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DOCKING STUDIES OF 1, 3, 7, 8 SUBSTITUTED XANTHINE DERIVATIVE ON A_2A AND A_2B ADENOSINE RECEPTOR

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ABSTRACT

Asthma is a chronic inflammatory disease of airways characterized by sudden attacks of laboured breathing, chest constriction, coughing and excess mucous production. Adenosine receptor was selected as a target as it displays multiple actions i.e. leukotriene antagonist, decrease inflammation, mast cell stabilizer and inhibit release of histamine. Xanthine was selected as a lead molecule as 1, 3, 8-substituted derivative have good selectivity but low to moderate affinity on A_2B and 1, 3, 7, 8-substituited derivative have good affinity on A_2A and A_2B receptor. Selective activation of A_2A AR has possible therapeutic approach for treatment of Asthma but have cardiovascular side effect specially diminishing B.P. Selective antagonism of A_2B may result adverse effect related to Cystic fibrosis. The purpose of this research was to propose a compound which acts on both A_2A and A_2B adenosine receptor. SAR, predictions using lipinski's rule of five, PASS and OSIRIS proposed 1-Allyl-3-ethyl-7-methyl-8-(3, 4, 5-trimethoxyphenyl) xanthine (1). Docking Simulation study of 1 done on A_2A and then, A_2A receptor was used to prepare model of A_2B receptor using Swiss pdb viewer and VMD software. Compound 1 showed all interactions on both [A_2A binding energy -6.29kcal/mol, binding affinity 14.11µM, on modified A_2A (A_2B receptor) binding energy -5.16 kcal/mol and binding affinity 64.54 µM]. So, it is concluded that compound 1 is potential antiasthmatic acting on both A_2A and A_2B and thus is expected to show minimal cardiovascular and cystic fibrosis side effects.

KEYWORDS

Asthma, Adenosine receptor A and B, Structure activity relationship, Molecular docking simulation and Xanthine derivative.

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INTRODUCTON

Asthma is a chronic inflammatory disease of airways, which can be characterized by sudden attacks of laboured breathing, chest constriction, coughing and excess mucous production[1]. The symptom of asthma can be treaed by number of ways but adenosine receptor as a target for xanthine is best choice for Asthma treatment because

adenosine receptor have multiple action i.e. Leukotriene antagonist, decrease the inflammation, Mast cell stabilizers and inhibition action on release of histamine[2].

Adenosine is an endogenous non-selective agonist, which activates all four subtypes of adenosine receptors (AR) i.e. A_1, A_2A, A_2B and A_3[3]. Adenosine receptors have been recognized as playing an important role in chronic inflammatory airway conditions like asthma, chronic obstructive pulmonary disease and fibrosis[4-6]. Experimental evidence, such as the increase in the adenosine concentration in hypoxia and cellular inflammation in the bronchoalveolar fluids of asthmatics and in plasma (upon contact with allergens), has highlighted the key role that adenosine and its A_2B receptors play in asthma[7,8]. At least half of the population of the world uses tea-containing xanthine: caffeine, small amount of theophylline and theobromine, prepared from the leaves of Thea sinensis. First half of the last century confirmed that methylxanthine share many pharmacological actions and differ only in potency. They are CNS stimulants predominantly caffeine, while theophylline has some CNS-stimulant properties, and theobromine possess only weak stimulant activity[9]. All these well-known drugs are xanthine (2, 6- dioxypurine) derivatives, easily chemically transformed to uric acid (2, 6, 8-trioxopurine). Theophylline is 1, 3-dimethyl xanthine, theobromine 3, 7-dimethyl xanthine and caffeine 1, 3, 7-trimethyl xanthine respectively[10].

Mechanism of action of xanthine derivative

The naturally occurring xanthine derivative, Caffeine and Theophylline are the classical adenosine receptor antagonists[11]. Adenosine released under conditions of cellular stress as seen in asthmatic airways may bind to one of its four AR[2].

A_1 AR activation has been implicated in several events including bronchoconstriction and mucus hypersecretion[12]. Activation of A_2A AR on the inflammatory cells mostly suppresses oxidative stress and proinflammatory cytokines, and may also inhibit the release of leukotrienes (LTs) and histamine from the mast cells[13]. Activation of A_2B AR leads to the release of LTs, histamine, proinflammatory cytokines and enzymes such as chymase and tryptase. LTs and histamine can directly cause smooth muscle contraction, while other mediators such as cytokines, LTs, tryptase and chymase may be chemoattractant for infiltration of leukocytes into the airway space, leading to airway inflammation[14,15]. A_3 AR activation may be involved in vasopermeability changes, mucus hypersecretion, elastase and superoxide anion release, and recruitment of eosinophils to the airways[2, 16-18].

Uses of xanthine other than asthma therapy

Xanthine derivatives are also therapeutically used as antiparkinsonism[19], AntiAlzheimer[20], vasodilators, antihypertensive[21], Acute Ischaemias[22], in diarrhea[23], in pathophysiological process (glaucoma and ischaemia)[24] and as anticancer[25]

Extensive studies have been performed on the 1, 3, 7, 8-substituted xanthine derivatives including structure activity relationships (SAR) of ligands of the A2A and A2B AR, we have screened a variety of xanthine derivatives substituted at the 1-, 3-, 7- and 8-positions. It was found that anellation at 1, 3, 7, 8-position of xanthine changed the profile of its AR activity. The Pharmacological evaluation of the series of novel xanthine derivatives with 1, 3, 7, 8-substituted generally demonstrated their antiasthmatic effect on AR.

Structure-activity studies have established that structural modifications at 1- and 3-positions of the xanthine nucleus do not greatly affect the binding ability of the compounds for adenosine receptors. Most N-7 substituents did not enhance affinity over hydrogen, except for 7-(2-chloroethyl), which enhanced the affinity of theophylline by 6.5-fold to 800nM[26]. However the most dramatic alterations in potency of the xanthine as antagonists of adenosine receptors result from substitution in the 8-position of this heterocyclic system[27,28]. Introduction of alkyl, cycloalkyl or a phenyl ring in the 8-position of 1, 3-dipropylxanthi-nes generate variety of potent and selective adenosine receptor antagonists[26-29].

Substitution of hydrogen at N-7 position favour A_2B AR selectivity[30] and methyl group favour A_2A and A_2B receptor affinity and decreases selectivity

for A_2B receptor[31]. Substitution of large alkyl group at N-1 than N-3, unsaturation in alkyl chain at N-1 position increase the affinity for A_2B receptor[32] and 8-phenyl analogue increase the affinity for A2A and A_2B receptor[33]. Substitution of -H on N-7 position and either polar group on benzene ring at meta position on C-8 position of xanthine or this polar group may be present at ortho position of methoxy group on benzene ring on C-8 position of xanthine, all these substituent favour A_2A receptor affinity[34].

Selective activation of A_2A AR could be a possible therapeutic approach for the treatment of asthma, but direct delivery to the lung will be required to circumvent cardiovascular side effect especially lowering of blood pressure[35].

Selective antagonism of A_2B AR may lead to adverse effects related to cystic fibrosis phenotype and cardiac preconditioning[36].

8-Phenyltheophylline is the parent member of a variety of potent adenosine receptor antagonists. It has been reported that appropriate substituents on the 8-phenyl ring not only affects the potency towards adenosine receptors but also the solubility properties[29]. The incorporation of polar substituents has been shown to improve the water solubility of 8-phenylxanthines and increase their usefulness as potential therapeutic agents[34,29].

In view of the above observation, it was decided to study the impact of good affinity on A2A and A2B receptor which is not selective at particular receptor. The new adenosine analogues of xanthine have structural variations at position 1 (allyl substituents), position 3 (ethyl substituents), position 7 (methyl substituent) and position 8 (3, 4, 5-trimethoxy phenyl substituents) of the xanthine nucleus. (Compound 1).

MATERIAL AND METHODS

Molecular docking simulation studies on A_2A adenosine receptor and ligand *XAC* molecule

Molecular docking simulations studies on A_2A adenosine receptor and ligand *XAC* molecule through software's Auto Grid 4 and Auto Dock 4. The crystal structure of A_2A receptor associated with bound ligand *XAC* was downloaded from RCSB Protein Data Bank portal. All primary information regarding receptor and structure (3REY.pdb) registered in the protein data bank was used. The bound ligand *XAC* was found within the receptor in its bioactive conformation. Figure No.4.

A_2A receptor processing

A_2A receptor processing was done through chimera software the downloaded protein had one chain, A. Chain A of downloaded protein consist of bound ligand *XAC*, which was separated by using software *Chimera*.

Ligand preparation

The ligand was separated from the receptor 3REY.pdb by means of *Chimera* software. [using Chem Draw™ Ultra 8.0 (Chembridge Soft Corporation, MA, USA). Figure No.5.

Grid box

Grid Box Formation using grid box (no.of grid points: 32x, 38y, 64z; spacing: 0.375; grid center: 47.506x, 24.104y, 33.375z), utilizing Autogrid.

The regions of interest used by Autodock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box had 3 thumbwheel widgets which let us change a number of points in x, y and z dimensions. The spacing between grid points could be adjusted with another thumbwheel, the value in the study taken was 0.365 A^0 and No. of points considered were 32, 38 and 64 points in the x, y and z dimensions and 47.506, 24.104 and 33.375 as x, y, z centers. (Figure No.6).

Manipulation in amino acid in A2A receptor

Manipulation in amino acid in A_2A receptor was done because crystallography structure of A_2B adenosine receptor are not available on pdb.org. After modification in A_2A receptor, this modified receptor can be used as A_2B adenosine receptor.

Mutation of amino acid

Amino acid ILE 80, LEU 249, MET 270 was mutate by LEU 80, ALA 270, VAL 249 respectively in A_2A receptor by using Swiss pdb Viewer software. Now, LEU 80, ALA 270, VAL 249 amino acids are present in receptor. This modified A_2A receptor was used as A_2B receptor.

Mutation of amino acid in A_2A receptor was done by Swiss pdb Viewer software. (Table No.1).

Minimization of modified A_2A receptor

Minimization using MM_2 using Operating system Windows XP], Receptor Preparation using Protein Data Bank (http: //www.rcsb. org/pdb). Minimization of protein is necessary because some of the amino acid change their conformation after modification of some of the amino acid in A_2A receptor. Software VMD is utilized for preparation of all necessary files required for minimization of protein.

Molecular docking simulation study of A_2B adenosine receptor

Crystal structure of A_2B receptor after molecular docking simulation along with water

The crystal structure of protein A_2B was prepared by modification of some of the protein in A_2A receptor.

Ligand preparation

All 2-D chemical structures were sketched in *Chem Draw*™ Ultra 8.0 (Chembridge Soft Corporation, MA, USA). These 2D structures were converted into 3D by *Chem3D*™ Ultra 8.0 (Chembridge Soft Corporation, MA, USA). These chemical structures were geometrically minimized through MM2 method by taking default dynamics parameters (step interval 2 fs, frame interval 10 fs) on a PC with operating system Windows XP. Electrostatic charges were assigned by Gastgeiger-Huckel method. These conformations were then utilized as starting conformations to perform molecular docking.

Receptor Preparation

The crystal structure of A_2B adenosine receptor was obtained by modification of some of the amino acid in A_2A adenosine receptor.

Grid box Formation

The binding pocket in the receptor was defined by a grid box (no.of grid points: 74x, 70y, 72z; spacing: 0.375; grid center: 31x, 25y, 19z). All extended conformations of ligands fit in the box. This was ensured by placing the grid box in the centre of the ligand.

Grid maps preparation

Valine 249 and Alanine 270 was selected as flexible residue during formation of grid box. *Autogrid* utility of the *Auto Dock* suite was run to prepare map files for different atom types in ligands and receptor viz. A, C, OA, N, NA, SA, HD. These map files are in turn taken up by *Auto Dock* for carrying docking simulations.

RESULTS AND DISCUSSION

Validation of molecular docking simulation process

Validation of docking programme was done by 3 parameters

(a) Binding energy of complexed structure

Binding energy of docked ligand should be in the range between -5 to -15Kcal/mol.

(b) Overlay of docked and crystallized ligands

The docked conformation of ligands should be perfectly overlayed with the crystal structure ligands of downloaded protein. This testing of the Autodock docking algorithm with ligands (already within receptor as complex) was completed successfully and the docked conformation of ligands were perfectly superimposed with reference structure of respective ligands, i.e. its respective crystal structures. The re-docking of this ligands were successfully achieved to get final results.

(c) Ligand-Protein Interactions

Similar interactions between the docked ligand and the receptor should be observed after d.

Table No.3 Result of interaction between *XAC* ligand and A_2A receptor

Figure No.12 a and b was compared, it was found that polar and hydrophobic interactions were same as shown in following Table No.3.

Table No.4 Result of interaction between proposed molecule and A_2A receptor

Figure No.12 and No.13 was compared, it was found that polar and hydrophobic interactions were same as shown in following Table No.4.

Table No.5 Result of interaction between proposed molecule (1) and A_2B receptor

Following result were observed in docking studies of A_2B adenosine receptor with proposed molecule.

Manipulation in amino acid in A_2A receptor

Manipulation in amino acid in A_2A receptor was successfully prepared. This model was used for further studies as A_2B receptor.

Minimization of protein

Root-Mean-Square-Deviation

After the minimization of protein calculation are terminated, results are recorded in the form of rmsdin*.dcd file. After the minimization of protein RMSD value was found to be 0.8 A^0.

Table No.1: Amino acid present in A_2A and A_2B receptor

S.No	Amino acid in A_2B receptor	Amino acid in A_2A receptor	Distance b/w ligand and amino acid	Inference
1	ASN 253	LEU 272	10.4	Not present in binding area
2	LEU 81	ILU 80	4.9	Present in binding area
3	LYS 170	GLU 169	9.1	Not Present in binding area
4	VAL 256	PHE 255	11.5	Not Present in binding area
5	ALA 271	MET 270	3.3	Present in binding area
6	ASN 267	ALA 265	7.4	Not Present in binding area
7	LYS 269	TRP 268	5.5	Not Present in binding area
8	LYS 267	PRO 266	8.2	Not Present in binding area
9	VAL 250	LEU 249	3.7	Present in binding area

Table No.2: Binding energy of various ligand after docking

S.No	Complex	Binding Energy (Kcal/mol)
1	Ligand XAC With A2A receptor	-7.39
2	1-Allyl-3-ethyl-7-methyl-8-(3, 4, 5-trimethoxyphenyl) xanthine With A2A receptor	-6.29
3	1-Allyl-3-ethyl-7-methyl-8-(3, 4, 5-trimethoxyphenyl) xanthine With A2B receptor	-5.16

Table No.3: Binding energy and result of interaction between *XAC* ligand and A_2A receptor

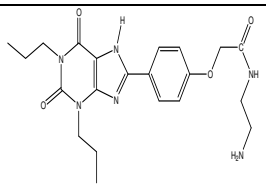
S.No	Ligand	Experimental K_i	Docked K_i	Binding Energy (Kcal/mol)	Polar interaction	Hydrophobic interaction
1	 XAC	7-64 nM	430nM	-7.39	ASN253	PHE168 MET177 ILE274

Table No.4: Result of interaction between proposed molecule and A_2A receptor

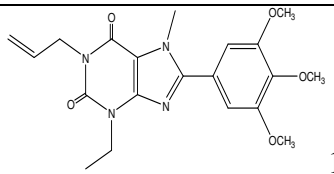
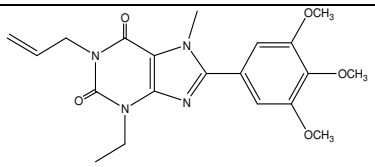
S.No	Ligand Compound 1	Docked K_i µM	Binding Energy (Kcal/mol)	Polar interaction	Hydrophobic interaction
1	 1-Allyl-3-ethyl-7-methyl-8-(3, 4, 5-trimethoxyphenyl) xanthine	14.11	-6.29	ASN253, GLU169, ALA59, ILE80	PHE168

Table No.5: Result of interaction between proposed molecule (1) and A_2B receptor

S.No	Ligand Compound 1	Docked K_i µM	Binding Energy (Kcal/mol)	Polar interaction	Hydrophobic interaction
1	 1-Allyl-3-ethyl-7-methyl-8-(3, 4, 5-trimethoxyphenyl) xanthine	64.58	-5.16	ASN284	PHE44

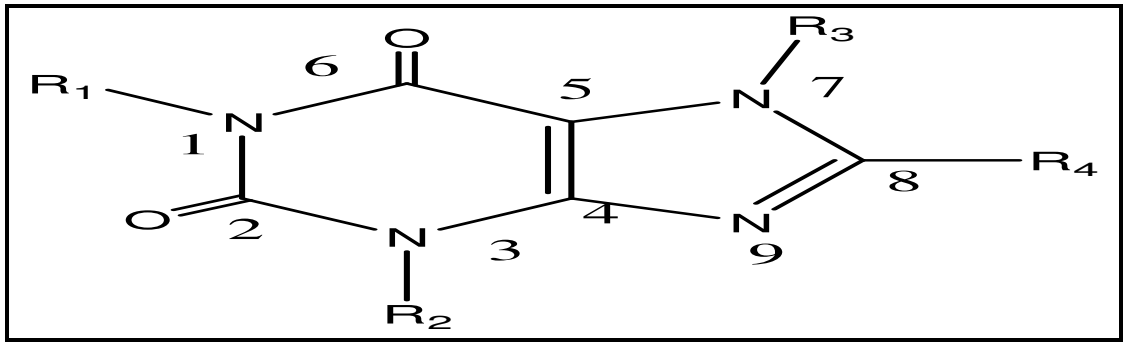
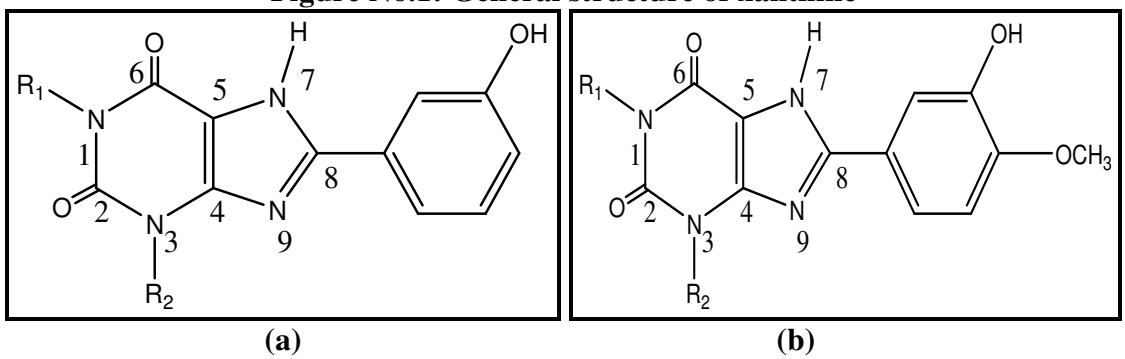


Figure No.1: General structure of xanthine



(a) **(b)**

Figure No.2: Polar group on benzene ring on C-8 position (a) at meta position (b) at ortho position of methoxy group

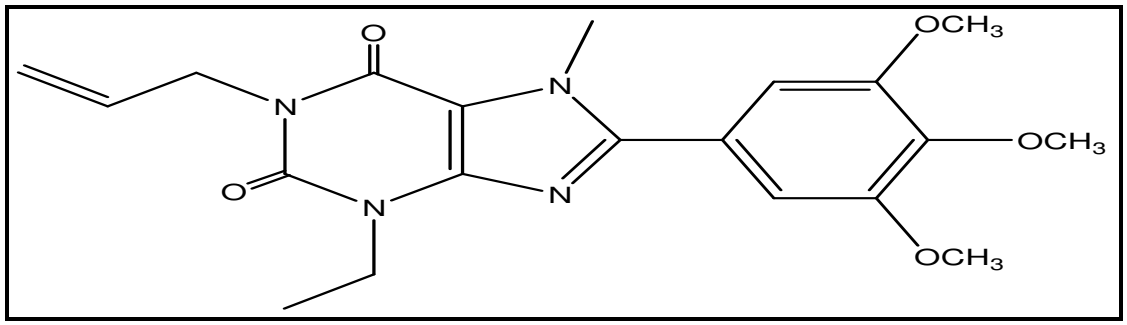


Figure No.3: 1-Allyl-3-ethyl-7-methyl-8-(3, 4, 5-trimethoxyphenyl) xanthine

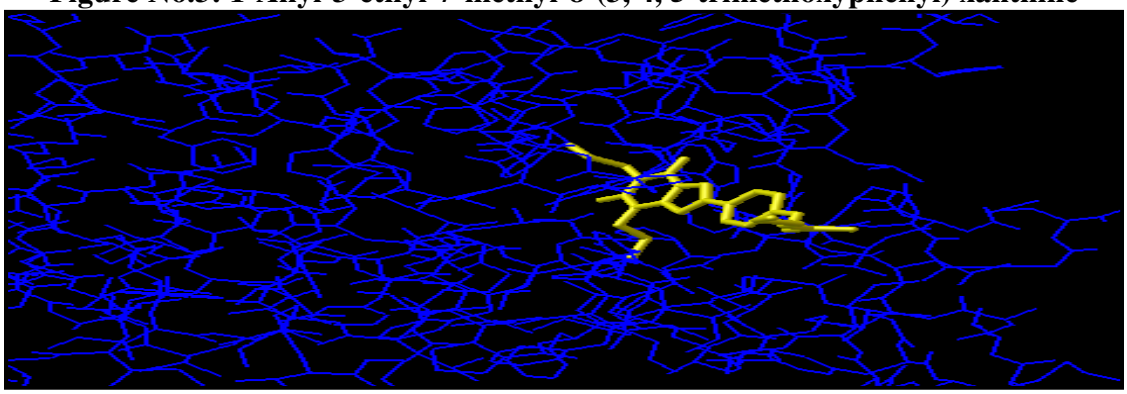


Figure No.4: Crystal structure of A_2A receptor associated with bound ligand *XAC*

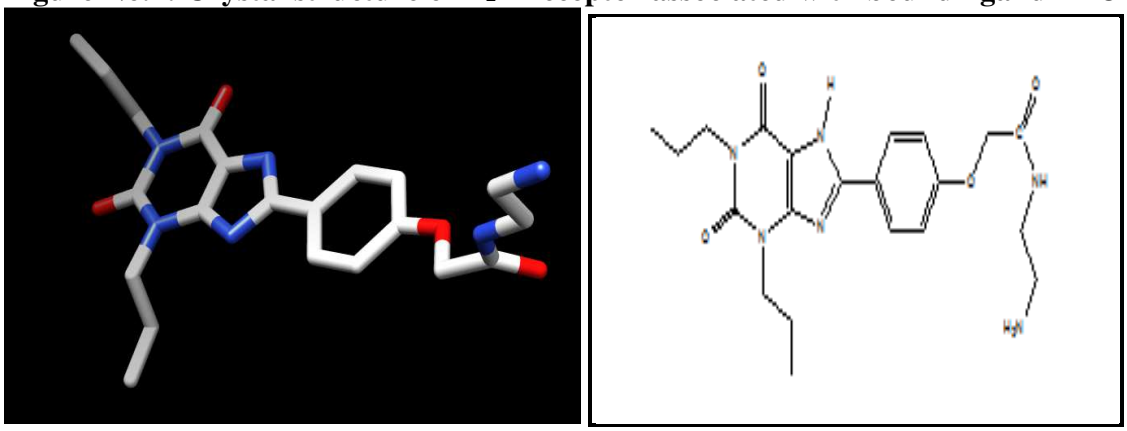


Figure No.5: Ligand *XAC* separated from A_2A receptor

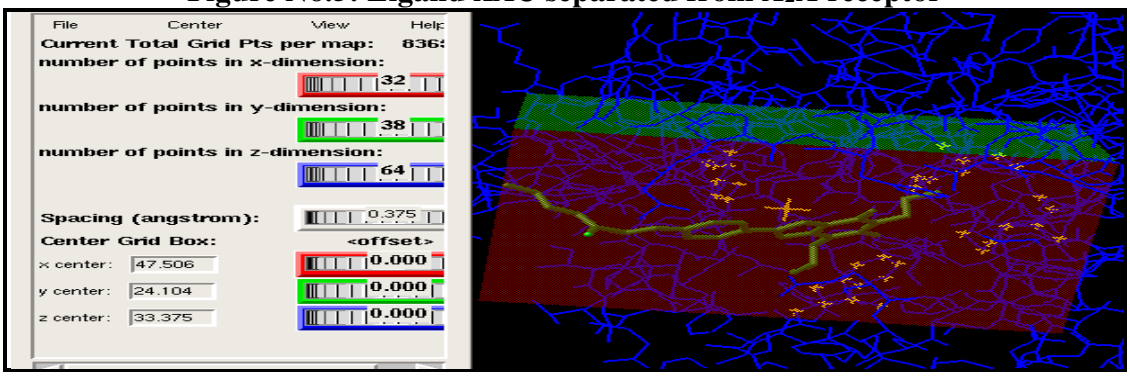


Figure No.6: Grid box covering all active sites in receptor
Amino acid (Yellow Colour) = ASN253, MET177, PHE168 and ILE274

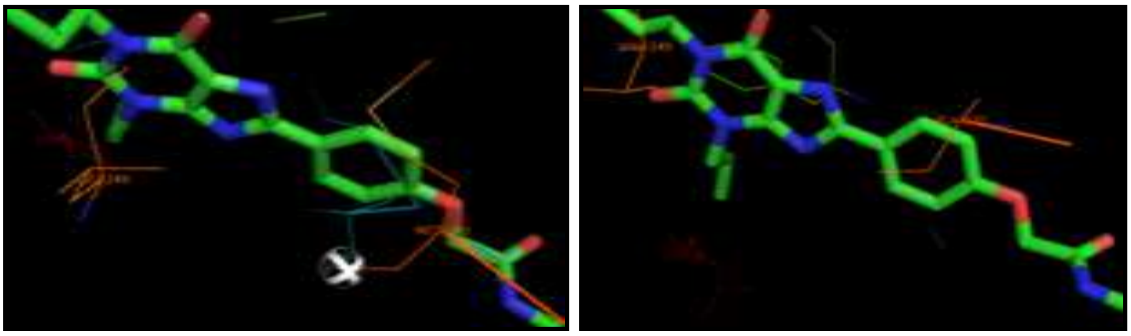


Figure No.7: A_2A receptor and A_2B receptor (after manipulation of amino acid in A_2A receptor)

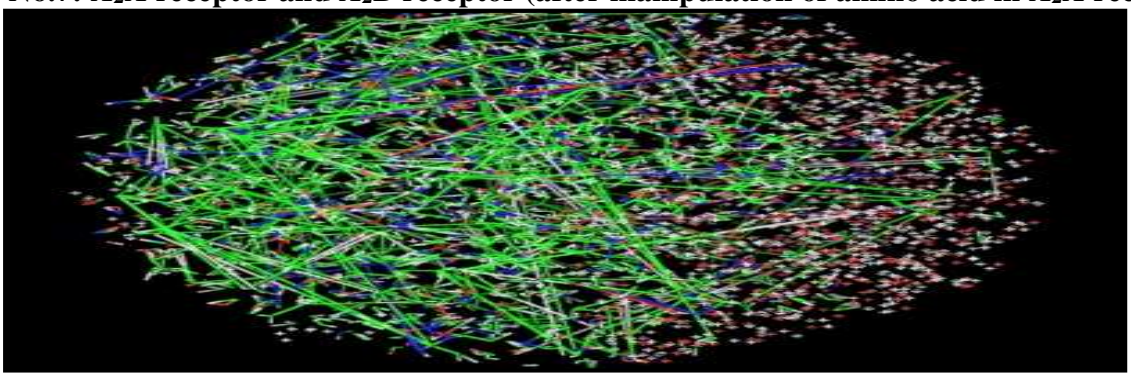


Figure No.8: Crystal structure of A_2B receptor after molecular docking simulation along with water

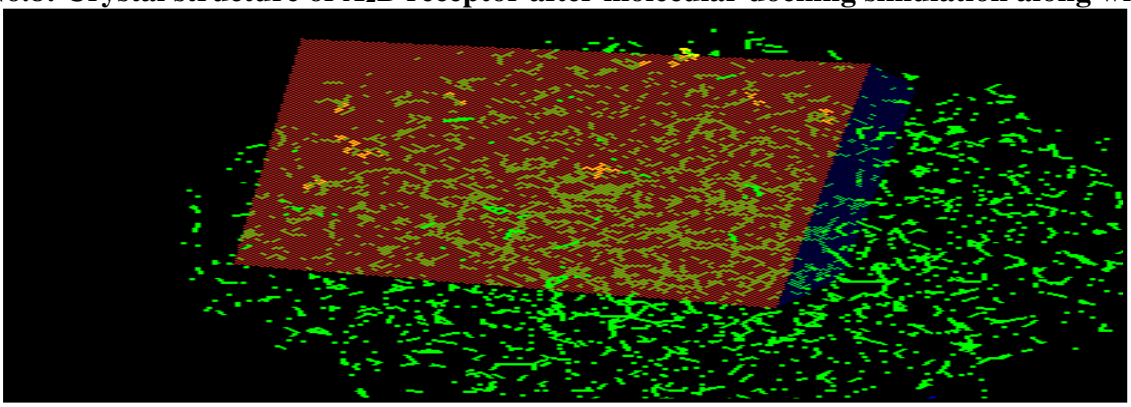


Figure No.9: Grid box covering all active site in receptor
Amino acid in grid box-Valine 249 and Alanine 270 (yellow colour)

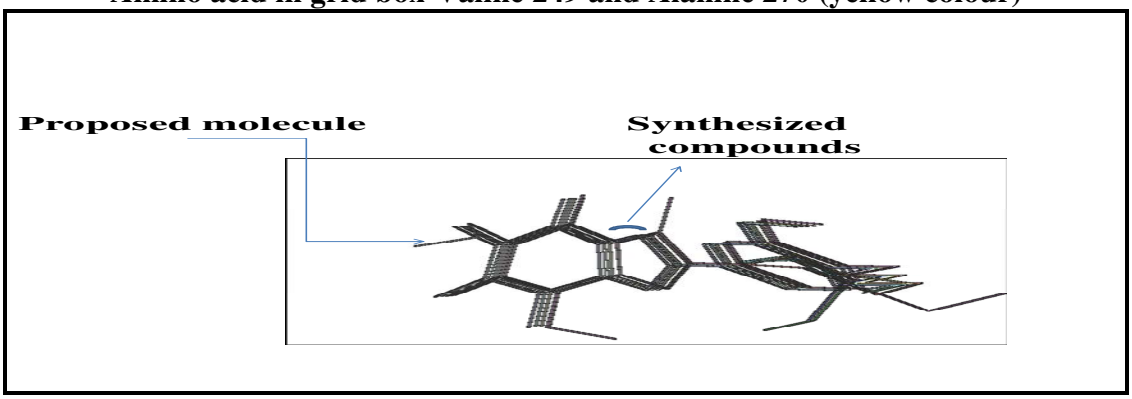


Figure No.10: Bioactive conformation of proposed molecule with reported synthesized compounds within A_2A receptor

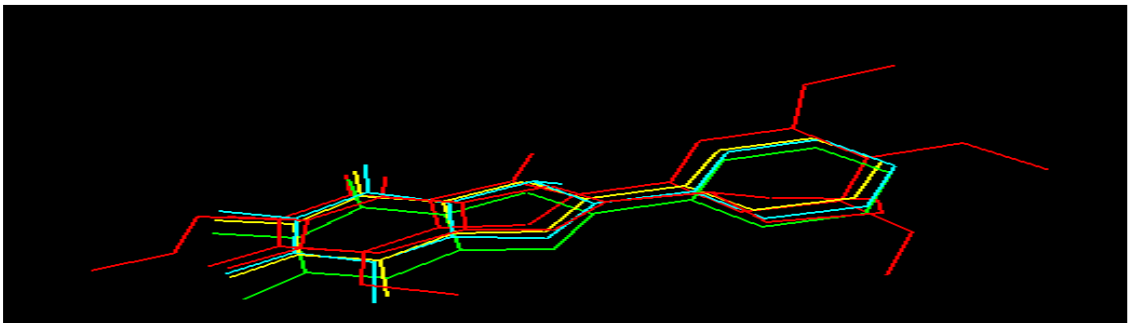
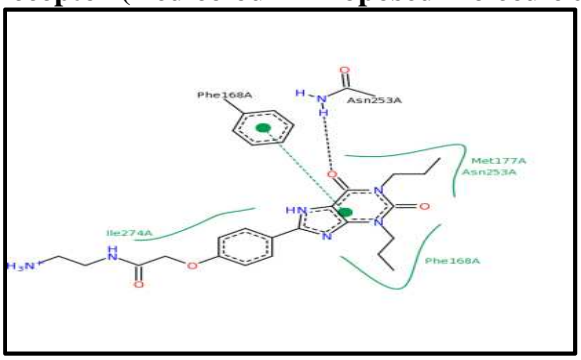
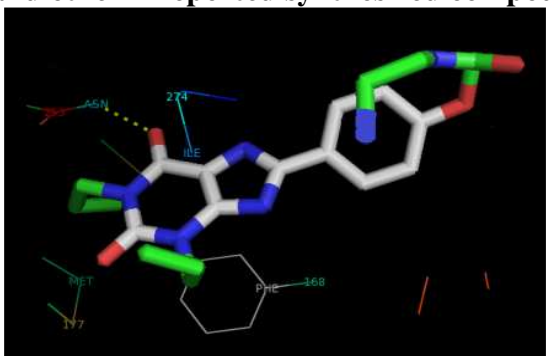


Figure No.11: Bioactive conformation of proposed molecule with reported synthesized compounds within A_2B receptor (Red colour - Proposed molecule and other - Reported synthesized compounds)





(a) (b)

Figure No.12: (a)-Two dimensional interaction of A_2A with *XAC* by pdb and (b)-Three dimensional binding mode of XAC within active site of receptor

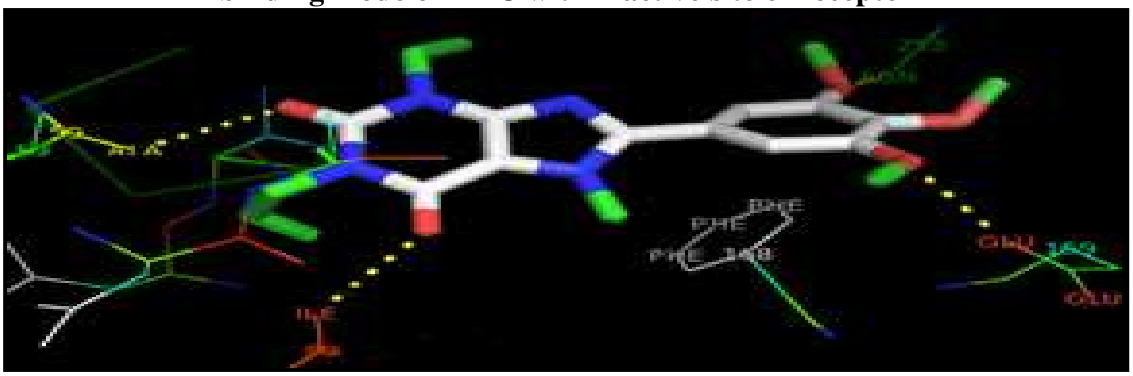


Figure No.13: Three dimensional binding mode of proposed molecule within active site of receptor

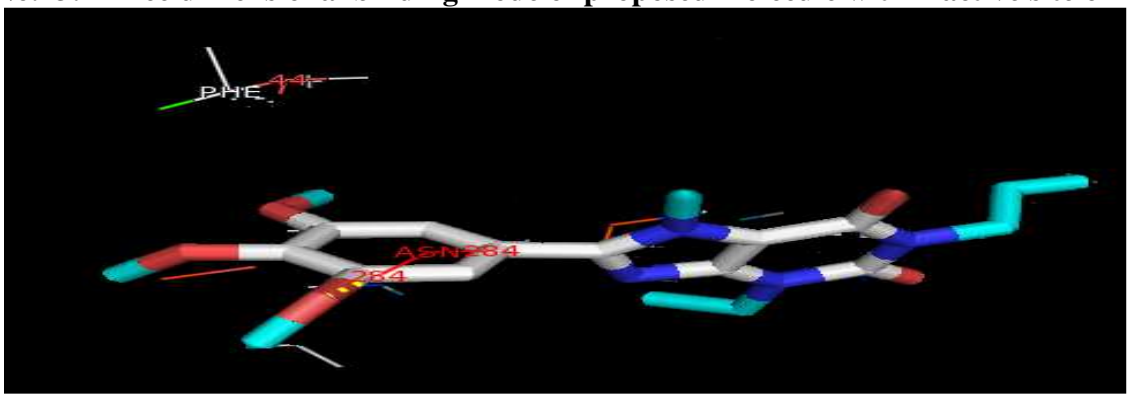


Figure No.14: Three dimensional binding mode of proposed molecule within A2B receptor

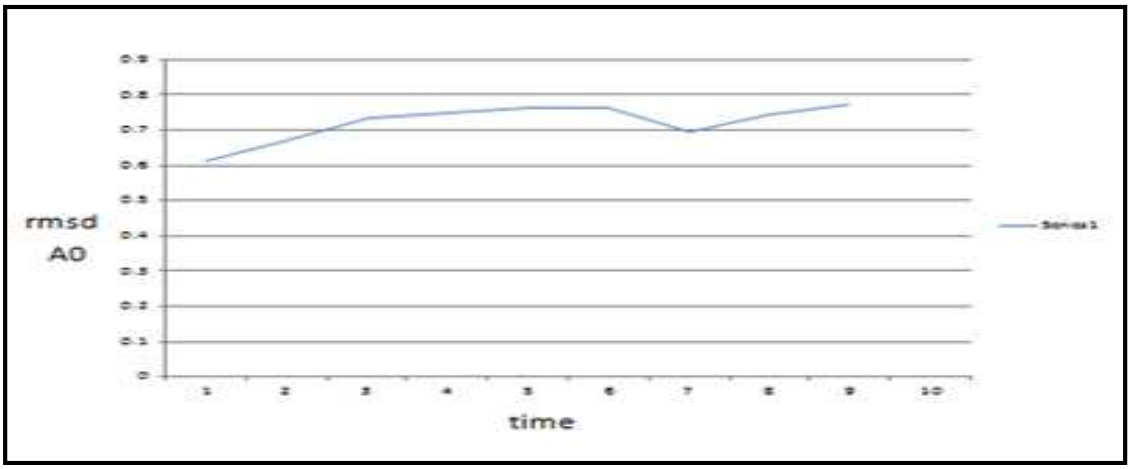


Figure No.15: Graph between RMSD and time

CONCLUSION

The aim of this article was to design potential antiasthmatic agents. Compound was proposed on the basis of SAR which act on both A_2A and A_2B receptor. The proposed compound was not selective for particular one receptor. This was beneficial for decreasing the side effect related to CVS. A docking simulation study for knowing binding affinity of proposed molecule (1) was done on A_2A receptor and modified A_2A receptor. Proposed molecule (1) showed all interaction with binding energy -6.29Kcal/mol and binding affinity 14.11µM on A_2A receptor and with binding energy -5.16Kcal/mol and binding affinity 64.58µM on modified A_2A receptor (A_2B receptor). A_2A receptor was used for prepare model of A_2B receptor. This model was prepared by using *Swiss pdb* viewer and *VMD* software. A_2A based model was used as A_2B receptor. Proposed compound (1) was free from CVS related side effect because of 1, 3, 7, 8-substitution. Proposed compound was free from unwanted side effects predicted by *PASS* and *osiris* like mutagenicity, carcinogenicity, hepatotoxicity and teratogenicity.

FUTURE ASPECTS

We can design new molecule by using structure activity relationship which act on adenosine receptor. SAR based design molecule can docked on adenosine receptor to treat asthma.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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