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Molecular Modelling Studies of Pyridazinone Derivatives as Antibutyrylcholinesterases

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Abstract: Background: Butyrylcholinesterase (BChE) is known serine hydrolase enzymes responsible for the hydrolysis of acetylcholine (ACh). Although the role of the other serine hydrolase enzyme, acetylcholinesterase (AChE) in cholinergic transmission is well known, the role of BChE has not been elucidated sufficiently. The hydrolysis of acetylcholine in the synaptic healthy brain cells mainly carried out by AChE, it is accepted that contribution to the hydrolysis of BChE is very low; but both AChE and BChE are known to play an active role in neuronal development and cholinergic transmission. Docking is a method that predicts the preferential orientation of a molecule (small molecule) to a second (protein) molecule when connected to form a stable complex. It is used to predict the affinity of small molecule drug candidates against protein targets, their binding to these proteins, and hence their biological activity. Objective: In this study, we examined a series of pyridazinone-derived compounds, previously synthesized by our research group, for the compatibility of BChE enzyme and some physicochemical properties of the compounds *in silico*. Method: The compounds were optimized by conjugated gradient method by creating three dimensional models with OPLS_2005 force field parameters with 2D Sketcher and MacroModel (Schrödinger, LLC, NY) software in Maestro (Schrödinger, LLC, NY). Results: When the activities of the compounds were compared with the physicochemical parameters calculated by computerized methods, some parameters were found to be directly related to the activity. Conclusion: This study supports that the researchers may use to calculate various physicochemical properties and to make molecular modeling studies before working with pyridazinone derivates.

Keywords: Butyrylcholinesterase (BChE), Molecular Modelling, Pyridazinone

1. Introduction

Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes in the serine hydrolase enzyme group are generally known as cholinesterases. Of these two types of cholinesterase enzyme in the human brain, AChE is encoded by chromosome 7 and BChE is encoded by chromosome 3. The role of AChE in cholinergic delivery is well known, but the role of BChE has not been elucidated. In healthy brain cells, synaptic acetylcholine (ACh) hydrolysis is mainly carried out by AChE, with little contribution of BChE to this hydrolysis [1-3].

Although the cholinesterase enzymes are encoded on different chromosomes, the amino acid sequences of both enzymes are similar in 65% of each other. While AChE is common in normal adult brain, BChE is present in limited amounts and AChE is responsible for 80% of cholinesterase activity in the brain and BChE is responsible for the remaining 20%. While BChE enzyme levels are high in the early stages of nervous system development, this level decreases in later stages. AChE is located in the cell body of the cholinergic neurons, axons and proximal to the dendritic extensions, while BChE is found in the cell body and dendrites [4, 5].

Although BChE has been shown to regulate cholinergic delivery in smooth muscles, its function in the nervous system is not well known. Recent studies on better understanding of BChE function have shown that mice without AChE gene

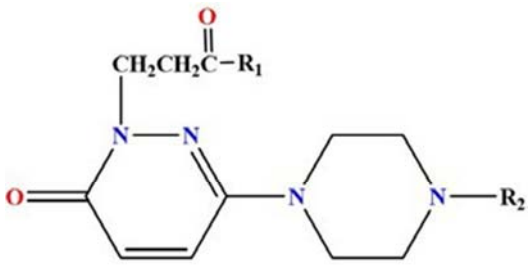
may develop to adulthood, although conditions related to peripheral or central cholinergic dysfunction such as tremor, ileus and weakness have emerged. Furthermore, mice are highly susceptible to butyrylcholinesterase inhibition and organophosphate effects [6]. This suggests that both AChE and BChE play an active role in neuronal development and cholinergic transmission.

Cholinesterase inhibitors inhibit the acetylcholine-degrading enzyme to ensure that the concentration of acetylcholine in the synapse remains high.

Both AChE and BChE inhibitor tacrine have improved cognitive function in some Alzheimer's patients as a result of clinical trials and have received FDA approval for Alzheimer's treatment [7]. However, the use of tacrine is limited as it causes liver damage. The efficacy of tacrine in Alzheimer's patients has led to the development of novel acetylcholinesterase inhibitor compounds. Donezepil, which was later approved for clinical use and only inhibited AChE, was found to improve perception and clinical functions for 21-81 weeks. Side effects of this drug are often caused by excessive cholinergic effects. Another cholinesterase inhibitors such as rivastigmine, eptastigmine and galantamine are approved by the FDA in recent years, are also used in the treatment; but these also show similar side effects [8-10].

While the targeted pharmacological effects are achieved with these synthetic analogues which are in the developmental stage, at the same time hepatotoxicity and known gastrointestinal side effects are prevented. In synthetically developed analogues, there are risks such as inability to obtain derivatives with potent and BBB permeability properties which present in naturally derived cholinesterase inhibitors or obtain compounds with unexpected pharmacological properties [1, 3].

From these considerations, it has been reported that compounds containing the pyridazinone ring as the main structure exhibit AChE/BChE inhibitor activity. The activities of the compounds obtained in our previous study which ethyl-6- substituted-3(2H)-pyridazinon-2-yl propionate (3a-e) and 6- substituted-3(2H)- pyridazinon-2-yl propionohydrazide (4a-e) derivatives were synthesized as AChE/BChE inhibitor. Ethyl 6-[4-(3- trifluoromethylphenyl) -piperazin]-3(2*H*)-pyridazinon-2-yl propionate 3e was found to be the most active compound in inhibition of both the AChE and BChE (Figure 1) [11].



R_1= ethoxy (3a-e), hydrazinyl (4a-e)
R_2= phenyl, 2-fluorophenyl, 4-fluorophenyl, 2-pyridyl, 3-trifluoromethyl

Figure 1. *Structure of compounds 3a-e, 4a-e.*

The compounds were optimized by conjugated gradient method by creating three dimensional models with OPLS_2005 force field parameters with 2D Sketcher and MacroModel (Schrödinger, LLC, NY) software in Maestro (Schrödinger, LLC, NY), Chem3D 15.0 and GaussView 5.0. [12]. The physicochemical properties of the compounds were calculated by QikProp (Schrödinger, LLC, NY) and drug similarity criteria (eg Lipinski's rule of five) was examined [13]. Crystal structure of BChE (PDB ID: 4BDS) was downloaded from Protein Data Bank (www.rcsb.org) and prepared using Protein Preparation Wizard of Maestro (v12.0, Schrödinger, LLC, New York, NY, 2014). Using Maestro's receptor grid forming panel, grid maps of the binding regions of proteins were generated. The remaining ligands were coupled to these maps 50 times in standard precision mode using Glide (Schrödinger, LLC, NY) software [14-16]. The obtained clamping poses were examined visually. The mean of BChE scores was calculated by considering the clamping score of the appropriate pose determined for each ligand [14].

2. Materials and Methods

The compounds were optimized by conjugated gradient method by creating three dimensional models with OPLS_2005 force field parameters with 2D Sketcher and MacroModel (Schrödinger, LLC, NY) software in Maestro (Schrödinger, LLC, NY), Chem3D 15.0 and GaussView 5.0. [12]. The physicochemical properties of the compounds were calculated by QikProp (Schrödinger, LLC, NY) and drug similarity criteria (eg Lipinski's rule of five) was examined [13]. Crystal structure of BChE (PDB ID: 4BDS) was downloaded from Protein Data Bank (www.rcsb.org) and prepared using Protein Preparation Wizard of Maestro (v12.0, Schrödinger, LLC, New York, NY, 2014).

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3. Result and Discussion

In docking study, physicochemical parameter werecalculated. Parameter value of the compounds and their steric parameter values, were homo, lumo, band gap, dipole moment and length were calculated using gauss view 5.0 program. logP and molar refractivity were calculated with chemdraw professional 15.0. The synthesized compounds were prepared in LigPrep (maestro, schrodinger 12.0). And also 227 parameters were calculated using the qikprop (maestro, schrodinger 12.0) software. When the activities of the compounds were compared with the physicochemical parameters calculated by computerized methods, some

parameters (Table 2) were found to be directly related to the activity.

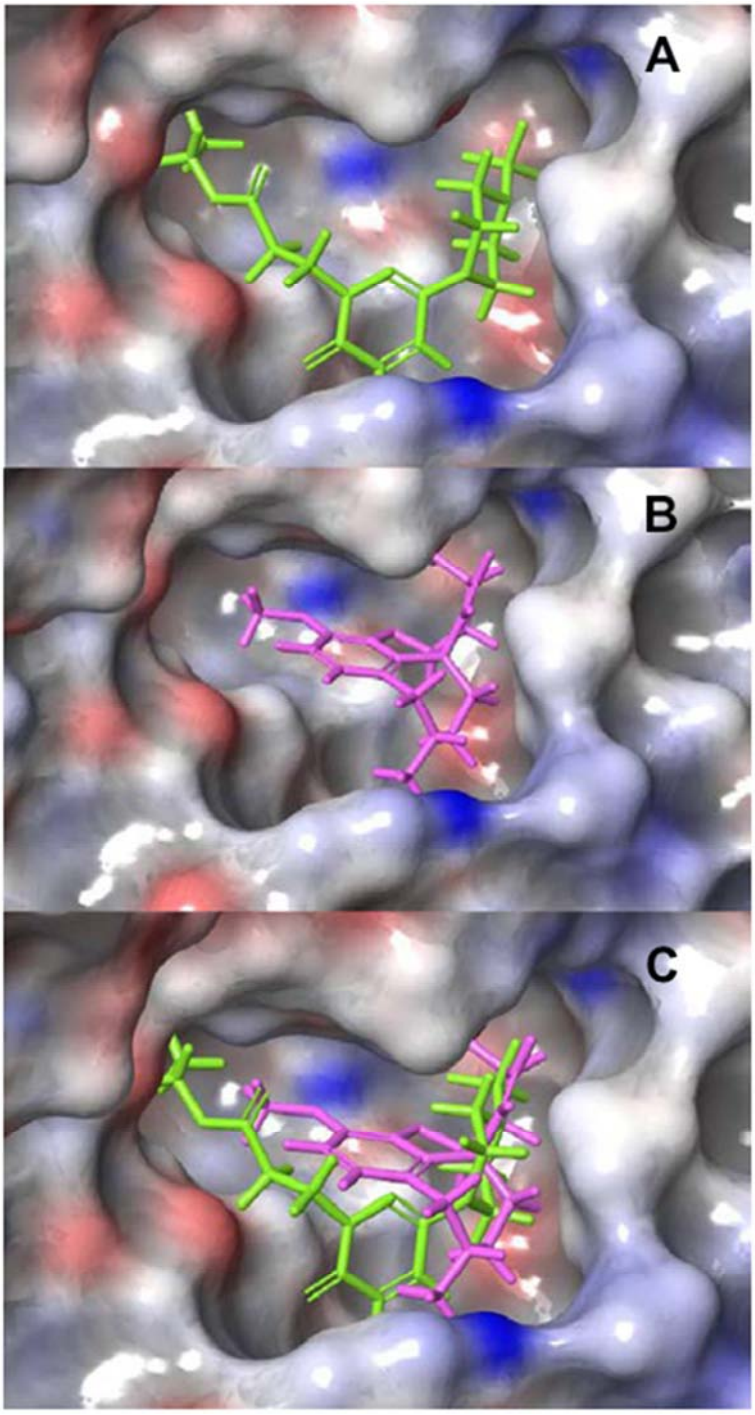

Figure 2. *Positions of compounds in the active site of the receptor A: 3e, B: galantamine, C: 3e and galantamine.*

Table 1. *% Inhibition and Docking scores of compounds.*

Compounds	% inhibition 0,5 mM	Docking score
galantamine	97.20 + 0.67	-8.51
3a	23.23+1.39	0
3b	32.30+1.26	7.372
3c	27.10+1.23	7.741
3d	62.23+1.23	6.982
3e	78.44+1.23	6.982
3d	62.23+1.23	6.982

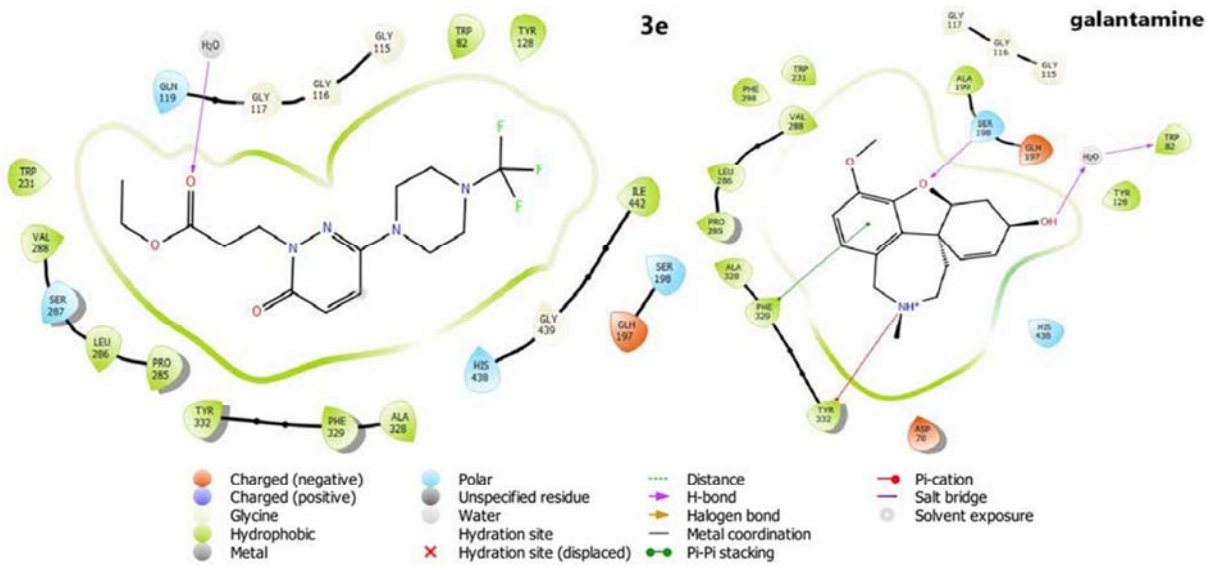

Figure 3. *2D interaction diagram from Glide for 3e and galantamine.*

Table 2. *Some physicochemical and pharmacokinetic properties of compounds.*

Comp.	FOSA	FISA	QPlohPw	QPPMDCK	PSA	logP
3a	348.2	103.2	8.32	515.8	81.08	2.12
3b	277.8	93.81	7.8	903.8	74.99	2.27
3c	345.1	94.6	8.08	894.2	80.60	2.27
3d	349.2	109.7	8.72	442.5	88.99	1.50
3e	313.9	89.8	6.74	688.9	74.77	1.69
4a	201.9	186.5	14.0	72.1	113.06	0.62
4b	197.6	186.7	13.9	97.5	113.02	0.78
4c	201.9	186.4	13.85	129.6	113.06	0.78
4d	206.9	191.2	14.52	64.6	121.39	0.01
4e	206.9	189.5	12.81	65.9	115.86	0.2

It has been found that the activity is completely lost when the polar surface areas of the compounds are 113 Å² and above. Furthermore, activity is destroyed when the log P values of the compounds are below 1.5. Table 2 clearly shows that FOSA and FISA values are also related to activity. As can be seen from these data, it is understood that physicochemical parameters are very important in activity and should be calculated before the compounds are synthesized.

The active compound (3a-e), docking studies were performed. In this study, it was aimed to determine the binding scores of the compounds in the crystal structure of the enzyme butyrylcholinesterase and the residues responsible for the activity in the binding region of the protein. (Figure 2 and Figure 3). Galantamine, which is used as a standard at *in vivo* studies, was compared with the interaction of compounds with protein. Galantamine, which is the most active at *in vivo* studies, has the highest docking score. Furthermore, the most active compound 3e has the best docking score after galantamine. Percentage inhibition and docking scores are indicated in Table 1.

4. Conclusion

Pyridazinone and its derivatives are frequently studied as acetylcholinesterase and butyrylcholinecholinesterase inhibitors. A large number of compounds are randomly synthesized and fail in activity. In this study we docked ten compounds which we previously reported to the catalytic site of the BChE. Docking studies showed that **3e** bound to the catalytic site of BChE with high affinity. Molecular modeling studies were also conducted for the galantamine, which is used as a reference compound at *in vitro* studies. The binding profiles of galantamine were found to be better in accordance with the activity results. For this reason, it will be beneficial for researchers to calculate various physicochemical properties and to make molecular modeling studies before working with compounds having similar scaffold.

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