Evaluation of the anti-Alzheimer's disease activity of N-ferrocenylmethyl-2-nitroaniline using bioinformatics tools

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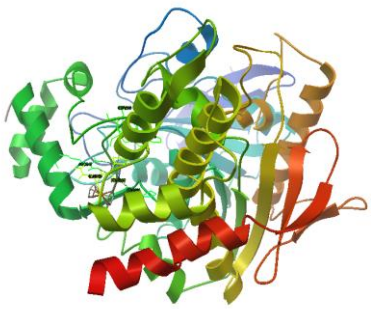
***Abstract*— Inhibition of acetylcholinesterase is currently regarded as the leading strategy against Alzheimer's disease. The principal objective of this project was to investigate the acetylcholinesterase inhibitory activity of N-ferrocenylmethyl-2-nitroaniline (2FMNA) using the bioinformatics tools to predict the relationship between them.**

In this research, we based on docking study of the interaction between N-ferrocenylmethyl-2-nitroaniline and the AChE by using the open source software AutoDock tools. The X-ray crystal structure of the enzyme AChE (PDB ID :5HF5) were obtained from Protein Data Bank (http://www.rcsb.org./pdb). The N-ferrocenylmethyl-2-nitroaniline structure chosen for docking was optimized with the Gaussian 09 software by the DFT method and the set of B3LYP / 6-311G ++ (d, p) bases.

The interaction parameters obtained from molecular docking show that the interaction between 2FMNA and the enzyme is of the electrostatic type.



The interaction between the ligand N-ferrocenylmethyl-2-nitroaniline and the receptor AChE.

Keywords*— N-ferrocenylmethyl-2-nitroaniline, molecular docking, enzyme acetylcholinesterase (AChE), Alzheimer's disease.

Introduction

Alzheimer's disease (AD) is known as the most common form of dementia and is a progressive neural disorder, characterised by memory loss and severe impairment of other intellectual capabilities. AD is connected with the reduced level of acetylcholine (Ach) and loss of cholinergic neurons in the brain. The acetylcholinesterase (AChE), an enzyme that breaks the neurotransmitter Ach into acetate and choline, hampers the normal neurotransmission. Cholinergic hypothesis of the disease states that the inhibition of AChE action may be one of the realistic approaches to the symptomatic management of AD.

Simultaneously, ferrocene and its derivatives have attracted great deal of attention due to their potential application in the treatment of various diseases such as malaria, fungal, bacterial infections, human immunodeficiency virus (HIV), cancer etc. Properties like stability in aqueous and aerobic medium, cell permeability, chemical modifications, and redox activity make it a biologically attractive system. Further, ferrocene itself is not cytotoxic.

In this work we have initiated an in silico study of the interaction between the N-ferrocenylmethyl-2-nitroaniline (2FMNA) derivative and the AChE enzyme (PDB code 5HF5) using the AutoDock tools software.

I. Materials and methods

1. The structure of 2FMNA selected for docking was optimized with Gaussian 09 software by the DFT method and the set of bases B3LYP / 6-311G ++ (d, p).

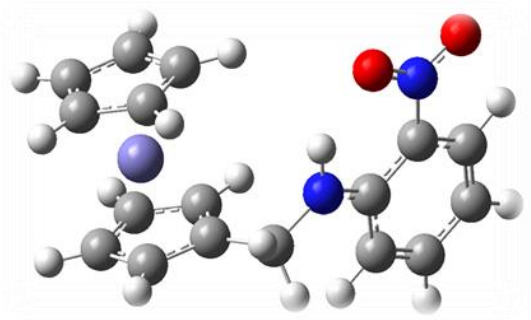


FIG 1. Structure of N-ferrocenylmethyl-2-nitroaniline.

2. The PDB file of AChE protein (PDB code 5HF5) has been downloaded from the protein database site www.rcsb.org

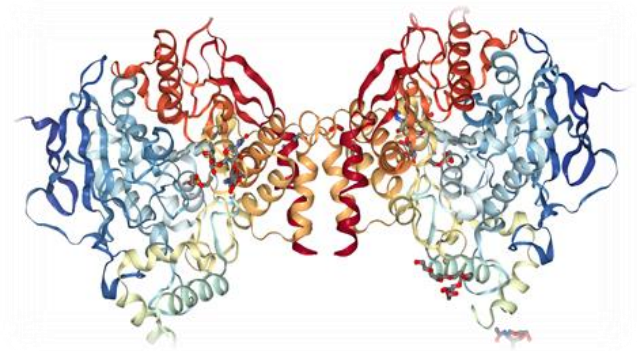


FIG 2. The X-ray crystal structure of the enzyme AChE.

3. Docking study was performed using AutoDock tools. The PDB files of 2FMNA was saved as PDBQT files, The crystal 3D structures of the receptors AChE was first prepared by using Discovery Studio Software, all water molecules, ligands and cofactors were deleted and the active site was defined. Then the polar hydrogen atoms were added. A grid box was generated using the AutoGrid tool, then the ligand was docked into the target receptor using AutoDock tool.

II. Results

The following figure shows the interaction of 2FMNA with AChE, this derivative forms one hydrogen bond with the amino acid PRO235, and two hydrogen bonds with ARG247.

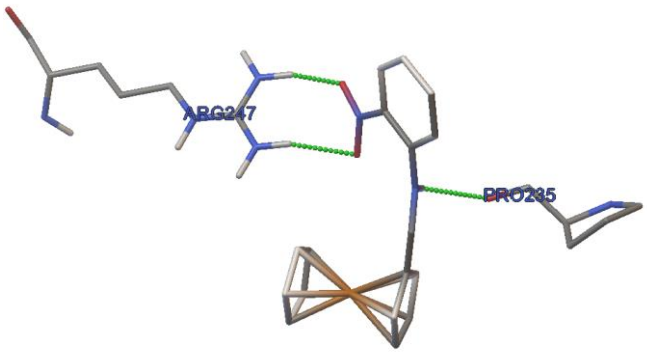


FIG3. Hydrogen bonding between 2FMNA ligand and AChE receptor residue (The H-bond interaction is represented by small green spheres)

Docking results of ligand 2FMNA with the receptor AChE showed that the ligand 2FMNA interact with the receptor AChE via three hydrogen bonds, the two first hydrogen bonds are formed between the HH12 and HH22 groups of the residue ARG247 and the oxygen atom of the ligand 2FMNA, the second is formed between the oxygen of the residue PRO235 and the HN group of the ligand. Fig. 3.

For better observation theses interactions are zoomed out in Fig. 5. And presented as secondary structure surface view in Fig. 4. Hydrogen bonds between AChE receptor and 2FMNA are also presented as small green spheres, Fig. 10a.

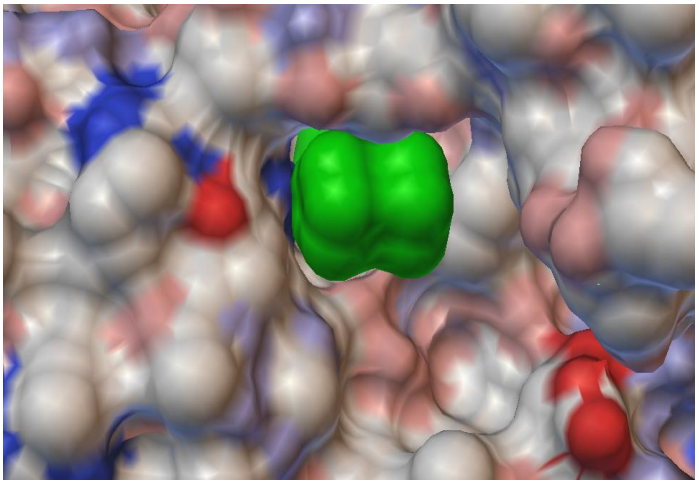
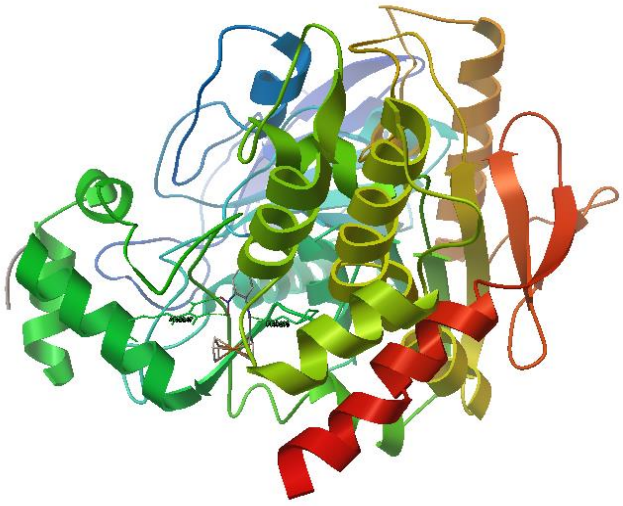
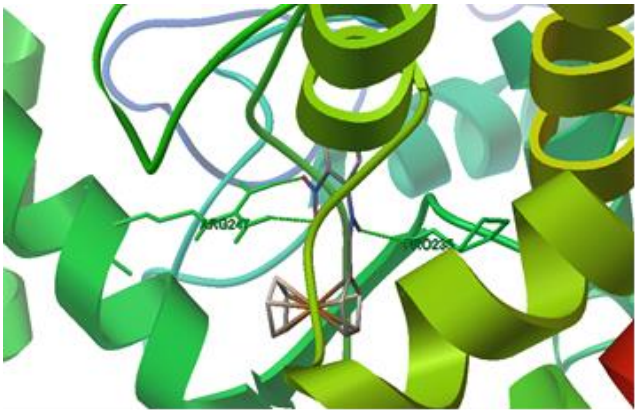


FIG 4. The interaction between the ligand 2FMNA and the receptor AChE, the secondary structure surface view



(a)



(b)

FIG 5. The interaction between the ligand 2FMNA and the receptor AChE, (a) secondary structure view, (b) zoomed view

The bond's lengths and energies values of the hydrogen bonds illustrated in Fig2 is tabulated in table 1.

it can be seen that the ligand FP binds strongly to the enzyme AChE by forming two hydrogen bonds with the residues Arg247 and one hydrogen bond with PRO235.

TABLE 1. LENGTHS AND ENERGIES VALUES OF HYDROGEN BONDS FORMED BETWEEN 2FMNA LIGAND AND ACHE RECEPTOR'S RESIDUES.

Bonds	Length (Å)	Energy (KJ.mol-1)
PRO235:O –2FMNA: HN	2.205	-1.27908
ARG247:HH12 – 2FMNA: O	1.787	-25.7948
ARG247:HH22– 2FMNA: O	2.077	-18.3627

The binding free energy and the binding constant of the docked structure of ligand 2FMNA with the receptors AChE summarised in Table 2.

The value of the obtained binding free energy indicates a high binding affinity of the studied ligand towards the receptors AChE. The binding constants K were calculated using the following equation 1.

$$\Delta G = -RT \ln K \quad (1)$$

Where ΔG is the binding free energy in KJ.mol-1, R is the gas constant, 8.32 J.mol-1K-1 and T is the absolute temperature, 298K.

TABLE 2. BINDING FREE ENERGY AND BINDING CONSTANT VALUES OBTAINED FOR ACHE- 2FMNA ADDUCT BY MOLECULAR DOCKING APPROACH

	-ΔG (KJ.mol^{-1})	**K(M^{-1})**
AChE –2FMNA	-24.36	10,099.10^{-1}

Conclusion

The interaction parameters obtained from molecular docking show that the interaction between 2FMNA and the enzyme is of the electrostatic type. Based on the fact that AChE receptor represent a drug target for AD treatment, it can be concluded that the studied ligand is qualified as potential drug candidature for AD.

REFERENCES

[1] DAS, Subrata, LASKAR, Monjur A., SARKER, Satyajit D., et al. Prediction of Anti‐Alzheimer's Activity of Flavonoids Targeting Acetylcholinesterase in silico. Phytochemical analysis, 2017, vol. 28, no 4, p. 324-331.

[2] H.M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig, I.N. Shindyalov, P.E. Bourne. The Protein Data Bank. Nucl. Acids Res. 28(1) (2000) 235-242

[3] G.M. Morris, H.Ruth, W. Lindstrom, M.F.Sanner, R.K. Belew, D.S. Goodsell, A.J. Olson, Software news and updates AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility. Journal of Computational Chemistry, 30(16) (2009), 2785–2791

[4] M.F.R. Fouda, M.M. Abd-Elzaher, R.A. Abdelsamaia, A.A. Labib, On the medicinal chemistry of ferrocene, Appl. Organomet. Chem. 21 (2007) 613e625.

[5] B. Maity, M. Roy, B. Banik, R. Majumdar, R.R. Dighe, A.R. Chakravarty, Ferrocene-Promoted Photoactivated DNA Cleavage and Anticancer Activity of Terpyridyl Copper(II) Phenanthroline Complexes, Organometallics, 29 (2010) 3632e3641.

[6] G. Jaouen, S. Top, A. Vessires, G. Leclercq, M. McGlinchey, J. The First Organometallic Selective Estrogen Receptor Modulators (SERMs) and Their Relevance to Breast Cancer, Curr. Med. Chem. 11 (2004) 2505e2517.

[8] M.J. Frisch et aal.. Gaussian, Inc., Wallingford CT, 2009.

[9] H.M. Berman et al., The Protein Data Bank, Nucl. Acids Res. 28(1) (2000) 235-242

[10] J. Zhang, Preparation, characterization, crystal structure and bioactivity determination of ferrocenyl–thiazoleacylhydrazones, Appl. Organomet. Chem. 22 (2008) 6e11.

[11] A.K. Kondapi, N. Satyanarayana, A.D. Saikrishna, A study of the Topoisomerase II activity in HIV-1 replication using the ferrocene derivatives as probes, Arch. Biochem. Biophys. 450 (2006) 123e132.

[12] C. Ornelas, Application of ferrocene and its derivatives in cancer research, New. J. Chem. 35 (2011) 1973e1985.

[13] Dassault Systèmes BIOVIA, Discovery Studio Modeling Environment, Release 2017, San Diego: Dassault Systèmes, 2016.

[14] Rajendra Prasad Paitandi, Rakesh Kumar Gupta, Roop Shikha Singh, Gunjan Sharma, Biplob Koch, Daya Shankar Pandey, Interaction of ferrocene appended Ru(II), Rh(III) and Ir(III) dipyrrinato complexes with DNA/protein, molecular docking and antitumor activity, European Journal of Medicinal Chemistry, 84 (2014) 17-29.