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Investigating the interactions of FCS-304 and other Monoamine Oxidase (MAO) A Inhibitors Using Molecular Docking

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ABSTRACT

4-propyl-2H-benzo[h]-chromen-2-one (FCS-304) is a derivative of coumarin which inhibits MAO-A. Selective MAO-A inhibitors are used in the treatment of neurological disorders such as depression. In this article, we have carried out molecular docking analysis of FCS-304 and other anti-depressent drugs to understand the structural features responsible for their potent anti-depressant activity. The analysis reveals that the majority of interactions of FCS-304 are either hydrophobic or steric in nature whereas other anti-depressent drugs like Clorgyline, Iproniazide etc. have interacted MAO-A isoform through hydrophobic as well as polar interactions. In agreement with the previous results the presence of hydrophobic group at position number 4 is quite favorable. The present analysis indicates that presence of hydrogen donor at the end of chain present at the position 4 and hydrophobic group at position 8 could be advantageous. The analysis is useful for future drug designing.

Keywords: MAO-A, FCS-304, Molecular docking, Drug Designing

INTRODUCTION

Coumarin (cromen-2-ona) is a major constituent of many natural as well as synthetic compounds. Not only coumarins are widely used in agricultural, paints, dye industries but have diverse pharmacological actions such as analgesic, anti-convulsant, neuro-protective, antidepressant etc [1-4]. Modern drug designing methods like QSAR, Molecular Docking etc. are widely used to understand the structural features responsible for pharmacological activities of

compounds [5]. The understanding can be utilized to increase the pharmacological properties of organic compounds.

In continuation of our earlier work [6] herein we report the docking analysis of FCS-304 and comparison of its docking pose with marketed drugs as inhibitors of MAO [5, 6]. The objectives of this work are: (1) to understand structural characters responsible for MAO-A activity of FCS-304 (2) to identify the types of interactions involved between FCS-304 with receptor site of Mao-A. (3) To compare docking pose of FCS-304 with marketed drugs (4) to analyze hydrophobic, electronic and steric characteristics of FCS-304.

MATERIALS AND METHODS

2 Experimental Protocols:

Computer-assisted simulated docking experiments were carried out in human MAO-A crystal structure (PDB ID: 2Z5X). Docking simulation study of FCS-304 using Argus Lab with the following protocol.

(1) Enzyme structure was checked for missing atoms, bonds and contacts. Ramchandran plot was plotted to check the health of protein. (2) Hydrogen atoms were added to enzyme structure. Bound ligands were manually deleted from the enzyme. (3) The ligand molecules were constructed using ACD Chem Sketch 11.0 and optimized structure was used for docking. (4) The active site was generated and ligands were docked within the MAO-A active site. (5) The lowest energy conformation was selected and subjected to an energy minimization.

RESULTS AND DISCUSSIONS

2.1 Modeling studies:

Molecular modeling study and conformational alignment studies of the FCS-304 were performed in order to rationalize the obtained biological results (Fig. 1). The complete molecular docking studies were performed using human MAO-A crystal structure (PDB ID: 2z5x).

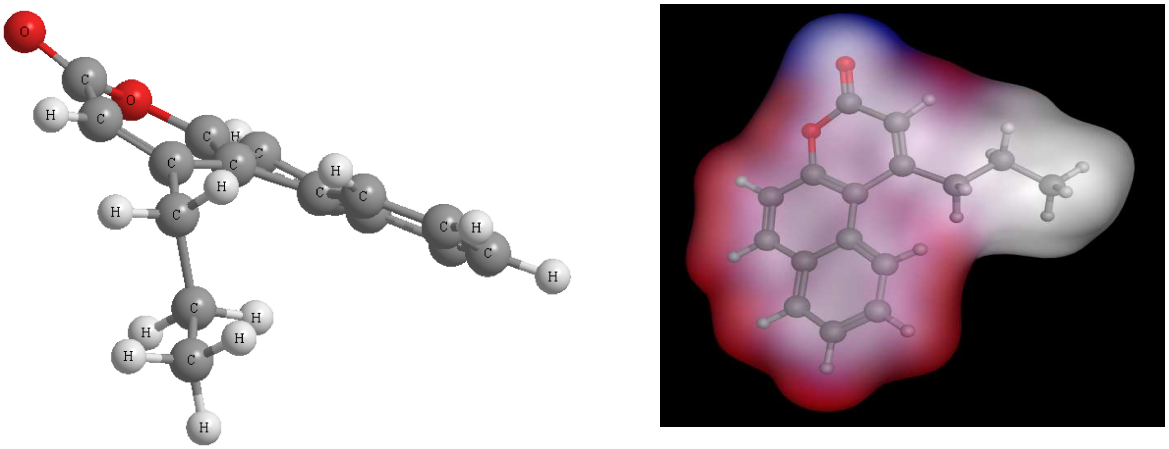
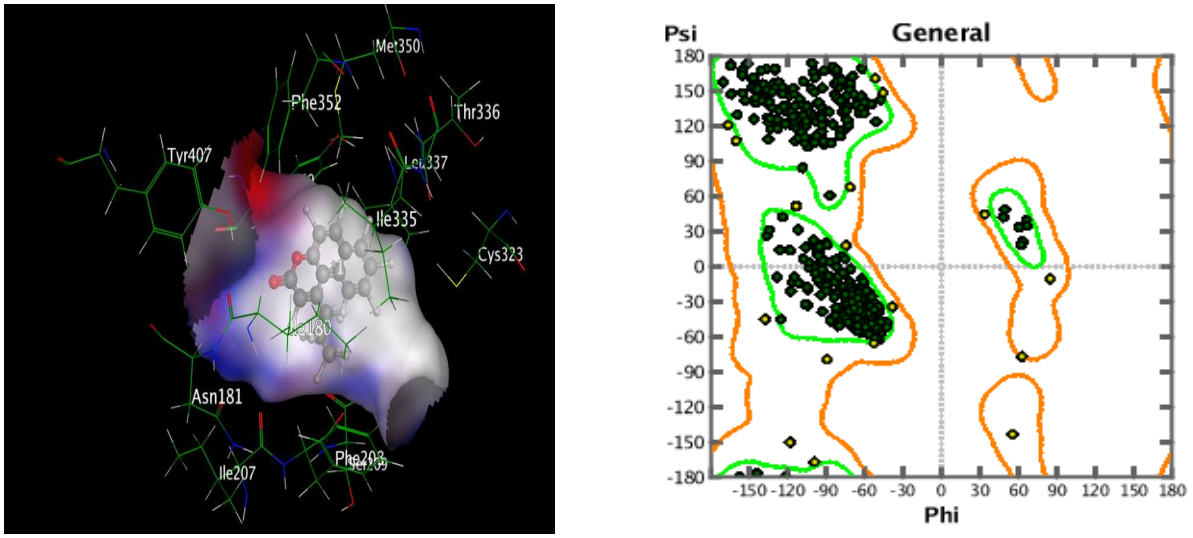


Figure 1. (a) Energy minimized 3D conformation and (b) Molecular surface areas of FCS-304 red= mild polar, blue= H-bonding and white = hydrophobic region

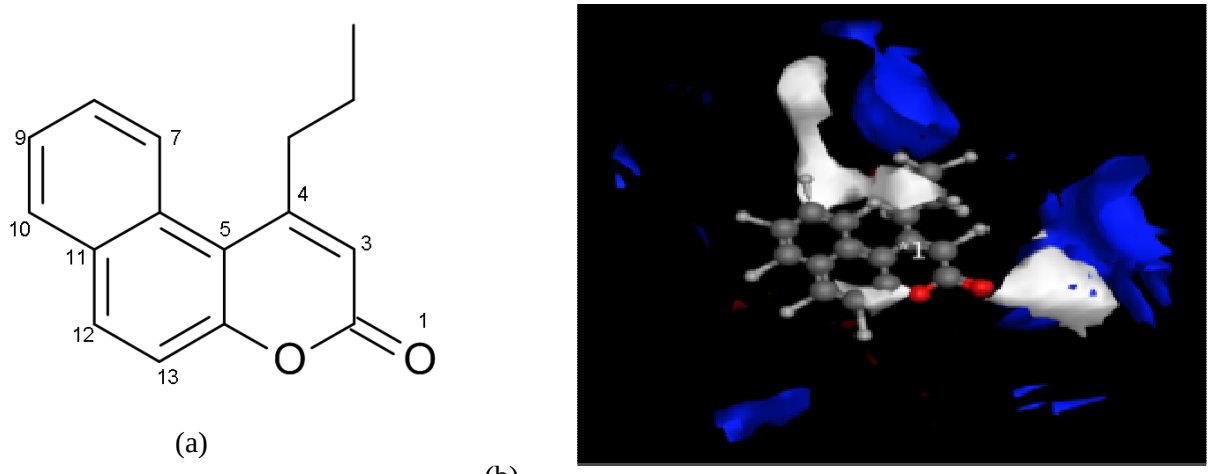
Before molecular docking the 3D structure of ligand was optimized. The pdb 2z5x was subjected to energy and residue optmisation. The health of protein was checked by plotting Ramchandran plot (Fig. 2).



(a) (b)

Figure 2: (a) Docking pose of FCS-304 in the active site of MAO-A (b) Ramchandran Plot for pdb 2z5x after energy and residue optimization.

Docking into the MAO-A active site revealed that the aliphatic chain at position 4 is responsible for hydrophobic interaction with Ile 180. In addition, the aromatic rings are also accountable for hydrophobic interaction with receptor. The polar part of molecule is more engaged in interaction with receptor. No H-bonding is present between FCS-304 and receptor (Fig.2). In order to get useful results that may be valuable in future drug designing we carried out receptor based electrostatic analysis also.

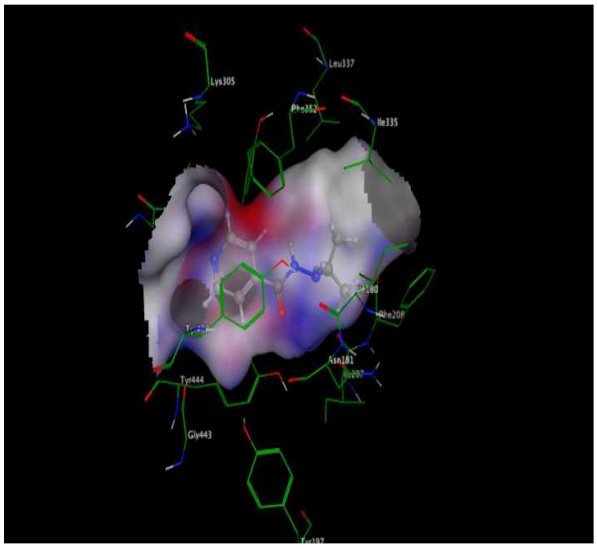


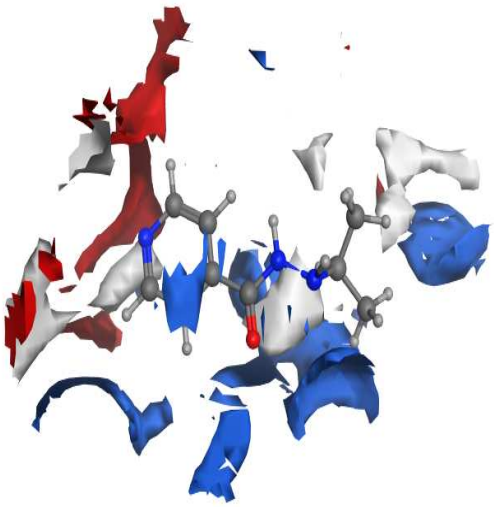
(a) (b)

Figure 3: (a) Structure of FCS-304 with numbering (b) Receptor based Electrostatics regions in the active site of MAO-A. Blue = donor, Red = acceptor and white = hydrophobic regions

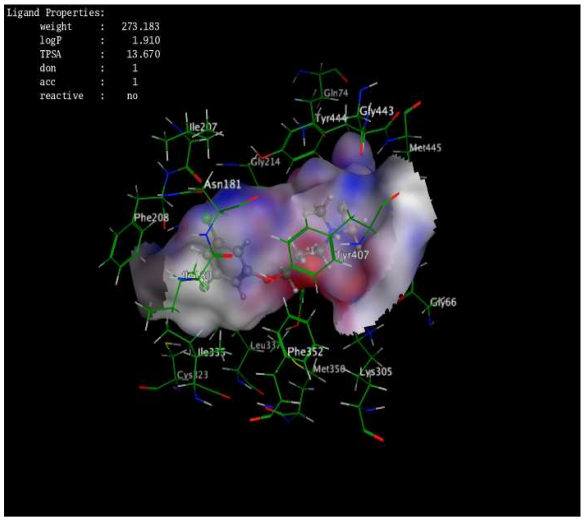
Figure 3 shows receptor based electrostatic regions around FCS-304. Interestingly, in agreement with the previous results [6], the presence of hydrophobic group at position number 4 is very favorable. A slight modification of chain at position 4 such as increasing the chain length with additional $–CH_2$-OH or simply –OH may increase interaction with receptor resulting in tighter binding with MAO-A. The present analysis indicates that presence of hydrogen donor at the end of chain present at the position 4 and hydrophobic group at position 8 could be advantageous.

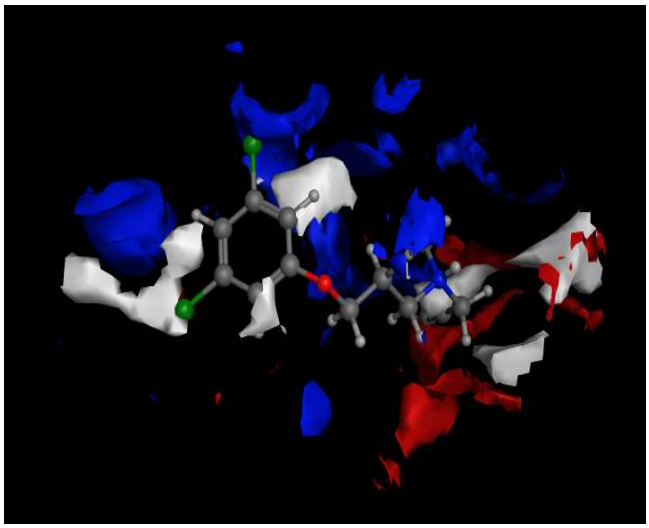
In order to get more productive and general results, we compared docking of FCS-304 with some marketed drugs like clorgyline, Iproniazide etc.; the docking poses show very interesting similarities and differences.





Iproniazide





Clorgyline

Figure 4: a) Docking pose (b) Receptor based electrostatic contour map

All MAO-A inhibitors have interact with residue like Tyr 407, Ile 180, Gln 215, Phe 208 etc. whereas clorogyline has additional interaction with Gly 67, Ala 68, Ile 207 that might be the reason behind making it to be very active even at very low concentration.

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REFERENCES

[1] RD Jawarkar, VH Masand, KN Patil, DT Mahajan , MH Youssoufi , TB Hadda, SL Kumbhare, *Der Pharm Chem*, Accepted manuscript.
[2]. SY Ariza, DC Rueda, J Rincón, EL Linares, MF Guerrero.*VITAE,* **2007**,14 (2), 51–58.

[3]. SY Kang, KY Lee, SH Sung, YC Kim. *Journal of Natural Products*, **2005**,68(1), 56–59.
[4]. Y Chen, LD Kong, X Xia, HF Kung, L Zhang, *Journal of Ethnopharmacology*, **2005**, 96 (3), 451–459.
[5]. VH Masand, KN Patil, DT Mahajan, RD Jawarkar, GM Nazerruddin, *Der Pharma Chemica*, **2010**, 2(4), 298-308.
[6]. NE Vergel, JL López, F Orallo, D Viña, DM Buitrago, E Olmo, JA Mico, MF Guerrero, *Life Sciences*, **2010**,86, 819–824.