



Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis and Molecular docking studies of Indole based compound (2-Methyl-1-Phenylsulfonyl-1h-Indol-3-yl)Phenylmethyl Acetate to nicotinic acetylcholine receptors

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ABSTRACT

Compounds having indole groups are biologically important compounds. Some of them are used as antimicrobial, antiviral, antitubercular, antiinflammatory, anticancer, antidiabetic, anticonvulsant agents. Because of the wide variety of the biological applications of the indoles, the synthesis of several substituted indoles and the study of their crystal, molecular structure and molecular docking studies, continue to be an interesting field of research. With this idea, crystals of indole derivatives are synthesized. The synthesized compounds are subjected to single crystal X-ray studies in order to investigate their molecular structure. Using Autodock v4.0, docking studies of the title derivative have been carried out to understand the possibility of these compounds to act as effective inhibitors.

Keywords: Indole, Neurotransmitter, Autodock v4.0, Docking, Nicotinic acetylcholine receptor.

INTRODUCTION

In the last several decades, indole derivatives have received considerable attention due to their wide range of applications. The small and simple Indole nucleus is present in compounds involved in research aimed at evaluating new products that possess interesting biological activities like antimicrobial, antiviral, antitubercular, anti-inflammatory, anticancer, antidiabetic, anticonvulsant, antimicrobial, antioxidant, antidepressant, anticonvulsant activities. Indole is used primarily in industry and research. Being an aromatic fused heterocyclic compound consisting of a six-membered benzene ring fused to five-membered nitrogen-containing pyrrole ring, indole finds use in research as a starting material for the synthesis of larger, usually bioactive structures [1]. The indolic amino acid tryptophan is the precursor of the neurotransmitter serotonin. However, studies suggest that the indole derivatives may have a beneficial effect to the accumulation of blood fat lipids associated with the disease [2]. Indole based compounds also found a wide application as a precursor in fine organic synthesis, leading to many different products, such as amine-, ether-, nitrile- and oxazole- derivatives [3, 4, 5, 6, 7], which were also proposed as therapeutic agents for coronary diseases such as ischemic heart disease, cardiac arrhythmia, hypertension and depression and even anticancer agents [8]. Indole undergoes electrophilic substitution, mainly at position 3. Substituted indoles are structural elements of the tryptophan-derived tryptamine alkaloids like the neurotransmitter serotonin, and melatonin. Neurotransmitters are endogenous chemicals that transmit signals from a neuron to a

target cell across a synapse. Release of neurotransmitters usually follows arrival of an action potential at the synapse, but may also follow graded electrical potentials. Neurotransmitters are synthesized from plentiful and simple precursors, such as amino acids, which are readily available from the diet and which require only a small number of biosynthetic steps to convert [9]. Otto Loewi is accredited for discovering acetylcholine (ACh)—the first known neurotransmitter [10]. Acetylcholine is one of many neurotransmitters in the autonomic nervous system (ANS) and the only neurotransmitter used in the motor division of the somatic nervous system. We report the synthesis and computational molecular docking studies of the (2-Methyl-1-Phenylsulfonyl-1h-Indol-3-Yl)Phenylmethyl Acetate (MPIPA) with nicotinic acetylcholine receptor. Nicotinic acetylcholine receptors and nAChRs are cholinergic receptors that form ligand-gated ion channels in the plasma membranes of certain neurons and on the postsynaptic side of the neuromuscular junction. Fig. 1 shows the releasing of acetylcholine from receptors and broken down by acetylcholinesterase.

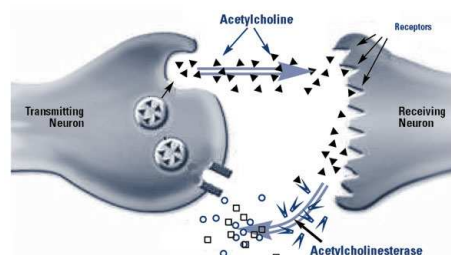


Fig.1 Releasing of acetylcholine from receptors and broken down by acetylcholinesterase

EXPERIMENTAL SECTION

2. Experimental

2.1 Compound Synthesis

To a solution of 1-phenylsulfonyl-(2-methyl-1*H*-indol-3-yl) (phenyl)methanol (0.5 g, 1.32 mmol) in dry DCM (20 ml) acetic anhydride (0.27 g, 2.64 mmol) and pyridine (0.2 g, 2.52 mmol) were added. It was then stirred at room temperature for 7 h under N₂ atmosphere. The reaction mixture was poured over crushed ice (100 g) containing 2 ml of Conc. HCl, extracted with CHCl₃ (3 × 10 ml) and dried (Na₂SO₄). Removal of solvent followed by recrystallization from CDCl₃ afforded the compound as crystals.

2.2 X-ray crystallographic analyses

A single crystal of the title complex suitable for X-ray structural analysis is selected from the crystals obtained above. All measurements were made on a Bruker Kappa APEX-II diffractometer with graphite monochromated Mo-K α radiation (0.71073 Å). The structure was solved by direct methods and refined by full-matrix least squares on F². All non-hydrogen atoms were refined anisotropically. The H atoms were introduced in calculated positions and refined with fixed geometry with respect to their carrier atoms [11].

2.3 Computational molecular docking studies

The X-ray crystal structure of Acetylcholine Binding Protein (AChBP) (PDB ID: 2XNU) was obtained from the RSCB Protein Data Bank (RSCB PDB). Acetylcholine binding protein (AChBP) as template for hierarchical in silico screening procedures to identify structurally novel ligands for the nicotinic receptors. The docking procedure was performed with version 4.0 of AutoDock program. It combines a rapid energy evaluation through pre-calculated grids of affinity potentials with a variety of search algorithms to find suitable binding positions for a ligand on a given protein. In AutoDock, the protein is required to be rigid, but the program allows torsion in the ligand. Results differing by less than 2.0 Å in positional root mean-square deviation (rmsd) were clustered together and represented the result with the most favorable free energy of binding.

The structure of the ligand is generated with ChemBiodraw 11.0. Atomic charges were assigned using the Gasteiger formalism, which is the type of atomic charge used in calibrating the Autodock empirical free energy function. Finally the compounds were set up for docking with the help of Autotors utility, the main purpose of which is to define the torsional degrees of freedom to be considered during the docking process.

The structure of the Acetylcholine Binding Protein (AChBP) (PDB: 2XNU) was setup as follows: Kollman charge and solvation parameters were added to the final protein file using the ADDSOL utility of AutoDock 4.0[12]. The

grid maps representing the protein in the actual docking process were calculated with AutoGrid. The grids were chosen to be sufficiently large to include not only the active site but also significant portions of the surrounding surface. The dimensions of the grids were thus 90 Å x 92 Å x 94 Å, with a spacing of 0.675 Å.

RESULTS AND DISCUSSION

3.1 X-ray structure analyses

The crystallographic data and refinement parameters are listed. The selected bond distances are given in table.1

Crystal data

Molecular Formula	C ₂₄ H ₂₁ NO ₄ S
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> (Å)	14.3655 (6) Å
<i>b</i> (Å)	8.3432 (4) Å
<i>c</i> (Å)	18.6261 (8) Å
Final R indices [<i>I</i> >2σ(<i>I</i>)]	R ₁ = 0.043
Goodness-of-fit on F ²	1.01

Table 1 Selected bond distances (Å).

Bond	Distance / Å	Bond	Distance / Å
C1—C2	1.369 (3)	C8—C9	1.438 (3)
C14—N1	1.418 (3)	C21—C22	1.373 (4)
C1—C6	1.378 (3)	C8—C16	1.493 (3)
C1—S1	1.747 (2)	C9—C14	1.386 (3)
C2—C3	1.398 (4)	C9—C10	1.389 (3)
C16—O3	1.448 (2)	C23—O4	1.184 (3)
C3—C4	1.354 (5)	C10—C11	1.375 (4)
C16—C17	1.510 (3)	C23—O3	1.339 (3)
C4—C5	1.349 (4)	C23—C24	1.481 (4)
C17—C22	1.373 (3)	C11—C12	1.379 (4)
C17—C18	1.377 (3)	C12—C13	1.364 (4)
C5—C6	1.368 (4)	N1—S1	1.665(17)
C18—C19	1.376 (4)	C13—C14	1.386 (3)
C19—C20	1.354 (5)	O1—S1	1.418(18)
C7—C8	1.339 (3)	O2—S1	1.413(19)
C7—N1	1.434 (3)		
C20—C21	1.362 (4)		
C7—C15	1.483 (3)		

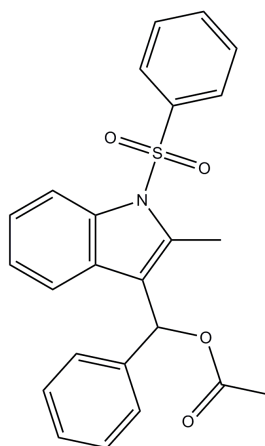


Fig.2 Schematic diagram of MPIPA

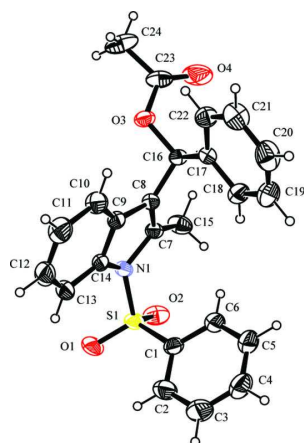


Fig.3 ORTEP diagram of MPIPA

3.2. Molecular docking studies

The structures of the target receptor binding sites of Acetylcholine binding protein (AChBP) (PDB ID: 2XNU) are obtained from the RCSB Protein Data Bank [13]. Then the possible binding sites of selected target receptors were searched using Q - site Finder to predict the ligand binding site and also whole protein structure assumed as a binding site.

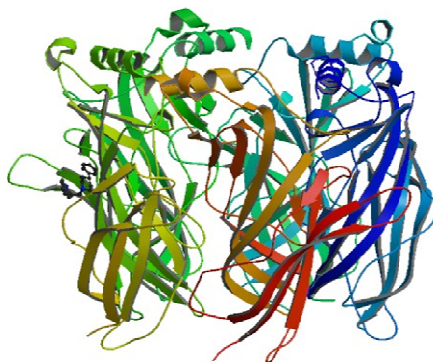


Fig 4 Protein structure of 2XNU

It works by binding hydrophobic probes to the protein and finding clusters of probes with the most favorable binding energy [14]. These include active sites located on protein surfaces and voids buried in the interior of proteins. Q-site Finder includes a graphical user interface, flexible interactive visualization, as well as on-the fly calculation for user uploader structures. The docking analyses of MPIPA were carried out by means of the Autodock tools (ADT) v1.5.4 and Autodock v4.0 program; (Autodock, Autogrid, Autotors, Copyright-1991-2000) from the Scripps Research Institute [15]. Gasteiger charges were computed and the Autodock atom types were defined using Autodock Tools, graphical user interface of Autodock supplied by MGL Tools [16]. The Lamarckian Genetic Algorithm (LGA), which is considered as one of the best docking methods available in Autodock [17, 18] was employed. This algorithm yields superior docking performance compared to simulated annealing or the simple genetic algorithm and the other search algorithms available in Autodock 4.0. To run autodock, we used a searching grid extended over the selected target proteins; polar hydrogens were added to the ligand moieties. Polar hydrogen charges of the Gasteiger - type were assigned and the nonpolar hydrogens were merged with the carbons and the internal degrees of freedom and torsions were set. Fig.2 shows the structure of MPIPA. Fig.4 shows the protein structure of 2XNU. MPIPA was docked to all the target protein complexes with the molecule considered as a rigid body and the ligands being flexible. The search was extended over the whole receptor protein used as blind docking. Affinity maps for all the atom types present, as well as an electrostatic map, were computed with a grid spacing of 0.635 Å. Evaluation of the results were done by sorting the different complexes with respect to the predicted binding energy.

RESULTS

The docking simulations in the active sites of 2XNU were performed by the Autodock program, which has been shown to successfully reproduce experimentally observed binding modes in terms of lowest docking energy. The target protein structures of 2XNU were docked with MPIPA which provided excellent results as were seen by the least values of the binding energy. The best possible binding modes of the MPIPA at targeted protein's active sites are displayed in Fig. 4 and their corresponding energy values are listed in Table 1 by using PyMOL tool v 1.1.

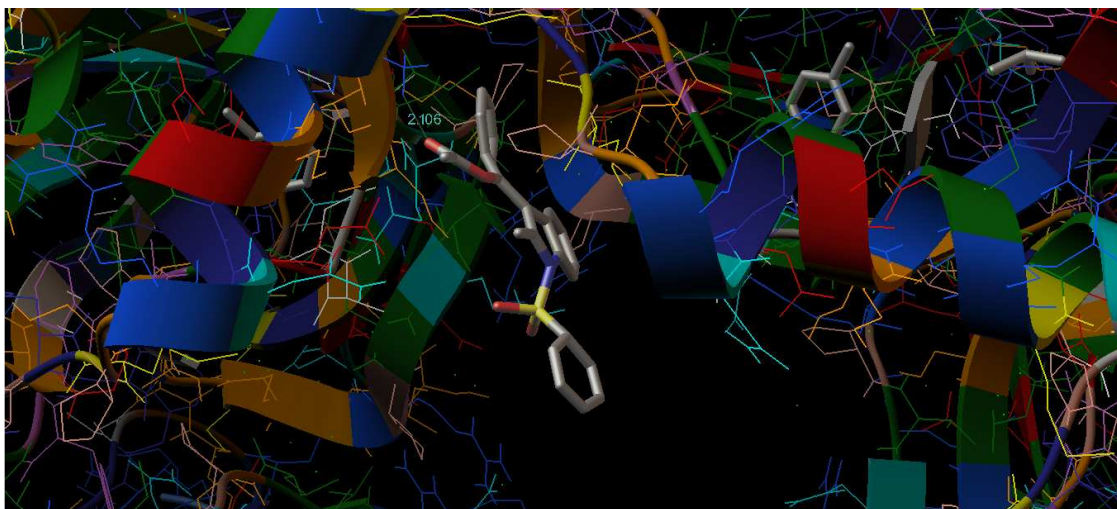


Fig.5 Binding interaction of MPIPA with Acetylcholine binding protein.

Here through Insilico approach it is predicted that MPIPA also shown to inhibit Acetylcholine binding protein as it has good Autodock score as -16.76 kcal/mol which is given in Table.2. A close view of the binding interactions of MPIPA with Acetylcholine binding protein is shown in Fig. 5. Hydrogen bond interaction also makes important contributions to the interactions between the ligand and the receptor. Here a maximum of one hydrogen bond formed between Acetylcholine binding protein and MPIPA. Thus the concept of protein-ligand interaction help in analyzing the binding properties of the receptor Acetylcholine binding protein with its inhibitors.

Table 2. Binding interaction Energy value of MPIPA with Acetylcholine protein

Compound	No. of H bonds	Residue/atom	Atom in compound	Bond length (Å, °)	Energy Value(kcal/mol)
MPIPA	1	LYS8:HZ2	O	2.106	-16.76

CONCLUSION

The protein-ligand interaction plays a significant role in structure based drug designing. Molecular docking study is used to clarify the binding mode of the medicinal compound MPIPA. Taken together; our docking results show that there is a positive correlation between the dock scores and the inhibition of Acetylcholine binding protein receptor.

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