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The potential effect of fluorinated compounds in the treatment of
Alzheimer's disease

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Abstract

Drug development for neurodegenerative diseases such as Alzheimer disease (AD) is a challenge not only due to the cellular molecular mechanisms involved but also because the inherent difficulty of most molecules to cross the blood-brain-barrier (BBB). To overcome these drawbacks, a promising approach is the development of fluorinated molecules and supramolecular assemblies.

This review focus on the therapeutic potential of new fluorinated molecules developed as active and selective agents for AD to achieve the desired properties in terms of pharmacokinetic/pharmacodynamics and BBB targeting. The methods to fluorinate organic molecules are described and a brief characterization of the mechanisms of AD progression and therapeutic approaches are also addressed.

The paradigm of cell biology knowledge and fluorine biochemistry is highlighted, such as organofluorine inhibitors of amyloid fibrillogenesis.

Keywords: Fluorine, Alzheimer's disease, therapeutic drugs, beta amyloid, aggregation mechanism

1. Introduction

Alzheimer's disease (AD) affects more than 35 million people and it is considered the most common form of dementia worldwide. In the United States, the estimates suggest that at every 72 seconds an individual develops AD. In 30 years, this rate probably will increase to one person developing the disease every 33 seconds and the number of people worldwide with the disease is probable to triple by the year of 2050, evidence that this disease is a serious public health problem [1].

The initial symptoms of AD are practically imperceptible and characteristically involve lapses of memory for recent events [2]. In addition, the performance for complex tasks and ability to acquire new information can be reduced [3]. Commonly an emotional control loss is observed in patients with AD, a symptom that may be accompanied by physical or verbal aggression. Over the time, the disease causes a progressive decline of the patient life with intense memory and cognition losses, leading to the immobility of the patients that succumb to respiratory difficulties. Normally, this disorder appears among people over the age of 65 years, with an average of eight year living after the appearance of the first symptoms [4].

Due to the impact of AD on the health care systems and also on the economy in worldwide, strategies for its early detection and treatment are an ambitious challenge in modern medicine. The existing treatments only attenuate the symptoms of the disease and, at the present, no therapies have been clinically proven to effectively prevent the progression of AD [5-15]. The existing therapeutics are all cholinergic agents, explicitly inhibitors of acetylcholinesterase, since AD causes considerable losses in cholinergic neurons [164]. These inhibitors increase the values of acetylcholine to keep the remaining cholinergic neurons. However this type of therapy does not stop the progressive loss of cholinergic neurons keep this therapy ineffective. Nowadays some drugs are commercialized: donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl) that are available as part of care for people with mild-to-moderate AD; and memantine (Ebixa) licensed for the treatment of moderate-to-severe AD [16].

2. The AD disease mechanism

Two pathophysiological hallmarks in the brain characterize this neuropathological disease: intracellular neurofibrillar tangles of hyperphosphorylated tau protein and extracellular accumulation of A β peptide (senile plaques) [3, 17, 18]. The peptide is aggregated as amyloid fibrils within the neuritic plaques and vascular deposits [19-25]. It is generally believed that A β precedes tau in the pathogenesis, i.e., A β causes the tau pathology [26].

The most abundant forms of A β peptide have 40 (~90%) and 42 (~10%) amino acids. From genetic and animal models, scientists have established a causative role of A β in AD [27, 28]. Several evidences indicate that the deposits maybe precede and induce the neuronal atrophy [6, 7, 29].

Nowadays it is believed that the degree of dementia of patients are associated with the concentration of soluble aggregates of the A β peptide [3, 17, 30]. The A β peptide derives from the amyloid precursor protein (APP) by consecutive activities of β - and γ -secretases [31-33], a process explained by a theory that was formulated 20 years ago: the cascade hypothesis [27]. This hypothesis has been the most influential in the AD research conducted by the academia and in the pharmaceutical industry [34].

Originally, when the amyloid cascade hypothesis was presented, the A β peptides and their aggregated forms were suggested to be responsible for initiating cellular events leading to the pathologic effects of AD. According to the first version of the amyloid cascade hypothesis, A β fibrils deposited in amyloid plaques were thought to cause neuronal dysfunction [27, 35]. Recently, studies support that diffusable A β oligomers including protofibrils and prefibrillar aggregates, are the major toxic species during the disease development and progression [36-38].

The transmembrane APP is an integral membrane protein with a single membrane-spanning domain, a large extracellular glycosylated N-terminus and a shorter cytoplasmic C-terminus that is expressed in many tissues and concentrated in the synapses of neurons. APP is produced in several different isomers ranging in size from 695 to 770 a.a.. The shorter sequence is the most abundant form in the brain [39]. This protein can be processed along two main pathways: non-amyloidogenic and amyloidogenic (Figure 1). Enzyme activities involved

in cleavage of APP at the α -, β - and γ -secretase sites have been identified. In the non-amyloidogenic pathway, APP is cleaved in its transmembrane region by the α -secretase, a proteolytic enzyme. This cleavage leads to the formation of a soluble APP fragment (sAPP α) and a C83 carboxy-terminal fragment. During the amyloidogenic pathway, A β is obtained by the cleavage of APP through the sequential actions of β - and γ -secretases. BACE1 (β -site APP-cleaving enzyme 1), a transmembranar aspartyl protease, is the major neuronal β -secretase and cleaves APP in the N-terminus, releasing secreted APP β and the 99-aminoacid C-terminal fragment of APP (C99) [40]. The γ -secretase cleaves the APP in the transmembrane region, produces the C-terminal end in the A β peptide, generating A β peptides ranging in length from 38 to 43 residues [41]. A β_{40} and A β_{42} are the most abundant isoforms [32]. The A β_{42} is characteristically produced by cleavage that occurs in the endoplasmic reticulum, while the A β_{40} is produced by cleavage in the trans-Golgi network [42]. After its production, A β may aggregate into oligomers, fibrils and finally in neurotoxic amyloid plaques by an unknown mechanism. The formation of toxic aggregates induces an inflammatory response and a situation of oxidative stress, which consequently causes the neuronal loss characteristic of AD [43-45].

Figure 1 - Amyloid cascade hypothesis

The sequence of 40 residues is normally produced more abundantly by cells (concentration of secreted $A\beta_{42}$ is 10-fold lower than that of $A\beta_{40}$) and its aggregation kinetic rate is much lower than that of the 42 ($A\beta_{40}$ at 20 μM is stable for 8 days or more whereas $A\beta_{42}$ aggregates immediately) [46, 47]. $A\beta_{42}$ is the most fibrillogenic sequence and is thus associated with disease states. The ratio $A\beta_{42}/A\beta_{40}$ has been related to the progression of AD as its increase is associated to the aggregation of $A\beta_{42}$ and consequently neurotoxicity [36]. The aggregation process of the $A\beta$ peptide conducts to the insoluble fibrils formation, that accumulate in senile plaques, deposits that characterize AD [48, 49]. In this state $A\beta$ is in a β -sheet conformation. The smaller aggregated intermediates are considered one of the more toxic species[3]. This species are called $A\beta$ oligomers. The oligomer process is very fast and is affected by many variables such as pH and temperature making the control of this process very difficult to achieve [50, 51].

This aggregation process has a nucleation-dependent mechanism in which partially folded forms of the peptide associate to form a stable nucleus [52, 53]. This nucleus acts as a template to sequester other intermediates to add to the growing thread of aggregated peptide

forming the protofibrils. The consecutive addition of partially folded intermediates to the ends of the chain leads to the formation of highly structured and insoluble amyloid fibrils. The time course of the conversion of the peptide into fibrils typically includes three phases: lag phase, elongation phase and plateau phase. In the first phase, the lag phase, the unfolding of A β and the formation of oligomers occur, which include β -sheet-rich species that act as nuclei for the formation of mature fibrils. In the elongation phase, once a nucleus is formed, the fibril growth is thought to proceed by the exponentially addition of monomers or oligomers to the growing nucleus. In the last phase, the plateau phase, the maximum fibril growth is reached (Figure 2).

Figure 2 - Representation of the A β peptide aggregation process.

A possible approach to circumvent AD is the inhibition of the β -peptide aggregation and fibrillation. This can be done either by prevention of the α - to- β structural transition through stabilization

of the normal state or by destabilization of the pathological fibrillar structure through the refolding of the β -peptide conformation into an α -helical rich state.

Until now, several groups developed different chemical compounds that inhibit A β aggregation or promote the disaggregation of the already formed fibrils [54-57]. There are several examples of molecules with these properties: β -cyclodextrin, hemin and related porphyrins, anthracycline 4'-iodo-4'-deoxydoxorubicin, hexadecyl-n-methylpiperidinium bromide, rifampicin, (-)-5,8-dihydroxy-3 α -methyl-2 α -(dipropylamino)-1,2,3,4-tetrahydronaphthalene and melatonin (a hormone that crosses the BBB and can block A β fibril formation) [58-60]. Also, it was demonstrated that natural occurring inositol stereoisomers stabilized the small A β aggregates [61].

Pharmacological intervention by inhibiting the function of the γ -secretase and β -secretase with a small molecule, and thus reducing A β levels, has been and remains a possible strategy. Though for AD treatment, the γ -secretase inhibition is a smart strategy, it has led to undesirable adverse events in clinical trials, such as notably gastrointestinal toxicity [62, 63]. These side effects are associated with blocking the processing of Notch, which are a transmembrane receptor signaling protein and also a γ -secretase substrate [64]. The modulation of γ -secretase is a possible strategy to avoid Notch-related toxicity. To selectively inhibit the production of A β_{42} while not affecting the production of A β_{40} or Notch processing, certain non-steroidal anti-inflammatory drugs (NSAIDs) were created [64-69] (figure 3).

Figure 3 - The amyloid cascade hypothesis suggests several possibilities of therapeutic intervention for disease modification [70]. Reprinted with permission from Gotz, J., et al., *Transgenic animal models of Alzheimer's disease and related disorders: Histopathology, behavior and therapy*. Mol Psychiatry, 2004. 9(7): p. 664-683. © 2004, Elsevier.

Regarding to β -secretase, BACE1 is a prime drug target for inhibiting the production of A β . BACE1 is an aspartic protease organized into an extracellular domain with signal peptide, composed by 501 amino acids

length, prodomain and catalytic domain, a transmembrane domain and a short cytoplasmic stretch of 22 amino acids. Its principal cleavage site in the APP extracellular domain forms the N-terminus of A β (position D672 of the longest APP isotype) [71]. The lack of A β generation in the brains of BACE1 deficient mice suggests that the therapeutic inhibition of BACE1 should reduce brain A β levels in humans for the treatment of AD. Additionally, BACE1 inhibitors may not be associated with mechanism-based toxicity [72].

Another attractive strategy to combat the AD is the use of therapeutic peptides (linear molecules with two or more a.a. residues, but less than 100) because of their high biological activity associated with low toxicity and high specificity [73]. These therapeutic peptides have many advantages including little unspecific binding to molecular structures other than the desired target, minimization of drug-drug interactions and negligible accumulation in tissues, reducing risks of complications due to metabolic products [43]. Today, around 70 therapeutic peptides to treat different types of diseases are on the market, 150 in clinical phases and more than 400 in the pre-clinics [73].

Substantial progress has already been made in discovering inhibitors of A β aggregation and a range of peptides, which block amyloid formation, were developed for therapeutic purposes [74-78]. Mostly, the inhibitors are focused on the internal A β sequence 16-22, KLVFFAE, because this region has been reported to be primarily responsible for the self-association and aggregation of the peptide [75, 79].

3. The effect of fluorine on physicochemical and conformational properties

The use of fluorine molecules in medicinal chemistry has been investigated over the last years. Compounds that contain fluorine atoms are of unique interest for medical applications due to their properties [15]. The substitution of various functional groups by fluorine has played and continues to play an important role in the development of more active, efficient and selective agents [80].

In fact, approximately 20%-25% of drugs in the pharmaceutical world contain at least one fluorine atom [15, 81-83]. During the last decades the appearance of fluorinated drugs brought significant advances into drug development, including steroidal and nonsteroidal anti-inflammatory and central nervous system drugs, anticancer agents, and antiviral agents [84, 85]. The drug design using fluorine substitution has culminated in the production of some of the key drugs available on the market. Although, no more than 13 naturally occurring organic compounds have been identified, and the majority of these are higher homologues of the fluoroacetic acid [86, 87]. Fast progress in this field is driven by the development of new fluorination reagents and methods increasing the range of synthetic fluorinated building blocks amenable to functional group manipulation [82, 83].

a. Fluorine properties

As predictable from its place on the periodic table of chemical elements, fluorine has the higher electronegativity in comparison with other halogens and presents a small atomic radius among these elements [80, 88-92]. Its inclusion in a molecule has a very strong effect on the acidity or basicity of proximal functional groups as could be concluded by the analysis of Table 1 [82, 83, 93].

Table 1 - Effect of fluorine substitution on pK_a and pK_b values [93]

Carboxylic acid	pK _a	Amine	pK _b
CH ₃ CO ₂ H	4.76	CH ₃ CH ₂ NH ₂	10.6
CH ₂ FCO ₂ H	2.59	CF ₃ CH ₂ NH ₂	5.7
CHF ₂ CO ₂ H	1.34	C ₆ H ₅ NH ₂	4.6
CF ₃ CO ₂ H	0.52		

b. Fluorine substitution

The use of a fluorine substituent on a stereogenic centre positioned vicinal to another electronegative group significantly influence the molecule conformation [94]. Due to the strong electron withdrawing capabilities of the fluorine, in the monofluorination or trifluoromethylation of saturated alkyl groups a decrease of the lipophilicity is observed. Contrary, the lipophilicity increases with aromatic fluorination, per/polyfluorination and fluorination adjacent to atoms with p-bonds. This phenomenon could be explained by the overlap between the fluorine 2s or 2p orbitals with the corresponding orbitals on carbon, making the C-F bond highly non-polarizable. The log P values analysis confirmed that fluorinated amide has a higher lipophilicity comparatively to its non-fluorinated counterpart (Table 1) [95]. A similar study was performed with fluorinated analogues of HIV-1 protease inhibitor with a commercial name Indinavir [96].

The physicochemical properties of the native drug can be modified by fluorine atoms through the change of electron distribution and, thereby, reducing the pKa. A lower pKa implies a greater hydrolytic stability [97]. In fact, a decrease in this parameter from a drug with an amine group, could improve the drug activity when the active form is the neutral species. Several examples clearly showed the correlation between the activity and the concentration of neutral species. The histidine H₂ receptor antagonist (mifentidine) presents two forms, the neutral, imidazole, with a pKa of 5.58 and the protonated, formamidinium, with a pKa of 8.88. With the addition of N-trifluorethyl to the molecule of mifentidine, the pKa of both forms decreased [pKa = 4.45 (imidazole); pKa = 6.14 (formamidinium)] (Figure 4). This transformation leads to a more active compound [97].

Figure 4 - a: Mifentidine chemical structure and b: N-trifluorethyl derivative

c. Fluorine metabolic improvement

Nowadays, contrarily to the by the natural carbon-fluorine bond formation, chemists have been developed several synthetic procedures for this purpose.

The use of fluorine to control the oxidative metabolism has become an important progress in the drug metabolic stability, a factor related to the bioavailability in body fluids. Although, due to the lipophilic nature most compounds are vulnerable to phase I metabolism enzymes [91]. The stronger carbon-fluorine link which has a stable dipole employs a localized effect on the nearby environment [91, 92, 97]. Studies suggest that the referred bond (van der Waals radius = 1.47 Å) is greater than the carbon-hydrogen bond (van der Waals radius = 1.20 Å), thus the substitution of hydrogen by fluorine is regarded as a bioisosteric way of introducing strong electron-withdrawing properties into molecules [80, 98, 99]. This is also used to control the biological half-life of a drug, longer to ¹⁸F-labeled ligands, and to avoid the development of potentially toxic products by oxidation [34, 97].

Furthermore, the drug binding affinity increase but the overall size of the molecule don't significantly change [92, 100].

Besides the alterations referred above, fluorine can also influence the interactions between a substrate and enzyme active sites, ligand receptor binding, translocation of molecules through biological membranes, and perturb other important biological properties [97].

d. Fluorine incorporation methods

Fluorine incorporation in a chemical structure can be accomplished by either electrophilic or nucleophilic attack, or the most frequently used method that involves a fluoro alkyl chain addition to the core structure of the drug [101, 102].

The substitution of H atoms with F atoms is different according to the charges of these two species. The formation of F⁺, specie that does not exist under normal conditions, is energetically unfavorable. So, if the loss of a proton is required in an enzyme-catalyzed

reaction, the substitution of fluorine in the hydrogen position effectively inhibit this process [97]. Contrary to this situation, F^- is a good leaving group when is possible the stabilization of the departing F^- by hydrogen bonding; instead loss of H^- is highly energetic [97].

The orthogonal reactivity of F^+ and H^+ as well as F^- and H^- has been exploited to design different types of drugs. In the 5-fluorouracil and DFMO mechanisms of action, as reviewed by Bégué and Bonnet-Delpon respectively, examples are found [80, 103].

Further, fluorinated imines are very useful tools for the introduction of fluorine atoms in complex structures [104-106]. Trifluoromethyl imines have been applied in the synthesis of protease inhibitors [107-109].

e. The effect of fluorine in the blood-brain barrier permeability

Other beneficial property of the fluorine substitution is the increase of blood-brain barrier (BBB) permeability due to changes in the lipophilicity or amine pKa that are of high interest in the design of central nervous system (CNS) active drugs [85, 110, 111]. Fluorine has an important and historical role in the development of antipsychotic drugs, also called neuroleptics or major tranquilizers. These drugs are used in the treatment of schizophrenia, mania and psychotic depression [112, 113]. In a study with 3-piperidinyldole antipsychotic drugs, it was found that fluorination decreased the basicity of the amine, thereby improving bioavailability [114]. The substitution of a proton or other univalent atom or group on a ligand with a fluorine atom can enhance receptor binding characteristics. The substitution on phenylephrine leads to 6-fluorophenylephrine, which showed an increase in potency at α -adrenoreceptors, making it a selective α -adrenergic agonist [92, 100].

The persistence of the researchers to develop new fluorinated medicinal and pharmaceutical agents created the need to develop new synthetic procedures to introduce fluorine. Then, the use of fluorine in drugs is now very common and new pharmaceutical agents that contain fluorine continues to rise [89, 97].

These innovations have been applied for the treatment of neurological disorders, as so AD, not only for the efficiency improvement but also for the capacity to cross the BBB.

4. The use of fluorine in Alzheimer's disease treatment

In order to inhibit the protein misfolding, compounds with fluorine atoms have been studied [44, 71, 115-119]. In the case of the AD, different types of molecules with fluorine atoms are designed and tested (Table 2). The efficiency is greater to higher fluorination rates: the 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) reconverted all the β -sheets into α -helices, and already predominantly at ≤ 15 vol.%. The HFIP is able to stabilize the α -helix structure [116] because A β peptide is delimited in aqueous solution by a hydration shell, as proposed by Vieira *et al* [44]. The internal part is strongly bound and oriented towards the protein. On the other hand, the outer part experiences a permanent exchange of water molecules with bulk water. The addition of TFE or HFIP to the solution promotes a competition between fluorinated alcohol and protein for water molecules. The water will reorganize the structure around $-\text{CF}_3$ groups in order to maximize the $-\text{OH}$ bonds. Around the hydrophobic groups a cage-like structure is formed [118]. Local clusters from hydrophobic alcohol are created in a certain concentration, and should be stronger than the hydrophobic force that maintains A β aggregates. Molecules of fluorinated alcohol can surround protein aggregates and infiltrate between them to separate the aggregated molecules from each other. Since parts of the A β_{40} have hydrophobic nature, hydrophobic integrations with fluorinated alcohol occur, causing the breakage of the A β -aggregate structure into single A β molecules.

Through another study, Torok *et al*, demonstrate the efficacy of a new class of organofluorine inhibitors on the inhibition of the *in vitro* self-assembly of A β_{40} peptide [15]. According with the authors, the introduction of a CF_3 group significantly increases the acidic nature of OH, which has an essential function in binding to the amyloid β peptide. Such modification turns the compounds described into potential drugs to AD [15].

Also, it was verified that the induction and the stabilization of helix structures in proteins is possible by a fluorinated alcohol 2,2,2-trifluoro ethanol (TFE) [117]. Ethanol by itself cannot refold β -sheets into α -helices for A β_{40} . Can just recreate helices from random coil at higher concentrations (≥ 50 vol.%). However the β -to- α refolding happens if ethanol is fluorinated (TFE) [44, 120, 121].

In another molecule, AZD3839, the introduction of fluorine near to the amidine moiety, improves the permeability properties in the brain, and reduces *in vivo* brain A β ₄₀ [122].

Recently, Loureiro *et al.* synthesized peptides containing fluorinated amino acids to inhibit the A β ₄₂ aggregation. The peptides were based on the sequence well known and well accepted β -sheet breaker peptide LVFFD. Valine was substituted by either 4,4,4-trifluorovaline or 4-fluoroproline, and phenylalanine at position 3 was replaced by 3,4,5-trifluorophenylalanine. Fluorination of the hydrophobic residue valine or phenylalanine is effective in preventing the A β ₄₂ aggregation [123].

Fustero *et al.* prepared novel fluorinated ethanolamines and studied their use as key fragments for the stereoselective synthesis of hydroxyethyl secondary amine (HEA)-type [107]. The designed drug, that resulted from the collaboration between Elan and Pfizer, is an example of a BACE1 inhibitor incorporating the HEA isostere [124].

HEA showed a high potency and cell permeability. In order to enhance its pharmacological profile, the authors suggest a further exploration around the chemical space. They propose the replacement of the hydrogen atoms at the benzylic position by fluorine atoms [94, 125, 126]. Formal fluorine shift (from the aryl to the benzylic position) should allow stereochemical permutations on the ethanolamine subunit [107].

1,3-oxazines, a class of BACE1 inhibitors, were analyzed by Hilpert *et al.*, and an extensive fluorine scan revealed the power of fluorine(s) to lower the pK_a and thereby dramatically change their pharmacological profile [71]. The introduction of two fluorine atoms into the headgroup of 1,3-oxazine reduced the pK_a considerably and led to noble *in vivo* activity. A lower pK_a will influence the enzymatic and cellular activity, hERG activity, P-glicoprotein efflux, and eventually the *in vivo* activity [71]. The drug produced, a CF₃-substituted oxazine was found to be an orally active BACE1 inhibitor with a relevant pharmacodynamic profile in wild-type mice and a long lasting A β _{40/42} reduction in the cerebrospinal fluid (CSF) at a dose as low as 1 mg/kg [71]. This model was used because the wild-type mice has a normal physiological level of APP expression, which can provide a better

physiological model for A β -peptide production than APP-transgenic organisms [71].

Several other BACE1 inhibitors were developed, showing that the introduction of a fluorine in the 2-position of the benzamide non-prime side led to an increase in cell activity [127]. The compound GSK188909 synthesized by Beswick *et al*, bear a meta-substituted benzyl amine prime side, and was identified as one of the first selective, nanomolar inhibitors in the cells expressing swedish (SWE) APP. Is important to understand that this extracellular protein presents a two amino acid substitution (at APP670 and 671), causing it to be more likely to undergo processing by β -secretase than the wild type APP, resulting in higher production of the amyloidogenic A β peptides.

In addition to *in vitro* capability, in an animal model of Alzheimer's disease (mice), GSK188909 also had a favorable pharmacokinetic profile which allowed them to determine whether a BACE1 inhibitor would lower amyloid production [127].

In another study, several fluoroalkyls were synthesized to probe the increased potency verified for compounds in the presence of fluorine, maintaining rates of permeability coupled with good to high levels of recovery. They also had diminutive levels of P-gp efflux activity. The authors have focused in the pharmacokinetic parameters and not only in the potency of the molecule. Thus, an orally inhibitor was developed with activity in *wildtype* preclinical guinea pig animal model [128].

A different example, retinoic acid receptor subtype- β 2 (RAR β 2) is thought to play a role in neurodegenerative diseases, such as AD, since has been linked to the induction of neural differentiation, motor axon out growth and neural patterning [129]. A series of agonists displaying high selectivity for RAR β 2 were designed and synthesized by Olsson *et al*. [129]. This team showed that fluorinated alkoxythiazole displayed a significant increase in activity at the RAR β 2. A biphenyl analogue was also tested by incorporating a fluorine atom, and the potency on RAR β 2 greatly increased [129]. Such results

might be explained by the lower pKa promoted with fluorine atom, thereby rendering the binding ligand-receptor more stable [100, 129]. Another strategy to combat the AD is to inhibit the tau protein phosphorylation, through the inhibition of glycogen synthase kinase-3 β (GSK-3 β), a serine/threonine kinase essential for the referred process. Saitoh and co-workers synthesised derivatives of 1,3,4-oxadiazole, GSK-3 β inhibitor [130]. Of these derivatives, the compound containing a 4-methoxy-3-(trifluoro-methyl)benzyl group and those containing 4-methoxyphenyl and 3-trifluoromethyl groups, showed single-digit nanomolar potent inhibitory activity [100].

1-[(3-Fluoro-4-pyridinyl)amino]-3-methyl-1(H)-indol-5-yl methyl carbamate (P10358) is a reversible acetylcholinesterase inhibitor with great potency which produces central cholinergic stimulation after oral and parental administration in rats and mice.

P10358 is a 2.5 times more potent acetylcholinesterase inhibitor *in vitro* than THA, another cholinesterase inhibitor from Cognex. [131]. The referred compound alters brain dopamine neurotransmission because it can increase the extracellular levels of dopamine and its metabolite HVA. Such mechanism of action could be used to treat others diseases like Parkinson [131, 132], making this a promising compound not only for AD. The pharmacological studies indicated that P10358 has a preclinical profile that may be also advantageous in the symptomatic treatment of AD. These studies demonstrated that the behavioral efficacy of P10358 in learning and memory paradigms is attributed specifically to brain AChE inhibition, since this compound has low affinity for a wide variety of other neurotransmitter receptors [131].

Moreover, novel polyhydroxylated (E)-stilbenes were synthesized with the objective of inhibiting the enzymes acetyl- and butyrylcholinesterase. One of them, with an extra fluorine substituent, presented an increased action when compared with other known inhibitors [133].

In another perspective for Alzheimer's disease treatment, some nonsteroidal anti-inflammatory drugs (NSAIDs) has been shown to modulate the activity of γ -secretase, the enzymatic complex responsible for the formation of A β [134-139].

The proposed mechanism for this effect is an allosteric modulation of presenilin-1, the principal component of the γ -secretase complex [140-144]. The inhibition of $A\beta_{42}$ production is independent from the anti-anticyclooxygenase (COX) activity, and it depends on the chemical structure of the NSAIDs, with some compounds displaying activity and others not [134, 140, 145, 146]. Sulindac and Flurbiprofen are two anti-inflammatory drugs with great potential for alzheimer's disease. Interesting, both molecules present a fluor atom on their structures. 1-(3',4'-Dichloro-2-fluoro[1,1'-biphenyl]-4-yl)-cyclopropanecarboxylic acid (CHF5074) is a new γ -secretase modulator, without COX and Notch-interfering activities in vitro. Imbimbo and his team tested the effects of chronic CHF5074 treatment on Tg2576 transgenic mice brains, with $A\beta$ pathology. In comparison with controls, CHF5074 treatment significantly reduced the area occupied by amyloid plaques and the number of plaques in cortex. Biochemical analysis confirmed the histopathological measures, with CHF5074-treated animals showing reduced total brain $A\beta_{40}/A\beta_{42}$ levels. Although, the size of the remaining plaques was not significantly affected by this treatment. These results suggest that CHF5074 is capable of inhibit the initiation of the formation of plaques but is less effective in inhibiting the growth of the plaques [146]. In a human neuroglioma cell line expressing swedish mutated form of amyloid precursor protein (H4swe), CHF5074 reduced $A\beta_{40}/A\beta_{42}$ secretion [146]. Besides the fluorine molecules presented here, other examples of the use of fluorine in AD could be find. Giacomelli *et al* performed adsorption studies of $A\beta$ solutions (containing either monomers or small oligomers) on poly(tetrafluoroethylene) surfaces. Their results showed that the fluorinated surface strongly promoted α -helix re-formation [121]. A comparable effect was found by Vieira *et al*, studying the solution of $A\beta$ in CF_3 -group-containing solvents [44]. Further, Rocha *et al* demonstrated that negatively charged nanosurfaces, including fluorinated surfaces, inhibit the conformational transition of $A\beta_{40}$ from unfolded to β -sheet that normally occurs. This could be explained by the interactions between the negatively charged groups and the polar side chains in unfolded peptide, inhibiting conformational transitions [147].

In a work developed by Saraiva *et al*, it was demonstrated the use of fluorinated nanoparticles (NPs) to avoid A β aggregation. In the presence of 8 mg/mL fluorinated NPs, microscopy analysis showed a homogeneous distribution of A β ₄₂ around the NPs, which indicates a strong interaction between them [148]. Fluorinated NPs might interact with important fragments for A β ₄₂ oligomerization in the very beginning of the nucleation step, preventing them from interaction with other peptide molecules, as suggested by atomic force microscopy (AFM). Also, A β dimers were not observed when the peptide was incubated with the fluorinated analogues. After 3 days A β monomers were not detected anymore. Furthermore, the NPs used in this work were able to attenuate the enzyme activation promoted by A β ₄₂ oligomers. Saraiva *et al* reported results that indicate that fluorinated NPs promote an increase in α -helical secondary structure of A β ₄₂. The NPs exert a combination of antioligomeric and antiapoptotic effects and increase cell viability in the presence of A β ₄₂ oligomers [148]. The trifluoromethyl group significantly increases the acidic nature of the carboxylic acid due to the introduction of the strong electron-withdrawing. The acidic character has a key role in the possibility of lysine residues (Lys₁₆ and Lys₂₈) bind to the peptide. The interaction between C-F bond and the side-chain amides of glutamine (Gln₁₅) and asparagine (Asn₂₇) residues are geometric preferable [149]. Consequently, the fluorinated NPs can interact with two patches of hydrophobic residues responsible for oligomerization (Leu₁₇-Ala₂₁ and Ala₃₀-Ala₄₂). Also they can be able to interact with residues in their vicinity by exploiting the same intermolecular interaction as in A β assembly and disrupting the potential for further aggregation [148]. Thus, fluorinated compounds might have a good bioavailability and influence the development of AD, including molecules, surfaces or even nanoparticles. The follow table can resume the several examples already described.

Table 2 - Fluorinated molecules, surfaces and nanoparticles developed for the AD treatment.

	Name	Site of action	Therapeutic effect	Clinical trial phase	Ref.
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Molecules	TFE	A β	Induce and stabilize helix structures	-	[117]
	HFIP		Reconvert all the β -sheet into α -helix	-	[150]
	5'-halogen substituted 3,3,3-trifluoromethyl-2-hydroxyl-(indol-3-yl)-propionic acid esters		Exhibited substantial activity in the disassembly of preformed fibrils	-	[151]
	AZD3839		In vivo brain reduction of A β_{40}	Phase 1 clinical trials completed	[122]
	LPfFFD-PEG LVFffFD-PEG LVfFFD-PEG		Induce and stabilize helix structures	Encapsulation of the peptides by the same group	[123]
	Fluorinated ethanolamines	β -secretase (BACE1)	Increase the permeability on cells	Preparation of additional fluorinated analogues by the same group	[107]
	1,3-Oxazines fluorinated derivative		Decrease of the pKa	Undergoing clinical evaluation	[71]
	GSK188909		Favour pharmacokinetic profile	The <i>in vivo</i> efficacy is currently being investigated further, through animal models.	[127]
	Fluorinated alkoxythiazole	RAR β 2	Increase the activity at the RAR β 2.	-	[129]
	GSK-3 β inhibitor fluorinated derivative	Tau protein	Potent inhibitory activity of GSK-3 β	Under further pharmacologic al evaluation	[130]

	P10358	Acetylcholinesterase	Produce central cholinergic stimulation	-	[131]
	CHF5074		Reduction of the amyloid plaques area and number	Under phase 2 clinical trials	[146]
Surfaces	Poly (tetrafluorethylene)	A β	Promotion of α -helix re-formation	-	[121]
Nanoparticles	Fluorinated nanoparticles	A β	Preventing the interaction of the A β_{42} with other peptide molecules	-	[147, 148]

Concluding remarks

Fluorine plays an important role in the diagnosis of many CNS diseases, including neurodegenerative disorders such as Alzheimer's disease. The incorporation of a fluorine atom into a compound modifies its physicochemical properties. The alteration can increase the binding affinity to a specific compound, can increase metabolic stability or even affect other administration, distribution, metabolism and excretion (ADME) properties.

The demands to develop new methods for introduction of fluorine into organic molecules have led to many simple and convenient procedures. This has increased the availability of fluorinated analogues such as biological evaluation. Even with the advances on this field, the role of fluorine in drug development and design continues capable to expand.

In this review, the attempt has been made to highlight the different fluorinated molecules already designed and synthesized and able to inhibit the β -amyloid peptide aggregation.

With this work we can expect that investigations using fluorinated compounds in the treatment of CNS disorders will continue to unabated. Potency, selectivity and bioavailability are crucial parameters to determine the utility of these compounds in AD.

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