The 9th International Electronic Conference on Medicinal Chemistry (ECMC 2023)
01–30 November 2023 | Online

Molecular docking analysis of enaminocarboxamide-based small molecules against Acetylcholinesterase, drug-likeness, and ADME prediction

Chaired by Dr. Alfredo Berzal-Herranz and Prof. Dr. Maria Emília Sousa

pharmaceuticals MDPI

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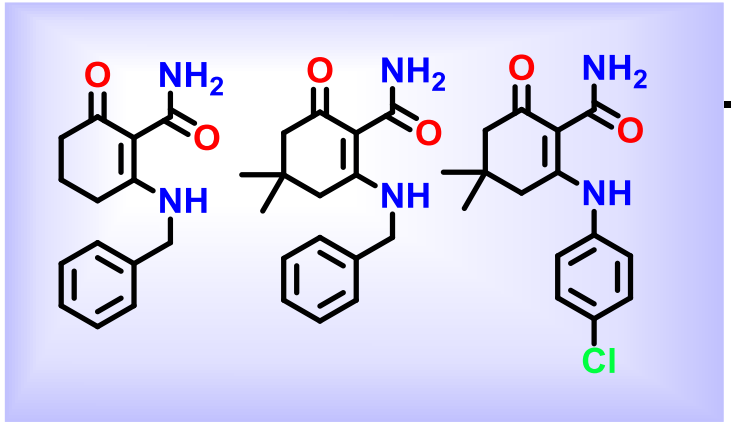
Graphical Abstract



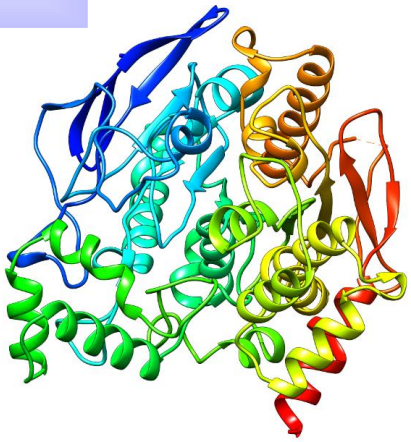
In silico study (Drug-Candidate)

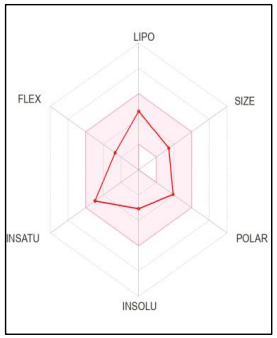
Molecular Docking

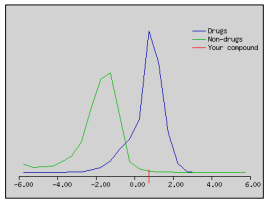
ADME Prediction with SwissADME

Drug-likeness with MolSoft

Investigation of enaminocarboxamide derivatives as AChE inhibitors anti Alzheimer's disease Agents







Abstract: Finding treatments to neurodegenerative diseases such as Alzheimer's disease AD is one of the biggest challenges for scientists working in the medicinal field, due to the fact that these pathologies are complex, difficult to prevent, and multifactorial. Indeed, AD progression involves different proteins and enzymes including Acetylcholinesterase AChE. There is no cure for AD, but there is symptomatic treatments in which the AChE inhibitors takes the major place, that is what made AChE the main drug target in the conception of new anti-AD agents.
Our interest was sought to a specific class of small molecules containing the enaminocarboxamide scaffold combining both enaminone and primary amide moieties. A docking simulation was performed to explore the binding mode of studied compounds and the active site of AChE (PDB: 1ACJ) using Schrödinger suite for the docking calculation and Chimera for the 3D visualization. The studied derivatives showed a great stability inside the cavity of AChE with a docking score included between -9.685 and -8.726 kcal.mol-1. This stability was supported by different interactions with the key residues of the active site including hydrogen bonds with His440, a water bridge with Trp84 as well as pi-pi stacking with Trp84 and Phe330. Additional interactions were perceived with Ser200 and Tyr121 residues. The promising results of docking simulation prompted us to complete the in silico investigation by predicting drug-likeness and ADME properties of the studied compounds using MolSoft and SwissADME as accurate predictive tools.

Keywords: Acetylcholinesterase; Alzheimer's disease, Docking simulation; Enaminocarboxamide

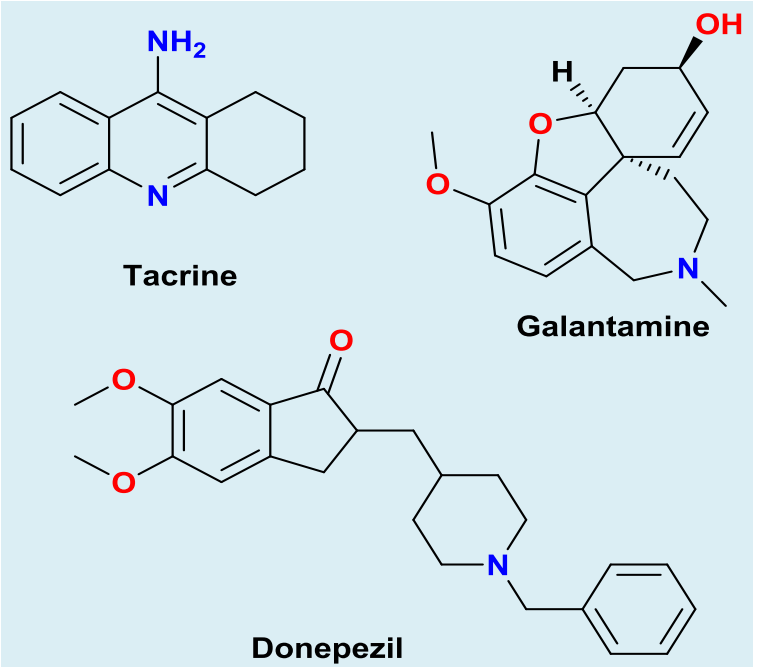
Introduction

Normal aging

Normal occasional memory loss

Alzheimer's patients

Memory loss that interrupts completing daily tasks
Problems in speaking
Confusion

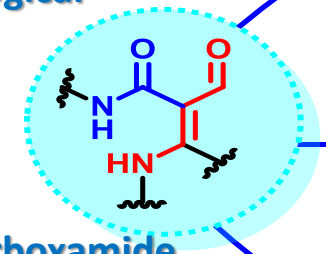


Main anti-AD agents are AChE inhibitors

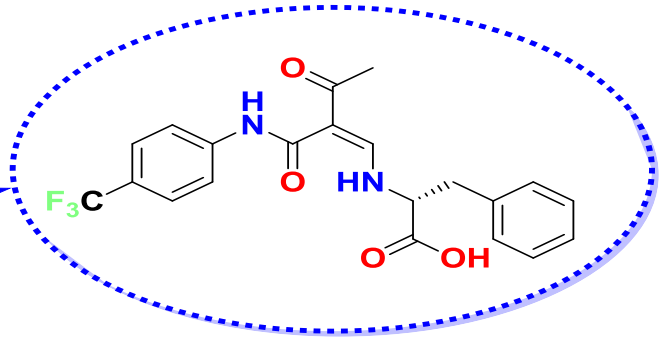
D.B. Hogan, Can J Psychiatry. 59, 618 (2014).

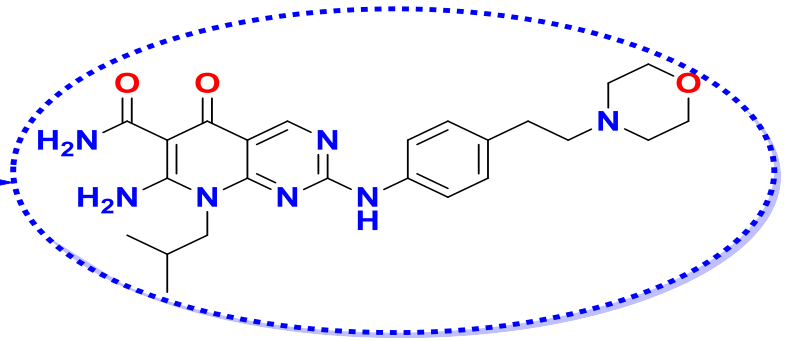
Introduction

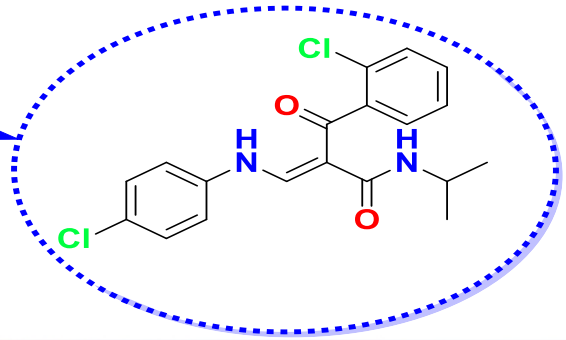
Pharmacological activities of enaminocarboxamide derivatives



- Anticancer
- CaMKII kinase inhibitor
- Anxiolytic

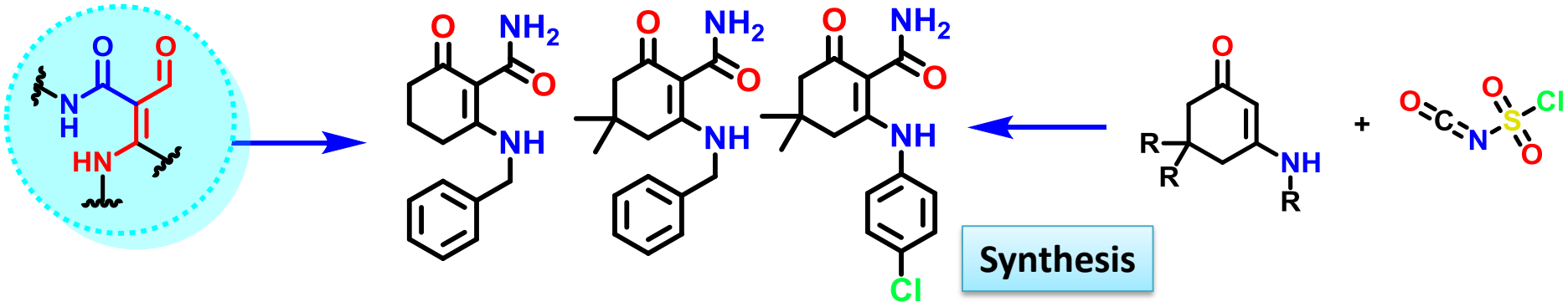






P. Subramamiam, C. Ramasubbu, S. Athiramu, S. Arumugam, M. Alagumuthu, Arch. Pharm. Chem. Life Sci. 352, 1800244 (2018).
P. Beauverger, G. Begis, S. Biscarrat, O. Duclos, G. McCort, US8975250B2. (2015).
D.J. Hogenkamp, T.B.C. Johnstone, J-C. Huang, W-Y. Li, M. Tran, E.R. Whittemore, R.E. Bagnera, K.W. Gee, J. Med. Chem. 50, 3369, (2007).

Introduction



In order to conceive new potentially active compounds as drug-candidates as anti-AD agents, we were interested in the *In silico* study of some enaminocarboxamide-derived compounds synthesized from enaminones and CSI[1], we performed a docking simulation to these compounds in the active site of AChE, and a prediction of pharmacokinetic properties.

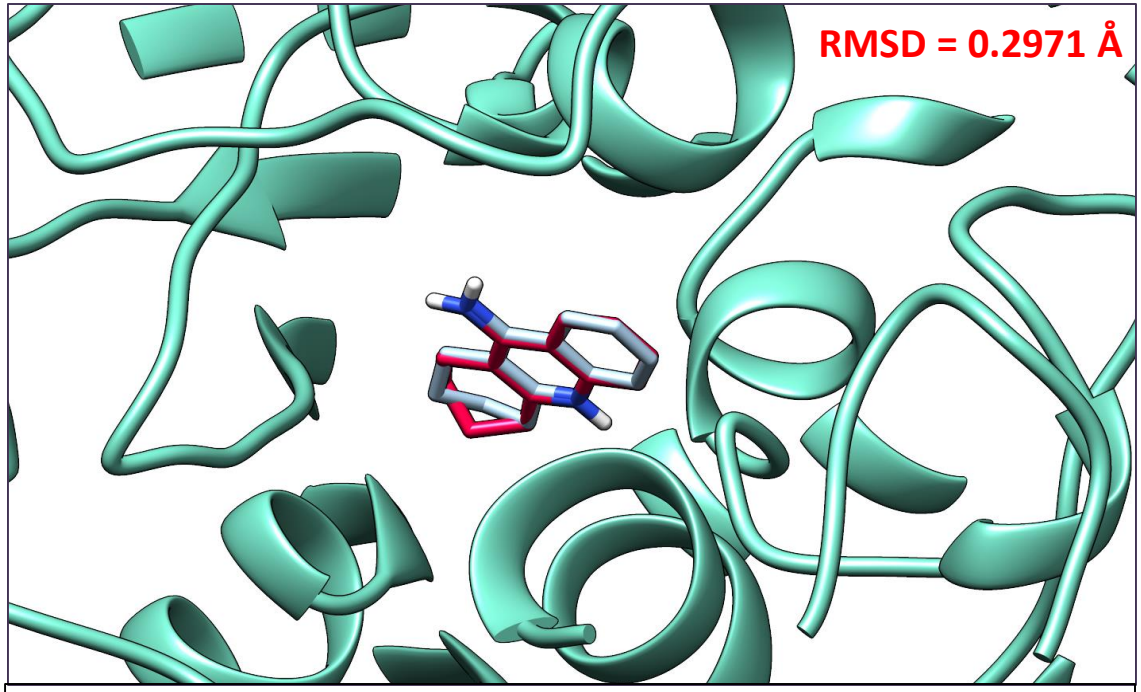
[1] Y. O. Bouone, A. Bouzina, N-E. Aouf, M. Ibrahim-Ouali, Res. Chem. Interm., 49, 1349 (2023).

Results and discussion

Molecular docking

Re-docking

Resolution of the crystal (PDB: 1ACJ): 2.80 Å



Superimposition of the co-crystalized ligand and the docked ligand.

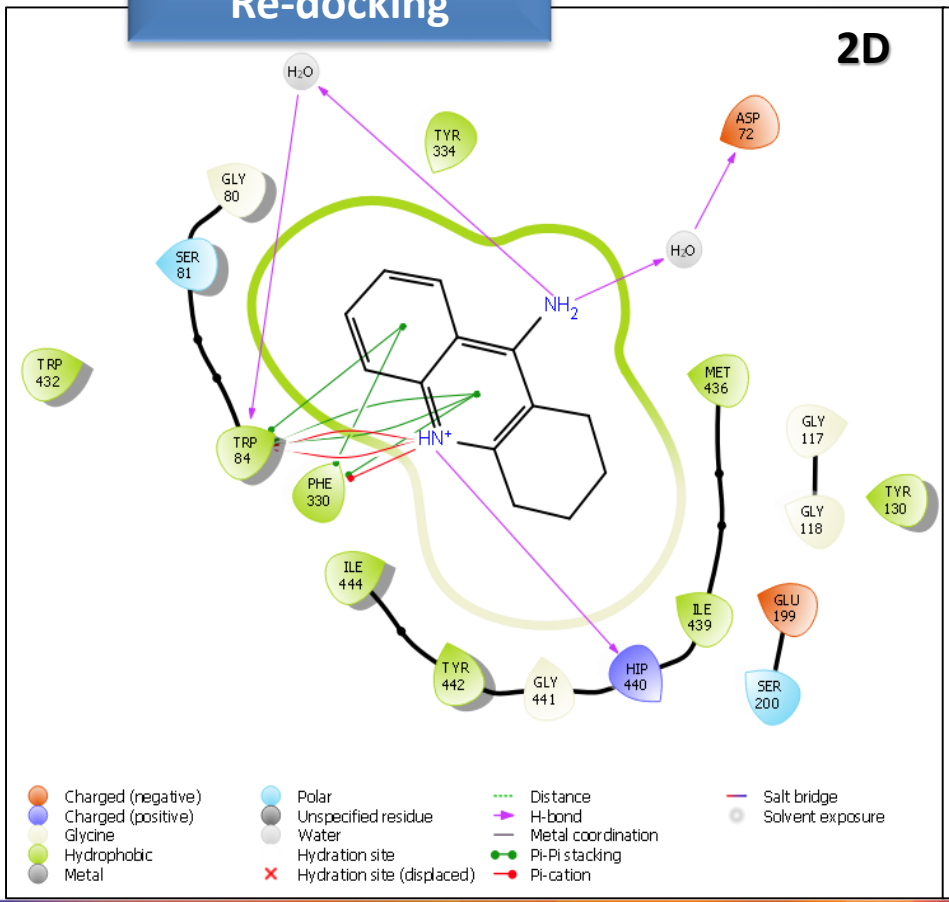
Validation of the docking protocol

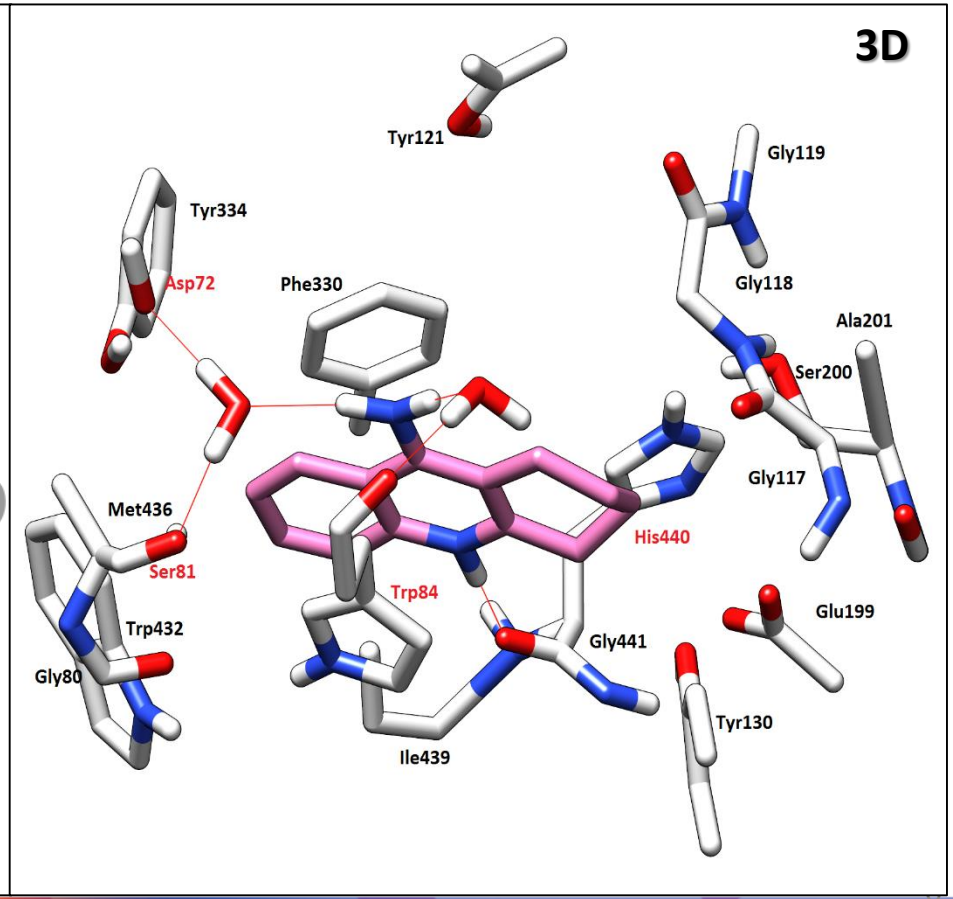
- PDB: 1ACJ
- Protein preparation with (protein preparation wizard): optimization In presence of water molecules
- Ligand preparation with (OPLS3) force field.
- Docking with SP (Standard precision).

Results and discussion

Molecular docking

Re-docking

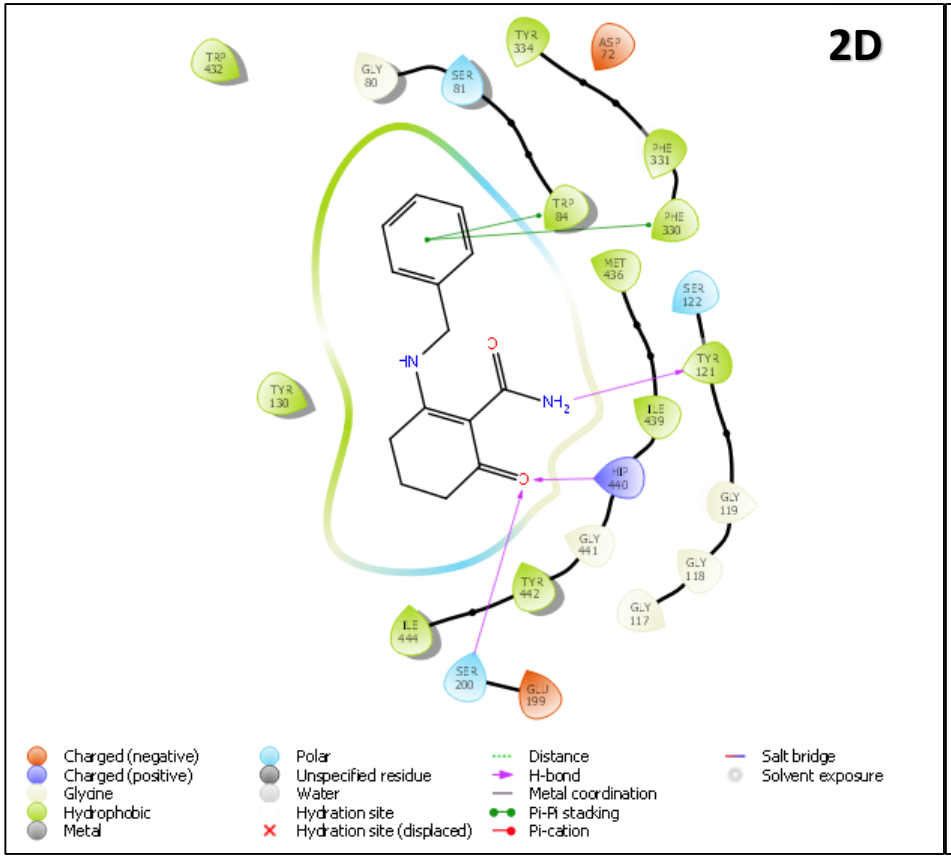


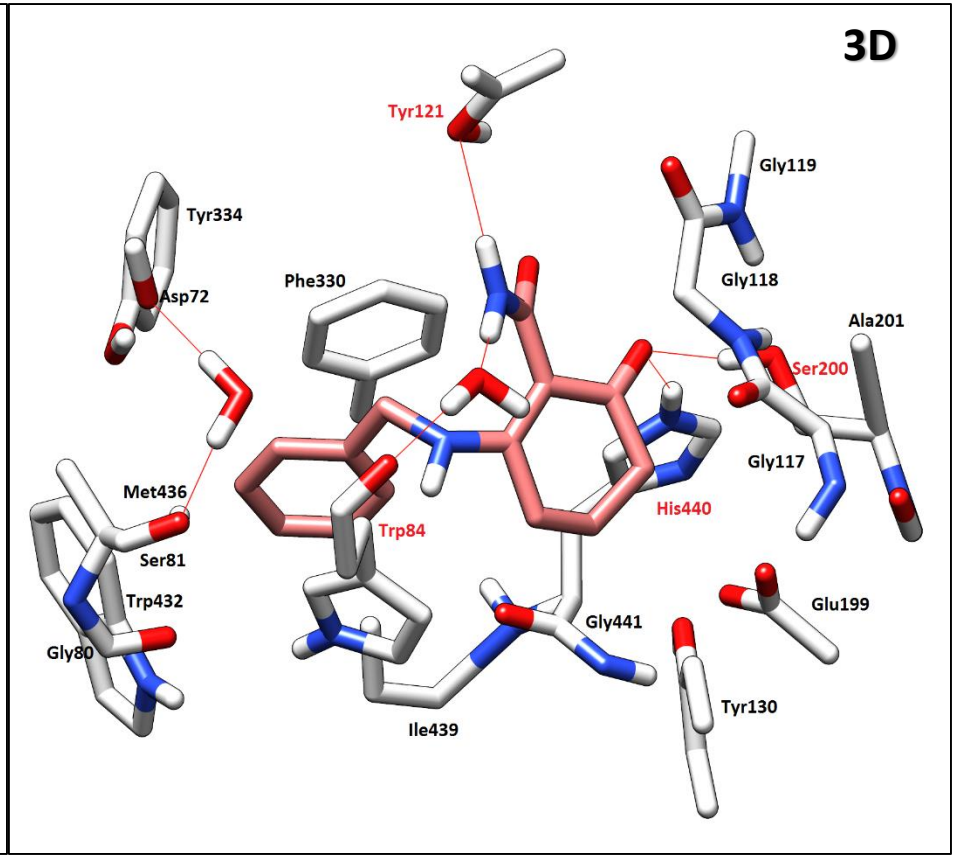


Results and discussion

Molecular docking

Compound 1

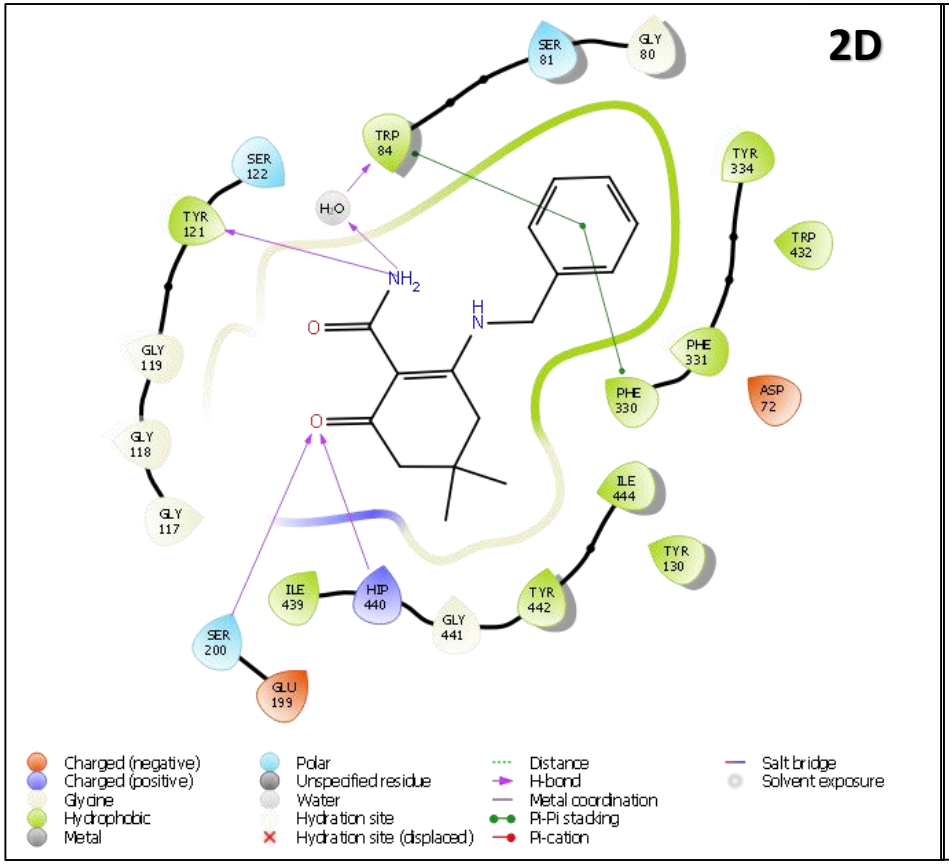


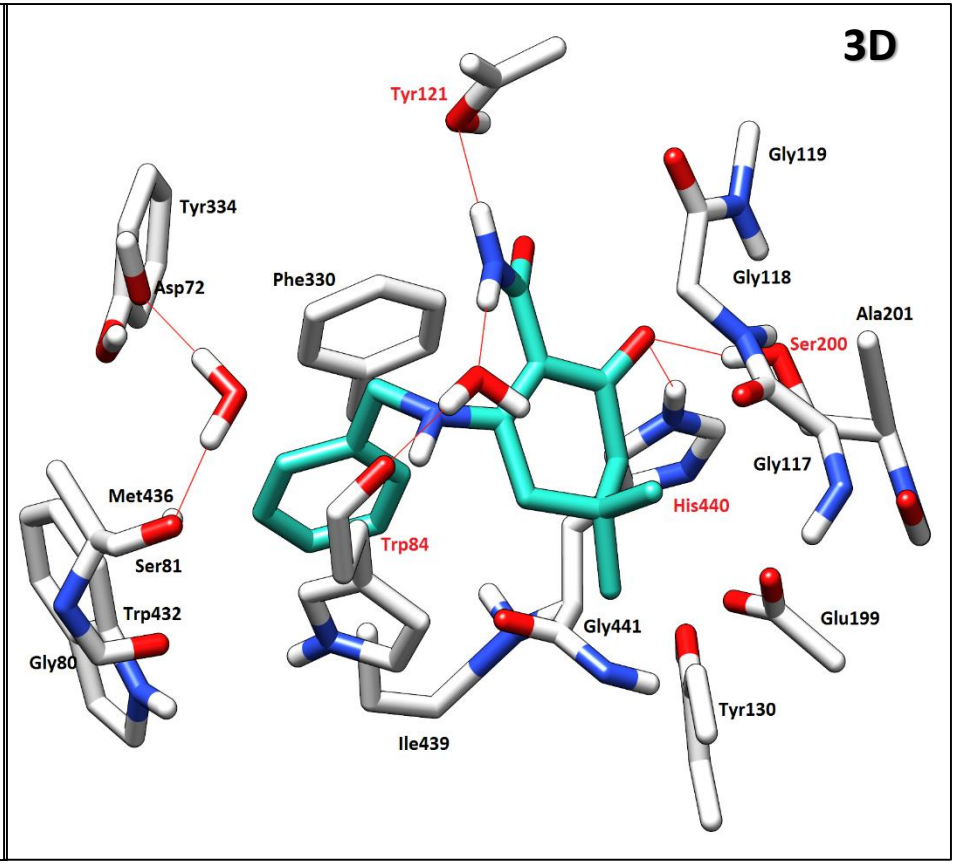


Results and discussion

Molecular docking

Compound 2

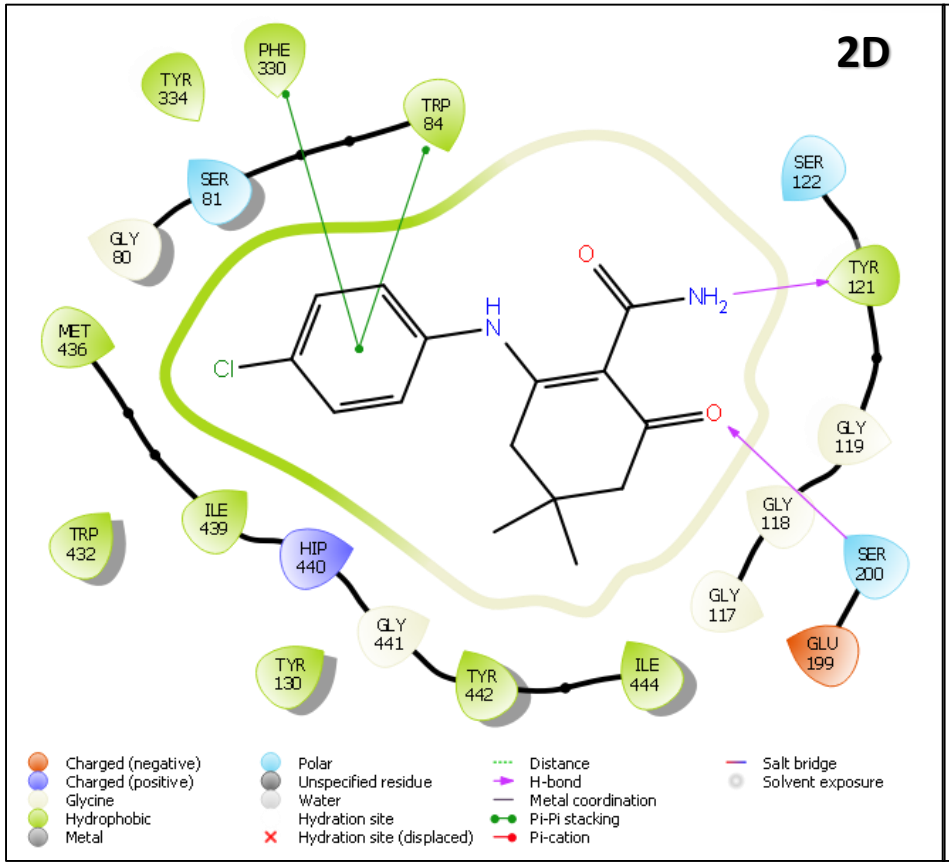


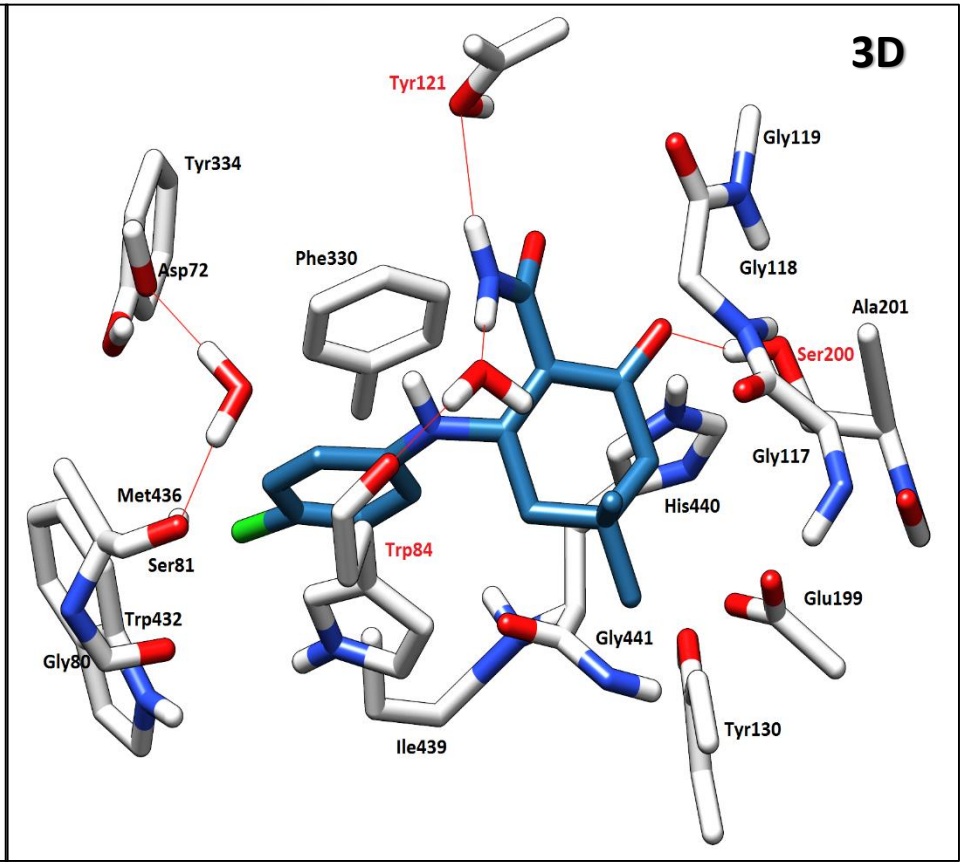


Results and discussion

Molecular docking

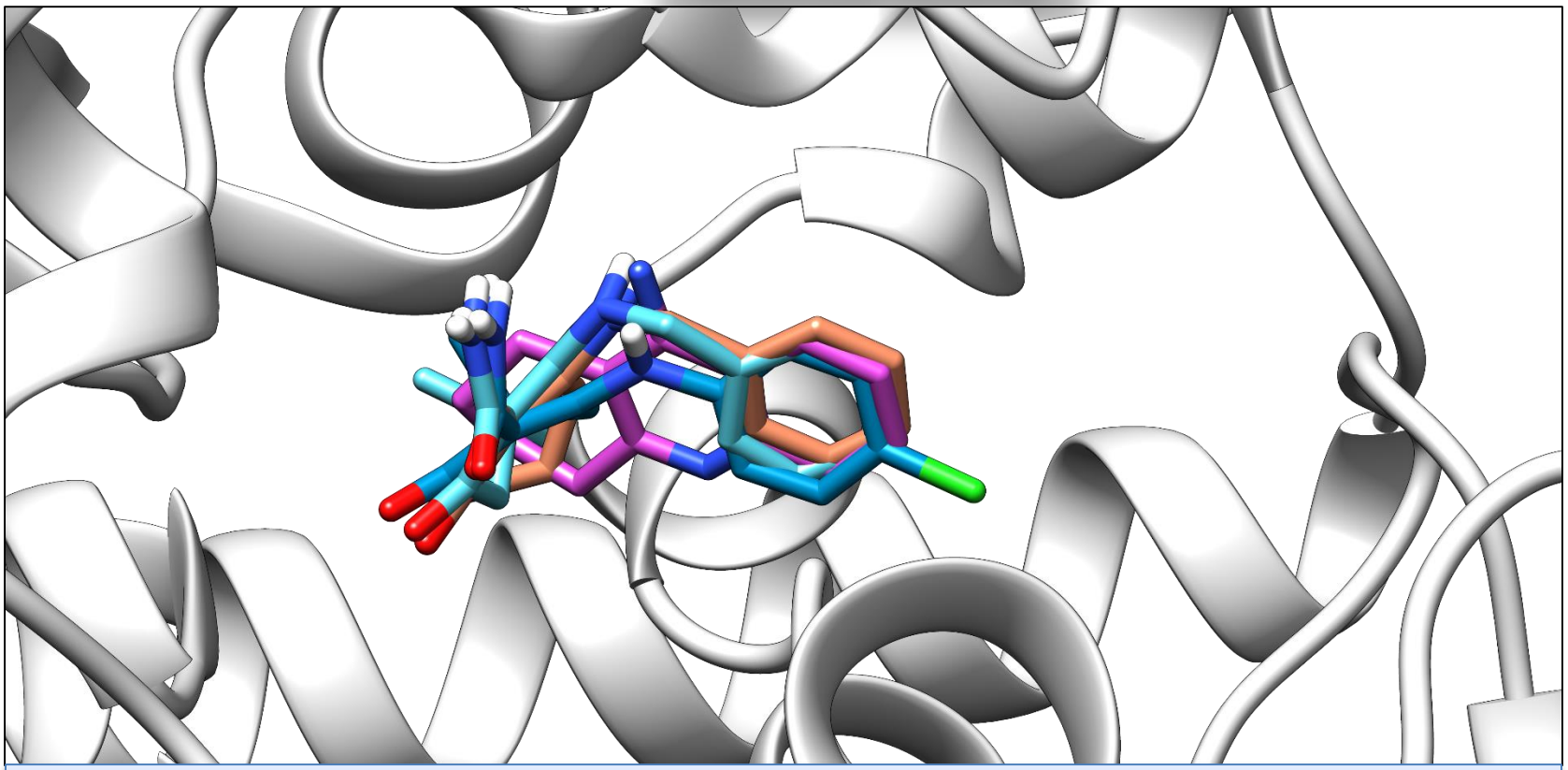
Compound 3





Results and discussion

Molecular docking



Superimposition of Tacrine and all the studied compounds in the active site of Acetylcholinesterase

Results and discussion

Molecular docking

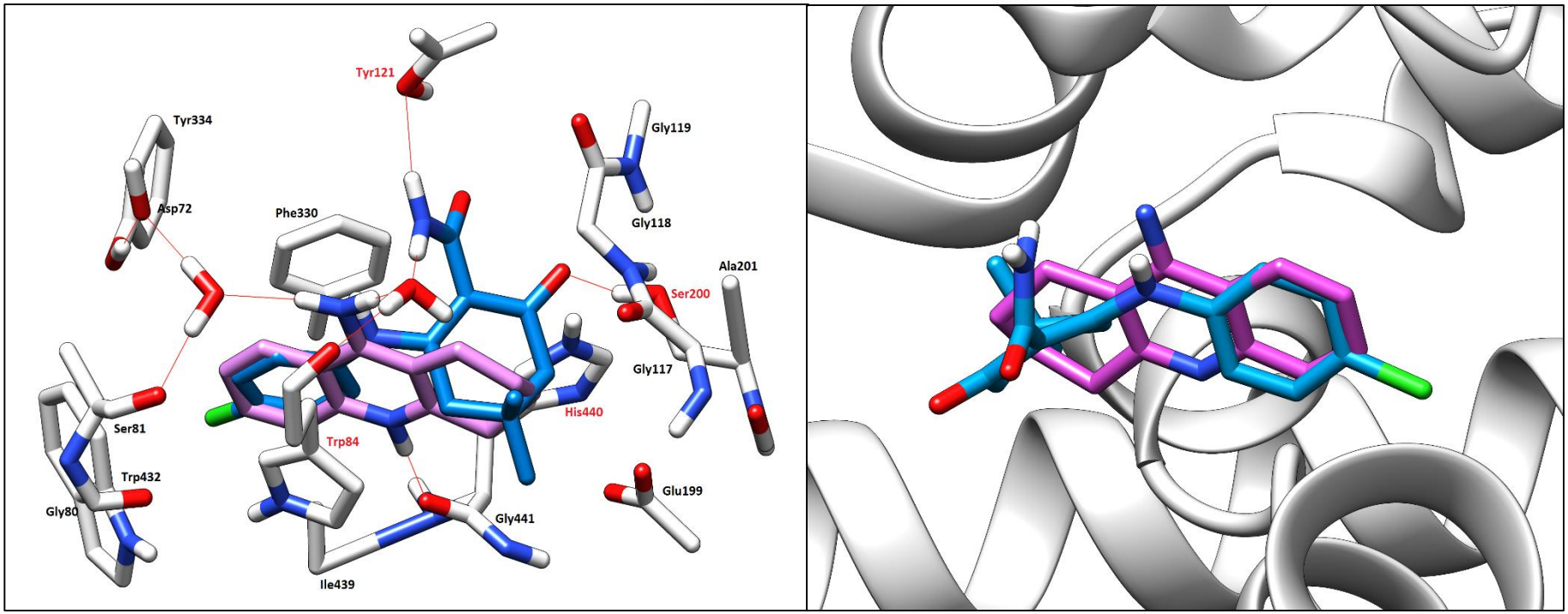
Entry	Docking score (kcal/mol)
1	-8.726
2	-9.178
3	-9.685
Tacrine	-10.567

Compound **3** showed the best docking score (-9.685) among the investigated compounds followed by compound 2 (-9.178) that formed interactions similar to those formed by the reference ligand

Entry	H bonds	Hydrophobic interactions
1	**His440**, Ser200, Tyr121	**pi-pi stacking (Trp84, Phe330)**
2	**His440**, Ser200, Tyr121, **H_2O-Trp84**	**pi-pi stacking (Trp84, Phe330)**
3	Ser200, Tyr121	**pi-pi stacking (Trp84, Phe330)**
Tacrine	**His440, H_2O-Asp72, H_2O-Trp84**	**pi-pi stacking (Trp84, Phe330)**

Results and discussion

Molecular docking



Superimposition of the co-crystallized ligand Tacrine (pink) and compound 3 (blue) with the best docking score inside the cavity of Acetylcholinesterase

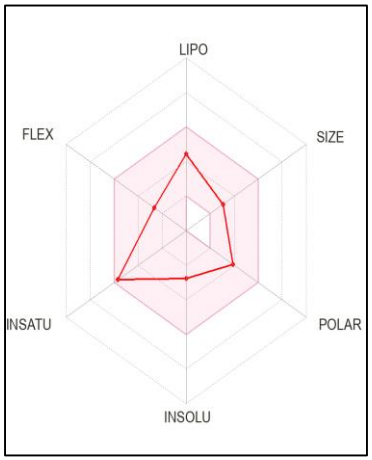
Results and discussion

ADME prediction

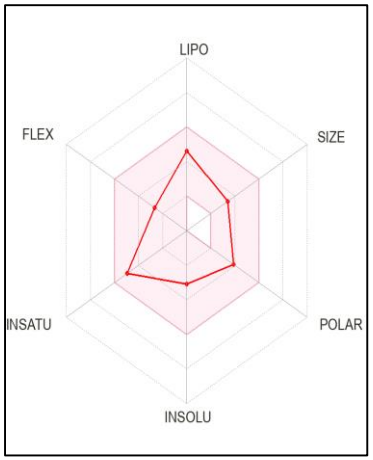
Property	1	2	3
MW (g/mole)	244.29	272.34 g/mol	292.76
Rotatable bonds	4	4	3
H-bond donor	2	2	2
H-bond acceptor	2	2	2
Violations	1	0	1
Log Po/W iLogP	1.85	2.16	1.84
Log S ESOL	-2.77	-3.10	-4.07
GI	High	High	High
BBB	No	Yes	Yes
Log Kp	-6.17 cm/s	-6.14 cm/s	-5.39 cm/s
Bioavailability Score	0.55	0.55	0.55
TPSA (˚A)	72.19 Å²	72.19 Å²	72.19 Å²

Results and discussion

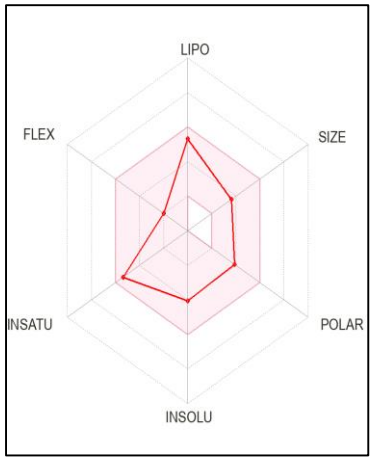
ADME prediction



Compound 1



Compound 2



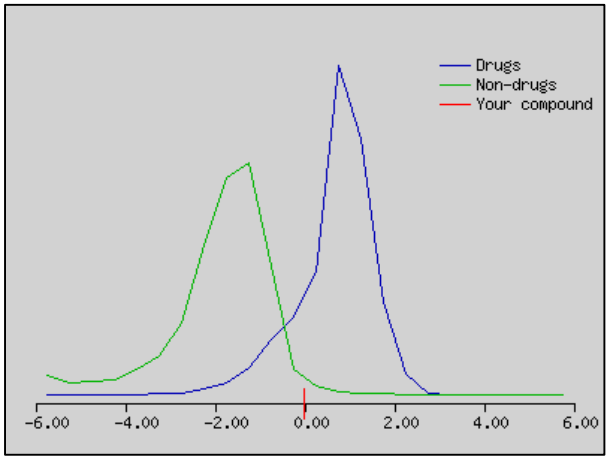
Compound 3

Bioavailability radars

Bioavailability radars of studied compounds show good results. All compounds are inside the optimal norms of flexibility, lipophilicity, solubility, polarity, size, and saturation.

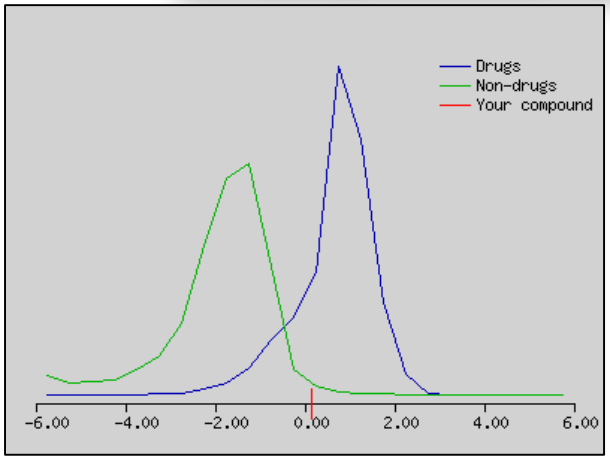
Results and discussion

Drug-likeness



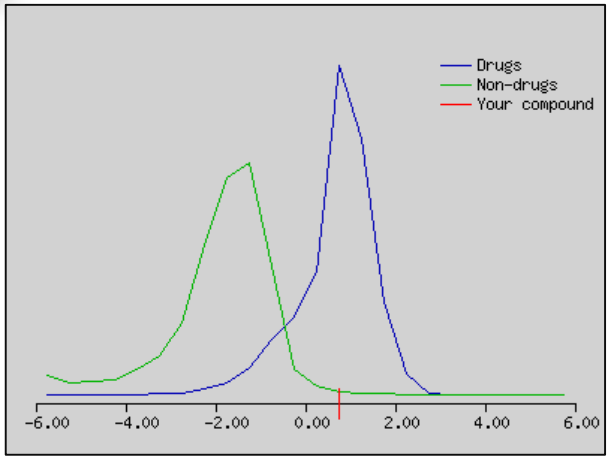
DLS : -0.00

Compound 1



DLS : 0.14

Compound 2



DLS : 0.75

Compound 3

Drug-likeness scores of studied compounds is included in the range 0-0.75 in which compound 3 got the highest score. All studied enaminocarboxamides appear within the drugs range (Blue plot).

Conclusions

Three small molecules containing the enaminocarboxamide moiety were subjected to an *in silico* study in order to investigate their potentiality to become drug-candidates.

A docking simulation was performed to explore the binding mode of the studied compounds within the cavity of the Acetylcholinesterase enzyme with the purpose of predicting their ability to act as anti-Alzheimer disease agents by inhibiting AChE. Results are considered as promising for compound 2 that showed a good docking score -9.178 and formed interactions with the key residues of the AChE active site.

An ADME prediction was carried out and indicated that all compounds are in the optimal ranges of bioavailability parameters. Further, compound 2 is drug-like according to Lipinski, Ghose, Veber, Egan, and Muegge rules while compound 1 and 3 respected all the previously cited rules except one. In addition, drug-likeness score according to MolSoft is higher for compound 2 and 3.

Acknowledgments

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