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γ-Secretase Inhibitors Selected by Molecular Docking, to Develop a New Drug Against Alzheimer's Disease

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Abstract

Background: Alzheimer´s disease (AD) is one of the most common forms of dementia, is characterized by memory loss and cognitive impairment that affects more than 30 million people worldwide. The pathogenesis of Alzheimer's disease is primary driven by brain accumulation of the amyloid β peptide generated from the amyloid-β precursor protein (APP) via cleavages by β- and γ-secretase. In this study, we propose an approach by molecular docking to select compounds as γ-secretase inhibitors for decreasing the APP generation.

Methods: We selected potential γ-secretase inhibitors by molecular docking in the potential site between Asp257, Lue268, Asp385, Ile387, Phe388, and Leu432 amino acids in presenilin-1 (PS-1), using a chemical library of over 500,000 compounds.

Results: Eight compounds (AZ1 – AZ8) were selected by molecular docking to develop γ-secretase inhibitors for decreasing the APP generation.

Conclusion: AZ1 – AZ8 compounds could be interacting in the potential site between Asp257, Lue268, Asp385, Ile387, Phe388, and Leu432 amino acids in PS-1. These compounds could specifically interact in the binding pocket in PS-1 to prevent/decrease the APP generation, to develop a new drug against Alzheimer's disease.

Keywords: Amyloid Beta-Protein Precursor, Amyloid Precursor Protein Secretases, Alzheimer's disease, Molecular Docking Simulation, Presenilin-1.

Introduction

Alzheimer´s disease (AD) is one of the most common forms of dementia, is characterized by memory loss and cognitive impairment that affects more than 30 million people worldwide (1), and the expectation in 2050 there will be 131 million cases (2). Alzheimer´s disease is known for neuronal loss and patients losing cognitive function. The pathogenesis of Alzheimer's disease is primary driven by brain accumulation of the β-amyloid peptides generated from the APP via cleavages by γ- and β-secretases (BACE-1) (3-7), both proteins are the ones who generate this disease which induces dystrophic neurites and progressive loss of synaptic and neuronal loss, chronic inflammation and oxidative damage (8), and the APP overexpression which by upregulating the proapoptotic proteins would result in the activation of apoptosis in neuronal cells, resulting in neuronal cell death (9-10).

γ-secretase was defined as a complex that cleaves the APP to produce mainly the amyloid β peptide (Aβ40 and Aβ42) in Alzheimer's disease (4, 10-11). The γ-secretase is formed by a complex consisting of four individual proteins: presenilin-1 (PS-1 or PSEN-1), nicastrin, anterior pharynx-

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defective 1 (APH-1), and presenilin enhancer 2 (PEN-2) (12-14). In Alzheimer's disease have been reported several mutations in PS-1, favoring the production of β-amyloid peptides (15-20), and the PS-1 Gene ID is 5663 (21).

There are compounds that inhibit β- and γ-secretase but they are not selective (14) (22), since they can affect the function of γ-secretase on the Notch peptide (23), since it is introduced into the cavity in which the APP is being cut. In addition, there are studies that using others proteins as therapeutic targets; Keap1-Nrf2 PPI inhibitor (24), β-secretases (BACE-1) inhibitor (5), SREBP2, GSK3B (25), or even in an allosteric site in γ-secretase (14), where the inhibitory effect could affect the generation of amyloid peptides or tau proteins (9-10).

In this study we used the γ-secretase as therapeutic target, due to there are many studies showing that an inhibitory effect has been achieved (1, 3, 14), and they identified the important amino acids in the active site (in PS-1) (14). For the molecular docking, we using the crystallographic structure of the γ-secretase complex with APP (26), and is described the Asp257, Lue268, Asp385, Ile387, Phe388 and Leu432 amino acids in the PS-1 to make the cleavage in the APP (11, 14, 20), to produce the β-amyloid peptides (Fig. 1).

This study proposes compounds selected by molecular docking as the basis for developing drugs that can help treat AD. The compounds could be selective to PS-1 to potentially inhibit the β-amyloid peptides generation.

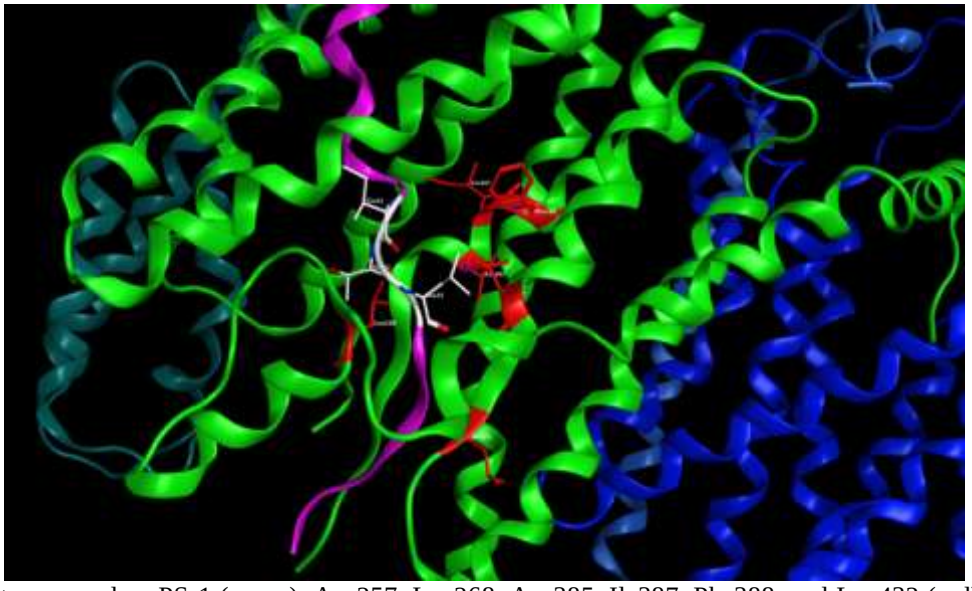

Fig. 1. γ-secretase complex. PS-1 (green), Asp257, Lue268, Asp385, Ile387, Phe388, and Leu432 (red). APP (pink), cleavage in the APP in Ile718, Thr719 and Leu720 amino acids (white).

Materials and Methods

Preparation of receptor protein and definition of binding site

The X-ray crystallographic structure of γ-secretase (from *Homo sapiens*) was obtained from the Protein Data Bank (PDB) (27) under PDB code 6IYC. The structure was used as protein target for a docking directed to the amino acids Asp257, Lue 268, Asp385, Ile387, Phe388 and Leu432 (11).The protonation and energy minimization of each PDB file was performed using Molecular Operating Environment (MOE) software with the default parameters, and the CHARMM27 Force Field used was (28).

Screening library

The EXPRESS-Pick Stock small molecule screening library from ChemBridge Corp (29) was used for docking. This small molecule screening collection comprising 502,350 chemical compounds that fulfill the druggable properties of Lipinski's rules (30-31) and cover a wide area of chemical space.

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Molecular docking

High-throughput virtual molecular docking was carried out by MOE, the potential binding site for the docking directed to the amino acids Asp257, Lue 268, Asp385, Ile387, Phe388 and Leu432 (11) (PDB 6IYC), and up to 100 conformers of each compound were generated for docking. A flexible ligand-rigid receptor molecular docking was performed with MOE-Dock, as we reported. Later the values of up to 30 conformers of each compound were analyzed, and the average $\Delta G_{binding}$ of each compound was determined, as previously reported (32-33). The analysis of ligand interaction per amino acid was conducted using PLIP (Protein Ligand Interaction Profiler) (34).

Selection of the best eight compounds

From the docking results, up to 30 conformers for each compound were analyzed to determine their $\Delta G_{binding}$ averages in order to select the best eight compounds as previously (35). Also computed was standard deviation (using Excel Microsoft-365 software), with these results, the best $\Delta G_{binding}$ averages were determined for interactions of PS-1 with each compound. The description of chemical properties using PhysChem - ACD/Labs (36), the theoretical toxicity (mutagenicity and carcinogenicity) (37), and LD50 (38) of each compound selected were determined.

Statistical analysis

Data were expressed as mean ± standard deviation (SD), averages and standard deviations were calculated in Excel (Microsoft).

Results

Selection of the best eight compounds by molecular docking

In this study, we used the EXPRESS-pick Collection library from Chembridge Corp. comprising 502,350 compounds, we generated up to 100 conformers of each one for performing the molecular docking (35) at the potential site between Asp257, Lue 268, Asp385, Ile387, Phe388 and Leu432 amino acids in PS-1 (in γ-secretase, Fig. 2). The best eight compounds were selected based on their average binding affinity ($\Delta G_{binding}$), calculated with the $\Delta G_{binding}$ of all conformers. After classifying and analyzing all compounds, we determined a range between −11.34 to −10.21 kcal/mol for the best eight compounds (Fig. 2), the eight compounds selected were labeled as AZ1 to AZ8. Each compound's interaction with γ-secretase was analyzed using its interaction report (Table 1) (34). All calculated $\Delta G_{binding}$ averages are related to the number of interactions from the results analyzed by molecular docking (mainly hydrogen bonding and hydrophobic interactions).

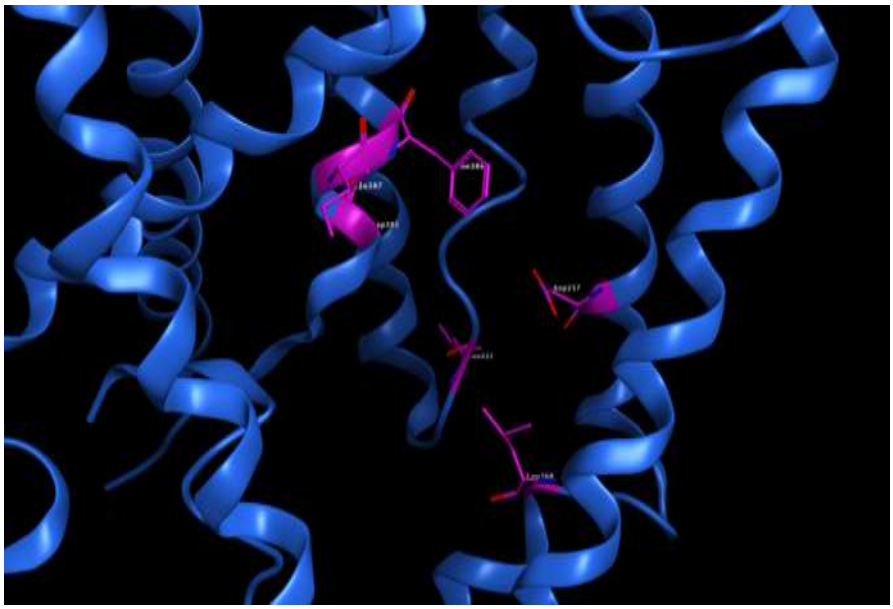

Fig. 2. PS-1 (blue) shows the potential site for molecular docking between Asp257, Lue 268, Asp385, Ile387, Phe388, and Leu432 amino acids (pink).

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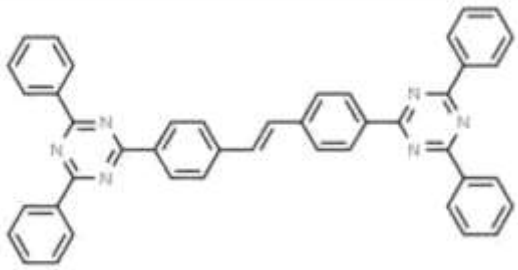
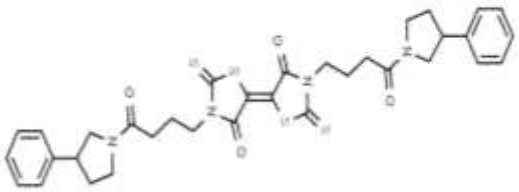
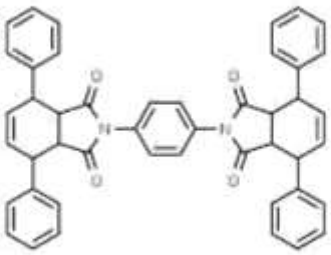
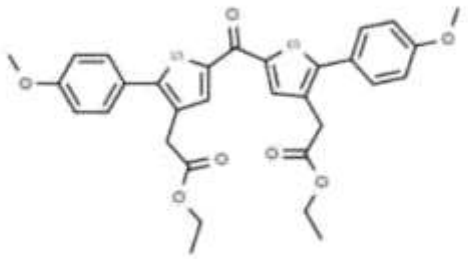
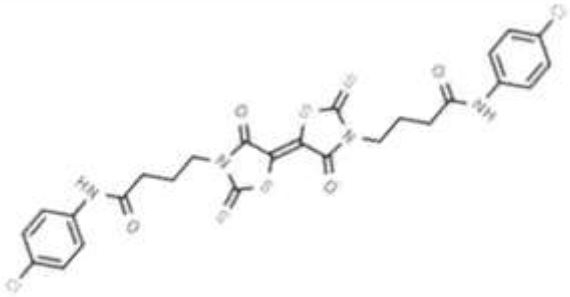
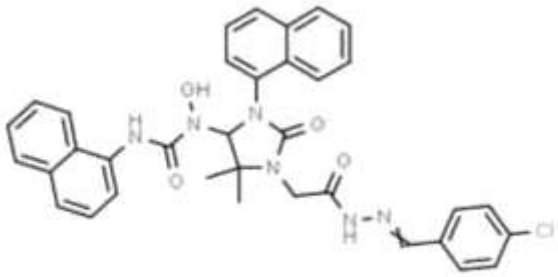
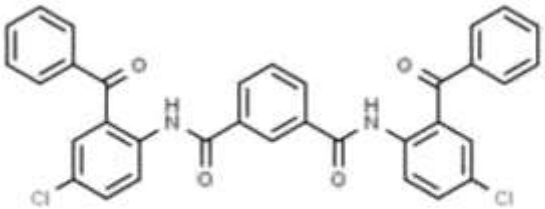
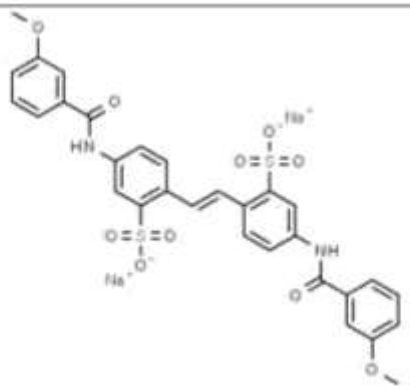
AZ1.- 5255391, 2065053	AZ2.- 5146422, 2830458
	
AZ3.- 5133445, 4420926	**AZ4.- 5130209, 2829055**
	
AZ5.- 5146452, 2830465	**AZ6.- 5138480, 9584934**
	
AZ7.- 5181388, 2179873	**AZ8.- 5102786, 5716987**
	

Fig. 3. ID ChemBridge Corp., PubChem CID, and structure of the eight selected compounds, AZ1 to AZ8.

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Table 1. Compound ID, PubChem CID, Canonical SMILES, interaction with amino acids in PS-1, number of conformers used and $\Delta G_{binding}$ average (kcal/mol) with standard deviation.

Compound ID and PubChem CID	Canonical SMILES	Interaction with residues in PS-1 (Table S2 – S9)	Number of conformers	Average of $\Delta G_{binding}$ and SD
AZ1 2065053	C1=CC=C(C=C1)C2=NC(=NC(=N2)C3=CC=C(C=C3)C=CC4=CC=C(C=C4)C5=NC(=NC(=N5)C6=CC=CC=C6)C7=CC=CC=C7)C8=CC=CC=C8	Phe237, Lys380, Gly382, Gly384, Ala431, Leu432	22	-11.34 ± 0.81
AZ2 2830458	C1CN(CC1C2=CC=CC=C2)C(=O)CCCN3C(=O)C(=C4C(=O)N(C(=S)S4)CCCC(=O)N5CCC(C5)C6=CC=CC=C6)SC3=S	Leu286, Lys380, Gly382, Gly384, Leu432, Ala434	30	-10.75 ± 1.13
AZ3 4420926	C1=CC=C(C=C1)C2C=CC(C3C2C(=O)N(C3=O)C4=CC=C(C=C4)N5C(=O)C6C(C=CC(C6C5=O)C7=CC=CC=C7)C8=CC=CC=C8)C9=CC=CC=C9	Lys380, Leu381, Gly382, Gly384, Leu432	28	-10.51 ± 1.32
AZ4 2829055	CCOC(=O)CC1=C(SC(=C1)C(=O)C2=CC(=C(S2)C3=CC=C(C=C3)OC)CC(=O)OCC)C4=CC=C(C=C4)OC	Leu268, Leu286, Leu381, Gly382, Gly384, Leu432	30	-10.36 ± 1.27
AZ5 2830465	C1=CC(=CC=C1NC(=O)CCCN2C(=O)C(=C3C(=O)N(C(=S)S3)CCCC(=O)NC4=CC=C(C=C4)Cl)SC2=S)Cl	Leu286, Lys380, Gly382, Gly384, Asp385, Leu432, Ala434	29	-10.34 ± 1.00
AZ6 9584934	CC1(C(N(C(=O)N1CC(=O)NN=CC2=CC=C(C=C2)Cl)C3=CC=CC4=CC=CC=C43)N(C(=O)NC5=CC=CC6=CC=CC=C65)O)C	Ile143, Leu268, Gly384, Leu432	25	-10.24 ± 1.00
AZ7 2179873	C1=CC=C(C=C1)C(=O)C2=C(C=CC(=C2)Cl)NC(=O)C3=CC(=CC=C3)C(=O)NC4=C(C=C(C=C4)Cl)C(=O)C5=CC=CC=C5	Leu381, Gly382, Gly384, Leu432, Ala434	28	-10.23 ± 0.86
AZ8 5716987	COC1=CC=CC(=C1)C(=O)NC2=CC(=C(C=C2)C=CC3=C(C=C(C=C3)NC(=O)C4=CC(=CC=C4)OC)S(=O)(=O)[O-])S(=O)(=O)[O-].[Na+].[Na+]	Met146, Phe237, Gly382, Gly384, Asp385, Ala434	26	-10.21 ± 0.41

Interaction of compounds AZ1–AZ8 with PS-1

Each compound's (AZ1–AZ8) interactions with PS-1 were analyzed using 22–30 conformers of each compound (Fig. 2). We determined the primary amino acids in PS-1 based on the molecular docking results: Ile143, Met146, Phe237, Lue268, Leu286, Lys380, Leu381, Gly382, Gly384, Asp385, Leu432, and Ala434

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amino acids that interact with compounds AZ1–AZ8 (Table 1). For these amino acids, the eight compounds showed greater interactions with the potential site (Fig. 2), particularly with Leu286, Lys380, Gly382, Gly384, Leu432, and Ala434 (mainly through hydrogen bonding and hydrophobic interactions for the conformers analyzed). Therefore, the compounds could block/hindering the APP cleavage (11, 14, 20).

Theoretical Cytotoxic effect of compounds AZ1-AZ8

We evaluated the theoretical cytotoxic effects of the eight compounds for potential use in AD. The compounds had good results in web-based theoretical toxicity evaluations with a theoretical median lethal dose (LD50) between 350 - 3000 mg/kg (38).

Discussion

We already mentioned that the AD does not have specific treatments, and the prevalence is increasing and an increase is expected in the near future (1, 2), highlighting the global importance of developing new treatments for AD (5, 14, 22, 23), and the development of drugs against different therapeutic targets has had a development in the last decades (against γ- and ß-secretases or even in a allosteric site) (3-6, 25). So, several new drug's studies (5, 14, 22, 23) and therapeutic targets; such as γ-secretase, GSK3B, BACE-1, SREBP2 were selected as targets for inhibition, to develop a drug against AD (14, 25).

The γ-secretase complex is a good therapeutic target due to its functions on the APP generation (3-4), it performs a process to release the amyloid peptide. γ-secretase complex makes a cleavage to generate peptides of 40 or 42 amino acids (Aβ40 and Aβ42), these peptides are toxic to neurons (4, 10, 11). So, the γ-secretase inhibition could presumably reduce Aβ peptides production and decreases the accumulation of Aβ peptides (amyloid plaques), to develop an effective treatment for AD. As already reported, it is important to achieve a selectivity to γ-secretase inhibition, for cleavage inhibition of APP-C99, without affect functions on Notch or other substrate, like Avagacestat, it exhibits a mayor preference for cleavage inhibition of APP-C99 over Notch (14).

We propose eight compounds by a in silico methodology reported (35), these compounds could blocking or hindering the active site in the PS-1 (as γ-secretase component and for its cleavage activity (14), Fig. 1). Since PS-1 functions represents a specific mechanism and justifies to use the γ-secretase as therapeutic target for developing drugs against AD (3, 4, 10, 11). So, we performed a molecular docking and used the ChemBridge Corp. chemical library (29) comprising >500,000 compounds directed in the potential site in PS-1 (Fig.2), that is the region for its cleavage activity (11, 14).

The molecular docking results showed that each compound's (AZ1–AZ8) interactions with PS-1 were between the Asp257, Lue268, Asp385, Ile387, Phe388, and Leu432 amino acids (Table 1), we determined the primary amino acids in PS-1 that interact with compounds AZ1–AZ8: Ile143, Met146, Phe237, Lue268, Leu286, Lys380, Leu381, Gly382, Gly384, Asp385, Leu432, and Ala434 (Table 1). For these amino acids, the eight compounds showed greater interactions with the potential site (Fig. 2), particularly with Leu 286, Lys380, Gly382, Gly384, Leu432, and Ala434.

For justify the in silico results of this study, we have to compare the interactions reported of two compounds with PS-1 (14). The inhibitory effect of compounds on PS-1 could be the blocking or hindering the cavity near of Pro433, Ala434, Leu435 amino acids, in the binding pocket in PS-1 (14, 39); specifically, Semagacestat has more interactions with Asp257 and Asp385, and Avagacestat has more interactions with Leu282 and Gly382 of PS-1. Generally, both compounds with interactions with Val261, Leu268, Val272, Leu418, Thr421, Leu425, and Ala434 amino acids, these amino acids occupies the binding pocket for the β-strand of APP-C99 (14). If we compare the interactions of AZ1 – AZ8 compounds (Leu 286, Lys380, Gly382, Gly384, Leu432, and Ala434 amino acids in PS-1) with the interactions of Semagacestat and Avagacestat as γ-secretase inhibitors (14),

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we propose that it is probable to get the γ-secretase inhibitor effect by AZ1 – AZ8 compounds (Table 1). In addition, we made a molecular docking using the Semagacestat and Avagacestat molecules in the same potential site in PSEN-1 (Fig. 2). The molecular docking results showed that both molecules (Semagacestat and Avagacestat) have lower average of ΔGbinding (-7.27 and -8.84 kcal/mol respectively, Fig. 4) than AZ1 – AZ8 compounds (-11.34 to -10.21 kcal/mol, Table 1), as well as the main amino acids are similar to all compounds (Tables 1 and 3). The probable interactions of AZ1 – AZ8 compounds with PS-1 (Table 1) are similar to the amino acids reported (14) and also in the docking realized with Semagacestat and Avagacestat (Fig. 4). These results are related to the effect that could be generated between some compound and PS-1, to explain the inhibitory effect observed experimentally (14), where it is reported that the interactions near of Asp257, Lue268, Asp385, and Leu432 amino acids are important to get the probably inhibition effect on γ-secretase (Fig. 5), due to these interactions, these could generate a displacing of the cavity for the substrate β-strand by a structurally change (14).

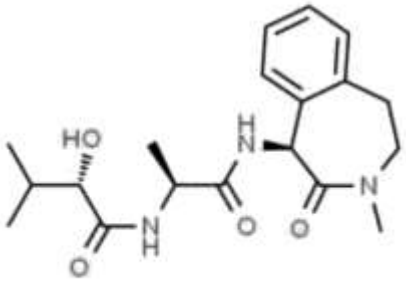
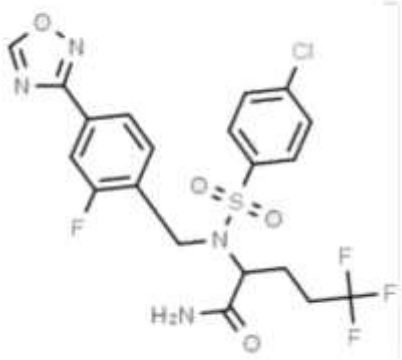
Compound and PubChem CID	Interaction with residues in PS-1 (Table S10, S11)	Number of conformers	Average of $\Delta G_{binding}$ and SD
Semagacestat 9843750 	Asp257, Lys380, Gly382, Gly384, Asp385, Leu432	29	-7.27 ± 0.76
Avagacestat 46883536 	Asp257, Leu286, Lys380, Leu381, Gly382	26	-8.84 ± 1.07

Fig. 4. Compound ID, PubChem CID, interaction with amino acids in PS-1, number of conformers used and $\Delta G_{binding}$ average (kcal/mol) with standard deviation.

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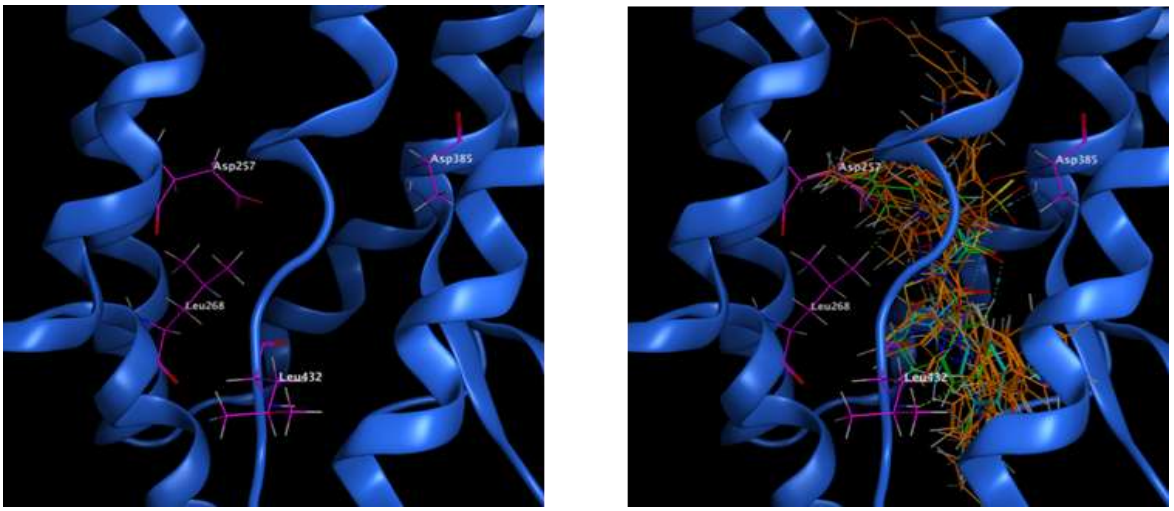

Fig. 5. PS-1 in γ-secretase (blue), Asp257, Lue268, Asp385, and Leu432 (pink). A) The main amino acids for the binding pocket, B) AZ1-AZ8 (orange), Semagacestat (green) and Avagacestat (cyan) in the binding pocket.

We recognize that the above correlations are by in silico results, and it is necessary to validate their interactions with experimental assays. We propose these eight compounds that could interact with this therapeutic target to develop a drug to treat AD. Also, we propose that these compounds are likely safe for use in humans because their theoretical toxicities studies were acceptable, determined by internet tools to predict their ADME and chemical properties.

As conclusion, we propose the AZ1 - AZ8 compounds as potential γ-secretase inhibitors and should be developed as new drugs to attend AD. These compounds could specifically interact in the binding pocket in PS-1 to prevent/decrease the APP generation to improve the neuron cell functions.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethics approval

Ethical approval is not required.

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