	134.0	134.1	134.6
C-7	123.7	123.8	123.8	123.8	124.1	123.8	123.5	123.4
C-8	126.0	125.7	125.7	125.8	125.9	126.6	127.5	125.8
C-9	180.6	181.0	180.9	180.9	181.1	176.6	176.5	181.1
2-CH ₃	7.4	—	—	—	—	—	—	—
C-4a	150.8	157.9	158.8	156.2	154.6	155.4	156.2	152.4
C-10a	155.6	155.9	155.9	156.0	155.9	156.1	156.3	156.1
C-8a	120.7	120.5	120.5	120.5	120.4	121.9	121.8	120.4
C-9a	103.6	103.0	104.1	103.5	104.0	108.6	115.2	102.6
C-1'	—	—	—	34.6	35.2	—	—	—
C-2'	—	—	—	16.7	17.2	—	—	—
C-3'	—	—	—	150.9	150.0	—	—	—
C-4'	44.0	43.3	92.6	—	—	16.8	15.3	16.4
3'-CH ₃	—	—	—	22.7	22.7	—	—	—
C-5'	90.4	91.1	42.9	112.2	112.3	31.6	30.9	31.6
C-6'	14.3	14.3	14.2	—	—	75.7	76.2	76.2
4'-CH ₃	25.9, 21.5	25.1, 20.6	28.5, 22.3	—	—	—	—	—
6'-CH ₃	—	—	—	—	—	26.7	27.0	26.9
C-1''	—	—	—	—	—	—	—	21.6
C-2''	—	—	—	—	—	—	—	122.4
C-3''	—	—	—	—	—	—	—	131.2
3''-CH ₃	—	—	—	—	—	—	—	25.8

^a Values in parts per million (δ_C).^b Measured in CDCl₃ at 75.47 MHz.^c Measured in CDCl₃ at 125.77 MHz. Assignments were confirmed by HSQC and HMBC experiments.

On the other hand, the new prenylated xanthenes **14** and **15** did not show characteristic proton and carbon signals of the 4',4',5'-trimethyldihydrofuran fused ring in their ¹H and ¹³C NMR spectra. Besides the singlets of the aromatic protons at δ_H 6.38 s and 6.30 s, respectively, for xanthone **14** and xanthone **15**, the ¹H and ¹³C NMR spectra showed the presence of the 3-methylbut-3-en-2-yl side chain as was evidenced by the signals of two vinyl protons at ca. δ_H 5.3 s, one allylic methyl group (δ_H 1.79 s; δ_C 22.7), one allylic methine proton (δ_H 4.13 q; δ_C 34.6 and δ_H 4.24 q; δ_C 35.2), and another methyl group (δ_H 1.43 d; δ_C 16.7 and δ_H 1.49 d; δ_C 17.2) on the methine carbon. That the prenyl side chain is on C-2 for the xanthone **14** was supported by the correlation between the methine proton of the side chain at δ_H 4.13 q (*J*=7.0 Hz) and the carbon signal at δ_C 160.8 (C-1) as well as between the signal of the methyl proton at δ_H 1.43 d (*J*=7.0 Hz) and the carbon signal at δ_C 111.3 (C-2) in the HMBC spectrum. On the contrary, the signal of the methine proton of the side chain at δ_H 4.24 q (*J*=6.9 Hz) was correlated with the carbon signal at δ_C 154.6 (C-4a) in xanthone **15**, confirming that the prenyl side chain is on C-4.

Finally, the existence of a 6',6'-dimethyldihydropyran fused ring in the prenylated xanthenes **19–21** was based on an observation of the two geminal methyl groups (δ_H ca. 1.40 s, δ_C ca. 27) and the two methylene groups (δ_H ca. 1.9 and 2.9; δ_C ca. 16 and 30) as well as an oxygen bearing quaternary carbon (δ_C ca. 76) in the ¹H and ¹³C NMR spectra. The EIHRMS gave a molecular formula C₁₈H₁₆O₃ for both xanthenes **19** and **20**. However, the 6',6'-dimethyldihydropyran fused ring on C-3 and C-4 in xanthone **19** was substantiated by the presence of the *ortho* coupled aromatic protons at δ_H 8.11 d (*J*=8.9 Hz, H-1) and 6.83 d (*J*=8.9 Hz, H-2), respectively. Furthermore, the HMBC spectrum showed a correlation between the proton signal of H-4' (δ_H 3.0 t, *J*=6.8 Hz) and the carbon signal of C-4a (δ_C 155.4). Instead, the ¹H NMR spectra of xanthone **20** showed two singlets of H-1 (δ_H 8.07) and H-4 (δ_H 6.82) and thus the 6',6'-dimethyldihydropyran fused ring must be on C-2 and C-3. This was confirmed by a correlation between the proton signal of H-4' (δ_H

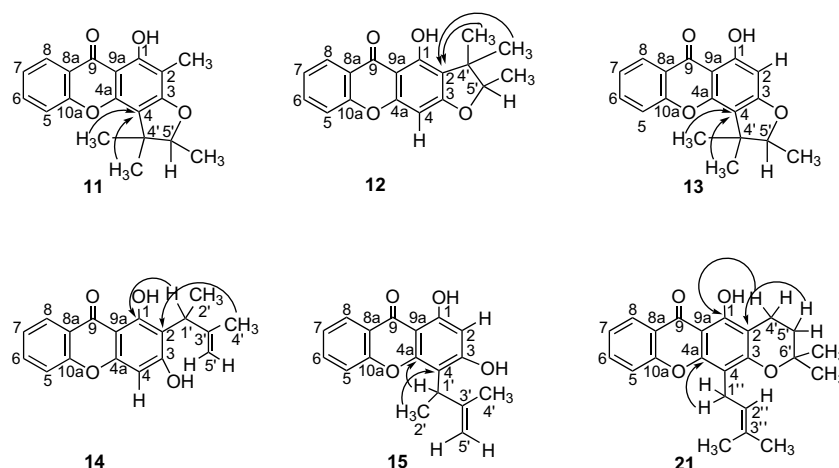


Figure 2. Main connectivities found in the HMBC of prenylated xanthenes **11–15** and **21**.

2.93 t, $J=6.8$ Hz) and the carbon signal at δ_C 126.6 (C-1) in the HMBC spectrum. The molecular formula $C_{23}H_{24}O_4$ (accurate mass 364.1675), obtained from EIHRMS, for the new xanthone **21** indicated the existence of two prenyl substituents. That the 6',6'-dimethyldihydropyran fused ring was on C-2 and C-3, like in xanthone **20**, was supported by the correlations between the proton signal of H-4' (δ_H 2.75 t, $J=6.9$ Hz) and the carbon signal at δ_C 158.4 (C-1) as well as between the proton signal at δ_H 1.89 t (H-5') and the carbon at δ_C 103.7 (C-2) in the HMBC spectra. Thus, another prenyl side chain must be on C-4. The nature of the prenyl side chain on C-4 was established as 3-methylbut-2-enyl by the characteristic proton and carbon chemical shifts from the ^1H and ^{13}C NMR spectra (Tables 3 and 4, respectively). The HMBC spectrum showed that the signal of the methylene protons at δ_H 3.48 (H-1'') gave cross peaks with both carbon signals at δ_C 152.4 (C-4a) and δ_C 159.3 (C-3).

3. Conclusions

Microwave-assisted organic synthesis (MAOS) was successfully applied in the synthesis of oxyprenylated xanthenes (**4** and **6**) from the hydroxyxanthone precursors (**1** and **2**) with the two folds increase of yields and remarkable shorter reaction times, when compared to the conventional heating conditions. Besides, the yields of diprenylated by-products did not suffer a significant alteration. Furthermore, we have applied the MW irradiation methodology to prepare dihydrofuranoxanthone derivatives from the oxyprenylated xanthenes precursors (**4** and **6**). When NMP was used as a solvent, the oxyprenylated xanthone **4** furnished the angular dihydrofuranoxanthone **11** with a very good yield (72%) while the oxyprenylated xanthone **6** gave the linear dihydrofuranoxanthone **12**, but with slightly higher yield than the previously described in the classical method. However, when the reaction was performed in *N,N*-DEA, the oxyprenylated xanthone **6** gave both linear (**12**) and angular (**13**) dihydrofuranoxanthenes, together with the previously unreported prenylated derivatives **14** and **15**, all in low yield. On the other hand, a combination of a MW irradiation with the Montmorillonite K10 clay was used in the one-pot synthesis of dihydropyranoxanthone derivatives directly from the hydroxyxanthone precursors without prior preparation of the oxyprenylated xanthone intermediates. One of the advantages of this methodology is the possibility to vary the conditions such as the type of clay, the absence or presence of solvent and the temperature. Besides being environmentally friendly, this methodology has proved to give a much higher yield (five to eight folds) of the angular dihydropyranoxanthone **16** from the hydroxyxanthone precursor **1**, when compared to the classical method in which zinc

chloride and high temperature heating are used. As this is the first report on the application of the combined MW irradiation and Montmorillonite K10 clay for the synthesis of prenylated xanthenes, it can open a new avenue for the environmentally friendly method to obtain other classes of bioactive compounds.

4. Experimental part

4.1. General methods

Purifications of compounds were performed by flash chromatography using Merck silica gel 60 (0.040–0.063 mm) and preparative thin layer chromatography (TLC) using Merck silica gel 60 (GF₂₅₄) plates. Reactions were monitored by TLC. MW reactions were performed using glassware setup for atmospheric-pressure reactions and also 12 mL and/or 50 mL closed glass reactors (internal reaction temperature measurement with a fiber-optic probe sensor) and were carried out using an Ethos MicroSYNTH 1600 Microwave Labstation from Milestone. Melting points were obtained in a Köfeler microscope and are uncorrected. IR spectra were measured on an ATI Mattson Genesis series FTIR (software: WinFirst v. 2.10) spectrophotometer in KBr microplates (cm^{-1}). UV spectra were taken in ethanol¹⁶ and were recorded on a Varian CARY 100 spectrophotometer: λ_{max} in nm (software: Cary Win UV v. 3.0). ^1H and ^{13}C NMR spectra were taken in $CDCl_3$ at room temperature, on Bruker Avance 300 and 500 instruments. Chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane (TMS) as an internal reference. ^1H NMR spectra were measured at 300.13 MHz and/or 500.13 MHz and assignment abbreviations are the following: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), and double doublet of doublets (ddd). ^{13}C NMR spectra were measured at 75.47 MHz and/or 125.77 MHz. ^{13}C NMR assignments were made by 2D HSQC and HMBC experiments (long-range C, H coupling constants were optimized to 7 and 1 Hz). HRMS spectra were recorded as EI (electronic impact) mode on a VG Autospec M spectrometer (m/z) at CACTI—University of Vigo. Prenyl bromide 95% and Montmorillonite K10 clay were purchased from Sigma Aldrich.

4.2. General procedure for the synthesis of prenylated xanthenes 4–9 under MW irradiation

A mixture of xanthenes **1** or **2** (2.00 mmol), prenyl bromide (4.00 mmol), K_2CO_3 (4.20 mmol) in acetone (90 mL), in a two-necked glassware apparatus, provided with magnetic stirring bar, fiber-optic temperature control, and reflux condenser, was heated

for 3×20 min according to the following microwave program: Power: 200 W; temperature: 62 °C; ramp time: 5 min; hold time: 15 min; final temperature 59 °C. After cooling, the solid was filtered and the solvent removed under reduced pressure and afforded the crude product that was purified by flash chromatography (SiO₂; hexane/EtOAc 99:1 or CH₂Cl₂/petroleum ether/Et₂O 1:96:3). The isolation of the components of the mixture was then carried out by preparative TLC (SiO₂; hexane/EtOAc 9:1 or CH₂Cl₂/petroleum ether/Et₂O 5:90:5 and hexane/EtOAc 8:2). Prenylated xanthenes **4**, **5** were crystallized from EtOH and prenylated xanthenes **6–9** were crystallized from CH₂Cl₂/petroleum ether (60–80). Compounds **4–9** were shown to possess spectroscopic and analytical data according to those previously reported.⁵ Compounds (yields): **4** (83%), **5** (5%), **6** (53%), **7** (1%), **8** (1%), **9** (2%).

4.3. General procedure for Claisen rearrangement of monoprenylated xanthenes **4** and **6** in NMP under MW irradiation

A solution of monoprenylated xanthenes **4** or **6** (0.35 mmol), in NMP (15 mL), was transferred to a two-necked glassware apparatus, provided with magnetic stirring bar, fiber-optic temperature control, and reflux condenser and heated for 2×30 min according to the following microwave program: step 1: 5 min, ramp to 202 °C, 800 W maximum power; step 2: 25 min, hold at 202 °C, 300 W maximum power. After completion of the reaction, the mixture was poured onto crushed ice, acidified (5 N HCl) and extracted successively with Et₂O and CH₂Cl₂. The organic layers were washed with water and dried. The crude products were purified by preparative TLC (SiO₂; hexane/EtOAc 25:1 or 95:5). Compounds **11** and **12** were crystallized from CH₂Cl₂/petroleum ether (60–80) and were identified by their spectroscopic and analytical data.

4.3.1. 5-Hydroxy-1,1,2,4-tetramethyl-1,2-dihydrofuro[2,3-*c*]xanthen-6-one (**11**)

Yield 72%; yellow solid; mp 194–196 °C (CH₂Cl₂/petroleum ether); UV (EtOH) $\lambda_{\max}$ (ϵ): 316, 259, 237, 214 (15,367, 20,445, 31,634, 27,394); (EtOH+NaOH): 404, 295, 281, 220 (5522, 16,463, 16,163, 37,818); (EtOH+AlCl₃): 330, 264, 236, 221 (20,248, 25,502, 36,680, 37,839); IR (KBr) $\nu_{\max}$: 2959, 2918, 2898, 2865, 1643, 1620, 1594, 1475, 1432, 1311, 1221, 1142, 1101, 762 cm⁻¹; ¹H NMR data, see Table 3; ¹³C NMR data, see Table 4; EIMS *m/z* (%): 310 (13, M⁺), 295 (100), 280 (20), 267 (17); EIHRMS *m/z*: calcd for C₁₉H₁₈O₄: 310.1205, found: 310.1215.

4.3.2. 4-Hydroxy-2,3,3-trimethyl-2,3-dihydrofuro[3,2-*b*]xanthen-5-one (**12**)

Yield 20%; yellow solid; mp 151–154 °C (CH₂Cl₂/petroleum ether); UV (EtOH) $\lambda_{\max}$ (ϵ): 313, 240, 222 (7933, 15,185, 12,215); (EtOH+NaOH): 390, 276, 217 (2267, 7881, 25,607); (EtOH+AlCl₃): 314, 240, 222 (9274, 17,822, 16,230); IR (KBr) $\nu_{\max}$: 3430, 2966, 2922, 2885, 1655, 1611, 1569, 1474, 1447, 1305, 1145, 821, 749 cm⁻¹; ¹H NMR data, see Table 3; ¹³C NMR data, see Table 4; EIMS *m/z* (%): 296 (32, M⁺), 281 (100), 266 (9), 253 (7), 88 (42); EIHRMS *m/z*: calcd for C₁₈H₁₆O₄: 296.1049, found: 296.1049.

4.4. General procedure for Claisen rearrangement of monoprenylated xanthone **6** in *N,N*-DEA under MW irradiation

A solution of the monoprenylated xanthone **6** (100 mg; 0.34 mmol), in *N,N*-DEA (4 mL), under nitrogen atmosphere, was irradiated for 3×15 min at 750 W and 225 °C. After completion of the reaction, the reaction mixture was diluted with water, acidified (5 N HCl), and extracted successively with petroleum ether, Et₂O, and CH₂Cl₂. The organic layers were washed with water and dried. The crude product was purified by flash chromatography (SiO₂;

hexane/EtOAc 95:5) and by preparative TLC (SiO₂; petroleum ether/Et₂O 95:5). Compounds **12–15** were identified by their spectroscopic and analytical data. Compound (yield): **12** (7%) was characterized as described above.

4.4.1. 5-Hydroxy-1,1,2-trimethyl-1,2-dihydrofuro[2,3-*c*]xanthen-6-one (**13**)

Yield 6%; yellow solid; mp 89–91 °C (CH₂Cl₂/petroleum ether); UV (EtOH) $\lambda_{\max}$ (ϵ): 313, 240, 223 (5763, 11,407, 9807); (EtOH+NaOH): 385, 274, 216 (1585, 6356, 45,659); (EtOH+AlCl₃): 329, 240, 223 (5437, 8785, 11,230); IR (KBr) $\nu_{\max}$: 3422, 2961, 2921, 2855, 1658, 1611, 1455, 1315, 1155, 1104, 832, 746 cm⁻¹; ¹H NMR data, see Table 3; ¹³C NMR data, see Table 4; EIMS *m/z* (%): 296 (46, M⁺), 281 (100), 253 (12), 237 (8), 84 (7); EIHRMS *m/z*: calcd for C₁₈H₁₆O₄: 296.1049, found: 296.1049.

4.4.2. 1,3-Dihydroxy-2-(3-methylbut-3-en-2-yl)-9H-xanthen-9-one (**14**)

Yield 5%; yellow solid; mp 192–195 °C (acetone); UV (EtOH) $\lambda_{\max}$ (ϵ): 312, 238, 217 (4756, 9985, 7985); (EtOH+NaOH): 373, 276, 215 (5526, 5437, 45,926); (EtOH+AlCl₃): 323, 238, 221 (4178, 8578, 9052); IR (KBr) $\nu_{\max}$: 3435, 2963, 2921, 1644, 1609, 1444, 1316, 1257, 1143, 1073, 749 cm⁻¹; ¹H NMR data, see Table 3; ¹³C NMR data, see Table 4; EIMS *m/z* (%): 296 (17, M⁺), 281 (100), 253 (13), 97 (15), 83 (18), 69 (29); EIHRMS *m/z*: calcd for C₁₈H₁₆O₄: 296.1049, found: 296.1046.

4.4.3. 1,3-Dihydroxy-4-(3-methylbut-3-en-2-yl)-9H-xanthen-9-one (**15**)

Yield 5%; yellow solid; mp 193 °C (decomp.); UV (EtOH) $\lambda_{\max}$ (ϵ): 312, 259, 236, 213 (13,234, 22,997, 30,178, 24,510); (EtOH+NaOH): 368, 285, 215 (12,582, 19,763, 94,896); (EtOH+AlCl₃): 416, 332, 274, 219 (4184, 16,409, 22,315, 30,772); IR (KBr) $\nu_{\max}$: 3401, 2960, 2922, 2853, 1646, 1607, 1422, 1222, 1143, 755 cm⁻¹; ¹H NMR data, see Table 3; ¹³C NMR data, see Table 4; EIMS *m/z* (%): 296 (52, M⁺), 281 (100), 253 (34), 225 (17), 213 (21), 149 (32), 69 (22); EIHRMS *m/z*: calcd for C₁₈H₁₆O₄: 296.1049; found: 296.1051.

4.5. General procedure for the synthesis of dihydropyranoxanthenes **16–21** with Montmorillonite K10 clay

A slurry of the K10 clay (20 equiv by weight) in CHCl₃ (ca. 50 mL) was treated with the xanthenes **1**, **2** or **3** (0.50 mmol), followed by the addition of prenyl bromide (1 mmol). The mixture was maintained under stirring at room temperature for 5 days. The reaction mixture was filtered under vacuum, washed with CH₂Cl₂, Me₂CO, and MeOH and the filtrate concentrated under vacuum. The recovered clay was reactivated by washing with MeOH. The crude product was purified by flash chromatography (SiO₂; petroleum ether/EtOAc) and by preparative TLC (SiO₂; petroleum ether/EtOAc or CH₂Cl₂). The products were identified by their spectroscopic and analytical data. Compounds (yields): **16**⁵ (51%), **17**⁵ (3%), **18**⁵ (9%).

4.5.1. 3,3-Dimethyl-2,3-dihydropyrano[2,3-*c*]xanthen-7(1H)-one (**19**)

Yield <2%; white solid; mp 158–160 °C (Me₂CO); IR (KBr) $\nu_{\max}$: 2962, 2924, 2854, 1648, 1611, 1463, 1431, 1345, 1265, 1228, 1159, 1114, 1061, 748 cm⁻¹; ¹H NMR data, see Table 3; ¹³C NMR data, see Table 4; EIMS *m/z* (%): 280 (31, M⁺), 265 (11), 225 (100); EIHRMS *m/z*: calcd for C₁₈H₁₆O₃: 280.1100, found: 280.1111.

4.5.2. 2,2-Dimethyl-3,4-dihydropyrano[3,2-*b*]xanthen-6(2H)-one (**20**)

Yield <2%; white solid; mp 135–138 °C (Me₂CO); IR (KBr) $\nu_{\max}$: 2964, 2921, 2852, 1655, 1615, 1460, 1311, 1272, 1154, 1115, 755 cm⁻¹;

^1H NMR data, see Table 3; ^{13}C NMR data, see Table 4; EIMS m/z (%): 280 (32, M^{++}), 265 (19), 225 (100); EIHRMS m/z : calcd for $\text{C}_{18}\text{H}_{16}\text{O}_3$: 280.1100, found: 280.1103.

4.5.3. 5-Hydroxy-2,2-dimethyl-12-(3-methylbut-2-enyl)-3,4-dihydropyrano[3,2-b]xanthen-6(2H)-one (**21**)

Yield <2% as a yellow solid; mp 96–99 °C (Me_2CO); UV (EtOH) λ_{max} (ϵ): 317, 261, 237, 217 (11,403, 17,541, 23,333, 23,716); (EtOH+NaOH): 410, 280, 214 (3479, 13,534, 60,000); (EtOH+ AlCl_3): 332, 265, 222 (10,674, 14,572, 24,681); IR (KBr) ν_{max} : 3441, 2967, 2920, 2855, 1646, 1611, 1580, 1473, 1434, 1224, 1159, 1109, 1037, 748 cm^{-1} ; ^1H NMR data, see Table 3; ^{13}C NMR data, see Table 4; EIMS m/z (%): 364 (25, M^{++}), 309 (21), 293 (49), 265 (29), 253 (100); EIHRMS m/z : calcd for $\text{C}_{23}\text{H}_{24}\text{O}_4$: 364.1675, found: 364.1675.

4.6. General procedure for the synthesis of dihydropyranoxanthenes **16–18** and **21** with Montmorillonite K10 clay and conventional heating

A slurry of the K10 clay (20 equiv by weight) in CHCl_3 (ca. 20 mL) was treated with the xanthenes **1** or **2** (0.40 mmol), followed by the addition of prenyl bromide (0.80 mmol), in a sealed tube. The mixture was maintained under stirring at 100 °C in an oil bath for 60 min. The reaction mixture was filtered under vacuum, washed with CH_2Cl_2 , Me_2CO , and MeOH, and the filtrate concentrated under vacuum. The recovered clay was reactivated by washing with MeOH. The crude product was purified by column chromatography (SiO_2 ; hexane/EtOAc) and by preparative TLC (SiO_2 ; hexane/EtOAc). The products were identified by their spectroscopic and analytical data. Compounds (yields): **16**⁵ (63%), **17**⁵ (7%), **18**⁵ (12%). Compound (yield): **21** (6%) was characterized as described above.

4.7. General procedure for the synthesis of dihydropyranoxanthenes **16–18** and **21** with dry Montmorillonite K10 clay and conventional heating

Montmorillonite K10 clay (2 g) was measured into a vial and heated in an oven at approximately 110 °C for 2 h. The activated clay was transferred to a desiccator and allowed to cool to room temperature. To the clay was added CHCl_3 (ca. 20 mL), xanthenes **1** or **2** (0.40 mmol), followed by the addition of prenyl bromide (0.80 mmol), in a sealed tube. The mixture was maintained under stirring at 100 °C in an oil bath for 60 min. The reaction mixture was filtered under vacuum, washed with CH_2Cl_2 , Me_2CO , and MeOH, and the filtrate concentrated under vacuum. The recovered clay was reactivated by washing with MeOH. The crude product was purified by column chromatography (SiO_2 ; hexane/EtOAc) and by preparative TLC (SiO_2 ; hexane/EtOAc). The products were identified by their spectroscopic and analytical data. Compounds (yields): **16**⁵ (63%), **17**⁵ (8%), **18**⁵ (18%). Compound (yield): **21** (7%) was characterized as described above.

4.8. General procedure for the synthesis of dihydropyranoxanthenes **16–21** with Montmorillonite K10 clay and MW irradiation without solvent

Xanthenes **1**, **2** or **3** (0.140 mmol) were mixed and grounded with K10 clay (20 equiv by weight) in a mortar. The mixture was transferred to a 12 mL closed microwave reactor and prenyl bromide (1.15 mmol) was added. The mixture under stirring was irradiated at 150 W for 20 min and final temperatures range were 110–150 °C. The reaction mixture was filtered under vacuum, washed with CH_2Cl_2 , Me_2CO , and MeOH, and the filtrate concentrated under vacuum. The recovered clay was reactivated by washing with MeOH. The crude product was purified by flash

chromatography (SiO_2 ; petroleum ether/EtOAc) and by preparative TLC (SiO_2 ; petroleum ether/EtOAc or CH_2Cl_2). The products were identified by their spectroscopic and analytical data. Compounds (yields): **16**⁵ (53%), **17**⁵ (<2%), **18**⁵ (<2%). Compounds (yields): **19** (9%), **20** (3%), **21** (<2%) were characterized as described above.

4.9. General procedure for the synthesis of dihydropyranoxanthenes **16–21** with commercial Montmorillonite K10 clay and MW irradiation with solvent

A slurry of the K10 clay (20 equiv by weight) in CHCl_3 (ca. 8 mL) was treated with the xanthenes **1**, **2** or **3** (0.140 mmol), followed by the addition of prenyl bromide (1.15 mmol), in a 12 mL closed microwave reactor. The mixture under stirring was irradiated at 150 W for 20 min and final temperatures range were 105–115 °C. The reaction mixture was filtered under vacuum, washed with CH_2Cl_2 , Me_2CO , and MeOH, and the filtrate concentrated under vacuum. The recovered clay was reactivated by washing with MeOH. The crude product was purified by flash chromatography (SiO_2 ; petroleum ether/EtOAc) and by preparative TLC (SiO_2 ; petroleum ether/EtOAc or CH_2Cl_2). The products were identified by their spectroscopic and analytical data. Compounds (yields): **16**⁵ (86%), **17**⁵ (10%), **18**⁵ (14%). Compounds (yields): **19** (25%), **20** (9%), **21** (4%) were characterized as described above.

4.10. General procedure for the synthesis of dihydropyranoxanthenes **17**, **18**, and **21** with dry Montmorillonite K10 clay and MW irradiation with solvent

Montmorillonite K10 clay (2 g) was measured into a vial and heated in an oven at approximately 110 °C for 2 h. The activated clay was transferred to a desiccator and allowed to cool to room temperature. To the clay was added CHCl_3 (ca. 11 mL), xanthone **2** (0.43 mmol), followed by the addition of prenyl bromide (0.86 mmol), in a 50 mL closed microwave reactor. The mixture under stirring was irradiated at 250 W for 20 min and the final temperature was 110 °C. The reaction mixture was filtered under vacuum, washed with CH_2Cl_2 , Me_2CO , and MeOH, and the filtrate concentrated under vacuum. The recovered clay was reactivated by washing with MeOH. The crude product was purified by flash chromatography (SiO_2 ; petroleum ether/EtOAc) and by preparative TLC (SiO_2 ; petroleum ether/EtOAc). The products were identified by their spectroscopic and analytical data. Compounds (yields): **17**⁵ (10%), **18**⁵ (20%). Compound (yield): **21** (5%) was characterized as described above.

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References and notes

- Pinto, M. M. M.; Sousa, M. E.; Nascimento, M. S. J. *Curr. Med. Chem.* **2005**, *12*, 2517.
- Pinto, M.; Castanheiro, R. In *Natural Prenylated Xanthenes: Chemistry and Biological Activities in Natural Products: Chemistry, Biochemistry and Pharmacology*; Brahmachari, G., Ed.; Narosa Publishing House: Nova Deli, India, 2008; Chapter 17, pp 520–676.
- Epifano, F.; Genovese, S.; Menghini, L.; Curini, M. *Phytochemistry* **2007**, *68*, 939.
- Subba Rao, G. S. R.; Raghavan, S. *J. Indian Inst. Sci.* **2001**, *81*, 393.
- Castanheiro, R. A. P.; Pinto, M. M. M.; Silva, A. M. S.; Cravo, S. M. M.; Gales, L.; Damas, A. M.; Pedro, M. M.; Nazareth, N.; Nascimento, M. S. J.; Eaton, G. *Bioorg. Med. Chem.* **2007**, *15*, 6080.

6. Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2005; Vol. 25, pp 9–55.
7. Oliver Kappe, C. *Angew. Chem., Int. Ed.* **2004**, 43, 6250.
8. Oliver Kappe, C.; Dallinger, D. *Nat. Rev. Drug Discov.* **2006**, 5, 51.
9. Nagendrappa, G. *Resonance* **2002**, 64.
10. Dintzner, M.; McClelland, K.; Morse, K.; Akroush, M. *Synlett* **2004**, 2028.
11. Mortoni, A.; Martinelli, M.; Piarulli, U.; Regalia, N.; Gagliardi, S. *Tetrahedron Lett.* **2004**, 45, 6623.
12. Jain, A. C.; Anand, S. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 329.
13. Cravo, S.; Castanheiro, R.; Pinto, M.; Pinto, D.; Silva, A. Abstracts Book, 41st IUPAC World Chemistry Congress, Turin, Italy, Aug 5–10, 2007.
14. Fernandes, E. G. R.; Silva, A. M. S.; Cavaleiro, J. A. S.; Silva, F. M.; Borges, M. F. M.; Pinto, M. M. *Magn. Reson. Chem.* **1998**, 36, 305.
15. Patel, G. N.; Trivedi, K. N. *J. Indian Chem. Soc.* **1988**, 65, 192.
16. Mesquita, A.; Corrêa, D.; Gottlieb, O.; Magalhães, M. *Anal. Chim. Acta* **1968**, 42, 311.

ANEXO VII

Submitted to *Acta Cryst. E*

1-Hydroxy-3-(3-methylbut-2-enyloxy)xanthone

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Abstract

The title compound C₁₈H₁₆O₅ is a monoprenylated xanthone. The xanthone skeleton exhibits a planar conformation and the isoprenyl side chain remains approximately in the mean plane of the xanthone moiety. The corresponding dihedral angle is 4.4°. The hydroxyl group bound to C1 forms an intramolecular hydrogen bond to O11 [H...O = 1.585 Å, O...O = 2.585 Å, and O—H...O = 160.5°]. In the crystal structure, the molecules are packed, with their planar skeletons planar to one another, into columns.

Related literature

For background literature and synthesis details, see: Pinto *et al.* (2005); Epifano *et al.* (2007) and Castanheiro *et al.* (2008, 2009). For related structures, see: Gales *et al.* (2001, 2005a,b)

Computing details

Data collection: XCALIBUR PX ULTRA, CrysAlis software; cell refinement: CrysAlis software; data reduction: *CrysAlis RED* application; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97* (Sheldrick, 1997).

1-Hydroxy-3-(3-methylbut-2-enyloxy)xanthone

Crystal data

C ₁₈ H ₁₆ O ₅	$\gamma = 79.039 (6)^\circ$
$M_r = 296.31$	$V = 735.54 (9) \text{ \AA}^3$
Triclinic, $P\bar{1}$	$Z = 2$
$a = 4.8199 (3) \text{ \AA}$	Mo $K\alpha$ radiation
$b = 11.7014 (8) \text{ \AA}$	$\mu = 0.09 \text{ mm}^{-1}$
$c = 13.6176 (10) \text{ \AA}$	$T = 295 \text{ K}$
$\alpha = 77.329 (6)^\circ$	$0.4 \times 0.2 \times 0.1 \text{ mm}$

Acta E preprint

$$\beta = 88.582 (6)^\circ$$

Data collection

Gemini PX Ultra CCD area-detector
diffractometer

2981 independent reflections

Absorption correction: none

1958 reflections with $I > 2\sigma(I)$

8520 measured reflections

$$R_{\text{int}} = 0.017$$

Refinement

$$R[F^2 > 2\sigma(F^2)] = 0.058$$

239 parameters

$$wR(F^2) = 0.191$$

H atoms treated by a mixture of
independent and constrained refinement

$$S = 1.09$$

$$\Delta\rho_{\text{max}} = 0.27 \text{ e } \text{\AA}^{-3}$$

2981 reflections

$$\Delta\rho_{\text{min}} = -0.23 \text{ e } \text{\AA}^{-3}$$

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References

- Castanheiro, R. A. P., Pinto, M. M. M., Silva, A. M. S., Cravo, S. M. M., Gales, L., Damas, A. M., Pedro, M. M., Nazareth, N., Nascimento, M. S. J. & Eaton, G. (2007). *Bioorg. Med. Chem.* 15, 6080-6088.
- Castanheiro, R. A. P., Pinto, M. M. M., Cravo, S. M. M., Pinto, D. C. G. A., Silva, A. M. S. & Kijjoo, A. (2009). *Tetrahedron* accepted for publication, DOI information: 10.1016/j.tet.2009.03.019.
- Epifano, F., Genovese, S., Menghini, L. & Curini, M. (2007). *Phytochemistry* 68, 939-953.
- Farrugia, L. J. (1997). *J. Appl. Cryst.* 30, 565.
- Gales, L., Sousa, M. E., Pinto, M. M., Kijjoo, A. & Damas, A. M. (2001). *Acta Cryst.* C57, 1319-1323.
- Gales, L. & Damas, A. M. (2005). *Curr. Med. Chem.* 12, 2499-2515.
- Gales, L., Sousa, M. E., Pinto, M. M. & Damas, A. M. (2005). *Acta Cryst.* E61, o2213-o2215.
- Pinto, M. M., Sousa, M. E. & Nascimento, M. S. (2005). *Curr. Med. Chem.* 12, 2517-2538.
- Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.

supplementary materials

1-Hydroxy-3-(3-methylbut-2-enyloxy)xanthone

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Comment

Prenylated xanthenes have been reported to mediate some important biological activities, concerning a large variety of targets with therapeutic value. Microwave irradiation was used for the first time to the synthesis of this prenylated xanthone. In fact, microwave-assisted heating under controlled conditions is an invaluable technology for medicinal chemistry because it often dramatically reduces reaction times.

Experimental

Prenylation was carried out using prenyl bromide in alkaline medium.

Refinement

Non-hydrogen atoms were refined anisotropically. The C4AX- and C4BX-bound hydrogen atoms were positioned with idealized geometry and refined on their parent carbon atom at distances of 0.96 Å, with $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$; the other hydrogen atoms were refined freely with isotropic displacement parameters.

Figures

Fig. 1. Molecular structure of the title compound with displacement ellipsoids shown at 50% probability for non-H atoms.

1-Hydroxy-3-(3-methylbut-2-enyloxy)xanthone

Crystal data

$\text{C}_{18}\text{H}_{16}\text{O}_4$	$Z = 2$
$M_r = 296.31$	$F_{000} = 312$
Triclinic, $P\bar{1}$	$D_x = 1.338 \text{ Mg m}^{-3}$
Hall symbol: -P 1	Mo $K\alpha$ radiation radiation
$a = 4.8199 (3) \text{ \AA}$	$\lambda = 0.71073 \text{ \AA}$
$b = 11.7014 (8) \text{ \AA}$	Cell parameters from 1141 reflections
$c = 13.6176 (10) \text{ \AA}$	$\theta = 4.0\text{--}24.3^\circ$
$\alpha = 77.329 (6)^\circ$	$\mu = 0.09 \text{ mm}^{-1}$
$\beta = 88.582 (6)^\circ$	$T = 295 \text{ K}$
$\gamma = 79.039 (6)^\circ$	Plate, yellow
$V = 735.54 (9) \text{ \AA}^3$	$0.4 \times 0.2 \times 0.1 \text{ mm}$

Data collection

Gemini PX Ultra CCD area-detector	1958 reflections with $I > 2\sigma(I)$

supplementary materials

diffractometer

Radiation source: fine-focus sealed tube

Monochromator: graphite

$T = 293$ K

ω and θ scans

Absorption correction: none

8520 measured reflections

2981 independent reflections

$$R_{\text{int}} = 0.017$$

$$\theta_{\text{max}} = 26.4^\circ$$

$$\theta_{\text{min}} = 2.6^\circ$$

$$h = -5 \rightarrow 6$$

$$k = -14 \rightarrow 14$$

$$l = -17 \rightarrow 16$$

Refinement

Refinement on F^2

Least-squares matrix: full

$$R[F^2 > 2\sigma(F^2)] = 0.058$$

$$wR(F^2) = 0.191$$

$$S = 1.09$$

2981 reflections

239 parameters

Primary atom site location: structure-invariant direct methods

Secondary atom site location: difference Fourier map

Hydrogen site location: inferred from neighbouring sites

H atoms treated by a mixture of independent and constrained refinement

$$w = 1/[\sigma^2(F_o^2) + (0.0996P)^2 + 0.1285P]$$

$$\text{where } P = (F_o^2 + 2F_c^2)/3$$

$$(\Delta/\sigma)_{\text{max}} < 0.001$$

$$\Delta\rho_{\text{max}} = 0.27 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\text{min}} = -0.23 \text{ e } \text{\AA}^{-3}$$

Extinction correction: none

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R -factor wR and goodness of fit S are based on F^2 , conventional R -factors R are based on F , with F set to zero for negative F^2 . The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating R -factors(gt) etc. and is not relevant to the choice of reflections for refinement. R -factors based on F^2 are statistically about twice as large as those based on F , and R -factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\text{\AA}^2$)

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
O10	0.1165 (3)	0.91548 (13)	0.36926 (11)	0.0547 (4)
C4	-0.1958 (5)	0.8489 (2)	0.49239 (16)	0.0536 (5)
C9A	-0.0291 (4)	0.72849 (18)	0.36981 (15)	0.0484 (5)
C3	-0.3524 (4)	0.76272 (19)	0.53769 (15)	0.0518 (5)
C4A	-0.0375 (4)	0.82959 (18)	0.41066 (15)	0.0476 (5)
C10A	0.2789 (4)	0.9025 (2)	0.28666 (15)	0.0512 (5)
O2	-0.4984 (3)	0.78583 (14)	0.61965 (12)	0.0644 (5)
O1	-0.2014 (4)	0.54763 (14)	0.38056 (14)	0.0688 (5)
C9	0.1391 (4)	0.7111 (2)	0.28356 (17)	0.0541 (5)

C8A	0.2964 (4)	0.80569 (19)	0.24173 (15)	0.0513 (5)
C2	−0.3536 (5)	0.6616 (2)	0.49979 (16)	0.0534 (5)
C1	−0.1952 (4)	0.64512 (18)	0.41735 (17)	0.0518 (5)
O11	0.1485 (4)	0.62249 (15)	0.24578 (14)	0.0726 (5)
C5	0.4288 (5)	0.9926 (2)	0.25011 (18)	0.0612 (6)
C8	0.4660 (5)	0.8009 (2)	0.15763 (18)	0.0629 (6)
C1X	−0.6458 (6)	0.6951 (2)	0.67345 (19)	0.0642 (7)
C6	0.5920 (5)	0.9855 (2)	0.16691 (19)	0.0686 (7)
C7	0.6119 (6)	0.8900 (2)	0.12033 (19)	0.0691 (7)
C2X	−0.7943 (6)	0.7402 (2)	0.7580 (2)	0.0712 (7)
C3X	−0.8476 (5)	0.6756 (2)	0.84543 (17)	0.0632 (6)
C4AX	−1.0140 (7)	0.7282 (3)	0.9247 (2)	0.0982 (10)
H4A1	−1.0295	0.6660	0.9825	0.147*
H4A2	−1.1994	0.7669	0.8986	0.147*
H4A3	−0.9195	0.7854	0.9438	0.147*
C4BX	−0.7566 (8)	0.5421 (3)	0.8721 (2)	0.1020 (11)
H4B1	−0.8165	0.5118	0.9390	0.153*
H4B2	−0.5545	0.5215	0.8692	0.153*
H4B3	−0.8408	0.5077	0.8253	0.153*
H2	−0.452 (5)	0.600 (2)	0.5299 (17)	0.064 (6)*
H4	−0.190 (5)	0.919 (3)	0.5185 (19)	0.076 (7)*
H6	0.683 (6)	1.050 (3)	0.141 (2)	0.087 (8)*
H5	0.412 (5)	1.053 (2)	0.2821 (19)	0.072 (7)*
H8	0.475 (5)	0.733 (2)	0.1245 (19)	0.069 (7)*
H7	0.725 (6)	0.894 (3)	0.065 (2)	0.092 (9)*
H1XA	−0.500 (5)	0.619 (2)	0.7018 (17)	0.066 (7)*
H1XB	−0.781 (6)	0.683 (3)	0.624 (2)	0.100 (9)*
H1	−0.076 (6)	0.556 (3)	0.334 (2)	0.082 (9)*
H2X	−0.873 (5)	0.831 (3)	0.7432 (19)	0.082 (8)*

Atomic displacement parameters ($\text{\AA}^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O10	0.0633 (9)	0.0528 (9)	0.0573 (8)	−0.0240 (7)	0.0174 (7)	−0.0223 (7)
C4	0.0636 (13)	0.0487 (12)	0.0574 (12)	−0.0212 (10)	0.0108 (10)	−0.0223 (10)
C9A	0.0485 (11)	0.0466 (12)	0.0529 (11)	−0.0093 (9)	−0.0036 (9)	−0.0158 (9)
C3	0.0570 (12)	0.0503 (12)	0.0522 (12)	−0.0163 (10)	0.0041 (10)	−0.0149 (9)
C4A	0.0512 (11)	0.0429 (11)	0.0519 (11)	−0.0136 (9)	0.0022 (9)	−0.0135 (9)
C10A	0.0507 (11)	0.0533 (12)	0.0505 (11)	−0.0099 (9)	0.0048 (9)	−0.0138 (9)
O2	0.0803 (10)	0.0635 (10)	0.0616 (9)	−0.0345 (8)	0.0254 (8)	−0.0244 (7)
O1	0.0853 (12)	0.0527 (10)	0.0811 (12)	−0.0269 (9)	0.0125 (10)	−0.0308 (8)
C9	0.0536 (12)	0.0522 (13)	0.0609 (13)	−0.0071 (10)	−0.0019 (10)	−0.0244 (10)
C8A	0.0493 (11)	0.0557 (13)	0.0500 (11)	−0.0054 (9)	0.0031 (9)	−0.0178 (10)
C2	0.0591 (13)	0.0479 (12)	0.0578 (13)	−0.0205 (10)	0.0014 (10)	−0.0123 (10)
C1	0.0563 (12)	0.0426 (11)	0.0602 (12)	−0.0122 (9)	−0.0054 (10)	−0.0159 (9)
O11	0.0791 (11)	0.0665 (11)	0.0864 (12)	−0.0190 (8)	0.0152 (9)	−0.0438 (9)
C5	0.0686 (15)	0.0567 (14)	0.0628 (14)	−0.0194 (11)	0.0140 (11)	−0.0178 (11)
C8	0.0666 (14)	0.0671 (15)	0.0564 (13)	−0.0068 (12)	0.0053 (11)	−0.0221 (12)

supplementary materials

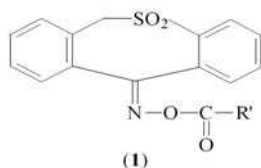
C1X	0.0757 (16)	0.0565 (15)	0.0645 (14)	−0.0260 (13)	0.0186 (13)	−0.0120 (12)
C6	0.0737 (16)	0.0662 (16)	0.0642 (14)	−0.0198 (13)	0.0164 (12)	−0.0069 (12)
C7	0.0736 (16)	0.0781 (18)	0.0542 (13)	−0.0119 (13)	0.0176 (12)	−0.0152 (12)
C2X	0.0772 (16)	0.0595 (16)	0.0788 (17)	−0.0194 (13)	0.0285 (13)	−0.0170 (13)
C3X	0.0727 (15)	0.0588 (14)	0.0614 (14)	−0.0208 (11)	0.0114 (11)	−0.0136 (11)
C4AX	0.126 (2)	0.084 (2)	0.0877 (19)	−0.0267 (18)	0.0455 (18)	−0.0227 (16)
C4BX	0.157 (3)	0.0733 (19)	0.0724 (18)	−0.0241 (19)	0.0241 (19)	−0.0104 (14)

Geometric parameters (Å, °)

O10—C10A	1.374 (2)	C5—C6	1.372 (4)
O10—C4A	1.376 (2)	C5—H5	0.90 (3)
C4—C4A	1.369 (3)	C8—C7	1.367 (4)
C4—C3	1.400 (3)	C8—H8	0.99 (3)
C4—H4	0.97 (3)	C1X—C2X	1.483 (4)
C9A—C4A	1.407 (3)	C1X—H1XA	1.03 (3)
C9A—C1	1.416 (3)	C1X—H1XB	1.00 (3)
C9A—C9	1.440 (3)	C6—C7	1.388 (4)
C3—O2	1.355 (3)	C6—H6	0.94 (3)
C3—C2	1.392 (3)	C7—H7	0.91 (3)
C10A—C5	1.387 (3)	C2X—C3X	1.311 (3)
C10A—C8A	1.389 (3)	C2X—H2X	1.03 (3)
O2—C1X	1.446 (3)	C3X—C4AX	1.499 (4)
O1—C1	1.348 (3)	C3X—C4BX	1.505 (4)
O1—H1	0.86 (3)	C4AX—H4A1	0.9600
C9—O11	1.247 (3)	C4AX—H4A2	0.9600
C9—C8A	1.465 (3)	C4AX—H4A3	0.9600
C8A—C8	1.396 (3)	C4BX—H4B1	0.9600
C2—C1	1.370 (3)	C4BX—H4B2	0.9600
C2—H2	0.95 (3)	C4BX—H4B3	0.9600
C10A—O10—C4A	119.45 (17)	C7—C8—C8A	120.4 (2)
C4A—C4—C3	118.0 (2)	C7—C8—H8	120.8 (14)
C4A—C4—H4	119.4 (15)	C8A—C8—H8	118.8 (14)
C3—C4—H4	122.5 (15)	O2—C1X—C2X	107.6 (2)
C4A—C9A—C1	116.74 (19)	O2—C1X—H1XA	108.9 (13)
C4A—C9A—C9	121.58 (19)	C2X—C1X—H1XA	109.3 (13)
C1—C9A—C9	121.67 (19)	O2—C1X—H1XB	106.2 (17)
O2—C3—C2	123.68 (19)	C2X—C1X—H1XB	111.9 (17)
O2—C3—C4	114.97 (19)	H1XA—C1X—H1XB	113 (2)
C2—C3—C4	121.3 (2)	C5—C6—C7	121.4 (2)
C4—C4A—O10	116.22 (18)	C5—C6—H6	117.1 (18)
C4—C4A—C9A	122.98 (19)	C7—C6—H6	121.4 (18)
O10—C4A—C9A	120.81 (18)	C8—C7—C6	119.7 (2)
O10—C10A—C5	115.8 (2)	C8—C7—H7	126 (2)
O10—C10A—C8A	123.08 (19)	C6—C7—H7	114.5 (19)
C5—C10A—C8A	121.2 (2)	C3X—C2X—C1X	126.3 (3)
C3—O2—C1X	116.93 (17)	C3X—C2X—H2X	118.2 (14)
C1—O1—H1	100 (2)	C1X—C2X—H2X	115.4 (14)
O11—C9—C9A	122.7 (2)	C2X—C3X—C4AX	122.7 (2)

O11—C9—C8A	121.9 (2)	C2X—C3X—C4BX	122.4 (2)
C9A—C9—C8A	115.42 (19)	C4AX—C3X—C4BX	114.8 (2)
C10A—C8A—C8	118.8 (2)	C3X—C4AX—H4A1	109.5
C10A—C8A—C9	119.65 (19)	C3X—C4AX—H4A2	109.5
C8—C8A—C9	121.5 (2)	H4A1—C4AX—H4A2	109.5
C1—C2—C3	119.4 (2)	C3X—C4AX—H4A3	109.5
C1—C2—H2	116.8 (15)	H4A1—C4AX—H4A3	109.5
C3—C2—H2	123.8 (15)	H4A2—C4AX—H4A3	109.5
O1—C1—C2	118.73 (19)	C3X—C4BX—H4B1	109.5
O1—C1—C9A	119.7 (2)	C3X—C4BX—H4B2	109.5
C2—C1—C9A	121.55 (19)	H4B1—C4BX—H4B2	109.5
C6—C5—C10A	118.5 (2)	C3X—C4BX—H4B3	109.5
C6—C5—H5	123.4 (16)	H4B1—C4BX—H4B3	109.5
C10A—C5—H5	118.0 (16)	H4B2—C4BX—H4B3	109.5
C4A—C4—C3—O2	178.36 (17)	C9A—C9—C8A—C10A	0.9 (3)
C4A—C4—C3—C2	−1.5 (3)	O11—C9—C8A—C8	−0.3 (3)
C3—C4—C4A—O10	−179.07 (17)	C9A—C9—C8A—C8	−179.45 (18)
C3—C4—C4A—C9A	1.0 (3)	O2—C3—C2—C1	−178.92 (19)
C10A—O10—C4A—C4	−179.57 (17)	C4—C3—C2—C1	0.9 (3)
C10A—O10—C4A—C9A	0.4 (3)	C3—C2—C1—O1	−179.07 (19)
C1—C9A—C4A—C4	0.1 (3)	C3—C2—C1—C9A	0.2 (3)
C9—C9A—C4A—C4	179.80 (19)	C4A—C9A—C1—O1	178.54 (18)
C1—C9A—C4A—O10	−179.84 (17)	C9—C9A—C1—O1	−1.1 (3)
C9—C9A—C4A—O10	−0.2 (3)	C4A—C9A—C1—C2	−0.7 (3)
C4A—O10—C10A—C5	−179.57 (18)	C9—C9A—C1—C2	179.59 (18)
C4A—O10—C10A—C8A	0.1 (3)	O10—C10A—C5—C6	−179.1 (2)
C2—C3—O2—C1X	4.4 (3)	C8A—C10A—C5—C6	1.2 (4)
C4—C3—O2—C1X	−175.4 (2)	C10A—C8A—C8—C7	0.0 (3)
C4A—C9A—C9—O11	−179.6 (2)	C9—C8A—C8—C7	−179.7 (2)
C1—C9A—C9—O11	0.1 (3)	C3—O2—C1X—C2X	−178.8 (2)
C4A—C9A—C9—C8A	−0.5 (3)	C10A—C5—C6—C7	−0.9 (4)
C1—C9A—C9—C8A	179.17 (18)	C8A—C8—C7—C6	0.3 (4)
O10—C10A—C8A—C8	179.61 (18)	C5—C6—C7—C8	0.1 (4)
C5—C10A—C8A—C8	−0.8 (3)	O2—C1X—C2X—C3X	−149.0 (3)
O10—C10A—C8A—C9	−0.7 (3)	C1X—C2X—C3X—C4AX	−176.4 (3)
C5—C10A—C8A—C9	178.9 (2)	C1X—C2X—C3X—C4BX	1.0 (5)
O11—C9—C8A—C10A	−180.0 (2)		

ANEXO VIII



where R' = monosubstituted aryl

The original compounds were obtained in 4 steps starting from the 6,11-dihydro-dibenzo[b,e]thiepin-11(6H)-one

The structures were elucidated by elemental analysis and spectral analysis. (proton and carbon NMR, IR).

The *in vitro* antimicrobial activity of some new compounds was tested; promising results were observed.

P219

NOVEL POTENTIAL NEUROPROTECTORS AND COGNITION ENHANCERS FROM NMDA-RECEPTOR ANTAGONISTS CLASS

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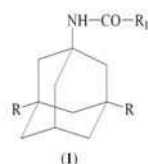
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Excitotoxicity has a main role in the pathogenesis of neurodegenerative diseases (as Alzheimer disease). An aberrant release of glutamate and a consequent overstimulation of glutamate receptors lead to brain cells death

Therefore, a major strategy has been focused on the search of agents able to antagonize the effects of glutamate (especially NMDA receptors antagonists).

Accordingly these researches, we obtained new original amino-adamantane derivatives with the general formula (1)



where R = H, CH₃

R₁ = mono- and disubstituted aryl

The new compounds were obtained by the acylation reaction of amino group from 1-aminoadamantane or 1-amino-3,5-dimethyl-adamantane (memantine) with chloride of substituted benzoic acids

The obtained compounds have been characterized by their physical properties. Their chemical structures were elucidated by elemental analysis, IR and ¹H- and ¹³C-NMR spectra.

The biological preliminary investigations by Y labyrinth test and by modified black and white box test were begun for some compounds.

P220

OPTIMIZATION OF SYNTHETIC METHODOLOGIES OF BIOLOGICAL ACTIVE PRENYLATED XANTHONES

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One of the main aims of drug optimization is to maximize interactions of the molecule with its target-binding site in order to improve activity and selectivity as well as minimize side effects.

Our research group has been focusing on the synthesis of prenylated xanthones because of their interesting activities, namely antitumor [1-2]. Although the oxygenation pattern of these derivatives can play an important role in their biological activity, the presence of the prenyl side chains seems also to be associated with this activity. Many properties of these compounds are thought to reside in their enhanced interaction with biological membranes and with target proteins when compared with their non-prenylated analogs [3]. For that reason, we have recently obtained prenylated xanthones through a classical prenylation method and evaluate their effect on the *in vitro* growth of human tumor cell lines [4]. In order to optimize the synthetic process to obtain these compounds, microwave assisted organic synthesis was used. Thus, we have obtained the prenylated derivatives **3-8**, by the reaction of dihydroxyxanthones **1-2** with prenyl bromide under microwave irradiation (**Fig.1**). The dihydrofuranoxanthones **9** and **10-11**, were also obtained by microwaves (MW), through Claisen rearrangement of monoprenylated derivatives **3** and **5**, respectively (**Fig.1**).

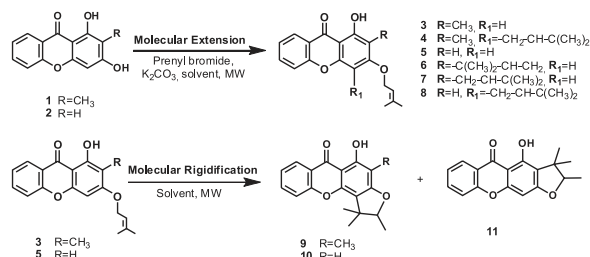


Fig. 1: General procedure for the synthesis of xanthone derivatives by microwave irradiation.

The effect of compounds **3-11** on the *in vitro* growth of three human tumor cell lines: MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung) and SF-268 (cen-

tral nervous system) showed for xanthonenes **6** and **7** a selective and potent growth inhibitory activity against the MCF-7 cell line, comparing with respective building block **2** [4]. Compounds **9-11** are undergoing biological assays.

References

- [1] Pinto, M., *et al. Curr. Med. Chem.* 2005, 12, 2517
- [2] Pinto, M.; Castanheiro, R.; "Natural Prenylated Xanthonenes: Chemistry and Biological Activities" in *Natural Products: Chemistry, Biochemistry and Pharmacology*, Ed. Brahmachari, G., Narosa Publishing House PVT. LTD., Nova Deli, India, 2007, chap. 17, *accepted for publication*
- [3] F. Epifano, *et al. Phytochemistry* 2007, 68, 939.
- [4] Castanheiro, R., *et al. Bioorg. Med. Chem.* 2007, 15, 6080.

Acknowledgments

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P221

CLASSIFICATION OF INSULIN RECEPTOR ACTIVATORS WITH SELF-ORGANIZING MAPS

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The binding of insulin to the extracellular part of the insulin receptor is a key step in the insulin signalling pathway. Upon binding, the receptor is autophosphorylated and the intracellular tyrosine kinase is activated. In 1999, Zhang *et al.* discovered a small molecule from a fungal extract which activates the human insulin receptor by binding directly to its intracellular domain [1]. This compound (L-783,281 or demethylasterriquinone B-1, DMAQ-B1) was shown to lower blood glucose levels in mouse models of type 2 diabetes mellitus.

During the last years, approximately 100 derivatives of this compound have been synthesized (e.g. [2] and [3]), most of them containing the original quinone substructure. Since this structural group might cause toxic side effects in long-term administration it would be beneficial to find active compounds with a different type of structure.

A method which was successfully used for finding new types of scaffolds is the clustering of compounds with self-organizing maps. This artificial neural network places objects with similar features into the same region of a map. The learning algorithm is unsupervised i.e. the group which the object belongs to is not known to the network at the time of training.

In this study, DMAQ-B1 and its derivatives were categorized as active or inactive according to their reported biological activity. Different sets of chemical descriptors were used as input vector for a self-organizing map.

These descriptors include general descriptors and subdivided van der Waals surface areas calculated with MOE (Chemical Computing Group) as well as 2D property-weighted autocorrelation vectors calculated with ADRI-ANA.Code (Molecular Networks). Varying map sizes and lengths of training were investigated. The resulting maps were examined on their ability to separate active and inactive compounds. This was done by calculating mathematical scores like the true-positive- and the true-negative-rate but also by visually inspection of the maps. Especially the 2D autocorrelation descriptors performed well in correctly classifying the compounds and may thus provide a versatile concept for virtual screening of databases for new activators of the insulin receptor.

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References

- [1] Zhang B, Salituro G, Szalkowski D, Li Z, Zhang Y, Royo I, Vilella D, Díez MT, Pelaez F, Rubi C, Kendall RL, Mao X, Griffin P, Calaycay J, Zierath JR, Heck JV, Smith RG, Moller DE. Discovery of a Small Molecule Insulin Mimetic with Antidiabetic Activity in Mice. *Science*. 1999;284(5416):974-7
- [2] Wood HB Jr, Black R, Salituro G, Szalkowski D, Li Z, Zhang Y, Moller DE, Zhang B, Jones AB. The basal SAR of a novel insulin receptor activator. *Bioorg Med Chem Lett*. 2000;10(11):1189-92
- [3] Pirrung MC, Liu Y, Deng L, Halstead DK, Li Z, May JF, Wedel M, Austin DA, Webster NJ. Methyl scanning: total synthesis of demethylasterriquinone B1 and derivatives for identification of sites of interaction with and isolation of its receptor(s). *J Am Chem Soc*. 2005;127(13):4609-24

P222

NEW ANTIMICROBIAL AGENTS: SYNTHESIS, IDENTIFICATION, AND BIOLOGICAL SCREENING

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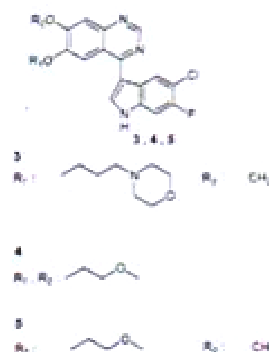
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The development of resistance to current antimicrobials continues to be a serious difficulty in the treatment of infectious diseases. Therefore, from day to day, the design and synthesis of new compounds having antimicrobial activity has become a high priority in biomedical research and continues to attract the attention of many scientists.

ANEXO IX



We present the syntheses of the compounds **3**, **4** and **5** in which the 4-anilino-moiety is exchanged by a substituted 3-indolyl heterocycle. Compounds **3**, **4** and **5** represents a more fundamental change in the pharmacophore and claim an excellent EGFR-tyrosine kinase- and a HER-2-tyrosine kinase inhibition activity.

A detailed discussion of the synthetic results will be presented together with NMR-spectral and x-ray results.

P231

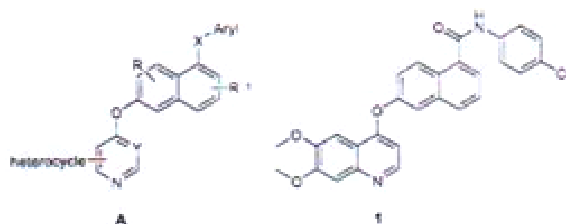
1,6-Naphthyls as a new class of potent KDR inhibitors

M. Potashman, M. Bajpai, D. Bauer, S. Bellon, G. Borg, J. Bready, D. Choquette, A. Coxon, T. DeMelfi, L. DiPietro, N. Doerr, J. Estrada, S. Flynn, J. Germain, J.C. Harmange, D. La, M. Morrison, V. Patel, S. Van Der Plas, A. Polverino, M. Potashman, D. Powers, C. Starnes, M. Weiss, D. Whittington, R. Zanon

AMGEN INC, Cambridge, MA; AMGEN INC, Thousand Oaks, CA.

Inhibition of VEGF-mediated angiogenesis has proven to be an effective therapeutic approach to treating human tumors in clinical trials. Endothelial cell proliferation and migration, two crucial steps in angiogenesis, are mediated through a specific VEGF receptor, the Kinase insert Domain containing Receptor (KDR). Inhibition of KDR kinase activity by small molecules has been shown to be a very promising way to interdict this VEGF pathway in human cancers.

Using a structure-based drug design approach, we identified a new series of KDR inhibitors. We will present the structure activity relationship for a series of 1,6-naphthyl-based KDR inhibitors (**A**). The pharmacokinetic properties and pharmacology of lead compound **1** will also be discussed.



P232

Inhibition of alpha, beta, delta, heta and zeta Protein Kinase C Isoforms by Xanthenes: Improvements Towards Selectivity

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The PKC isoenzymes are related to very important biological actions mainly in tumorigenesis. Clarification of the role of individual PKC isoforms in the cell has been difficult by the lack of selective PKC activators and inhibitors [1]. Xanthone derivatives have been reported to mediate several important biological activities, namely PKC modulation [2-4]. Molecular modifications in the xanthone scaffold were developed in order to improve potency and/or selectivity towards PKC modulation on the activators **1-2** and inhibitors **3-4** (Fig. 1).

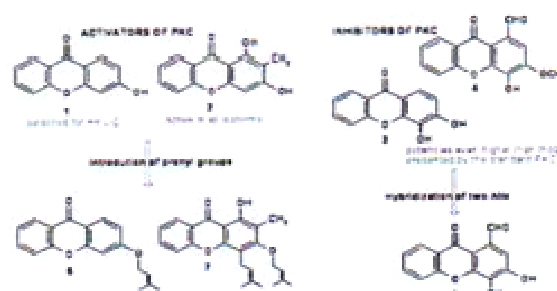


Fig. 1. Strategy for improving potency /selectivity in PKC modulators.

The modulatory activity of 1-formyl-3,4-dihydroxyxanthone (**5**) and two prenylated xanthone derivatives (**6-7**) on isoforms α , β , δ , η and ζ of protein kinase C (PKC) was evaluated using an *in vivo* yeast assay. Xanthenes **5** and **7** caused an effect compatible with PKC inhibition, similar to that elicited by known PKC inhibitors (chelerythrine and NPC 15437), and presented differences on their potency and selectivity towards the distinct isoforms tested. The present results revealed 1-hydroxy-2-methyl-4-(3-methylbut-2-enyl)-3-(3-methylbut-2-enyloxy) (**7**) xanthone as a new η -isoform-specific PKC inhibitor.

[1] Webb BLJ, Hirst SJ, Giembyez MA. Br J Pharmacol 2000;130:1433-1452.

[2] Saraiva L, Fresco P, Pinto E, Sousa E, Pinto M, Gonçalves J. Bioorg Med Chem 2003;11:1215-1225.

[3] Saraiva L, Fresco P, Pinto E, Sousa E, Pinto M, Gonçalves J. Bioorg Med Chem 2002;10:3219-3227.

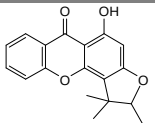
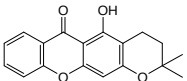
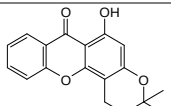
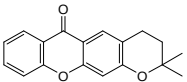
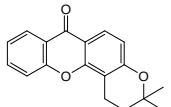
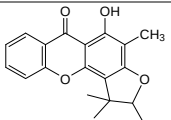
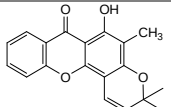
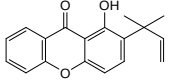
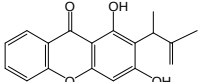
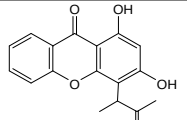
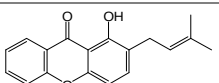
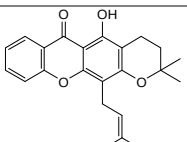
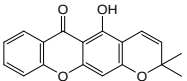
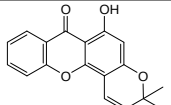
[4] Saraiva L, Fresco P, Pinto E, Sousa E, Pinto M, Gonçalves J. J Enzyme Inhib Med Chem 2003;18:357-370.

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ANEXO X

Anexo de Estruturas

Nome IUPAC	Nome Trivial	Estrutura	Sigla X e XP na Tese	Número correspondente no artigo		
				Anexo IV	Anexo V	Anexo VI
1,3-di-hidroxi-2-metil-9H-xanten-9-ona	1,3-di-hidroxi-2-metilxantona		X1	1	1	1
1-hidroxi-9H-xanten-9-ona	1-hidroxixantona		X2	-	9	-
3-hidroxi-9H-xanten-9-ona	3-hidroxixantona		X20	-	-	3
1,3-di-hidroxi-9H-xanten-9-ona	1,3-di-hidroxixantona		X38	2	2	2
1-hidroxi-2-metil-4-(3-metilbut-2-enil)-3-(3-metilbut-2-eniloxi)-9H-xanten-9-ona	1-hidroxi-2-metil-4-(3-metilbut-2-enil)-3-(3-metilbut-2-eniloxi)xantona		XP1	3	-	5
1-hidroxi-2-metil-3-(3-metilbut-2-eniloxi)-9H-xanten-9-ona	1-hidroxi-2-metil-3-(3-metilbut-2-eniloxi)xantona		XP2	4	-	4
1-hidroxi-3-(3-metilbut-2-eniloxi)-9H-xanten-9-ona	1-hidroxi-3-(3-metilbut-2-eniloxi)xantona		XP3	5	-	6
1-hidroxi-3-(3-metilbut-2-eniloxi)-2-(1,1-dimetilprop-2-enil)-9H-xanten-9-ona	1-hidroxi-3-(3-metilbut-2-eniloxi)-2-(1,1-dimetilprop-2-enil)xantona		XP4	6	-	7
1-hidroxi-2-(3-metilbut-2-enil)-3-(3-metilbut-2-eniloxi)-9H-xanten-9-ona	1-hidroxi-2-(3-metilbut-2-enil)-3-(3-metilbut-2-eniloxi)xantona		XP5	7	-	8
3-(3-metilbut-2-eniloxi)-9H-xanten-9-ona	3-(3-metilbut-2-eniloxi)xantona		XP6	-	-	10
1-hidroxi-4-(3-metilbut-2-enil)-3-(3-metilbut-2-eniloxi)-9H-xanten-9-ona	1-hidroxi-4-(3-metilbut-2-enil)-3-(3-metilbut-2-eniloxi)xantona		XP7	8	-	9
6-hidroxi-3,3,5-trimetil-2,3-di-hidropirano[2,3-c]xanten-7(1H)-ona	1-hidroxi-2,6',6'-trimetil-4',5'-di-hidropirano (2',3':3,4) xantona		XP8	9	3	16
4-hidroxi-2,3,3-trimetil-2,3-di-hidrofuro[3,2-b]xanten-5-ona	1-hidroxi-4',4',5'-trimetil-4',5'-di-hidrofurano (2',3':3,2) xantona		XP9	-	-	12

Nome IUPAC	Nome Trivial	Estrutura	Sigla X e XP na Tese	Número correspondente no artigo		
				Anexo IV	Anexo V	Anexo VI
5-hidroxi-1,1,2-trimetil-1,2-dihidrofuro[2,3-c] xanten-6-ona	1-hidroxi-4',4',5'-trimetil-4',5'-dihidrofurano (2',3':3,4) xantona		XP10	-	-	13
5-hidroxi-2,2-dimetil-3,4-dihidropirano [3,2-b] xanten-6(2H)-ona	1-hidroxi-6',6'-dimetil-4',5'-dihidropirano (2',3':3,2) xantona		XP11	11	5	18
6-hidroxi-3,3-dimetil-2,3-dihidropirano[2,3-c] xanten-7(1H)-ona	1-hidroxi-6',6'-dimetil-4',5'-dihidropirano (2',3':3,4) xantona		XP12	10	4	17
2,2-dimetil-3,4-dihidropirano[3,2-b] xanten-6(2H)-ona	6',6'-dimetil-4',5'-dihidropirano (2',3':3,2) xantona		XP16	-	-	20
3,3-dimetil-2,3-dihidropirano[2,3-c] xanten-7(1H)-ona	6',6'-dimetil-4',5'-dihidropirano (2',3':3,4) xantona		XP17	-	-	19
5-hidroxi-1,1,2,4-tetrametil-1,2-dihidrofuro[2,3-c] xanten-6-ona	1-hidroxi-2,4',4',5'-tetrametil-4',5'-dihidrofurano (2',3':3,4) xantona		XP18	-	-	11
6-hidroxi-3,3,5-trimetilpirano[2,3-c] xanten-7(3H)-ona	1-hidroxi-2,6',6'-trimetilpirano (2',3':3,4) xantona		XP19	-	6	-
1-hidroxi-2-(1,1-dimetilprop-2-enil)-9H-xanten-9-ona	1-hidroxi-2-(1,1-dimetilprop-2-enil)xantona		XP20	-	10	-
1,3-di-hidroxi-2-(1,2-dimetilprop-2-enil)-9H-xanten-9-ona	1,3-di-hidroxi-2-(1,2-dimetilprop-2-enil)xantona		XP21	-	-	14
1,3-di-hidroxi-4-(1,2-dimetilprop-2-enil)-9H-xanten-9-ona	1,3-di-hidroxi-4-(1,2-dimetilprop-2-enil)xantona		XP22	-	-	15
1-hidroxi-2-(3-metilbut-2-enil)-9H-xanten-9-ona	1-hidroxi-2-(3-metilbut-2-enil)xantona		XP23	-	11	-
5-hidroxi-2,2-dimetil-12-(3-metilbut-2-enil)-3,4-dihidropirano[3,2-b] xanten-6(2H)-ona	1-hidroxi-4-(3-metilbut-2-enil)-6',6'-dimetil-4',5'-dihidropirano (2',3':3,2) xantona		XP24	-	-	21
5-hidroxi-2,2-dimetilpirano[3,2-b] xanten-6(2H)-ona	1-hidroxi-6',6'-dimetilpirano(2',3':3,2) xantona		XP25	-	8	-
6-hidroxi-3,3-dimetilpirano[2,3-c] xanten-7(3H)-ona	1-hidroxi-6',6'-dimetilpirano(2',3':3,4) xantona		XP26	-	7	-