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Pharmacophore Distance Mapping and Docking Study of Some Benzimidazole Analogs as A_{2A} Receptor Antagonists

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ABSTRACT
Extracellular adenosine regulates a wide range of functions in higher organisms, in which the effects are mediated by a family of four class A (rhodopsin-like) GPCRs, *a*, adenosine receptors known as A_1, A_{2A}, A_{2B}, and A_3. A_{2A} antagonists, either alone or in combination with dopamine agonists, can have a role in the treatment of neurodegenerative movement disorders such as Parkinson's disease and Huntington's disease. The concept of a pharmacophore is widely used in modern drug design and it is generally defined as the 3D arrangement of certain features in the ligand that are responsible for its activity against a particular protein target. Docking involves, the process of fitting the ligand into receptor, and the compounds which fit in them properly are assumed to be active for that receptor and it gives corresponding docking scores.

Keywords: Pharmacophore, Docking, Adenosine Receptor, Parkinson's disease, Huntington's disease.

INTRODUCTION

Computer-assisted molecular modeling (CAMM) is relatively new and rapidly developing tool in drug design. [2] The concept of a pharmacophore is widely used in modern drug design and it is generally defined as the 3D arrangement of certain features in the ligand that are responsible for its activity against a particular protein target. [1-3] The importance of the pharmacophore stems from the fact that once it has been identified, it can be used to rationally design new ligand that contain it and thus have a greater chance of producing the desired pharmacological effect.

Adenosine receptors detect local changes in concentration of adenosine, they are seven spanning proteins coupled to various G-protein. [6-9, 14] A_{2A} receptors have role in antiinflammation and also exert effect on neural communication, promote coronary vasodilators and have anti-platelet effects, CNS effects may be favorable in patients with Huntington's chorea [4-6, 10-11] and agonist may inhibit psychosis. Accordingly, the pharmaceutical industry has made a substantial investment in recent years to develop selective, orally available A_{2A} antagonists. [12-13] Systematic medicinal chemistry coupled to model-interpreted bioassay provided the platform for receptor-based new drug discovery for over 30 years.

In present study we have calculated the pharmacophoric distance of benzimidazole analogs and docked these analogs on the A_{2A} receptor [PDB 3EML] [17] by using glide module of Schrödinger. Glide searches for favorable interactions between one or more molecule and the receptor, usally a protein.

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MATERIALS AND METHODS

One of the most important concepts in ligand-based design is the active analog approach. It was developed to derive a pharmacophoric pattern ("pharmacophore") from a set of ligands and, in addition, to obtain an (indirect) view of the receptor binding site. The common volume of the active ligands is the pharmacophoric region, whereas the combined volume of active ligands denotes the space that is available in the receptor including accessory sites for accommodating ligands. Docking is an example of structure based drug design [SBBD], receptor-ligand concept is basically as old as lock and key, the interaction between the ligand -receptor may be reversible or irreversible. Pharmacophore distance mapping measures minimum distance required by the atoms of the molecule for good binding in the receptor and thus activity. [15]

Pharmacophore Distance Mapping:

- Chem. Office 10 was used to draw the structure of 25 compounds selected.
- Energy minimizations were carried out. It is a process of changing the geometry of a structure to reduce its energy, the lower energy states are of interest because the molecules preferentially adopt that stage and will be stable.

- Molecular dynamics module of Chem. Office 10 3D Ultra was used to carry out the dynamics for each molecule.
- Distance mapping was carried out after each run.
- Standard deviations were calculated.

Parameters Followed:

Job Type: Minimize energy to minimum RMS gradient of 0.100,

Job Type: Molecular Dynamics, Step Interval: 2.0 Fs. Frame Interval: 10 fs, Terminate after 10000 Steps, Heating/Cooling Rate: 1.00 Kcal/atom/ps, Target Temperature: 300 Kelvin.

Similarly all the compounds were treated and distance mapping was performed (Table-1).

Docking Studies [16-18]

Molecular docking is basically a conformational sampling procedure in which various docked conformations are explored to identify the right one. Docking program used by us was Glide. Glide searches for favorable interactions between one or more ligand molecules and a receptor molecule, usually a protein. The combination of position and orientation of a ligand relative to the receptor, along with its conformation in flexible docking, is referred to as a *ligand pose*. The ligand poses that Glide generates pass through a series of hierarchical filters that evaluate the ligand's interaction with the receptor. The initial filters test the spatial fit of the ligand to the defined active site, and examine the complementarity of ligand-receptor interactions using a grid-based method patterned after the empirical ChemScore function. Final scoring is then carried out on the energy-minimized poses. By default, Schrödinger's proprietary Glide Score multi-ligand scoring function is used to score the poses. [16]

Receptor Structure Preparation:

The crystal structure of A_{2A} receptor subunit was obtained from Protein Data Bank (PDB entry code (3EML). [17-18] The structure was then manually corrected using the builder module of Maestro (Molecular Modeling Program) this involved the adding of missing residues (GLN 148- HIS 155), hydrogen atoms, appropriate bond-order, as well as removing of water, and fixing proper atom-types (according to atomic hybridization). [17] The manually inspected and corrected structure of A_{2A} was then subjected to a single run by Glide protein preparation program to optimize the structure and ensure its chemical correctness. The prepared model structure of A_{2A} is shown in Fig. 1 along with ligand to highlight the active site location.

Ligand Structure Preparation

For docking experiments, ligand molecules were drawn in Chem. Office 10.0 and after minimization exported as PDB file (3D-structure file) [17] to use in the advance molecular modeling program "Schrodinger". The starting conformation for all of the ligands was obtained by Polak-Ribiere Conjugate Gradient (PRCG) energy minimization using Macro model. Similarly reference ligand (Fig. 2) is prepared for the docking parameter calibration. [18]

RESULT

From the Table 1 obtained for pharmacophore distance mapping, it is seen that the distance between the pharmacophore with other atoms should be in a range of 4.1328±0.7676 to 4.7438±0.1987 for showing maximal activity. Docking Calibration: First we performed the docking of the reference ligand (X, Fig. 2) into the active site of A_{2A}. Docking was performed and few compounds were found to be active giving good GS score (Table 2) while few found to be inactive. From our results it is seen that compound 2 and 4c [Fig. 3, 4], though small in size than the crystal ligand, fit into the pocket of active site and are supposed to show activity while compounds like 3m and 5a [Fig. 5] do not fit into the pocket and are supposed to be inactive. So the compounds 2 and 4c are supposed to have maximal activity and the distance between the pharmacophore and other atom should be in the range of 4.1328±0.7676 to 4.7438±0.1987.

Table 1: Pharmacophoric Distance Mapping

S. No.	Atom from which distance is being mapped	Atom through which distance is being mapped	Distance mapped	Average
1	C1	C2	1.399	5.8179
		C3	2.392	
		C4	2.713	
		N9	4.787	
		N10	5.805	
		C13	8.000	
		C14	9.147	
		C15	9.158	
		C16	8.018	
		N17	6.760	
2	C5	C2	2.763	4.5887
		C3	2.425	
		C4	1.401	
		N9	2.484	
		N10	3.587	
		C13	6.093	
		C14	7.366	
		C15	7.648	
		C16	6.727	
		N17	5.393	
3	N6	C2	2.413	5.0396
		C3	2.797	
		C4	2.394	
		N9	3.659	
		N10	4.556	
		C13	6.665	
		C14	7.814	
		C15	7.860	
		C16	6.761	
		N17	5.477	

Pharmacophoric Distance: 4.4101±0.7877

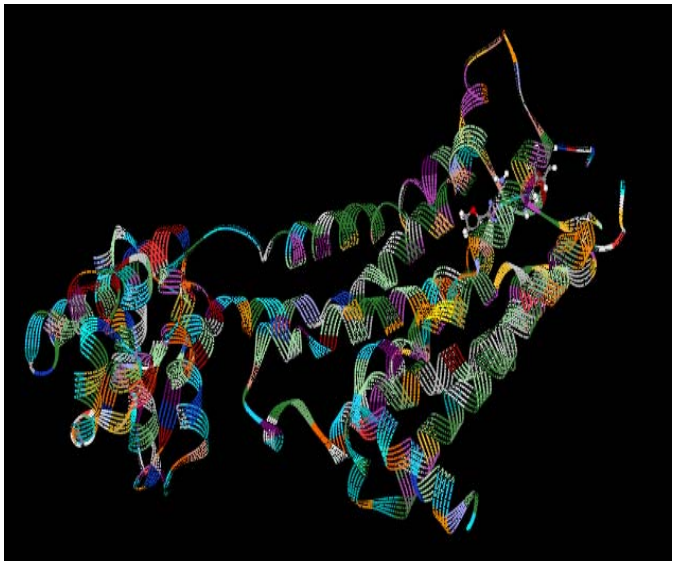
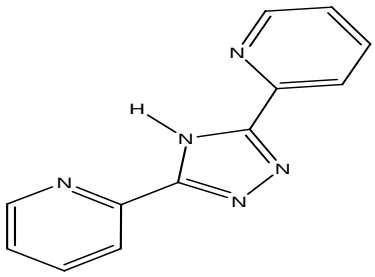
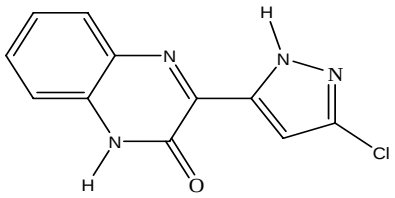
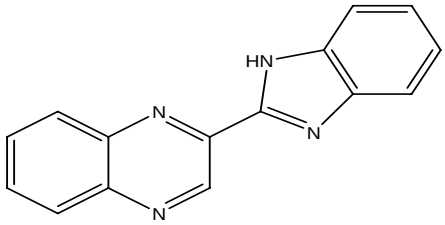
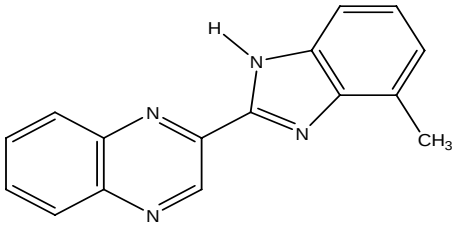
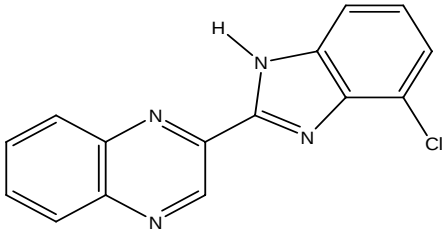
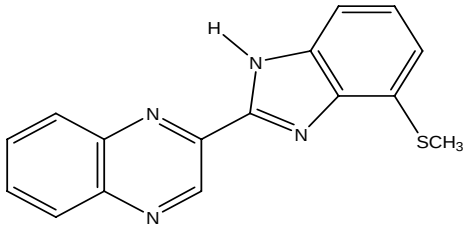
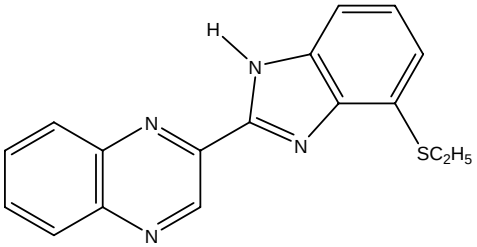
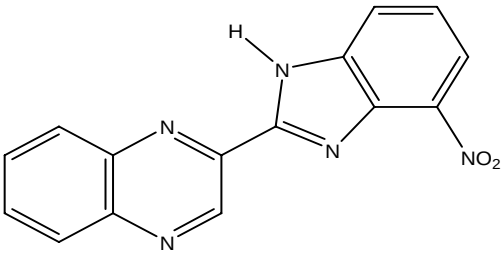
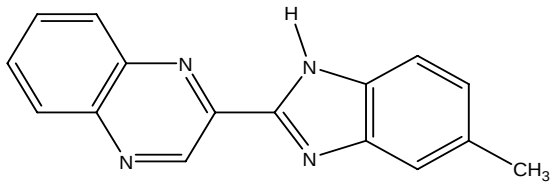
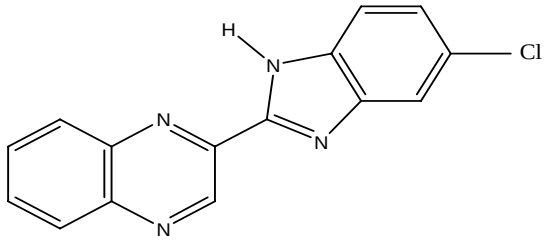
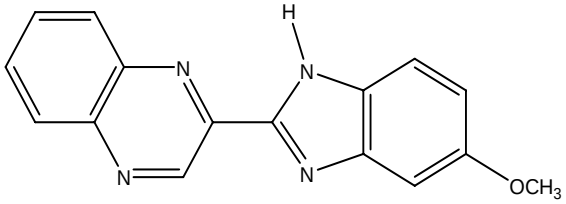
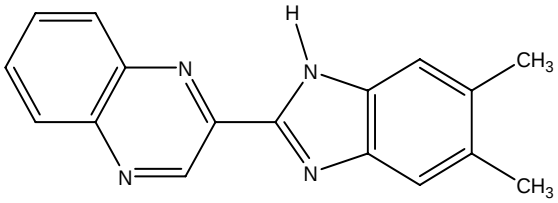
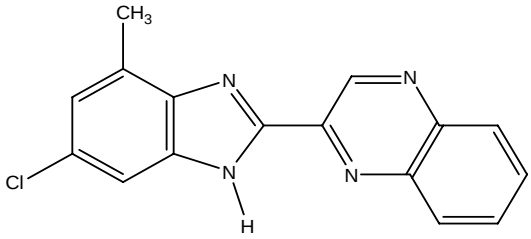
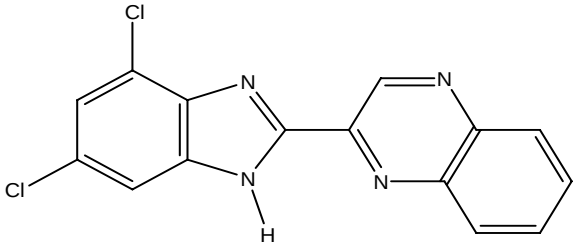
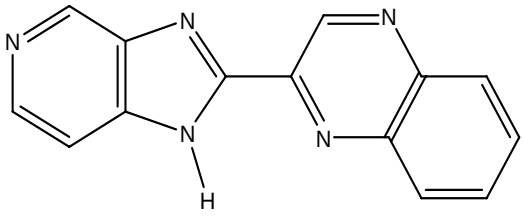
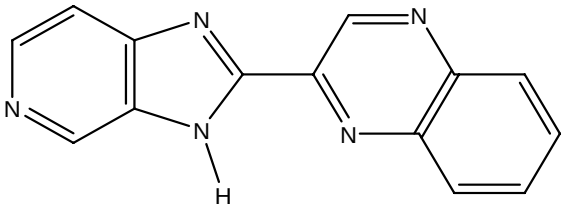
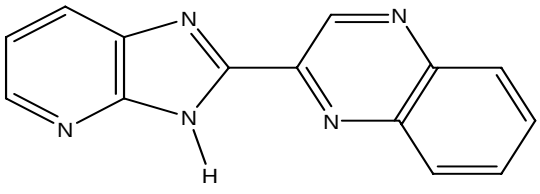
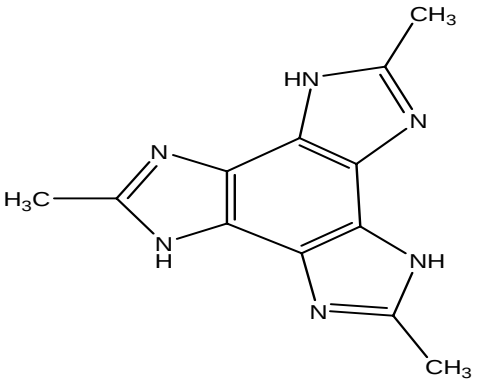
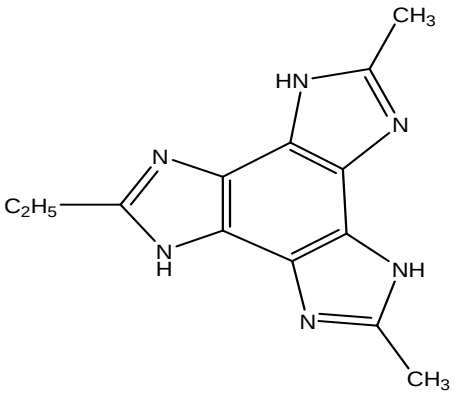
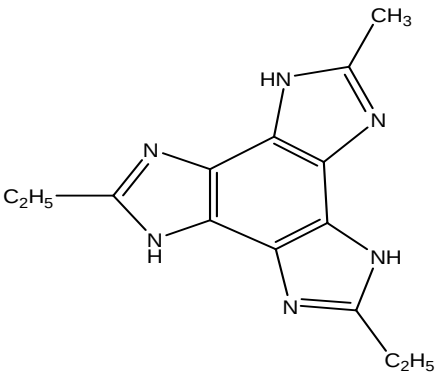
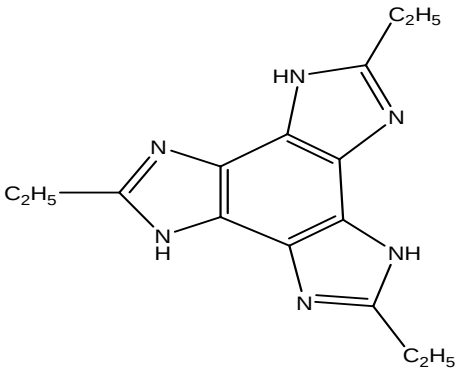
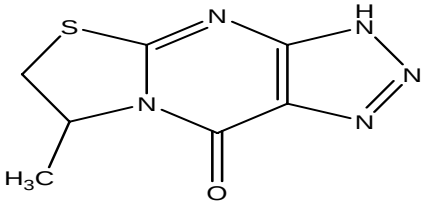
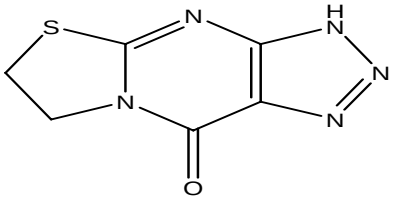


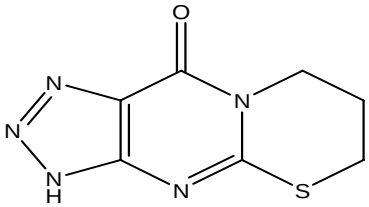
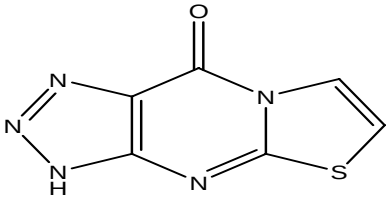
Fig 1. The prepared receptor structure showing the crystal ligand

Table 2: Glide Score and Pharmacophoric Distances

S. No.	Structure code	Structure	Glide score	Pharmacophoric distance
1.	1		-6.24	4.4101±0.7877
2.	2		-6.94	4.1328±0.7676
3.	3a		-6.24	4.3375±0.2958
4.	3b		-6.31	4.3474±0.2388
5	3c		-6.44	4.3705±0.2002
6.	3d		-6.56	4.3719±0.2072
7	3e		-6.32	4.6781±0.2906
8.	3f		-6.71	4.5783±0.2081

9	3g		-6.62	4.6352±0.2354
10	3h		-6.19	4.5673±0.2256
11	3i		-6.20	4.6573±0.2143
12	3j		-6.53	4.5437±0.2086
13	3k		-6.47	4.5867±0.2167
14	3l		-6.44	4.5761±0.2097
15	3m		-5.97	4.2599±0.2366
16	3n		-6.15	4.3167±0.2245
17	3o		-6.31	4.2765±0.2134

18	4a		-6.47	4.5038±0.2133
19	4b		-6.64	4.5174±0.2022
20	4c		-6.88	4.7438±0.1987
21	4d		-6.82	4.4756±0.2314
22	5a		-6.13	4.5644±0.2031
23	5b		-6.34	4.4533±0.2101

24	5c		-6.58	4.3976±0.2353
25	5d		-6.21	4.5362±0.2231

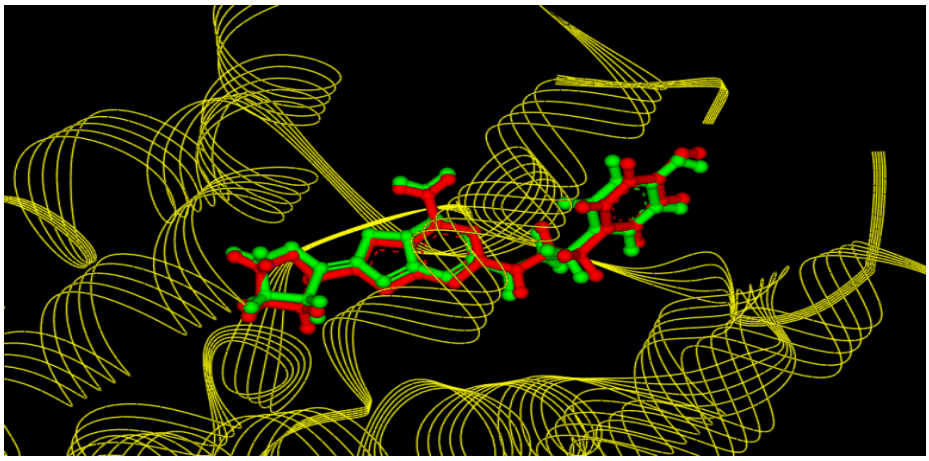


Fig 2: Docking calibration: the reference ligand (in green) fitting into the crystal ligand (in red) or the active site.

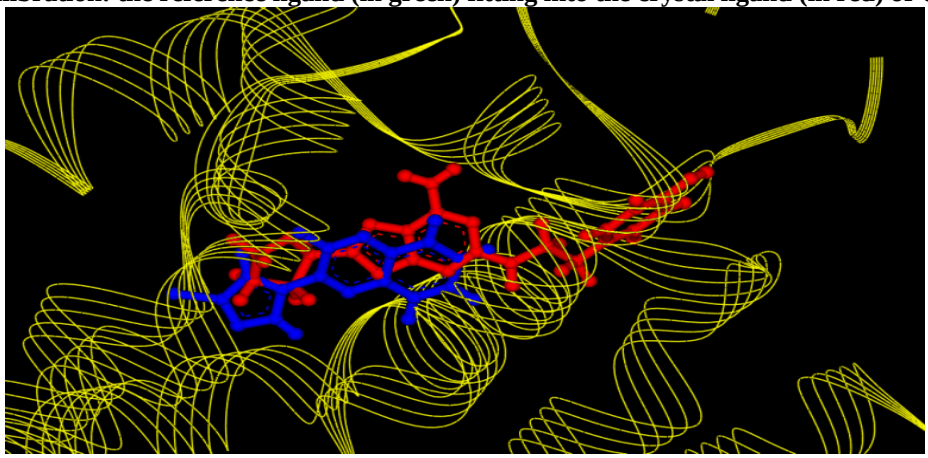


Fig 3: Docking of compound 2 (in blue) to the active site (in red).

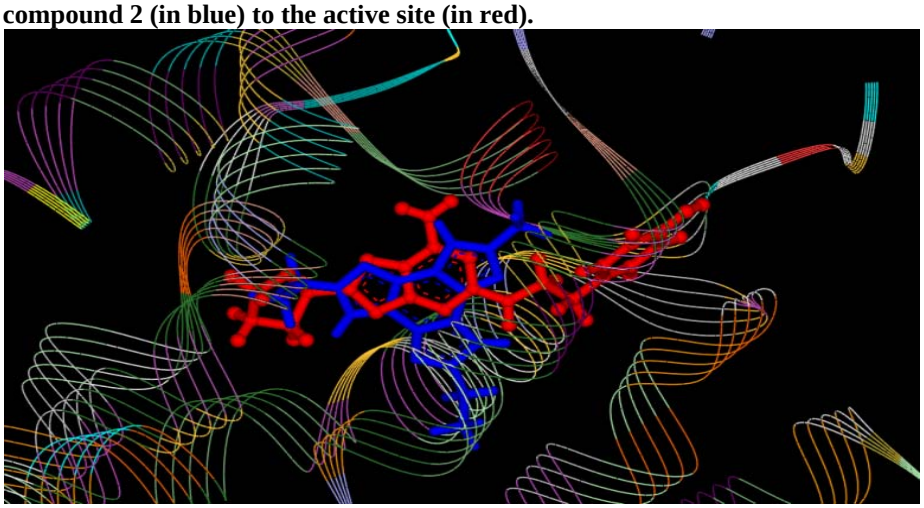


Fig 4: Docking of compound 4c (blue) to the active site (red)

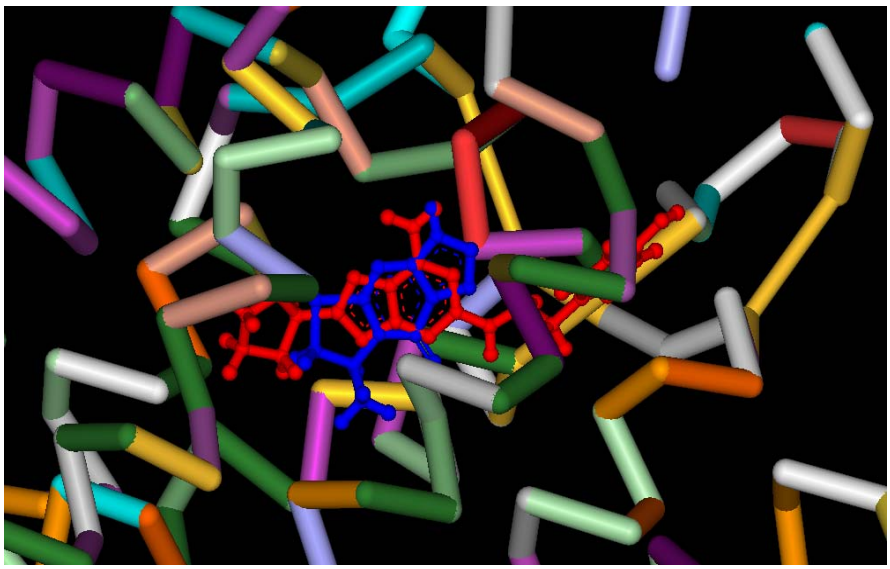


Fig 5: Docking of compound 5a (blue) to the active site (red)

DISCUSSION

From the above work carried out it is clear that use of drug design softwares is of great importance and should be employed for a rational drug design. And for this study the compounds should be designed which have pharmacohoric distance of 4.1328±0.7676 to 4.7438±0.1987 for showing maximal activity and as from the results compounds with good docking scores (2, 4c) [Fig. 3, 4] can be synthesized and tested for the activity similarly there derivatives can be docked and one with good fit with receptor can be explored keeping synthetic feasibility in mind.

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