IN SILICO STUDY OF NOVEL CHALCONE DERIVATIVES AS ANTICHOLINESTERASE CANDIDATE

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Abstract. *Alzheimer's disease (AD) is a deadly neurodegenerative disorder affecting the majority of elderly people in the world. One of the pivotal factors of the disease is the increasing level of acetylcholinesterase enzyme that inhibits acetylcholine activity in the brain that disrupts brain function. Chalcones are phytochemicals that have a wide spectrum of biological activities, including inhibition of AChE. A series of newly candidate chalcone derivatives (5-6) were studied for their acetylcholinesterase inhibitory activities against Alzheimer disease. The binding energy of all the synthesized compounds to the target protein (4M0E) was found to be higher than the reference inhibitor of dihydrotanshinone (-9.23 kcal/mol). Based on the molecular docking result compounds 6 (-11.91 kcal/mole) and 8 (-11.30 kcal/mol) have the highest binding energy among all synthesized compounds. In this study, it was found that the change at the aromatic ring by introducing substitutions of the electron-withdrawing small group (chlorine) and electron-donating group (methoxy) at the specific position play an outstanding role of their biological activities.*

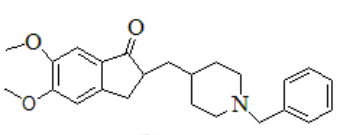
Keywords: *Alzheimer's disease, chalcone, chalcone derivatives, acetylcholinesterase, molecular docking.*

Nowadays, many scientists struggle to develop new compounds as drugs that are able to treat Alzheimer disease. AD is prompt to nerve cell breakdown, death and tissue loss throughout the brain (Carro *et al.,* 2017). This disease attracts researchers' attention to discover new powerful medicines to therapy Alzheimer's sickness more effectively. Currently, three drugs are allowed for the remedy of mild to moderate AD: donepezil (Pfizer, New York, NY, and USA), rivastigmine (Novartis, Beer, Basel, Switzerland) and galantamine (Janssen, Beerse, Belgium). These medicines have been considered to be standard and for the initial stage of AD therapy (Zhuang *et al.,* 2018). Moreover, currently, donepezil is used for the remedy of intense AD in the USA. These medicines are cholinesterase inhibitors that stop acetylcholine breakdown, a chemical messenger significant for learning and retention (Guo *et al.,* 2019). Some of the current drugs have some side effects such as regurgitation, diarrhoea and stomachic cramp. Some of the prescribed drugs with the maximum repeatedly damaging effect were dizziness, headache and confusion (Agrawal *et al.,* 2018). Study prove that combining α, β-unsaturated ketones into a particular molecule structure can enhance anti-Alzheimer and anticancer activity of the compounds (Reddy and Reddy, 2011). So, their chemistry has attracted attention all around the world, since this type of compounds containing keto-ethylenic (CO-CH=CH-) active group have industrial and biological application (Hazarkhani *et al.,* 2010). Researchers try to design medicinal drugs to treat fatal AD using molecular docking. The drug development project is one of the most complex, time-consuming, and financing burden tasks. The reason for drastic enhancement in the drug cost was a high rate of failure project in the pharmaceutical discovery (Sethi *et al.*, 2019). Molecular docking is one of the most important methods in the molecular modelling field. It has the ability, with the rapid development of pharmacology, network-based drug discovery is deemed to be a more cost-effective and promising drug development strategy. Synthesis of potential new anti-Alzheimer agents based on chalcone will be useful to humankind and pharmacological studies. The role of the electron-withdrawing and electron-donate groups in specific position of the

structure was evaluated by molecular docking. So therefore the key objective of this study was to design new chalcone derivatives (**1, 2, 3 and 4**) as target compounds for the treatment of Alzheimer's disease using molecular docking.

Molecular Docking

The strategy of molecular docking seeks to estimate the best ligand style which has a good binding affinity toward the target protein. It is able to generate a range of potential conformations or orientations of the ligand inside the protein binding site (Nithin *et al.*, 2018). This technique can predict both the ligand-protein binding affinity and the protein-ligand complex structure, which is good knowledge for providing the proposed drugs (Song *et al.*, 2020). The molecular docking process consists of two steps (Chaudhary *et al.*, 2020). The first step in the docking calculation is to obtain a target structure that typi cally co-nsists of a large biological molecule. The purpose of molecular docking is to give a prediction of the ligand-protein complex structure using computational methods. In this study, acetylcholinesterase was chosen as protein structure and a bulky group and halogen bearing chalcone as a ligand. It was important to review previous research to design a suitable drug candidate for Alzheimer treatment based on the structure (De Freitas Silva *et al.*, 2018). Donepezil **(5)** is one of the drugs approved by the FDA to treat Alzheimer disease. Donepezil is a prescription medication used to relieve the symptoms of Alzheimer's disease (AD) (Ghosh, Jana *et al*. 2019). The docking process of donepezil has been performed using Auto Dock 4.2 due to know its binding energy and interaction with the protein AChE. This research discovered the donepezil drug molecule's binding model inside the AChE gorge (De Freitas Silva *et al.*, 2018). The result showed that donepezil **(1)** exhibited high free energy score (-10.6 kcal/mol). Hydrophobic interaction of donepezil with AChE plays important role in ligand protein binding. This involves π-cation interaction with amino acid Trp86 residue and π-π stacking interaction between aromatic residues and aromatic groups present in donepezil. Ionic interaction between Asp74 residue and donepezil also contributed to the higher binding energy (Frye, Nilsen, Tønjum, & Ambur, 2013). In both increasing and reducing the binding energy of a compound, the position of water as a ligand is very important. While waters close to interactive residues (F295, Y121, Y341 and Y337) have been reported to mediate the donepezil piperidine ring flip or hydrogen bond in 4EY7 to induce tight binding. The x-ray position of the waters may be of limited use for the energetics of donepezil derivatives or related scaffolds resulting from donepezil core hopping. Donepezil's hydrophobic interactions with AChE have a major role in ligand-protein binding. This includes π-interaction with two amino acid Tyr341 and Tyr337 residue and π-π staking interaction between aromatic residue and aromatic group present in the donepezil (Jang *et al.*, 2018). Aljohani *et al*. (2020) reported molecular docking result of chalcone **(2)** using AutoDock 4.2 software. Torpedo california acetylcholinesterase (TcAChE) (PDB id: 1EVE) was chosen as enzyme for the docking study. The docking result showed that the chalcone **(2)** exhibited higher binding energy (-13.29 kcal/mol) than standard drug donepezil **(1)** (-10.00 kcal/mol). From the analysis of the molecular docking result, the chalcone **(2)** interacted with residue Trp84, Gly118, Glu199 and Tyr121. The chalcone **(2)** showed there was considerable flexibility of the chalcone **(2)** molecule that facilities the hydrophobic interaction with Trp84 which was in anionic site of the AChE. Moreover, the chalcone **(2)** formed hydrogen bond with residue Gly118, Glu199 and Tyr121 that were in peripheral anionic site. The docking result revealed that the chalcone **(2)** was bond within the active site of the target protein, hence it exhibited higher binding energy than reference drug (Aljohani *et al*., 2020).



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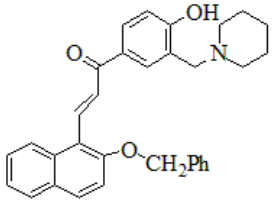

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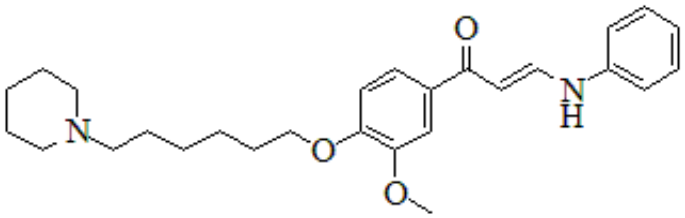
Liu *et al.* (2017) used Molecular Operating Environment (MOE) software package to conduct molecular docking study in order to get information about the interaction of chalcone derivatives with acetylcholinesterase. The x-ray crystal sucture of AChE was retrieved from PDB (PDB id: 1EVE) and rivastigmine were used as reference drug. They found compound **(3)** interacted with AChE via multiple sites. The π-cation interaction took place between the nitrogen of piperidine ring and residue Trp84 of the catalytic active site (CAS). At the top of peripheral anionic site (PAS) the aromatic rings bound with Tyr334 and Trp279 via a π- π stacking effect. Meanwhile, compound **(3)** exhibited a weaker binding affinity toward BuChE which only Gly66 and Tyr67 were bound with BuChE via a π-cation interaction. Based on the above result, compound **(3)** weaker binding affinity with BuChE showed good selectivity in inhibiting AChE (Liu *et al*., 2017).



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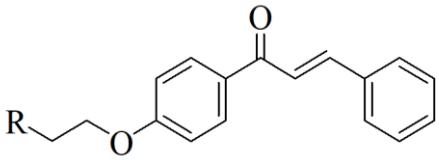
Compound **(4)** is an example of chalcone which showed powerful inhibition and excellent selectivity toward AChE. The compound **(4)** showed more binding to AChE compared to BuChE. This observation may rationalize the potent inhibition activity of the proposed compound toward AChE. It appears that the structure of the compound plays a pivotal role in the inhibition activity of the compound (Liu *et al.*, 2016).



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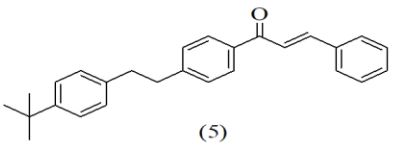
Research methodology

The process for the discovery of a new potential anti-Alzheimer possible drug candidate which involves computational section. Firstly, compounds **(5)**, **(6)**, **(7)** and **(8)** were predicted for their biological activity by using molecular docking. Next, the targeted compounds were synthesized and characterized. Acetylcholinesterase was chosen as a protein for anti-Alzheimer drug evaluation. The acetylcholinesterase 3D structure was downloaded from Protein Data Bank with PDB code 4M0E and then server save v6.0 (https://www.rcsb.org/structure/4M0E) was utilized to assess the protein. The protein was verified for PROCHECK, ERRAT and Verify3D (Cheung *et al.,* 2013). Stereochemical, anomalies, sequence fitness to structure and characteristic non-bonded interaction were tested of the target protein by utilizing web server tools, PROCHECK (Frateschi *et al.*, 2012), ERRAT (Colovos and Yeates, 1993), and Verify3D (Grotthuss *et al.*, 2003) respectively. PROCHECK is a computational program that evaluates the stereochemistry of a protein. Also, it is used to choose a reliable model structure for molecular docking analysis, this software analyzes the tertiary structure of the model based on the local geometry (Pandey *et al.*, 2015). In this research, the backbone conformation of AChE amino acids was evaluated by examining the Phi

ϕ and Psi dihedral angles of the PROCHECK analysis was used to achieve the Ramachandran plot. In the plot, the percentage of residues present in the steric allowed and disallowed regions was determined. This plot also provides other information including the position of AChE amino acid which participates in the stability of the AChE (Laskowski *et al.*, 2018). Verify 3D profile was applied to investigate the fitness of the AChE 3D structure with its own amino acid sequence (1D). The obtained profile provides crucial details on the fitting of the AChE primary sequence into its tertiary structure (Swain and Behera, 2014). Eventually, the selected structure of AChE crystal structure validity further was evaluated by ERRAT. ERRAT is a type of programmer used to validate protein structure that is particularly useful for the development of crystallographic modelling and refinement. The software examines the statistics of non-bonded interactions between different type of atom. The ERRAT program created a single output plot that gave the value of the error function versus. Location of a 9-residue sliding window. In comparison to statistics from highly refined systems, the error values were determined to provide confidence limits. This was highly beneficial in choosing reliability decisions (Bhargava *et al.*, 2014).



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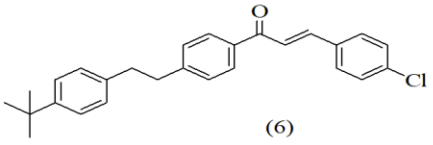

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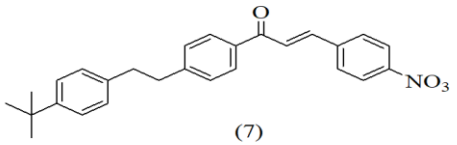

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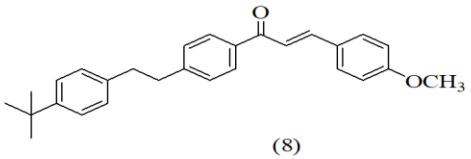

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Findings

The results expressed that chalcone derivatives bearing electron-withdrawing and electron donate groups play a crucial role in term of enzyme inhibition. On the other side, the superimpose structure showed that the synthesized compounds stacked with the active site of the target protein and the proposed compound of **(5)** overlap well with the reference inhibitor (dihydrotanshinone), Figure 3.5 represented the compound **(5)** as a green colour structure and reference inhibitor (dihydrotanshinone) as cyan colour.

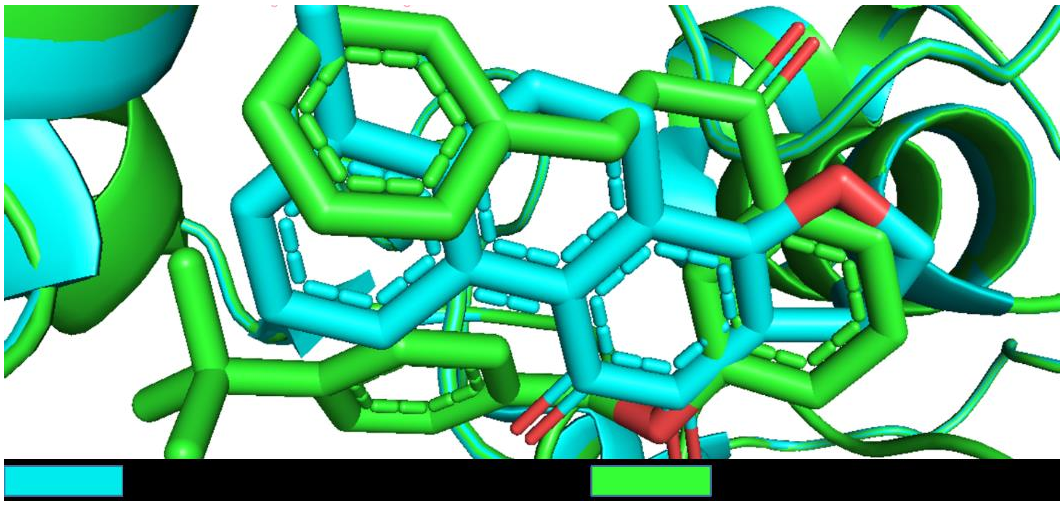

Figure 1. Dock model of the ligand **(5)** along with real crystal structure

The docking result revealed that the best conformation model among other conformations with a high binding energy value of -11.99 kcal/mol was recorded in the DLG file. Visualization the best conformation of the docked ligand with the real crystal structure of

protein superimpose structure was obtained by using pymol. As the result, the synthesized ligand bound well with the active site of the protein. Furthermore, it showed that the overlapping between the synthesized ligand and reference drug (dihydrotanshinone) was observed in Figure 1.

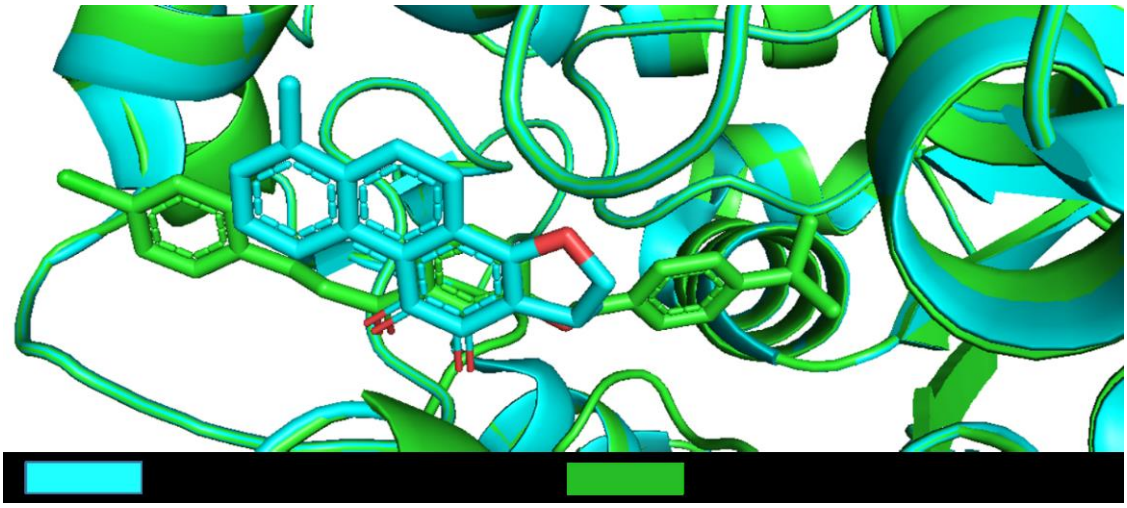

Figure 2. Dock model of the ligand **(6)** along with real crystal structure

The docking result exhibited that the best conformation model of the **(7)** having the energy value -10 kcal/mol which was recorded in the DLG file of the docking result. Visualization of the synthesized ligand with the target protein were done by using the pymol software. As a result, compound **7** appeared on the same side with the reference drug (dihydrotanshinone) and indicated that the compound **7** bound to the active site of the protein, Figure 3.7 represented the compound **7** as a green colour structure and reference inhibitor (dihydrotanshinone) as the cyan colour.

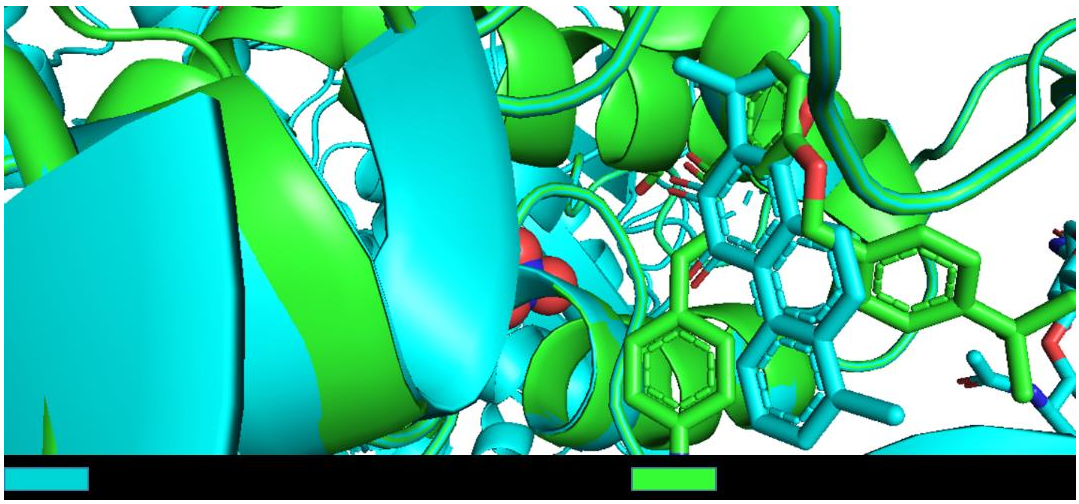

Figure 3. Dock model of the ligand **(7)** along with real crystal structure

It was recorded from the docking result that the compound **8** best conformation model bind with the active site of the target protein with the -11.30 kcal/mole energy value. In the end to compare the best-fit conformation model of the proposed ligand with the reference drug, the pymol software based on the superimpose structure showed that the suggested structure of the ligand overlaps with the reference drug (dihydrotanshinone).

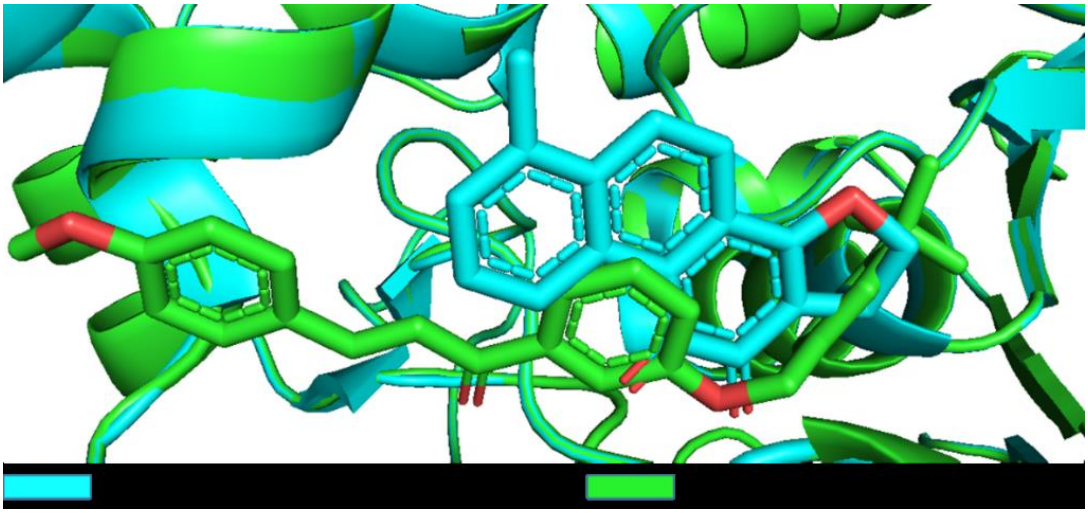

Figure 4. Dock model of the ligand (8) along with real crystal structure

From the docking result it can be interpreted that there are four different synthesized compounds with four different electron withdrawing groups and electron donate groups and the synthesized ligands exhibited different binding energy values. Their structure-activity relation (SAR) showed that compound with both electron-withdrawing group and electron-donating substituents increased the inhibition activity of the compounds. Based on literature acetylcholinesterase has small gorge site and it reacted with small molecules. As it can be observed in Table 1 that smaller electron-withdrawing groups such as chlorine attached with chalcone B ring in compound **6** was favoured to increase the binding energy than a large group such as NO2 which is present in compound **7** in the same position. Likewise, electron donating groups such as (CH3O-) also increase the binding energy of the compound. As it can be observed in Table 1.

Table 1. Assessment of the binding interaction of chalcone derivatives with AChE

Protein	Synthesized compounds	Substituents	Reference Drug	Binding Energy (Kcal/mol)	Inhibition Constant (Nm)
4M0E	5	4-H		-10.56	18.22
	6	4-Cl		-11.99	3.16
	7	4-NO_2		-10.02	44.87
	8	4-OMe		-11.30	5.18
			Dihydrotanshinone	-9.23	175.03

On the basis of the docking outcome study, it showed that compound **6** has the highest binding energy (-11.9 kcal/mol) while compound **5** has the lowest binding energy value (-10.02 kcal/mol). Visualizer discovery studio (2017) was utilized to analyze the interaction of hydrophobic and hydrogen bonds between AChE protein and ligands.

Discussion

In the beginning, the 3D structure of the AChE and ligands **(5)**, **(6)**, **(7)**, and **(8)** were evaluated and analysed. Molecular of four chalcone derivatives **(5)**, **(6)**, **(7)**, and **(8)** which consist of different substituents with the AChE protein was performed.

Acetylcholinesterase 3D Structure Evaluation

In this study, the protein x-ray crystal structure of acetylcholinesterase was obtained with a good resolution of 2.00 Å and validation from PDB bank server using PDB code 4M0E (https://www.rcsb.org/structure/4M0E). The structure was further evaluated by using PROCHECK, Verify 3D and ERRAT.

The PROCHECK software was the key structure validation method for several years. It also evaluates the stereochemistry of the protein 3D structure, by checking the geometry of protein structure and compare them to other well-refined structures determined at comparable resolution (Wlodawer, 2017). Ramachandran plot (Fig-

ure 3.1) is one of these PostScript plots produced by PROCHECK, based on the structure of acetylcholinesterase. The rotations are represented by the torsion angles phi and psi respectively. Phi and psi angles cause spheres to collide, and this corresponds to sterically disallowed conformation of the polypeptide backbone.

From the Figure 3.1, the white areas in the Ramachandran plot corresponds to sterically disallowed region where the conformation of the backbone atoms come close than the sum of van der Waals radii. These regions allow for the glycine 26residues only which has lack in its side chain (a side chain that consist of α -H). In the graph the allowed region was represented by red which referred to a two-conformational named alpha-helical and beta-sheet conformations. In these regions there are no steric clashes. The quality of the 3D model evaluated based on this allowed region. The yellow areas referred to the allowed regions, where the atoms are allowed to move a little closer to each other. The Ramachandran plot was summarized the distribution of phi and psi dihedral angles of the amino acid residues. Polypeptide main chain showed that 91.4% of the most favored area was occupied by the residue. On the other side, 8.3% residue found to lie in the additional allow regions and residue in generally allowed region found 0.2% and 0.1% was found within the disallowed region (figure 3.1). It can be concluded from the plot that a total 99.9% amino acid residues were located in the allowable regions. It is worthwhile noting that the 4M0E extracted structure was appeared the good quality model based on the located of the residue in the most favored region. Based on the ascertained information from the Verify 3D structure shown that 99.62 % had the averaged 3D-1D score > = 0.2 (Figure 3.2) and the obtained information rely on how well the primary sequence fits into the tertiary, for this purpose the evaluation took place to change the structure by transferring the 3D to 1D. It was proved that the model of acetylcholinesterase was a good choice since it had a promising quality and appeared satisfactory result based on that it was above 90%. Different colored regions exhibited the different feature of the amino acid eg; the red and pale yellow colour represents as most favoured additionally allowed and generously allowed respectively while the white region represents as the disallowed region.

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Table 2. Evaluation summary of acetyl cholinesterase 3D structure

Evaluation Tool	Evaluation Criteria	Score %	Cut-off %
ERRAT	Non-bonded	91%	50%
Verify 3D	Fitness 1D in 3D	99.62%	85%
Procheck	Stereochemistry	100%	90%

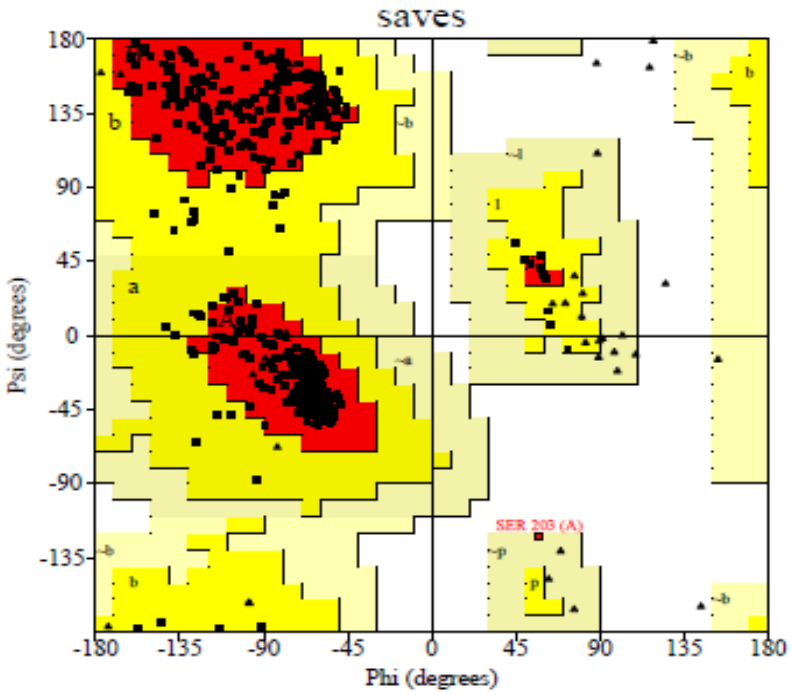

Figure 5. Ramachandran plot of AChE structure showing the Phi and Psi angle distribution of the amino acid residues. Red, yellow, and white coloured regions represent most favoured, additionally allowed and disallowed regioins respectively.

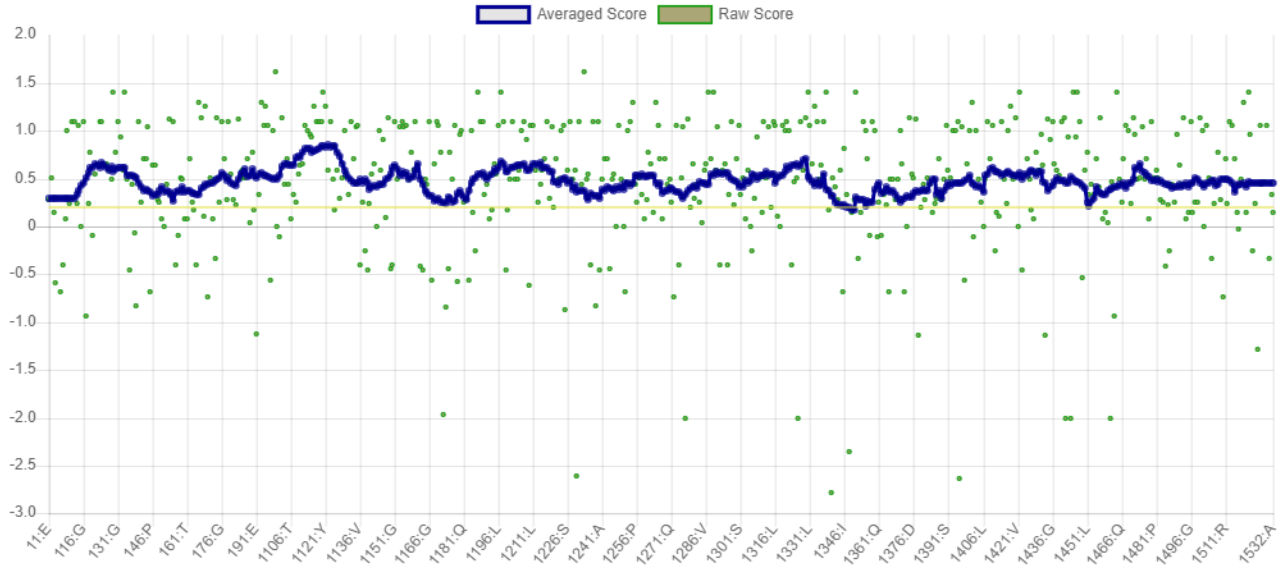

Figure 6. Verify the 3D plot of the AChE structure

ERRAT is a program for the verification of protein structures determined by crystallography. The ERRAT software is used to distinguish between regions correctly and incorrectly determined based on characteristic atomic interaction (Ke *et al.*, 2015). The programme of ERRAT analyzes the relative frequencies of various types. Three types of atoms considered (C, N and O), and consequently six types of 28 interaction are possible (CC, CN, CO, NN, NO, and OO). Error-values are shown as a function of the location of the 9-residue sliding window. In the downloaded structure of AChE, the error function is based on statistics of non-bonded atom-atom interactions (compared to a database of reliable high-resolution structures) (Bemani *et al.*, 2018). Finally, based on the data obtained from ERRAT, it was stated that the overall quality factor was approximately 91%. On the other side, the calculated error value falls below the 95% rejection limit (Figure 3.3). Commonly the excellent high-resolution structure produces value around 95%

or high. As long as, for lower resolution (2.5 to 3 Å) the overall quality factor is 91. Thus, this study surpassed the minimum of 50% cut-off. Therefore, the ERRAT obtained information result approved the quality and trustworthy structural analysis extracted 3D structure of AChE protein.

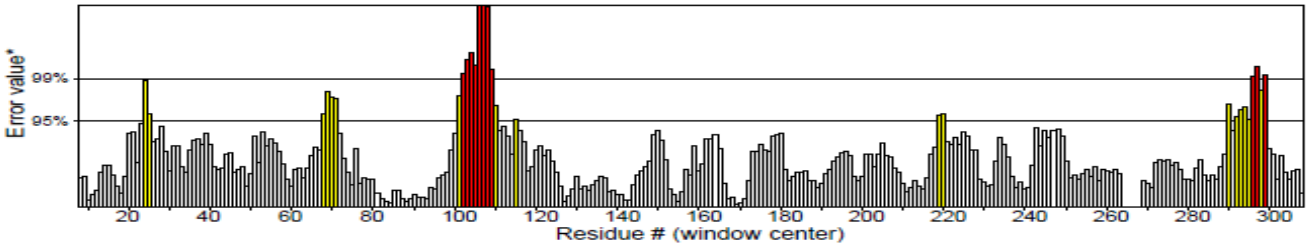

Figure 7. ERRAT plot of 4M0E structure

In this research, for molecular docking ligands were initially prepared using ChemDraw, Pymol and Avogadro program. The ligands 2D structures were designed using ChemDraw 15.1. For the stable conformation of the ligands, the Avogadro program was used to minimize the synthesized ligands structural energy for the molecular docking process. From the literature compounds that having a small electron-withdrawing group, electron donates group and aromatic substituent possess higher binding energy than -10.0 Kcal/mol and enhance inhibition activity of the compound against AChE in silico study. Compound (**1**), (**2**), (**3**) and (**4**) were chosen as ligands to bind with the active site of the AChE. Their 3D structures were designed using Pymol software.

Docking analysis was conducted for all synthesized chalcone derivatives. In this research, the virtual result of interaction the chalcone derivatives with targeted protein of human acetylcholinesterase (4M0E) was analyzed based on their binding energy. The binding energy statistics showed different binding affinity of the synthesized compounds with the targeted protein according to their chemical structure.

Conclusion

Molecular docking was successfully performed for all designed compounds and concluded that synthesized compounds **(5)**, **(6)**, **(7)**, and **(8)** exhibited different binding energy with targeted protein (4M0E) using Autodock 4.2. Among the proposed chalcone derivatives **(6)** and **(8)** showed the highest binding energy value (-11.91 kcal/mol) and (-11.30 kcal/mol) due to good binding interactions between the target protein and the peripheral active site of acetylcholinesterase consisting of hydrophobic and hydrogen bond interactions. Accordingly, ligands **(6)** and **(8)** are possible excellent candidates for acetylcholinesterase inhibitor since they show better binding energy compared to the reference drug.

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References

1. Agrawal M., Saraf S., Saraf S., Antimisiaris S. G., Chougule M. B., Shoyele S. A., and Alexander, A. (2018). Nose-to-brain drug delivery: An update on clinical challenges and progress towards approval of anti-Alzheimer drugs // Journal of controlled release, 281, 139-177.

2. Bemani P., Mohammadi, M., and Hakakian, A. (2018). Anti-ROR1 scFv-EndoG as a Novel Anti-Cancer Therapeutic Drug // Asian Pacific Journal of Cancer Prevention: APJCP, 19 (1), 97-102.

3. Bhargava K., Nath R., Seth P.K., Pant K.K., and Dixit R.K. (2014). Molecular Docking studies of D2 Dopamine receptor with Risperidone derivatives // Bioinformation, 10 (1), 8-12.

4. Carro E., Bartolomé F., Bermejo-Pareja F., Villarejo-Galende A., Molina J.A., Ortiz P., Calero M., Rabano A., Cantero J. L., and Orive G. (2017). Early diagnosis of mild cognitive impairment and Alzheimer's disease based on salivary lactoferrin // Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 8, 131-138.

5. Colovos Chris, and Todd O. Yeates. (1993). Verification of protein structures: patterns of non-bonded atomic interactions // Protein science, 2.9, 1511-1519.

6. Cheung J., Gary E.N., Shiomi K., and Rosenberry T.L. (2013). Structures of human acetylcholinesterase bound to dihydrotanshinone I and territrem B show peripheral site flexibility // ACS medicinal chemistry letters, 4 (11), 1091-1096.

7. Cui X., Guo Ye., Fang Jh. et al. (2019). Donepezil, a drug for Alzheimer's disease, promotes oligodendrocyte generation and remyelination // Acta Pharmacol Sin, 40, 1386-1393

8. Frateschi S., Keppner A., Malsure S., Iwaszkiewicz J., Sergi C., Merillat A.-M., Fowler-Jaeger N., Randrianarison N., Planès C., and Hummler E. (2012). Mutations of the Serine Protease CAP1/Prss8 Lead to Reduced Embryonic Viability, Skin Defects, and Decreased ENaC Activity // The American Journal of Pathology, 181 (2), 605-615.

9. Grotthuss M. v., Pas J., Wyrwicz L., Ginalski K., and Rychlewski L. (2003). Application of 3D-Jury, GRDB, and Verify3D in fold recognition // Proteins: Structure, Function, and Bioinformatics, 53 (S6), 418-423.

10. Ke, Y.-Y., Singh, V. K., Coumar, M. S., Hsu, Y. C., Wang, W.-C., Song, J.-S., Chen, C.-H., Lin, W.-H., Wu, S.-H., Hsu, J. T. A., Shih, C., and Hsieh, H.-P. (2015). Homology modeling of DFG-in FMS-like tyrosine kinase 3 (FLT3) and structure-based virtual screening for inhibitor identification // Scientific Reports, 5 (1), 1-12.

11. Pandey B., Kaur A., Gupta, O. P., Sharma, I., and Sharma, P. (2015). Identification of HSP20 gene family in wheat and barley and their differential expression profiling under heat stress // Applied Biochemistry and Biotechnology, 175 (5), 2427-2446.

12. Reddy, E. P., and Reddy, M. R. (2011). Alpha, beta-unsaturated sulfones, sulfoxides, sulfonimides, sulfinimides, acylsulfonamides and acylsulfinamides and therapeutic uses thereof: Google Patents 1-20.

13. Swain, P., and Behera, L. (2014). Comparative Structural Analysis of Dep1 Protein in Oryza Sativa // Research & Reviews: A Journal of Bioinformatics, 1 (2), 43-47.

14. Hazarkhani, H., Kumar, P., Kondiram, K. S., and Shafi Gadwal, I. M. (2010). 'Highly selective Claisen-Schmidt condensation catalyzed by silica chloride under solvent-free reaction conditions // Synthetic Communications, 40 (19), 2887-2896.

15. Ke, Y.-Y., Singh, V. K., Coumar, M. S., Hsu, Y. C., Wang, W.-C., Song, J.-S., Chen, C.-H., Lin, W.-H., Wu, S.-H., Hsu, J. T. A., Shih, C., and Hsieh, H.-P. (2015). Homology modeling of DFG-in FMS-like tyrosine kinase 3 (FLT3) and structure-based virtual screening for inhibitor identification // Scientific Reports, 5 (1), 1-12.

16. Laskowski, R. A., Jabłońska, J., Pravda, L., Vařeková, R. S., and Thornton, J. M. (2018). PDBsum: Structural summaries of PDB entries // Protein Science, 27 (1), 129-134.

17. Sethi, A., Joshi, K., Sasikala, K., and Alvala, M. (2019). Molecular docking in modern drug Discovery: Principles and recent applications // Drug Discovery Develop, 27-39.

18. Wlodawer, A. (2017). Stereochemistry and validation of macromolecular structures // In Protein Crystallography, 595-610.

19. Zhang, X., Rakesh, K. P., Bukhari, S. N. A., Balakrishna, M., Manukumar, H. M., and Qin, H.-L. (2018). Multi-targetable chalcone analogs to treat deadly Alzheimer's disease: Current view and upcoming advice // Bioorganic Chemistry, 80, 86-93.

IN SILICO ИССЛЕДОВАНИЕ НОВЫХ ПРОИЗВОДНЫХ ХАЛКОНОВ В КАЧЕСТВЕ КАНДИДАТОВ НА АНТИХОЛИНЭСТЕРАЗНУЮ АКТИВНОСТЬ

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Аннотация. *Болезнь Альцгеймера (БА) – это смертельно опасное нейродегенеративное заболевание, поражающее большинство пожилых людей во всём мире. Одним из ключевых факторов развития болезни является повышение уровня фермента ацетилхолинэстеразы (АХЭ), который подавляет активность ацетилхолина в головном мозге, нарушая его функции. Халконы – это фитохимические соединения, обладающие широким спектром биологической активности, включая ингибирование АХЭ. В данном исследовании были изучены новые производные халконов (соединения 5-6) на их активность ингибирования ацетилхолинэстеразы при болезни Альцгеймера. Энергия связывания всех синтезированных соединений с целевым белком (4M0E) оказалась выше, чем у референтного ингибитора дигидротаншинона (-9,23 ккал/моль). Согласно результатам молекулярного докинга, соединения 6 (-11,91 ккал/моль) и 8 (-11,30 ккал/моль) показали наивысшую энергию связывания среди всех синтезированных соединений. Исследование показало, что замены в ароматическом кольце – введение электронно-акцепторной (хлор) и электронно-донорной (метокси) групп в определённые позиции – играют важную роль в биологической активности этих соединений.*

Ключевые слова: *болезнь Альцгеймера, халькона, производные халькона, ацетилхолинэстераза, молекулярный докинг.*