



Computational Analysis of Sulfonamide-Based Compounds by Molecular Docking and ADME/T in the Inhibition of Acetylcholinesterase (AChE) in Alzheimer's Disease

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Abstract

Alzheimer's disease is a long-term neurodegenerative disease that degenerates brain cells and causes severe cognitive impairment in humans. Acetylcholinesterase inhibition is a common approach to improve the well-being of AD patients by increasing the duration of acetylcholine in cholinergic synapses. Despite the development of drugs with this utility, none of them is still clinically significant. In this sense, it is sought through studies the development of new drugs, as well as to improve the pharmacological activity of the compounds already used. Six compounds of the sulfonamida's base (sulfafurazole, sulfadiazine, sulfamethazine, sulfasalazine, sulfamethoxazole and sulfacetamide), already used for the treatment of other pathologies, were investigated by computational methods to know the molecular docking and analysis of absorption, distribution, metabolism and excretion (ADME). The results showed that these compounds presented a good interaction in relation to acetylcholinesterase (AChE) and a relative affinity to the inhibition sites of the enzyme. The *in silico* study showed that these drugs have a good human intestinal absorption, besides not being toxic, carcinogenic, mutagenic and neither have inhibitory capacity of cytochrome P (CYP).

Subject Areas

Bioinformatics

Keywords

Alzheimer, AChE, Sulfonamides, Docking, ADMET

1. Introduction

Alzheimer's disease (AD) was first described and diagnosed by Dr. Alois Alzheimer in 1907 [1] [2]. It is a chronic disease characterized by severe, chronic, incurable and progressive neurodegenerative disorder that has peculiar symptoms such as memory loss, impaired language and cognition accompanied by abnormal behavior, irreversible cognitive impairment and personality changes [3] and that mainly affects the senile population aged approximately over 65 years [4]. It is the most common cause of dementia accounting for up to 80% of cases of senile dementia and affecting 55 million people worldwide (data for 2021) [5] [6] [7] and, therefore, age is a major risk factor for the disease [8] and life expectancy is about 7 to 10 years in individuals diagnosed with the disease between 60 and 70 years of age [7].

In the present moment, the main cause and mechanism of this disease have not been totally elucidated and therefore there is no preventive or curative treatment. The most accepted thesis worldwide is that this dementia is characterized by neuronal death, which usually correlates with the appearance of important neuropathological changes, including acetylcholine deficiency, extracellular deposition of β -amyloid ($A\beta$ plaques), intracellular neurofibrillary tangles by hyperphosphorylated tau protein deposits, neuroinflammation and widespread loss of neuronality [9]. In addition, there are certain factors that potentiate the disease such as hyperchlorination of central nervous system neuron protein, and oxidative stress, the main cause being related to the low concentration of Acetylcholine (ACh) [10] [11] [12] which has direct links with learning and memory function. ACh is a biomolecule responsible for the transport of neuronal signals to the brain. Being that hydrolysis at a cholinacetyl group is catalysed by acetylcholinesterase (AChE) into choline and acetic acid which causes termination of neurotransmission signal that has direct links with learning and memory function [13] [14].

Therefore cholinesterase inhibitors have been the bet to reduce the symptoms of AD. Some of these drugs such as tacrine (Cognex[®]) and donepezil (Aricept[®]) have already been approved by the United States Food and Drug Administration (USFDA) to cure the symptoms of the disease [11] [14]. However much of the AChE inhibitors known in the market exhibit some adverse effects such as nausea, gastrointestinal disturbances, diarrhoea, muscle weakness, syncope and weight loss [15]. In addition, tacrine has also been discontinued in the United States because of its problem with toxicity [16] [17].

It has been reported that several compounds including sulfonamides and their derivatives have aroused interest in new drug development as they exhibit multi-target actions against a variety of diseases [18]. Moreover this class of compounds and their derivatives generate bioactive compounds (drugs) with various purposes therefore aroused interest in the development of new drugs, exhibiting antioxidant, antimicrobial, antifungal, antiviral (anti-HIV) activity, anti-inflammatory and others, in addition to other disorders of the central nervous system

(CNS), diabetes, various types of cancer and tumors [19] [20] [21] [22], as well as in the treatment of some mental disorders such as schizophrenia, depression, including some other dementias [23].

In the search for new effective treatments, the inhibitory potential of six drugs derived from the sulfamide group was investigated by *in silico* analysis by molecular docking and ADME analysis, tracing their respective interactions with respect to the enzyme acetylcholinesterase (AChE), besides obtaining important information of the pharmacokinetic properties of these substances when absorbed in the human organism.

2. Methodology

Molecular docking study on the enzyme-drug binding system and the binding energy of sulfonamide derivatives with human acetylcholinesterase was performed using UCSF Chimera Tools 1.15 [24] and AutoDock Vina program software [25] to understand their interactions at the active site of the enzyme. This large-scale coupling tool allows for structure prediction and lower energy ranking results of the conformations of the enzymes in relation to the ligands. The chemical structures of the ligands were refined using the same program. BIOVIA Discovery Studio Visualizer 4.5 was used for visualization of the formed structures.

2.1. Preparation of the Receptor

The three-dimensional crystal structure of human acetylcholinesterase (AChE) was obtained from the Protein Data Bank PDB (<https://www.pdb.org/>) identified with PDB ID: 1EVE. The pdb file of the crystal structure was prepared on the UCSF Chimera Tools platform. All graphical presentations of the 3D models were prepared using this same program. The two-dimensional (2D) structures of the amino acid sequences present in the enzyme interacting with the sulfonamides were produced using Discovery Studio Visualizer 4.5.

For the enzyme complexes, any non-protein molecules, such as water or solvents, were deleted. Kollman charges and polar hydrogens were added to the structure of the enzymes because they were missing from the PDB file. These hydrogen atoms are important because they are involved in the structure of the ligand. The pdb files of the edited enzymes and ligands were saved as pdbqt files because they served as input for the AutoDock Vina simulation.

2.2. Ligand Selection

The 3D structures of the ligands such as: sulfafurazole (CID: 5344), sulfadiazine (CID: 5215), sulfamethazine (CID: 5327), sulfasalazine (CID: 5339), sulfamethoxazole (CID: 5329) and sulfacetamide (CID: 5320) as well as that of the control drug (donepezil) (CID: 3152) were obtained from PubChem (Bolton *et al.*, 2008) and edited in UCSF Chimera Tools 1.15 program before molecular docking. The chemical structures of the ligands used in this study are shown in (Figure 1).

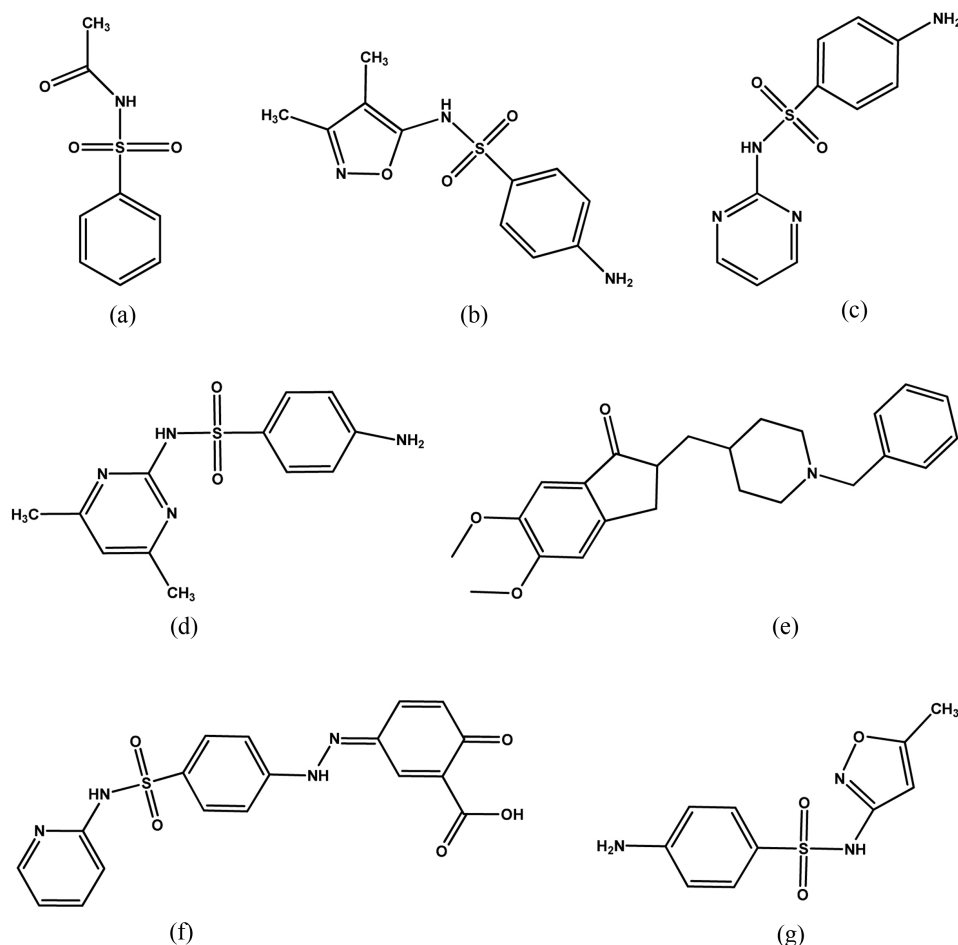


Figure 1. Structure of ligands (sulfonamides) and control drug—donepezil (e) used in the treatment of Alzheimer's disease, sulfasalazine (f), sulfafurazole (b), sulfamethazine (sulfadimidine) (d), sulfadiazine (c), sulfacetamide (a), sulfamethoxazole (g).

2.3. Grid Box Formation

The PDB files of the receptor (AChE) (**Figure 2**) and the ligands (substrates) were edited using the UCSF Chimera Tools program version 1.15. A grid parameter was set to define a space for which the ligand interacted to the receptor. The grid box was performed to cover the entire active site of the receptors. For recognition of receptor-ligand binding sites, $30 \text{ \AA} \times 30 \text{ \AA} \times 30 \text{ \AA} \times 30 \text{ \AA}$ grid box size configuration was defined with x, y and z dimensions, while the grid box centre coordinate adopted was 1.81, 66.16, 63.20 \AA . The pdb files of the edited enzymes and ligands were saved as pdbqt files as they served as input to the AutoDock Vina simulation.

2.4. Molecular Docking

Molecular docking was performed to predict the non-covalent binding of AChE (receptor) with its substrates (ligands) to determine the subsite structure. Molecular docking was used to calculate the mode of engagement of the enzyme-derivative sulfonamide complex.



Figure 2. 3D crystallographic conformation of target molecule: AChE (PDB ID: 1EVE), in ligand bound form. Ribbons represent the target molecule backbone and ligands are represented in stick style.

2.5. The ADME/T Predictions

The ADME/T (absorption, distribution, metabolism, excretion and toxicity) analyses were performed using SWISSADME server (<http://www.swissadme.ch/>). The ADME/T for each of the ligand molecules predict their various pharmacokinetic and pharmacodynamic properties including human intestinal adsorption, AMES toxicity, cytochrome P (CYP) inhibitory capacity, carcinogenicity, mutagenicity, Caco-2 permeability using always PreADMET server (<http://preadmet.bmdrc.org/>) and admetSAR (<http://lmmd.ecust.edu.cn:8000/>).

3. Results and Discussion

Nine resulting substrate conformations at the respective enzyme active sites were generated after each run in the AutoDock Vina program. The best conformations were chosen among the nine resulting ones based on low binding energy as well as binding accuracy when compared to the experimentally resolved crystal structure of the protein and ligand complex. The binding energy values obtained by molecular docking are shown in **Table 1**. Among all the ligands analysed in the assay, sulfasalazine showed the lowest binding energy of -10.2 kcal/mol indicating better binding, followed by the ligands sulfafurazole and sulfamethazine both with a binding energy of -9.4 kcal/mol. The next ligand following the series was sulfadiazine and sulfamethoxazole with binding energies of -9.1 kcal/mol and -8.9 kcal/mol, respectively. The highest binding energy -7.7 kcal/mol and thus the weakest binding among the test ligands, was observed with sulfacetamide. Nevertheless these obtained binding energy values suggest a strong complexing activity with AChE.

All ligands were successfully coupled to the active site of human acetylcholinesterase, interacting with its catalytic triad (Ser200, His440 and Glu327) and the main amino acid residues of the aromatic cage (Trp 84, Phe 330 and Tyr334) [12] [26], which are important active sites responsible for conferring a strong

Table 1. Values of the binding energies of sulphonamide-based compounds with the Acetylcholinesterase (AChE) enzyme determined by molecular docking.

| Ligand | DONEZ* | SAL ^a | FUR ^b | METAZ ^c | DIAZ ^d | METOX ^e | CETAM ^f |
|--------------------------------------|--------|------------------|------------------|--------------------|-------------------|--------------------|--------------------|
| ΔG (kcal·mol ⁻¹) | -11.0 | -10.2 | -9.4 | -9.4 | -9.1 | -8.9 | -7.7 |

a = sulfasalazine; b = sulfafurazol; c = sulfamethazine; d = sulfadiazine; e = sulfamethoxazole; f = sulfacetamide. *control drug = donepezil.

inhibition tendency by the analyzed ligands. The types of interaction between the ligands with the residues have been assembled in **Table 2**. In turn the representations of the ligands coupled to the specific amino acids of the AChE active site are shown in **Figures 3-8**. Moreover, the sulfonamides demonstrated a certain specificity of the ligands with the ligand site of AChE and their inhibitory potential against AChE, being observed an additional advantage with respect to the reference drug (donepezil), which, according to the study presented by [27], does not have direct interactions with the catalytic triad, which is the most important site related to the inhibition of acetylcholinesterase (AChE), although its binding energy with the active site is higher than the molecules of the group of sulphonamides investigated. Although the basic nucleus of all the structures is the same, most of the compounds have good values of efficient energy and do not present large differences in energy fluctuations.

The study of pharmacokinetic properties such as absorption, distribution, metabolism, excretion and toxicity (ADMET) of any molecule classified as a drug candidate is considered important before proceeding to *in vivo* testing. These fundamental parameters particularly determine the activity within the body of the studied substance [28].

The pharmacokinetic process of a drug answers whether a drug is able to reach the site of action. The pharmacodynamic process provides the answer whether or not a drug is able to produce the required pharmacological effect, in addition to a drug's ability to reach the site of action.

The absorption of a drug molecule, proposed for oral administration, depends on the extent of its transport through the walls of the gastrointestinal tract (GIT). Human intestinal absorption or HIA % is another crucial factor that helps predict the feasibility of absorption of a drug from the small intestine. To this end, simulated absorption using Caco-2 intestinal cell lines is considered.

Among the investigated properties, the blood-brain barrier (BBB) permeability is the most important, as it takes into account the passage of most compounds from the blood to the brain, *i.e.*, it is important when choosing drugs intended for the central nervous system, such as in Alzheimer's disease. Of the drugs analyzed, sulfadimidine performed the best taking into account the binding energy values, discussed above, and the ADME/T test (**Table 3**). In addition, all other molecules were shown to have an inhibitory potential with respect to AchE.

The sulfasalazine besides having the highest score in the parameter binding energy between the sulfonamides analyzed and good specificity with respect to

Table 2. Types of interactions between ligands and amino acid residues of AChE.

| Ligands | Types of interactions with amino acid residues | | | |
|--------------------|--|----------------|---|---|
| | Hydrogen bonds | Electrostatics | Hydrophobic | Van der Waals |
| CETAM ^f | Asp 72 | | Trp 84, Phe 330 | Tyr 334, Tyr 121, Tyr 70, Ser 122, His 440, Ser 81, Phe 331 |
| FUR ^b | | | Trp 84, Phe 330, Ile 439, Tyr 442 | Tyr 121, Gly 118, Phe 330, Ser 200, His 440, Gly 441, Gly 119, Phe 288, Phe 331, Phe 290 |
| DIAZ ^d | | Tyr 334 | Phe 330, Trp 84 | Ser 286, Leu 287, Phe 288, His 440, Tyr 121, Phe 331, Phe 290, Ile 287, Trp 279 |
| METAZ ^c | Glu 199, Tyr 121 | | Tyr 70, Phe 330, Phe 331, Tyr 334 | Ile 444, Asp 72, Ser 200, Tyr 130, Tyr 116, Phe 290, Gly 123, Trp 84, Ser 122, Gly 118 |
| SAL ^a | Trp 84, Gly 117 | Asp 72 | Phe 331, Phe 330, Tyr 334, Trp 84, Gly 117, His 440 | Ser 200, Phe 290, Ser 200, His 440, Glu 199, Tyr 130, Leu 127, Ser 124, Tyr 116, Gly 123, Gly 118, Ser 122, Asn 85, Tyr 121 Trp 279 |
| METOX ^e | Phe 330 | Trp 84 | Trp 84, Phe 330, Phe 331, Tyr 334, Tyr 121, Tyr 70 | Ser 81, Asp 72, Ser 122, Gly 118 |

a = sulfasalazine; b = sulfafurazol; c = sulfamethazine; d = sulfadiazine; e = sulfamethoxazole; f = sulfacetamide.

Table 3. *In-silico* metabolism, absorption, excretion, toxicity and distribution profile obtained from admetSAR server.

| Properties | Sulfasalazine | Sulfafurazol | Sulfadimidine | Sulfadiazine | Sulfamethoxazole | Sulfacetamide |
|-----------------------------|---------------|---------------|---------------|---------------|------------------|---------------|
| Blood-Brain Barrier | BBB+ | BBB+ | BBB+ | BBB+ | BBB+ | BBB+ |
| Human Intestinal Absorption | HIA+ | HIA+ | HIA+ | HIA+ | HIA+ | HIA+ |
| Caco-2 Permeability | Caco2- | Caco2- | Caco2+ | Caco2+ | Caco2- | Caco2- |
| P-glycoprotein Substrate | Non-substrate | Non-substrate | Non-substrate | Non-substrate | Non-Substrate | Non-Substrate |
| CYP450 2C9 Substrate | Non-substrate | Non-substrate | Non-substrate | Non-substrate | Non-substrate | Non-substrate |
| CYP450 2D6 Substrate | Non-substrate | Non-substrate | Non-substrate | Non-substrate | Non-substrate | Non-substrate |
| CYP450 3A4 Substrate | Non-substrate | Non-substrate | Non-substrate | Non-substrate | Non-substrate | Non-substrate |
| CYP450 1A2 Inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor |
| CYP450 2C9 Inhibitor | Inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor |
| CYP450 2C19 Inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor |

Continued

| | | | | | | |
|-------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| CYP450 3A4 Inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor |
| CYP Inhibitory Promiscuity | Low CYP Inhibitory Promiscuity | Low CYP Inhibitory Promiscuity | Low CYP Inhibitory Promiscuity | Low CYP Inhibitory Promiscuity | Low CYP Inhibitory Promiscuity | Low CYP Inhibitory Promiscuity |
| AMES Toxicity | Non AMES toxic | Non AMES toxic | Non AMES toxic | Non AMES toxic | Non AMES toxic | Non AMES toxic |
| Carcinogens | Non-Carcinogens | Non-Carcinogens | Non-Carcinogens | Non-Carcinogens | Non-Carcinogens | Non-Carcinogens |
| Biodegradation | Not ready biodegradable | Not ready biodegradable | Ready biodegradable | Ready biodegradable | Not ready biodegradable | Not ready biodegradable |
| Acute Oral Toxicity | III | IV | III | III | IV | III |
| Carcinogenicity (Three-class) | Non-required | Non-required | Non-required | Non-required | Non-required | Non-required |

BBB: Blood Brain Barrier; value closer to 1 represents better permeability through BBB. (2) HIA: Human Intestinal Permeability; value closer to 1 represents better absorption through intestine. (3) Caco-2: Human Intestinal Cell Line used for *in-silico* simulation.

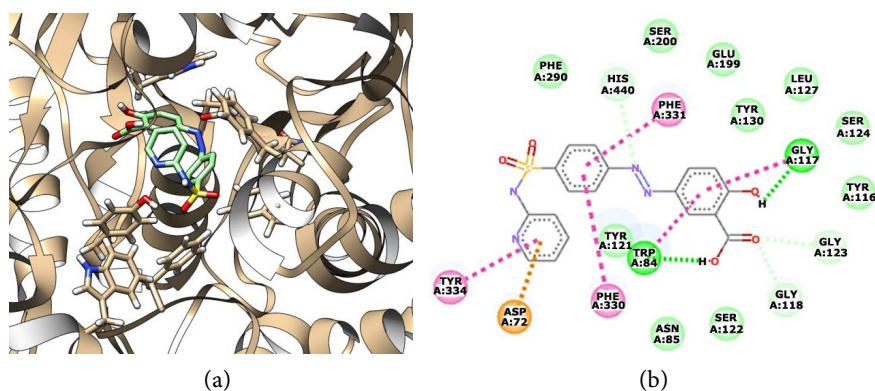


Figure 3. (a) Sulfasalazine interacting with AChE. (b) Interactions with amino acid residues of the catalytic site.

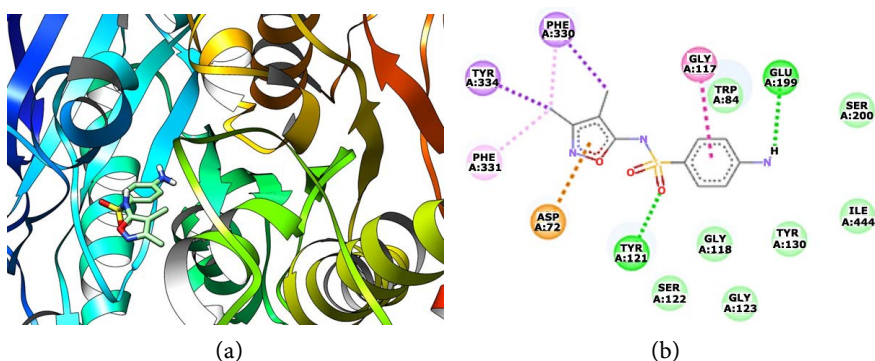


Figure 4. (a) Sulfafurazole interacting with AChE. (b) Interactions with amino acid residues of the catalytic site.

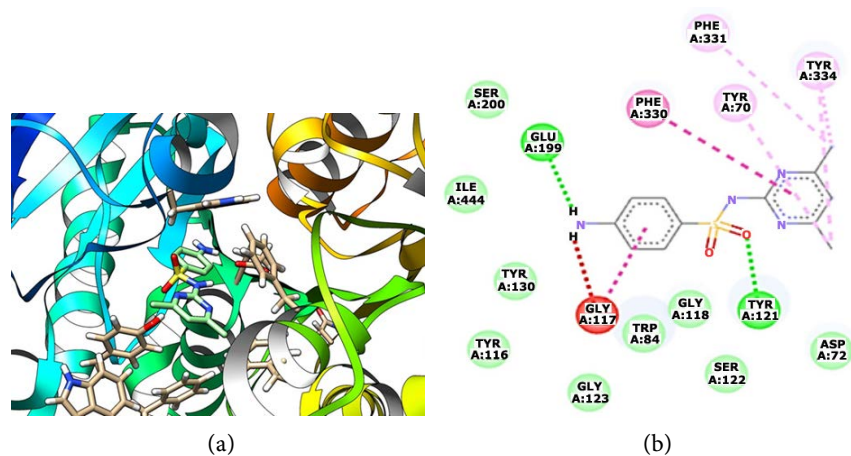


Figure 5. (a) Sulfamethazine interacting with AChE. (b) Interactions with amino acid residues of the catalytic site.

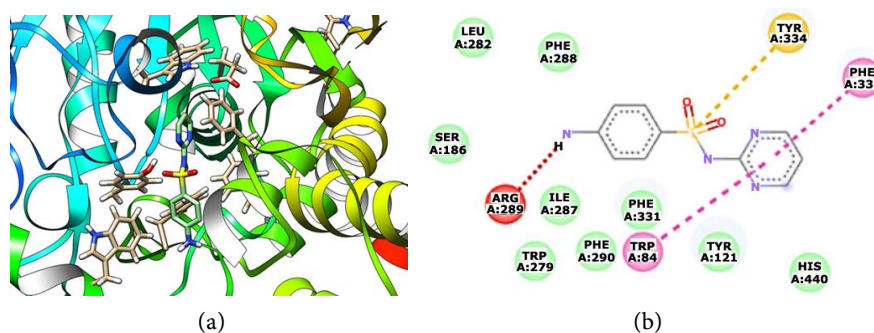


Figure 6. (a) Sulfadiazine interacting with AChE. (b) Interactions with amino acid residues of the catalytic site.

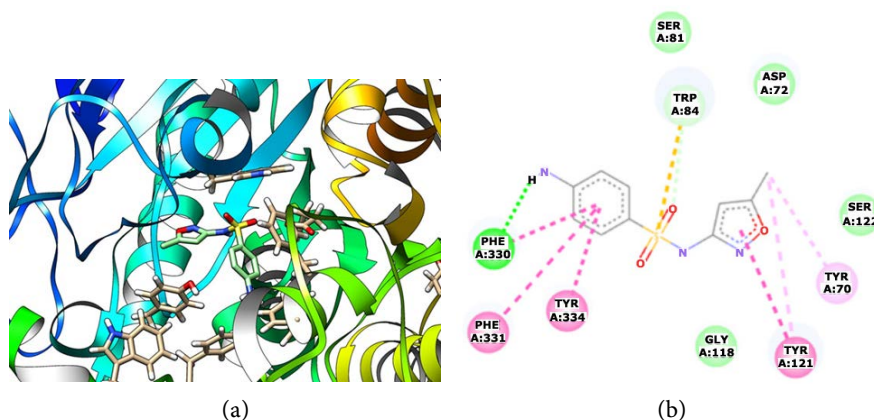


Figure 7. (a) Sulfamethoxazole interacting with AChE. (b) Interactions with amino acid residues of the catalytic site.

site interaction responsible for inhibition of AChE has a good permeability in the blood-brain barrier which is crucial for the development of drugs that target mainly brain cells, for example in Alzheimer's disease. It is important to note that all the ligand molecules are highly absorbable in human intestinal tissue and are not inhibitory to any of the cytochromes listed in **Table 3**, with the exception

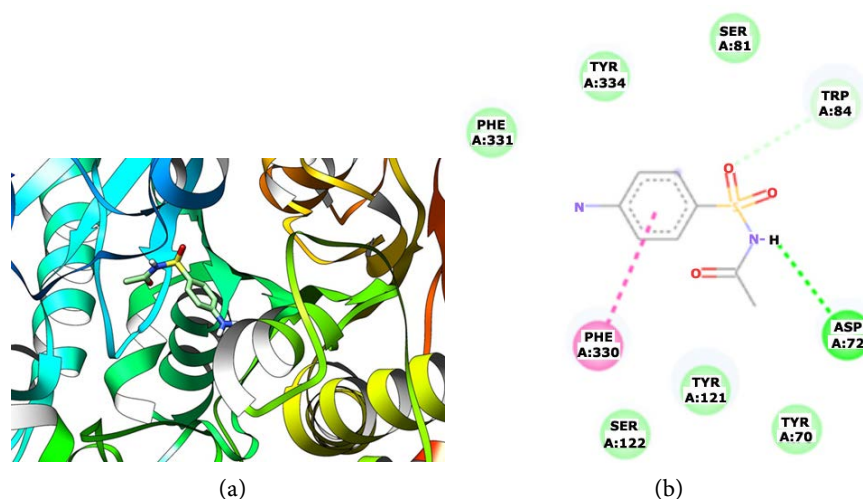


Figure 8. (a) Sulfacetamide interacting with AChE. (b) Interactions with amino acid residues of the catalytic site.

of sulfasalazine which has CYP450 cytochrome inhibitory capacity. Only sulfadimidine and sulfadiazine are biodegradable in biological media. None of the sulfonamides tested positive for mutagenesis, carcinogenicity and therefore carcinogenicity testing is not necessary. Moreover, none of these compounds induces significant acute oral toxicity, which may be an advantage over drugs already approved for the treatment of the disease, such as donezepil.

4. Conclusions

The different structures of the sulfonamide group molecules were investigated by molecular docking and ADMET techniques, presenting results with good affinities of interaction with residues of the catalytic site of the AChE enzyme, these are responsible for inhibiting in a reversible way the promising biological target in Alzheimer's disease therapy.

Despite the present *in silico* study, further computational and experimental investigations (*in vitro*, *in vivo* and clinical trials) are necessary to prove the inhibitory effect and the correct dosage of these compounds. However, the results of this work encourage even more advances in research regarding the treatment of Alzheimer's disease and highlight the importance of these for further research in the discovery of new therapies and the synthesis of new drugs with better efficacy.

Conflicts of Interest

The authors declare no conflicts of interest.

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