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Molecular Docking Analysis and ADMET Properties of Isoquinoline Derivatives as Potential Acetylcholinesterase Inhibitors

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Abstract. Alzheimer's disease (AD) are the progressive necrosis of central cholinergic neurons, followed by intra and hippocampal acetylcholine (ACh) levels. Acetylcholinesterase Enzyme (AChE) is an enzyme that is responsible for the metabolic breakdown of acetylcholine (ACh). The hydrolysis of ACh by excess amount of AChE decreases the amount of ACh in the brain, thus interfering with the normal brain functions. Modelling of seven isoquinoline derivative compounds is done by using Computer-Assisted Drug Design (CADD) such as molecular docking and ADMET properties calculation. The results obtained show that compound **13**, **14**, **16**, and **17** have a lower binding energy about -9 kcal/mol. It can be caused due to the more electron donating groups in these compounds. ADMET properties calculation is attempted to evaluate the interaction between the four compounds (**13**, **14**, **16**, and **17**) when entering the body systems. ADMET calculation result is showing that compounds **13** and **14** fulfill the parameter in adsorption properties while the others are not. Indicating that compounds **13** and **14** are potential to be Alzheimer's drug. This result is in line with experimental study.

Introduction

Among numerous infections influencing present-day humanities, dementia is quite possibly the most severe health problem (Ajala et al., 2022). Alzheimer's Disease (AD) was first described by Alois Alzheimer in 1907, has become one of the most prevalent dementia type diseases in the world which is increasing its number rapidly (Sarkar et al., 2021). AD is mainly prevalent in the older population (>65 years of age) (Wang et al., 2021). Based on Alzheimer's Disease International, currently, about 55 million people worldwide are suffering from this AD and the number is predicted to reach 78 million by 2030 and 131,5 million by 2050 (Gauthier et al., 2021).

One of the clinical manifestations of AD are the progressive necrosis of central cholinergic neurons, followed by intra and hippocampal acetylcholine (ACh) levels and also by the accumulation of ß-amyloid in some parts of the brain (Ahfid et al., 2021) which comprises the formation and aggregation of the ß-amyloid peptide (Aß) caused by the hydrolysis of the amyloid precursor protein (APP) by ß-secretase 1 (BACE-1) (Saglık et al., 2020). Beside these, in the familial and congenital cases, genetic factors play critical roles (Sarkar et al., 2021).

The cholinergic concern with Acetylcholine (ACh) which is regulated by two enzymes, acetylcholinesterase (AChE) and choline acetyltransferase (ChAT). ACh is synthesized by ChAT which catalyzes the transfer of an acetyl group from acetyl co-enzyme A (Ac-CoA) to choline (Ch) in the presynaptic neuron (Sarkar et al., 2021). AChE is an enzyme that is responsible for the metabolic breakdown of ACh into inactive compounds which are acetate and choline (Reubun et al., 2020). The hydrolysis of ACh by excess amount of AChE decreases the amount of ACh in the brain, thus interfering with the normal brain functions (Sarkar et al., 2020). AChE inhibitors (AChEi)

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increase synaptic ACh levels and improve cholinergic function in the brain (Andrieu et al., 2015). Donepezil is one of Food and Drug Administration (FDA)-approved drugs that is currently used for mild to moderate AD treatment targeting the AChE. However the drug has several side effects, therefore scientists are searching for more effective agents with lesser side effects (Sarkar et al., 2021).

Isoquinoline is an *N*-heterocyclic aromatic organic compound, which is a structural isomer of quinoline compound (Gujjarappa, 2020). Isoquinolines are a large class of medically active compounds with many bioactivity such as antitumour, antimicrobial, antiinflammatory, antifungal, antioxidant, and also neurochemical agent and can act as enzyme inhibitors (Jacob et al., 2016). Markmee et al., (2006) have designed and synthesized some isoquinoline derivatives, isolated from the root of *Stephania tetrandra* S and evaluated against AChE. By this result some of isoquinoline derivatives have a good activity against AChE. However, in silico study for those compounds had never been conducted. In this study, some isoquinoline derivatives were designed, modeled and screened for AD effectiveness and drug-likeness assessment by molecular docking and ADMET calculation stage. In the context of developing future strategies, molecular docking and ADMET studies have become critical methods (Said et al., 2022). Molecular docking is a widely accepted and used technique in drug R&D which reduces both time and costs of lead discovery processes. By simulating the interaction between ligand and receptor in the computer software, the docking system assigns scoring functions to the bound ligands which reflect their binding affinity. The lower docking score represents the greater binding affinity (Sarkar et al., 2021). Thereafter, the pharmacodynamics and physicochemical characteristics of the best selected ligands were predicted by determining their drug-likeness properties by the ADMET test.

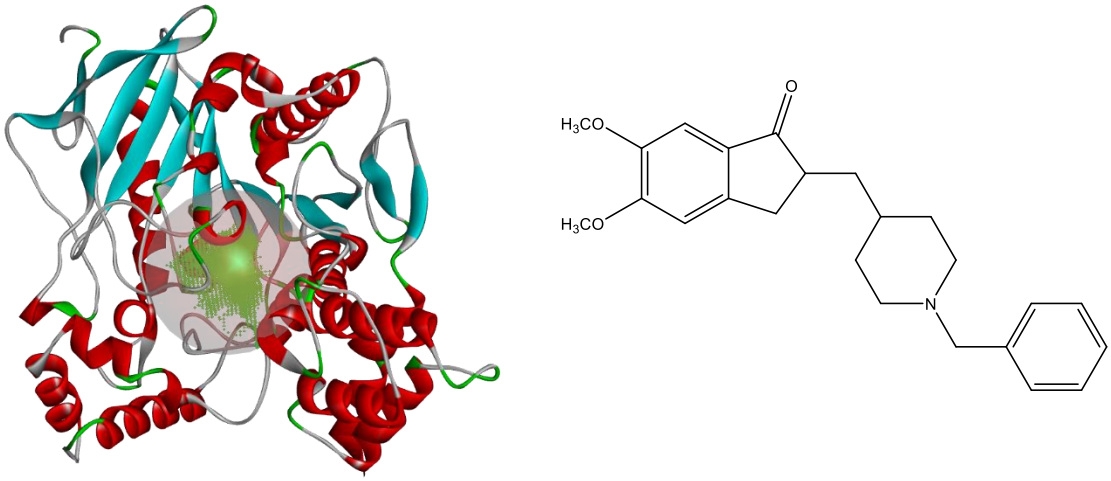
Experimental

Molecular Docking of Isoquinoline Derivatives

All ligands **11**-**17** (Table 1) was build using Avogadro version 1.2.0 software (Hanwell et al., 2012) and optimized using DFT B3LYP 6-31G in ORCA software (Neese et al., 2020). All ligands were formatted in pdb format file and prepared to dock in Chimera software (Pettersen et al., 2004). Protein structure of Acetylcholinesterase used in this study was downloaded in protein data bank using ID 1EVE (Figure 1). The unwanted residues were removed and prepare to dock in Chimera. Molecular docking protocol was set in the active site of the enzyme and used grid size 50 x 50 x50 Å and spacing 0.375 Å in AutoDock4 with the help of AutoDockTools (Morris et al., 2009). The Lamarckian Algorithm was used to produce 10 conformations and visualized the 2D interaction in Discovery Studio Visualizer program (Dassault System, 2009).

Calculation of ADMET Properties

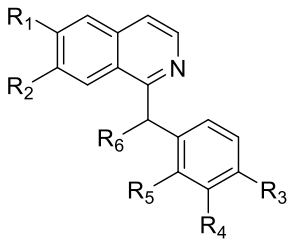
All ligand files were converted into smiles format using Open Babel program (O'Boyle et al., 2011). The smiles format of each ligand was converted to smiles format and inserted to pkCSM web server (Pires et al., 2015). ADMET property was chose to calculate all of property of adsorption, distribution, metabolism, excretion, and toxicity.



(a) (b)

Figure 1. (a) 3D-Structure of Acetylcholinesterase enzyme and its active site (green sphere); **(b)** E2020 as standard ligand

Table 1. List of isoquinoline derivatives as potential acetylcholinesterase inhibitor (Markmee, et al, 2006)



Ligands	R_1	R_2	R_3	R_4	R_5	R_6
11	H	H	OCH_3	H	H	OH
12	H	H	H	H	OCH_3	OH
13	OCH_3	OCH_3	H	H	OCH_3	OH
14	OCH_3	OCH_3	OCH_3	OCH_3	H	OH
15	OCH_3	OCH_3	H	H	H	=O
16	OCH_3	OCH_3	OCH_3	OCH_3	H	=O
17	OCH_3	OCH_3	OCH_3	OCH_3	H	H

Result and Discussion

Test Molecular Docking Analysis

Molecular docking conducted by ligand targets are 7 isoquinoline derivatives with AChE as the target protein (PDB code: 1EVE). Molecular docking analysis observed by the binding energy (ΔG), inhibition constant (Ki), and interaction between isoquinoline derivatives with AChE as the receptor of target protein.

Table 2. Docking result of isoquinoline derivatives in acetylcholinesterase enzyme

Compounds	Binding Energy (kcal/mol)	Inhibition Constant (nM)	H-Bond Interaction Residue
11	-8.60	498.59	Tyr334; Asp72
12	-8.30	829.46	Tyr121; Ser122
13	-9.11	209.48	Tyr121; Tyr130; Glu199
14	-9.27	160.96	Tyr121
15	-8.93	285.36	Asp72
16	-9.80	65.22	Asp72
17	-9.05	233.75	Asp72
E2020	-11.18	6.37	Tyr130; Trp84

Standard ligand used in this study is E2020 compound which is known as acetylcholinesterase inhibitor and had been used as Alzheimer's drug. Based on the results of the molecular docking of isoquinoline derivatives, all of isoquinoline derivatives still had a higher binding energy than the standard ligand (E2020) but there were 4 compounds (**13, 14, 16, and 17)** had a binding energy near the standard ligand and potential to be used as a new inhibitors.

As a ligand-receptor in the lowest energy condition, the molecule will be in the stable condition, thus the ΔG getting lower (Suhadi et al., 2021). The value of the bond energy formed is a calculation of the conformation of the ligand formed in a macromolecule (Susanti et al., 2019). Compound **16** has many methoxy groups (OCH_3) attached as side chain groups, compared to compound **11** which only has one methoxy group. Compounds with methoxy substituents are more polar, so they will affect the stability of interactions between ligands and receptors because of their hydrophilic characters (Widiyanti et al., 2021). In addition, the presence of a methoxy group as a side chain in benzene compounds increases the stability of the structure as an electron driving group. Therefore, compound **16** has the lowest energy value when compared all derivative compounds. The difference in bond energy values is also influenced by differences in the binding of the ligand to the amino acid on the receptor as a determinant of the most stable molecular geometry.

Both Tyr and Asp residue interaction reveal that these compounds are well accommodated in the active site of enzymes and strongly interact within hydrophobic interactions as well as hydrophilic interactions with the reseptor (Aarjane et al., 2021). Furthermore, visualization observations were carried out as shown in Figure 2 to determine the amino acids that play a role in the inhibition of the AChE. The result of these visualization observations is the interaction of amino acid residues with ligands. The presence of amino acid interactions involved allows contact between alpha-glucosidase ligands so that it has inhibitory activity as shown (Sari et al., 2020). Each ligand

has Van Der Waals interaction bonds and hydrogen interaction bonds. As shown in Figure 2 (a), it reveals hydrogen interaction bond between compounds **13** and amino acid residue of Tyr121, Tyr130, and also Glu199. Furthermore, compound **14** has an interaction with Tyr121 and unfavorable interaction in Gln69. Compounds 16 and 17 show a similar hydrogen bond interaction in Asp72 indicating the similarity position of binding through AChE receptor.

Active site of Acetylcholinesterase enzyme found in some of residues such as Trp84, Trp279, Phe330, Trp279, Glu185, Phe331, and Phe290 (Kryger et al., 1999). These residues were found by the interaction of E2020 in the active site of the enzyme. Comparing the docking result of tested ligands and standard ligand, it was shown that all tested ligands were in the active site of the enzyme due to the same residues interaction.

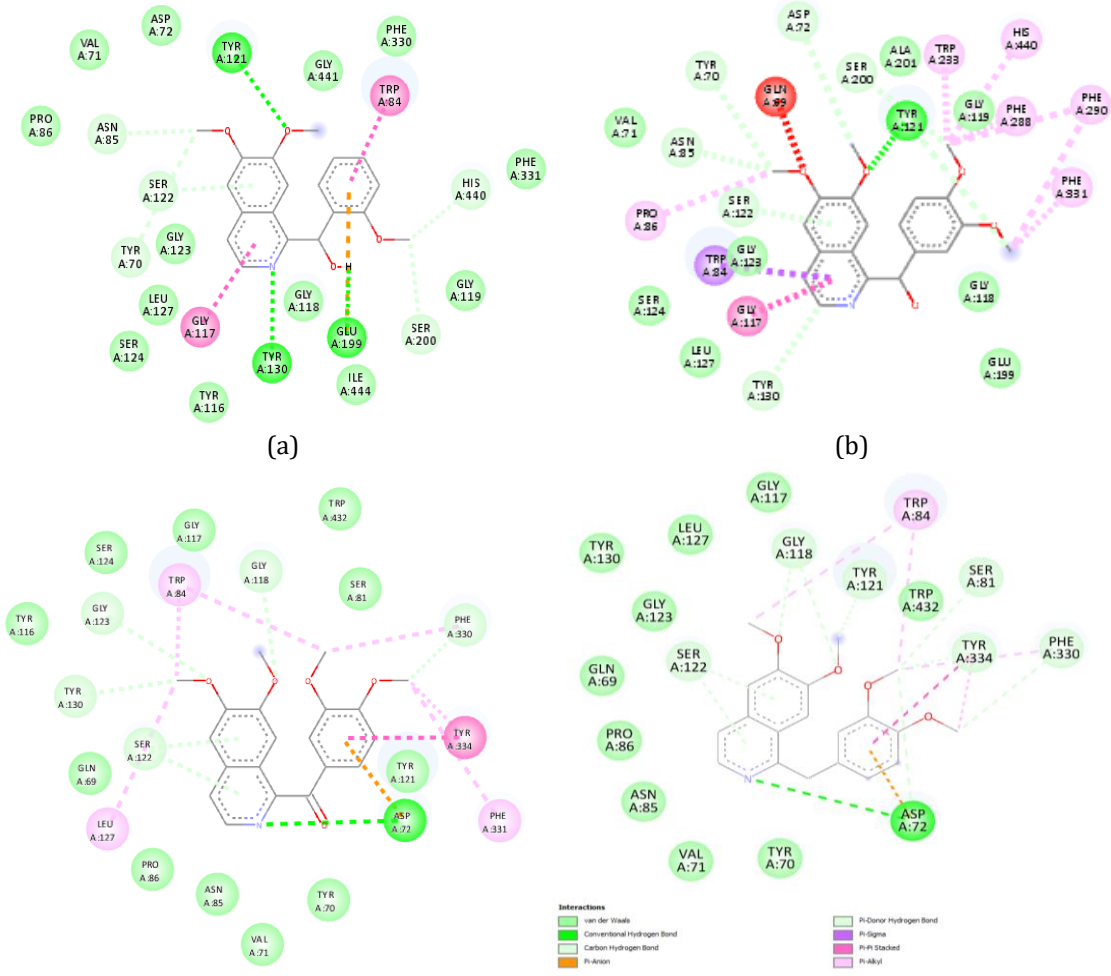


Figure 2. Interaction of isoquinoline derivatives ligand (a-d) continued is **13, 14, 16,** and **17** compound on binding side of AChE as receptor protein

ADMET Properties

Calculation of ADMET properties is shown in Table 3. There are 4 properties calculate in Lipinski rule and all ligands are fulfill all the threshold parameters indicating that all ligands have a good solubility and permeability in human body. Parameter in the other properties such as distribution, metabolism, excretion, and toxicity of each ligands showed that all ligands only fulfil some of parameters. In adsorption parameters, a compound is considered to have a high $CaCO_2$ permeability (greater than 0.9), high intestinal absorption (> 30%), act as the substrate and inhibitor of P-glycoprotein. By this threshold parameters, it can be shown that only **13** and **14** compounds that satisfy the standard of absorption parameters. In distribution parameters, the compounds should have low volume of distribution (VDss) (< -0.15), blood-brain barrier (BBB) lower than 0.3 and it is shown that only compounds **14** and **16** fulfill these parameters. In metabolism parameters, a compound is considered to be

cytochrome P450 inhibitor by inhibiting CYP2D6 or CYP3A4 substrate. Result of calculation show that all of compounds are likely to be CYP3A4 substrate and inhibitor of CYP1A2 and CYP2C19. In excretion parameters, a compound is likely to be an organic cation transporter 2 (OCT2) substrate and all of compound act as renal OCT2 substrate. AMES toxicity assessing mutagenic property of the compound in bacteria and all compounds show non-toxic property and skin sensitisation.

Table 3. Result of ADMET calculation properties

	Properties	Ligands						
		11	**12**	**13**	**14**	**15**	**16**	**17**
Lipinski rule	**Molecular Weight (≤500)**	265.312	265.312	325.364	355.39	295.338	353.374	339.391
	Log P (≤5)	3.3251	3.3251	3.3423	3.3509	3.3337	3.5002	3.86
	Acceptors H-Bond (≤ 10)	3	3	5	6	4	6	5
	Donors H-Bond (≤5)	1	1	1	1	1	0	0
Adsorption	**$CaCO_2$ Permeability (log Papp in 10^{-6} cm/s)**	1.903	1.803	1.323	1.13	1.276	1.294	1.376
	Intestinal absorption (% absorbed)	95.406	95.661	95.663	95.521	95.509	98.481	98.474
	P-glycoprotein substrate (Yes/No)	Yes	Yes	Yes	Yes	Yes	No	No
	P-glycoprotein I inhibitor (Yes/No)	No	No	Yes	Yes	No	Yes	Yes
	P-glycoprotein II inhibitor (Yes/No)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Distribution	**VDss (Log L/kg)**	-0.01	0.072	-0.068	-0.068	0.297	-0.111	0.143
	BBB permeability (Log BB)	0.125	0.612	0.44	-0.729	0.656	-0.263	0.139
Metabolism	**CYP2D6 substrate (Yes/No)**	No	No	No	No	No	No	No
	CYP3A4 substrate (Yes/No)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	CYP1A2 inhibitor (Yes/No)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	CYP2C19 inhibitor (Yes/No)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	CYP2C9 inhibitor (Yes/No)	No	No	Yes	Yes	Yes	Yes	Yes
	CYP2D6 inhibitor (Yes/No)	No	No	No	No	No	No	No
	CYP3A4 inhibitor (Yes/No)	No	No	No	No	No	No	No
Excretion	**Total Clearance (Log ml/min/kg)**	0.173	0.293	0.309	0.219	0.225	0.677	0.355
	Renal OCT2 substrate (Yes/No)	Yes	Yes	Yes	Yes	Yes	No	Yes
Toxicity	**AMES Toxicity (Yes/No)**	No	No	No	No	No	No	No
	Max. Tolerated dose (Log mg/kg/day)	0.134	0.388	0.554	0.509	0.131	0.724	0.611
	hERG I inhibitor (Yes/No)	No	No	No	No	No	No	No
	hERG II inhibitor (Yes/No)	No	No	No	No	No	Yes	Yes
	Hepatoxicity (Yes/No)	No	No	Yes	Yes	Yes	No	Yes
	Skin Sensitisation (Yes/No)	No	No	No	No	No	No	No
	T.Pyriformis toxicity (log ug/L)	1.057	0.72	0.517	0.43	0.631	0.369	0.534
	Minnow toxicity (Log mM)	0.885	0.548	0.705	1.432	0.643	0.914	-0.049

Conclusion

Molecular docking analysis through isoquinoline derivatives resulted that there are 4 compounds that have a low binding energy (13, 14, 16, 17). Compound 16 has the most potential as an inhibitor to a receptor protein AChE has played a role in Alzheimer's disease with a value of binding energy is -9,8 kcal/mol. Further analysis is done using ADMET properties calculation and resulting those compounds (13 and 14) are potential to be use as acetylcholinesterase Inhibitors

Conflict of Interest

The authors declare that there is no conflict of interest.

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