Journal of the Serbian Chemical Society
JSCS@tmf.bg.ac.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *87* (3) 293–306 (2022)
JSCS–5522
Original scientific paper
Published 1 October 2021

Benzene-1,3-diol derivatives as the inhibitors of butyrylcholinesterase: An emergent target of Alzheimer's disease

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(Received 16 April, revised 21 August, accepted 23 August 2021)

Abstract: Molecular docking is a powerful and significant approach for the identification of lead molecules on the basis of virtual screening. With it a large number of compounds can be tested and based on the scoring function and ranking, the conclusion can be made about how the selected compounds can inhibit the targeted protein/receptor. Considering the importance of selective inhibitors of cholinesterase in the treatment of Alzheimer disease, this research is focused on the determination of the mechanism of binding interactions of few benzene-1,3-diol derivatives within the active site of both acetyl-cholinesterase (AChE) and butyrylcholinesterase (BChE). All the selective ligands were found to have a greater binding affinity with the BChE when compared to that of AChE, by an average value of ~−28.4 and ~−12.5 kJ/mol, respectively. The results suggested that the identified inhibitors can be used as the lead compounds for the development of novel inhibitors of the targeted enzymes against some specific diseases, thus opening the possibility of new therapeutic strategies.

Keywords: molecular docking; acetyl-cholinesterase (AChE); butyrylcholinesterase (BChE); active pocket.

INTRODUCTION

Alzheimer's disease (AD), a neurodegenerative disorder, is characterized by the significant decrease in the level of acetylcholine (ACh) neurotransmitter.[1,2]

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https://doi.org/10.2298/JSC210416073D

This neurotransmitter (ACh) plays a significant role in the normal processes of learning and memory,activating muscarinic and nicotinic receptors of the central nervous system.[3,4] The acetyl-cholinesterase (AChE) and the butyrylcholineesterase (BChE) are well-studied enzymes that are involved in the hydrolysis of ACh to acetate and choline in the synaptic cleft.[5,6] The major signs and symptoms of AD include dementia, confusion, memory lapses, misinterpreting of the spatial relationships, and the decline in the ability to speak, write, think, reason, making decisions and planning. Personality and behavioural changes have also been observed including depression, anxiety, agitation, social isolation, mood swings, diurnal rhythm disturbances and delusions.[7,8] AD is characterized by various markers in the brain including a large number of amyloid plaques surrounded by the neurofibrillary tangles, vascular damage from plaque deposition and neuronal cell degradation. The main component of plaques is amyloid β protein and also the major cause of AD. The deposition of this notorious protein leads to the development of other symptoms.[9,10] Head injuries, progression of age, sequelae of delivery, ataxic fever, paralysis, mania, apoplexy, mercury abuse, wine abuse, political upheavals, unhappy love, dietary excess, masturbation, unfulfilled love, domestic problems, poverty and fears are among the causes of AD that emerged in the last century.[11,12]

Recent research has revealed that in the brain of patients suffering from AD, the level of AChE is considerably reduced whereas that of BChE increases, thus, aggravating the toxicity of β-amyloid peptide. In such instances, it is possible that BChE may be more suitable target than AChE.[13] Both AChE and BChE share 53 % amino acid sequence similarities of their active sites.[14] Recently, the increased level of BChE has been studied in AD patients therefore resulted in the increased β-amyloid peptide toxicity.[15] It is not surprising that cholinesterase inhibitors have shown better results in the treatment of AD than any other strategy explored.[16] Hence, the search for the discovery of novel cholinesterase inhibitors (ChE) is expected to continue in future since the current ChEs inhibitors are reported to have some side effects.[17] The availability of several crystal structures of both ChEs (in complexes) with different inhibitors provides the possibility to apply the docking protocol to explore the protein inhibitor complexes in terms of the nature of their interactions.[18] Although there are considerable efforts being made for understanding the etiology of the neurodegenerative disorder (AD) but the development of novel inhibitor of specific target remain as an important concern in the treatment of patient. The main challenge in the development of the inhibitors of the selected targets is their potency, selectivity and drug-ability. Therefore, there is a need of deep understanding of the structure activity relationships and functions of the selective inhibitors of selected enzymes.[19]

Over the past few years, the high-throughput screening (HTS) has become a cornerstone technology of pharmaceutical research[20] but it is very expensive and

technically impossible to screen a huge library of chemical compounds using these biochemical techniques (high throughput screening). In this regard, computational methodologies have become a vital element of many drug discovery programmes, from the hit identification to the lead optimization and beyond.[21] The high throughput computational screening using pharmacophore based virtual screening, molecular docking and quantum computational studies are among the most cost-effective technique through which millions of compounds can be screened rapidly.[22] Many heterocyclic compounds have been synthesized and reported for their potential to inhibit the targeted enzymes, but their molecular target was not fully defined. Among those heterocyclic derivatives, quinolones and dibenzoazepine have been found as the most attractive scaffolds due to their broad range of biochemical activities, such as angiotensin converting enzyme (ACE) inhibitor along with anti-convulsant, neuroprotective and anti-inflammatory properties.[23]

The current study is designed to relate the interest of some benzene-1,3-diol obtained from natural source as cholinesterase inhibitors, but more selective as BChE inhibitors. The structures were drawn using ACD/ChemSketch 12.01, and 3D optimized.[24] The study comprises the smart approach by using computational 4.2 software.[26] Moreover, the ADMET studies were also performed using ADMET tools to find value added product in short time without wasting of chemicals. The crystal structure of both enzymes co-crystalized with their inhibitors were obtained from the protein data bank.[25] The selected compounds were further explored along with novel inhibitors to determine the possible binding interactions of different amino acids within the active site of both enzymes, respectively, using Autodock LAB 2.0.[27] The deep understanding of the structure activity relationships and functions of the identified inhibitors/drug-like molecules provide a great hope for the development of future novel drugs.

EXPERIMENTAL

In order to gain insight into the binding interactions, the molecular docking studies of the selected compounds were performed using AutoDock 4.2.[26] The crystal structure of the human AChE (PDB ID 4BDT) bound to standard inhibitor huprine W and human BChE (PDB ID 4BDS) bound to standard inhibitor tacrine, Fig. 1, were downloaded from RCSB Protein Data Bank and used for docking studies.[25] The visual inspection for the binding pattern was done using the Discovery Studio Visualizer software, Version 17.2.[28]

Docking procedure

Ligand preparation. The selected compound structures were downloaded in Spatial Data File (SDF) format from PubChem.[29] The structures of the compounds were drawn using ACD/ChemSketch 12.01, and 3D optimized.[24] The 3D structures were converted to PDB format which were further processed by Autodock 4.2. The International Union of Pure and Applied Chemistry (IUPAC) name and InChIKey of the selected compounds are mentioned in Table I and their respective structures are given in the Supplementary material to this paper.

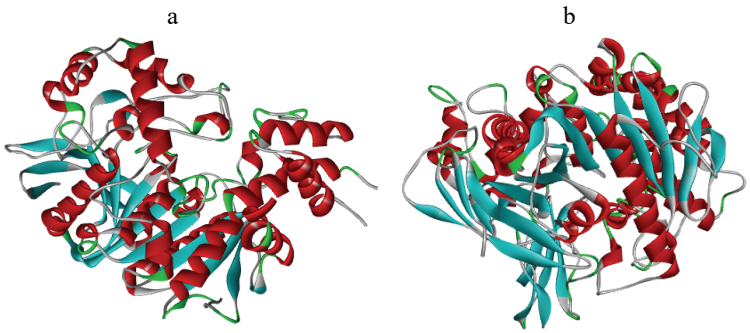

Fig. 1. Crystal structure of: a) human AChE (PDB ID 4BDT) and b) human BChE (PDB ID 4BDS) from Protein Data Bank (https://www.rcsb.org/search).[25]

Table I. List of the selected compounds for study

PubChem CID	Code	IUPAC name	InChIKey
5054	**1a**	Benzene-1,3-diol	GHMLBKRAJCXXBS-UHFFFAOYSA-N
10333	**1b**	4-Methylbenzene-1,3-diol	FNYDIAAMUCQQDE-UHFFFAOYSA-N
17927	**1c**	4-Ethylbenzene-1,3-diol	VGMJYYDKPUPTID-UHFFFAOYSA-N
87874	**1d**	4-Propylbenzene-1,3-diol	DJDHQJFHXLBJNF-UHFFFAOYSA-N
205912	**1e**	4-Butylbenzene-1,3-diol	CSHZYWUPJWVTMQ-UHFFFAOYSA-N
3610	**1f**	4-Hexylbenzene-1,3-diol	WFJIVOKAWHGMBH-UHFFFAOYSA-N
3014087	**1g**	4-Tert-butylbenzene-1,3-diol	YBKODUYVZRLSOK-UHFFFAOYSA-N
75294	**1h**	4-Benzylbenzene-1,3-diol	QVFIWTNWKHFVEH-UHFFFAOYSA-N
11171903	**1i**	4-(1-Phenylethyl)benzene-1,3-diol	PQSXNIMHIHYFEE-UHFFFAOYSA-N
24849532	**1j**	4-[2-(2,4-Dihydroxyphenyl)ethyl]-benzene-1,3-diol	WKIFTWPZTZUMRN-UHFFFAOYSA-N

Preparation of enzyme (receptor)

Before docking, the protein structure was prepared and refined using Autodock 4.2.[26] The standard preparation steps included the removal of co-crystal ligands and water molecules, followed by the addition of hydrogen and gasteiger partial charges to the protein structure. The protein was set to be rigid and ligands were allowed to dock within the activation loop of selected protein. The active site of a protein was determined by selecting a dimension grid of 60×60×60 Å^3 around the co-crystal ligands, *i.e.*, huprine W in case of AChE and tacrine in case of BChE.

Molecular docking

After preparation of the ligand and the ptrotein files, the Autogrid and Autodock utility of Autodock 4.2 programme were used for docking protocols. The software used the in-house default forcefield and the Lamarckian genetic algorithm (LGA), as a search parameter. LGA is a type of random or stochastic docking The algorithm, which actually deals with the calculation of random changes in flexible parts of the ligand, further determines its interaction with the amino acid residues of active site pocket. The Autodock 4.2 software calculates the different energy parameters and stores them, accordingly. The number of poses were set to 100 and population size was set upto 300. The high number of poses is a good practice to increase

the accuracy of the result. After the docking, top ten docked conformation with the best ligand–protein interaction and high binding energy were selected for the comparison with co-crystal standard ligand.

Visual inspection

The structures of each selected compound against AChE and BChE were visualized and inspected for the best fit orientation within the active pocket of the enzyme, respectively. This was done using Discovery Studio Visualizer software, version 17.2.

Drug likeness evaluation and calculated ADME properties

The absorption, distribution, metabolism and excretion (ADME) properties for all the tested compounds were calculated using online the integrated tool ADMET LAB 2.0.[27] All the synthesized compounds showed moderate ADME properties as shown later on.

RESULTS AND DISCUSSION

Potential binding site in receptors

The commercially available Molecular Operating Environment 2015.10 (MOE) software[30] was used for the prediction of the most potential active site where the selected ligand can bind and interact within the activation loop of targeted proteins *i.e.*, both AChE and BchE (Fig. 2).

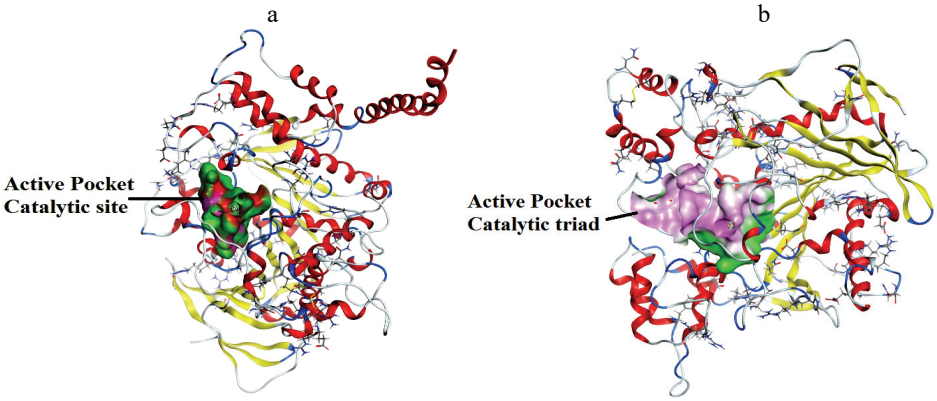

Fig. 2. Binding site prediction of: a) human AChE (PDB ID 4BDT) and b) human BChE (PDB ID 4BDS) using MOE 2015.10.

The active pocket of AChE contained total 36 amino acid residues including; GLN71, TYR72, VAL73, ASP74, GLY82, THR83, TRP86, ASN87, PRO88, TYR119, GLY120, GLY121 GLY122, TYR124, SER125, GLY126, ALA127, LEU130, TYR133, GLU202, SER203, ALA204, TRP236, PHE295, PHE297, SER336, TYR337, PHE338, TYR341, LEU437, TRP439, PRO446, HIS447, GLY448, TYR449 and ILE451. Similarly the active pocket of BChE contained total 45 amino acid residues and includes; GLN67, ASN68, ILE69, ASP70, GLN71, SER72, GLY78, SER79, TRP82, ASN83, PRO84, TYR114, GLY115, GLY116, GLY117, GLN119, THR120, GLY121, THR122, LEU125, TYR128,

GLU197, SER198, TRP231, GLU276, ALA277, VAL280, TYR282, GLY283, THR284, PRO285, LEU286, SER287, VAL288, ASN289, ALA328, PHE329, TYR332, PHE398, TRP430, MET437, HIS431, GLY439, TYR440 and ILE442. The selected ligands formed hydrogen bonding with the amino acid residues of the active pockets. In comparison to AChE, the ligands formed maximum interactions with amino the acid residues of BChE, thus ultimately resulted in the improved binding energies.

Docking analysis studies

In-silico study was conducted using Autodock 4.2 and the visualization of docked conformations were carried out using Discovery Studio Visualizer 17.2. The selected derivatives of benzene-1,3-diol were docked within the activation loop of AChE and BChE enzymes. The most possible 2D and 3D binding interactions of the docked conformations were obtained using Discovery Studio visualizer 17.2. All the ligands selected showed comparable interactions and docking scores with both enzymes, when compared to the standard donepezil. The interactions are given in the Figs. 3 and 4 and docking scores are displayed in Table II.

Visual inspection

The structure of each selected compound against AChE and BChE was visualized for best fit orientation within the active pocket of the enzyme, respectively. Particularly the compounds **1h**, **1i** and **1j** formed stable protein-ligand complex with both enzymes. The results are given in Figs. 3 and 4.

AChE docking studies

In terms of the detailed docking interaction studies, only three potent compounds **1h**, **1i** and **1j** are being discussed here. All the detailed discussion of other compounds are provided in Supplementary material to this paper.

The docked conformation of compound **1h**, **1i** and **1j** showed considerable inhibitory potential of AChE enzyme (Fig. 3). The docking scores of these three compounds were found to be best among all other compounds which were –21.68, –22.02 and –22.60 kJ/mol, respectively. It was seen that compound **1h** contain an aromatic ring as a substituent at 4^{th} position of the core aromatic ring. It was notable that the presence of aromatic ring has significantly increased the docking energy. It might be due to the resonance effect of an aromatic ring. Moreover, the substituted aromatic ring was also involved in alkyl interaction with LEU76 and VAL340. Similarly, compound **1i** contain phenyl ethyl as substituent. This substitution has significantly improved the binding energy, which might be due to positive inductive electron donating effect of ethyl group and the interaction of phenyl ring with LEU76 of the active site. Moreover, the resonating π-electrons of the benzene ring was also involved in the binding interactions with amino acid residues which further improved its docking energy. According to the

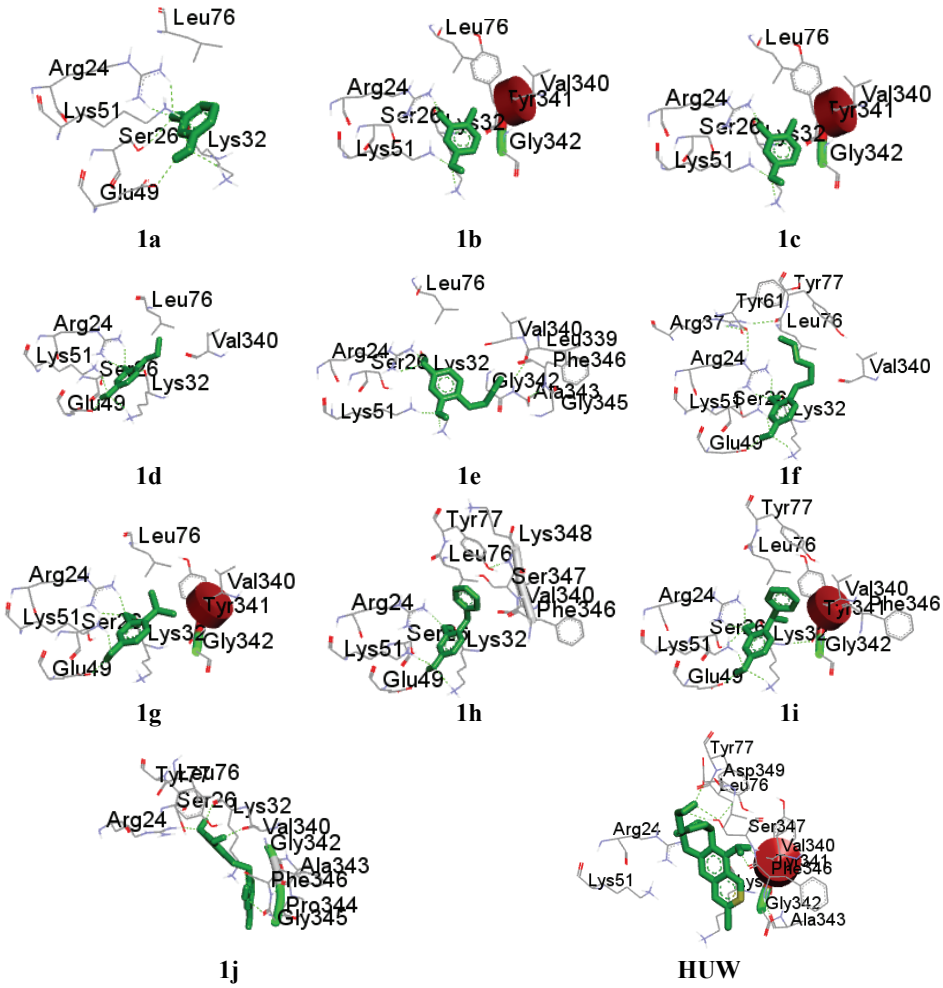

Fig. 3. Protein-ligand complex formed by docked structures of AChE inhibitors.

free binding energy score, compound **1j** was found to be the most potent derivative among all compounds. It was found that the amino acid residues which were involved in bonding and non-bonding interactions with compound **1j** were LYS32, ARG24, VAL340, PHE346, PRO344, LEU76, SER26, TYR77, ALA343 and GLY342. It was observed that the parent compound was substituted with the ethyl phenyl ring which had two hydroxyl groups at ortho position. Previously it was observed that hydroxyl groups were responsible for establishing strong hydrogen bonding with the amino acids of active site. Whereas, the benzene ring was itself involved in strong π-cation and π-sigma bonding with amino acid residues of the active site. Similarly, in the present compound two benzene rings, one ethyl group and 4 hydroxyl groups have significantly contributed to the most pot-

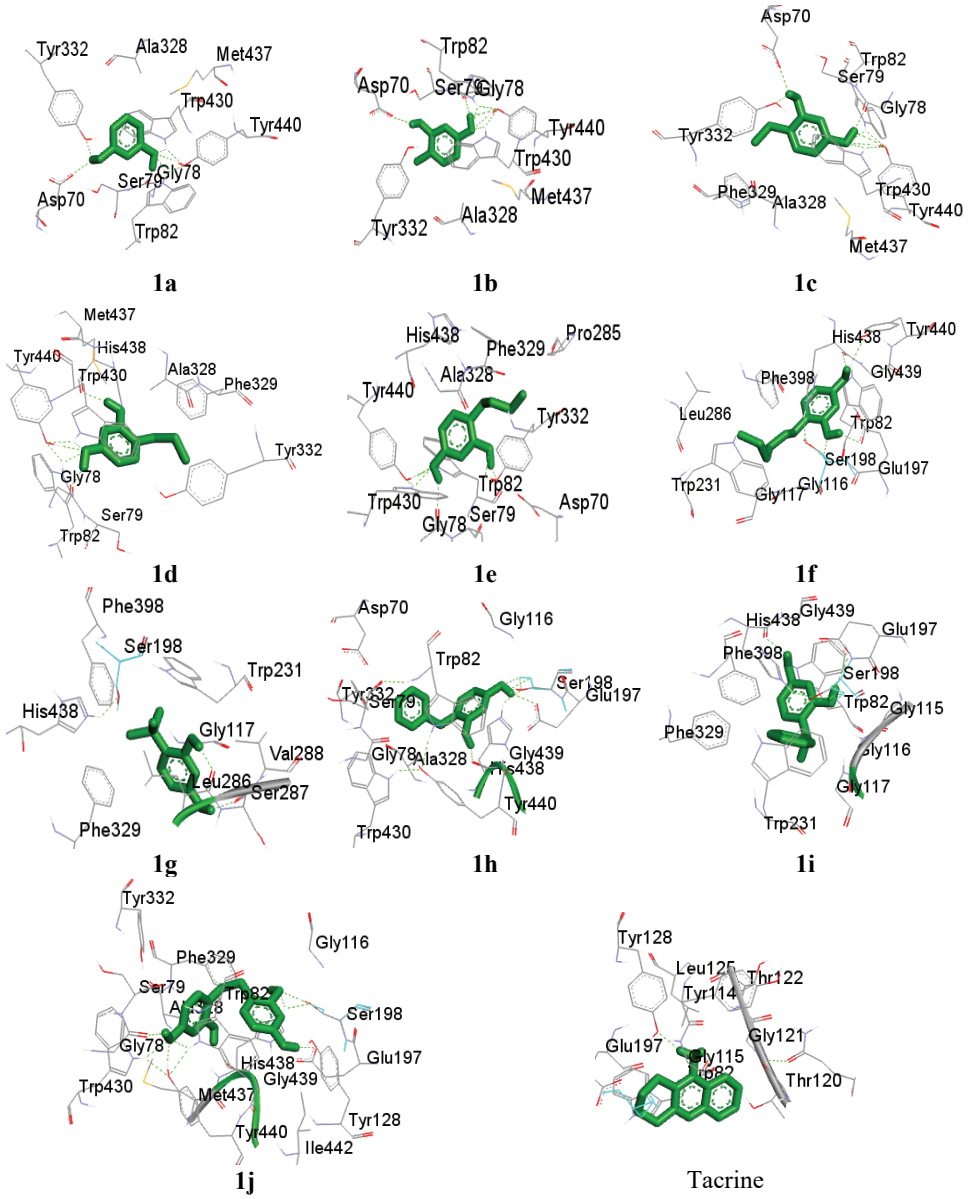

Fig. 4. Protein-ligand complex formed by docked structures of BChE inhibitors.

ent inhibitory potential of the compound. It can be seen that the hydroxyl groups of both rings were involved in hydrogen bonding with LYS32, ARG24, VAL340 and PHE346, respectively. Whereas, the aromatic rings were involved in π-alkyl and π-cation interactions. These factors corresponded to the highest inhibiting

potential of the compound. The detailed 2D interactions of AChE enzyme with all compounds are shown in Supplementary material.

TABLE II. Docking score of selected compounds by considering bound and unbound states of the ligand; **Hup** – huprine, **Tac** – tacrine, **Don** – donepezil

No.	Code	Acetylcholinesterase (AChE)		Butyrylcholinesterase (BChE)		Selectivity for BchE[a]
		Docking score, kJ/mol	Predicted inhibition constant, μM	Docking score, kJ/mol	Predicted inhibition constant, μM	
1.	**1a**	–6.69	2300	–17.58	836.67	2.8
2.	**1b**	–12.60	989.03	–20.68	472.10	2.0
3.	**1c**	–17.04	527.89	–20.89	309.80	1.7
4.	**1d**	–17.20	818.97	–23.19	171.02	4.8
5.	**1e**	–18.50	572.90	–24.82	174.55	3.3
6.	**1f**	–20.59	247.72	–25.03	81.68	3.0
7.	**1g**	–20.05	306.32	–23.19	87.16	3.5
8.	**1h**	–21.68	95.91	–25.07	40.86	2.3
9.	**1i**	–22.02	43.04	–26.92	27.24	1.5
10.	**1j**	–22.60	109.61	–29.14	9.30	12.1
11	**Hup**	–29.01	8.38	–	–	–
12	**Tac**	–	–	–28.84	8.8	–
Ctrl.	**Don**	–30.14	2.67	–32.65	0.035	89

[a]Selectivity index defined as *IC*[AChE]/*IC*[BChE]

Co-crystal ligand of AChE enzyme showed the binding energy of –29.01 kJ/mol. It was notable that the standard compound also possessed the aromatic moiety in its structure, which was responsible for the formation of π-alkyl and π-cation interactions with the amino acids residues. Whereas, the prescence of single hydroxyl group was contributing toward the formation of hydrogen bonding with amino acid residue of the active site. So, it is well understood that the presence of hydroxyl group, aromatic ring and electron donating alkyl groups are important determinants of the anti-cholinesterase activity of the compound (see Supplementary material).

BChE docking studies

In the terms of detailed docking interaction studies, only three potent compounds **1h**, **1i** and **1j** are being discussed here. All the detailed discussion of other compounds are provided in separate Supplementary material.

The docked conformation of compound **1h**, **1i** and **1j** showed the significant inhibitory potential against BChE enzyme (Fig. 4). The inhibitory potential of these derivatives were most potent against the BChE enzyme. The docking scores of these three compounds were found to be best among all other compounds, which were –25.07, –26.92 and –29.14 kJ/mol, respectively. These scores were found to be higher than the docking scores obtained with AChE enzyme which further strengthens the fact that these derivatives are more selective and potent

toward the BChE enzyme. Compound **1h** contain the aromatic ring as a substituent. The substituted aromatic ring was involved in an alkyl interaction with GLY115. Similarly, the compound **1i** contained the phenyl ethyl group as a substituent. This substitution has significantly improved the binding energy which might be due to the positive inductive electron donating effect of the ethyl group and the interaction of phenyl ring with ALA328 of the active site. Moreover, the resonating π-electrons of benzene ring were also involved in the binding interactions with amino acid residues, which further improved its docking energy.

According to the free binding energy score, the compound **1j** was found to be the most potent derivative among all compounds which has the docking score of 29.14 kJ/mol, with the predicted inhibitory constant value of 9.30 μM against BChE enzyme. It was found that the amino acid residues which were involved in bonding and non-bonding interactions with compound **1j** were as follows GLU197, GLY116, GLY117, LEU286, HIS438, TRP231, GLY439, TRP82 and VAL288. It can be observed that the parent compound was substituted with the ethyl phenyl ring, having two hydroxyl groups at *ortho* position. Previously, it was observed that the hydroxyl groups were mainly responsible for establishing strong hydrogen bonding with the amino acids of active site. Whereas, the benzene ring was itself involved in strong π-cation and π-sigma bonding, with the amino acid residues. Similarly, in the present compounds, two benzene rings, one ethyl group and 4 hydroxyl groups significantly contributed to most potent inhibitory potential of the derivative. It can be seen that hydroxyl groups of both rings were involved in hydrogen bonding with GLU197, GLY117, GLY116 and LEU286, respectively. Whereas, the aromatic rings were involved in π-alkyl and π-cation interactions. These factors corresponded to the highest inhibiting potential of **1j** compound. The detailed 2D interactions of BChE enzyme with all compounds are shown in Supplementary material.

The co-crystal ligand tacrine, of BChE enzyme, showed the binding energy of -28.84 kJ/mol. It was notable that the compound **1j** showed much better binding conformation than the standard tacrine. It was evident that the standard and the potent derivatives possessed the aromatic moiety in their structures which was responsible for the formation of stablizing hydrophobic interactions, *i.e.*, π-alkyl and π-cation interactions with the amino acids residues. Whereas, the prescence of hydroxyl group was contributing toward the formation of hydrogen bonding with the amino acid residue of active site. It was observed that the potent 1,3-diol derivatives possessed a larger number of hydroxyl groups, which caused more hydrogen bondings with the amino acid residues of active site. So it was concluded that the presence of hydroxyl group, the aromatic ring and the electron donating alkyl group were the important determinants for the anti-cholinesterase activity of the compounds (see Supplementary material).

Drug likeness evaluation and calculated ADME properties

During the drug discovery process, the determination of ADME properties of drug like molecule is a very important step. These properties were calculated by using online tool ADMET LAB 2.0. The octanol–water distribution coefficients (*S* + log *P* and *M*log *P*), the pH dependent octanol–water distribution coefficient (*S* + log *D*), the number of hydrogen bond donors (*HBDH*), the hydrogen bond acceptor (the sum of nitrogen and oxygen atoms) *MNO* and the topological polar surface area (*TPSA*) were determined for each molecule.

Among all the properties, the *TPSA* is a valuable molecular descriptor, which is used for the calculation of drug absorption properties. The *TPSA* value of less than 60 Å^2 gives prediction that the molecule has sufficient bioavailability properties, but if the value exceeds 140 Å^2, the molecule is considered as undesirable. Similarly the compounds with the molecular weight <500, *HBDH* < 10, *MNO* < 5 and log *P* < 5 are considered to be orally bio-available with a favourable ADME profile. All the selected compounds exhibited promising ADME properties, within the limits of Lipinski's rule of 5. The properties of the selected compounds are displayed in Table III.

TABLE III. Calculated ADME properties of the selected compounds

Compound	*MWt*	*S*+log *P*	*S*+log *D*	*M*log *P*	*HBDH*	*MNO*	*TPSA*
1a	110.11	0.751	0.736	0.893	2	2	40.46
1b	124.14	1.109	1.098	1.246	2	2	40.46
1c	138.16	1.595	1.588	1.58	2	2	40.46
1d	152.19	2.109	2.103	1.897	2	2	40.46
1e	166.22	2.664	2.66	2.2	2	2	40.46
1f	194.27	3.791	3.788	2.773	2	2	40.46
1g	166.22	2.647	2.644	2.2	2	2	40.46
1h	200.23	2.897	2.891	2.786	2	2	40.46
1i	214.26l	3.201	3.197	3.05	2	2	40.46
1j	246.26	1.882	1.871	1.942	4	4	80.92

CONCLUSION

The structure based virtual screening was employed to study the protein––ligand interactions for the identification of new BChE inhibitors, which could be a starting point for a promising lead candidate in the treatment of AD. The Pubchem database was filtered, treated, and subsequently screened against both AChE and BChE protein. Moreover, their predicted inhibition constant values were also in correlation with their binding energy values. Among the different derivatives, 4-(1-phenylethyl)benzene-1,3-diol (**1i**) and 4-[2-(2,4-dihydroxyphenyl) ethyl]benzene-1,3-diol (**1j**) showed strong inhibition and strong interactions with BChE. Thus, these compounds could be the starting point for the future development of novel inhibitors of BChE.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/10672, or from the corresponding author on request.

ИЗВОД

ДЕРИВАТИ БЕНЗЕН-1,3-ДИОЛА КАО ИНХИБИТОРИ БУТИРИЛХОЛИНЕСТЕРАЗЕ: НОВА МЕТА У АЛЦХАЈМЕРОВОЈ БОЛЕСТИ

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Молекулско моделовање (Molecular docking) је снажан и значајан приступ у идентификовању водећих молекула (lead molecules) на основу виртуелног скрининга. На овај начин, велики број једињења може да буде испитан, и на основу добијених резултата једињења могу да буду рангирана и може се претпоставити како одабрана једињења могу инхибирати циљани протеин. Имајући у виду важност постизања селективне инхибиције холинестераза, у овом истраживању фокусирали смо се на одређивање механизма везивних интеракција неколико деривата бензен-1,3-диола у активном месту ацетилхолинестеразе (AChE) и бутирилхолинестеразе (BChE). Показано је да сви одабрани лиганди имају већи афинитет за везивање са бутирилхолинестеразом (BChE) у поређењу са цетилхолинестеразом (AChE), са просечним вредностима −28,4 и −12,5 kJ/mol, редом. Резултати нашег истраживања указују да идентификовани инхибитори могу бити узети као водећи кандидати за развој нових инхибитора циљаних ензима у третману специфичних болести, и на тај начин се отвара могућност за нове терапеутске стратегије.

(Примљено 16. априла, ревидирано 21. августа, прихваћено 23. августа 2021)

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