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In-Silico Design of Purine 2, 6 Diones as Phosphodiesterase Inhibitors

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Sreeja S.[1], Vani V.[2], Akhila A. [3], Anagha S.Anil [4], Rizwan Bin Nizar M. [5], Sapna Sivanthie Suresh Kumar* [6]

[1] Associate Professor, Department of Pharmaceutical Chemistry, Mar Dioscorus College of Pharmacy, Thiruvananthapuram, Kerala-695017, India
[2]Associate Professor, Department of Pharmaceutical Chemistry,Mar Dioscorus College of Pharmacy, Thiruvananthapuram, Kerala-695017, India
[3]Research Scholar, Department of Pharmaceutical Chemistry, Mar Dioscorus College of Pharmacy, Thiruvananthapuram, Kerala-695017, India
[4] Research Scholar, Department of Pharmaceutical Chemistry,Mar Dioscorus College of Pharmacy, Thiruvananthapuram, Kerala-695017, India
[5]Research Scholar, Department of Pharmaceutical Chemistry,Mar Dioscorus College of Pharmacy, Thiruvananthapuram, Kerala-695017, India
[6] Research Scholar, Department of Pharmaceutical Chemistry,Mar Dioscorus College of Pharmacy, Thiruvananthapuram, Kerala-695017, India

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ABSTRACT

Phosphodiesterase inhibitors (PDE) are found in various parts of the lung cells. The enzymes PDE 3, PDE 4, PDE 5 and PDE 7 are mainly associated with asthma. It has been evident that PDE inhibitors can be used as an add-on treatment. This enhances the interest in discovery of PDE inhibitors to ensure a better safety profile. Theophylline, a non-specific phosphodiesterase inhibitor, is a methyl xanthine derivative containing the nucleus 1 H -Purine 2,6 diones. The nucleus is a bicyclic, heterocyclic compound that catalyse the secondary messengers in asthma. 1H-Purine-2,6-diones is a product of purine degradation, whose derivatives can be used as mild stimulants and bronchodilators. In this current research we focus on In-silico modelling of 1H-Purine-2,6-dione derivatives to enhance its phosphodiesterase inhibitory action through various substitutions in N7 position of the nucleus. The various methodologies applied include conversion of two dimensional structure to three dimensional using Novopro Biosciences online tools. Binding affinity was determined by docking using Autodock and the final visualization and PyMol for envision of the output. Theophylline was selected as the standard molecule and the ligands that shows upstanding docking score with phosphodiesterase inhibitors are selected as a promising anti - asthmatic agents.

INTRODUCTION

Bronchial Asthma or Asthma is a chronic inflammatory disease that affects the airways leading to episodes of difficulty in breathing. The disease leads to inflammation of the airways which is triggered by dust, smoke, pet dander or cold air. Other factors like pollen, air pollutants, smoke, foods, respiratory infections and even medications can lead to asthma or asthma attacks. Asthma is not just a single disease but it's categorized into different types. The treatment and management is based on the type of asthma. These can be allergic, aspirin-induced, occupational, steroid - resistant, exercise-induced, cough variant or night time asthma. Some cases of having both symptoms of chronic pulmonary disease (COPD) and asthma have been reported, collectively Asthma - COPD overlap Syndrome (ACOS). Asthma symptoms varies from person to person may be a persistent cough, especially at night, wheezing during exhalation and inhalation, shortness or difficulty in breathing or chest tightness.

Anti-asthmatic drugs can be for quick relief or long term medications. The former can be used to relieve acute asthma and later is for prophylactic measures. Anti-asthmatic drugs can be β2 agonists, anti-muscarinics, corticosteroids, leukotriene inhibitors, xanthines or any of these combinations. Theophylline is well known for its bronchodilation and respiratory stimulant activity. After oral absorption, drug is easily absorbed. The peak concentration is obtained in due course in sustained release tablets. Theophylline is metabolized to 3-methylxanthine by hepatic cytochrome P-450 (CYP-45). As per the report in recents newspapers, over 90% of asthma patients are in a need of right medication. India has about 34.3 million asthmatics which constitutes the 12.9% of global cases. The clinical relevance of a better asthmatic drug is indispensable.

Phosphodiesterases (PDE) are isoenzymes expressed in lungs. These catalyse the hydrolysis of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). PDE isozymes can be targeted to provide different beneficial biological responses. So, we focus on multiple variants in a complex signaling network. PDEs are found in different lung cell types such as vascular smooth muscle cells, epithelial cells, fibroblasts, inflammatory and immune cells which include eosinophils, monocytes, neutrophils, macrophages, T-lymphocytes and B-lymphocytes. Cyclic AMP is an important second messenger in asthma. When the cAMP level rises, it causes the relaxation of the ASM and inhibits numerous immune and inflammatory responses. Increased cAMP levels affect the mucociliary

clearance directly through the activation and acceleration of ciliary motility and indirectly affects the allergic or other inflammation. cGMP is second messenger in asthma because it regulates the vascular smooth muscle relaxation.

Our motive is to design new molecules having and ability to inhibit PDE using 1H-Purine 2,6 diones using the softwares like Chemsketch, Syntelly, Molinspiration, PASS online, AutoDock and PyMol as phosphodiesterase (PDE) inhibitors. Purine 2,6 diones or xanthine nucleus is a bicyclic, heterocyclic compound containing pyrimidine ring fused with imidazole ring. The antiasthmatic drugs like theophylline and aminophylline also possess xanthine nucleus.

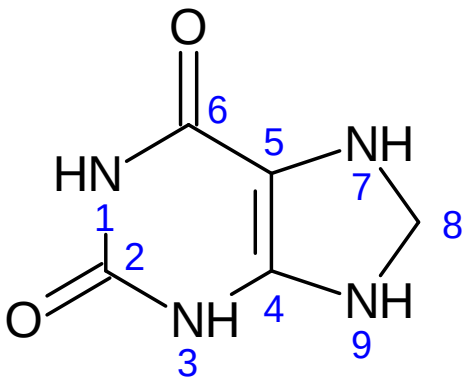


Fig 1.1 1 H purine 2,6 diones (Xanthine nucleus)

Materials and Methods

Computation Platform and Software

Software used for Insilico design are ACD Chemsketch, Molinspiration, PASS online NovoPro Lab, PyMol, AutoDock, etc.

Table 2.1. Software Used for Drug Designing

SOFTWARE USED	USAGE
ACD Chemsketch	Drawing
SMILES (Simplified Molecular Input Line Entry System)	To translate a chemical's 3D structure into a string of symbols, ie., easily understood by computer software
Molinspiration	Calculate drug likeness properties
PASS online	Predict the biological activity of the molecule
PDB (Protein Data Bank)	To obtain target proteins (receptor)
PubChem	To obtain the 3D structure of standard drug
NovoPro Biosciences Inc.	Converting derivatives smiles to PDB
Autodock	Docking
PyMol	Visualizing

ACD Chemsketch

ACD Chemsketch is a molecular modelling program used to create and modify images of chemical structures. This allows molecules and molecular models displayed in two and three dimensions, to understand the structure of chemical bonds and the nature of the functional groups. The program offers some advanced features that allows the molecules rotate and apply color to improve visualization. With this program it is possible to write and perform chemical equations, diagrams, laboratories and chemical equations, diagrams, laboratories and chemical structures of various entity.

Molinspiration

Molinspiration is a cheminformatic software tool, aiding molecule manipulation and processing. It allows visualization of collection of molecules encoded as SMILES.

PASS online. Molinspiration tools are platform independent and may run on any PC, Mac, LINUX machine. Molinspiration property calculator enables interactive calculation of molecular properties. The molinspiration values depicts whether the molecule follows the Lipinski rule of five. According to the Lipinski rule of five, an orally active drug has no more than one violation of the following criteria. The criterias are as follows:

1. No more than 5 hydrogen bond donors, i.e., n.HDO $\leq$ 5

2. No more than 10 hydrogen bond acceptors, i.e., n.HDA $\leq$ 10

3. No more than 5 rotational bonds, i.e., n.rotb $\leq$ 5

4. A molecular mass less than 500

5. A calculated octanol-water partition coefficient (ClogP) does not exceed 5

PDB (Protein Data Bank)

The protein data bank is a database for 3 dimensional structure data. It is mainly used for obtaining the data of large biological molecules like proteins and nucleic acid. The data in PDB is available after X-ray crystallography, NMR spectroscopy, cryo-electron microscopy and submitted by biologists and biochemists from all over the world. The database is freely accessible on the internet via the websites of its member organisations (PDBe, PDBj, RCSB and BMRB). The PDB is controlled by Worldwide Protein Data Bank (wwPDB).

NovoPro Biosciences Inc.

NovoPro Biosciences provide online tools conversion of SMILES to 3D structure. The 3D structure can be downloaded in any one of the desired formats like .pdb, .mol, .sdf. The various derivatives can be converted to SMILES and their 3D structures can be computed.

AutoDock

AutoDock is a molecular modeling simulation software. It is effective for protein - ligand docking. AutoDock 4 is available under the GNU General Public License. This application is one of the most cited docking software applications. It consist of two main programs. AutoDock is for docking of the ligand to a set of grids describing the target protein. Auto Grid can be used for pre-calculating these grids. To performing the docking processes, the ligand and protein molecule has to undergo certain preparations.

Protein Preparation

The X-ray crystal structures obtained from PDB database as a raw is not suitable for molecular docking studies. An ideal PDB structure contains only heavy atoms, waters, cofactors, metal ions. These can be multimeric and at the same time these do not possess

about bond orders, topologies or formal ionic charge . Hence, the raw PDB structure should be prepared in a suitable manner for docking. Protein preparation was attained by means of Autodock. Upon deletion of chains. Substructures, addition of hydrogen and Kollman charges a minimized force field of energy was obtained.

Ligand Preparation

A standard drug of the selected activity and showing the binding properties is selected for PubMed database. The selected ligand can be downloaded in .sdf format and visualized in Pymol and was opened in AutoDock. Then the molecule is reduced to a structure containing a single chain. It is then subjected to elimination of water, addition of Kollman charges and addition of hydrogen atoms. The ligand is now charged and ready for docking.

PyMol

PyMol is an open source and also a proprietary molecular visualization system. With PyMOl, high quality 3D images of small molecules and biological macromolecules are obtained. The software is an open source but proprietary molecular visualization system. The images of docked complex has been visualized by PyMol.

Scheme of Work

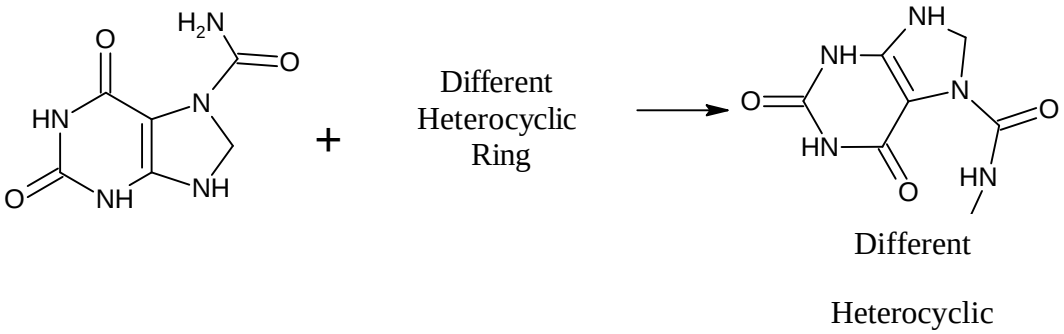
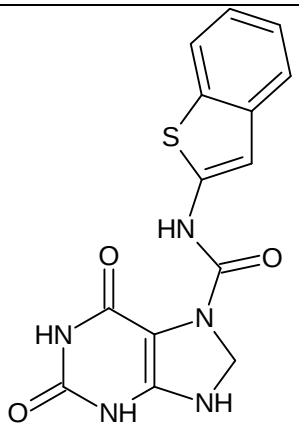
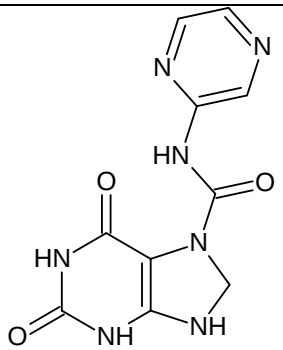
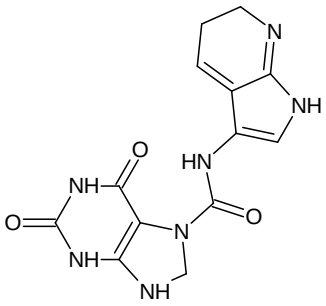
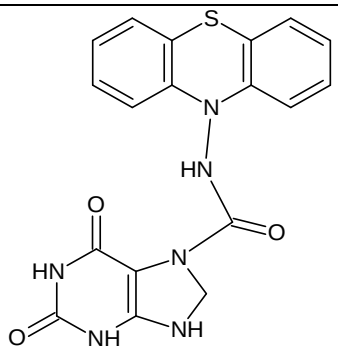


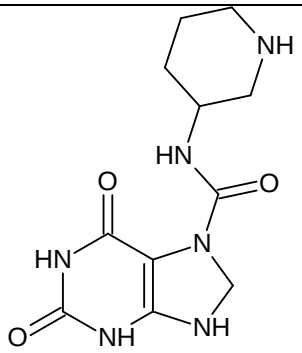
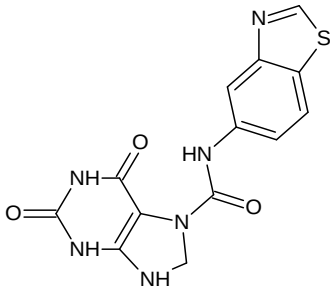
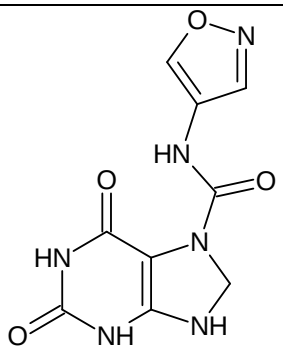
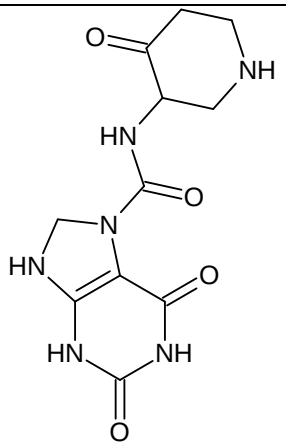
Fig 2.1. Scheme of Work

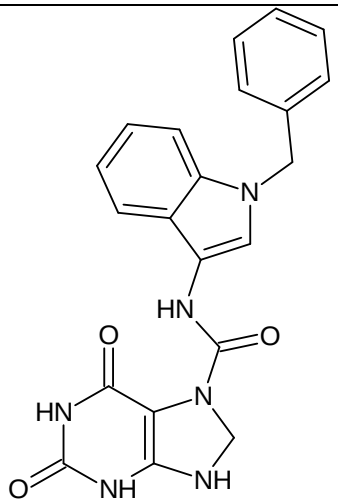
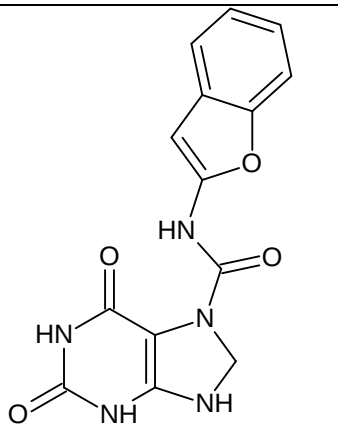
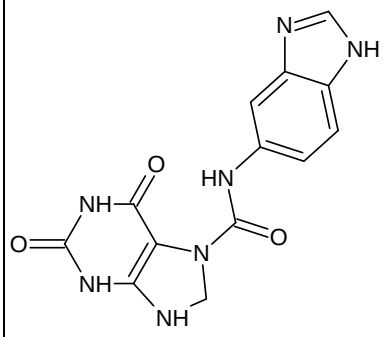
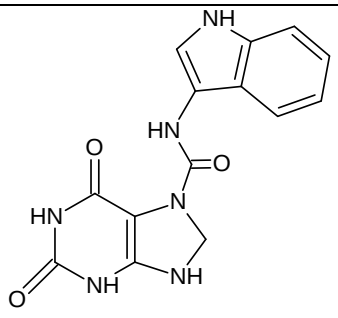
Results and Discussions

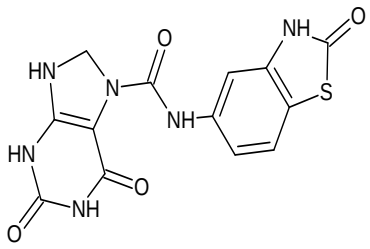
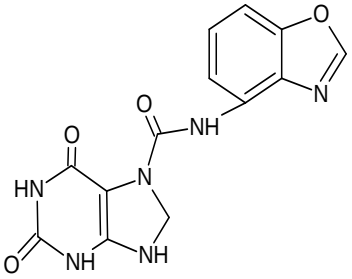
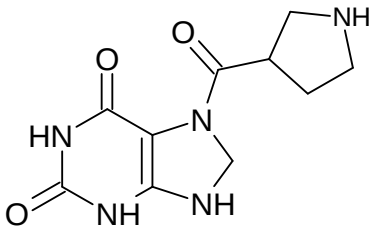
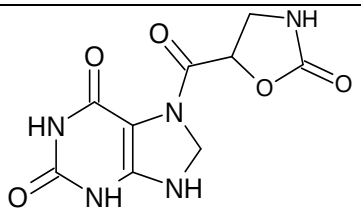
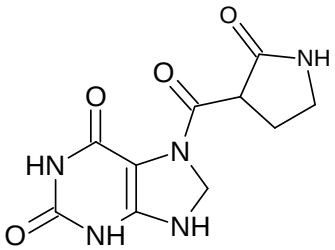
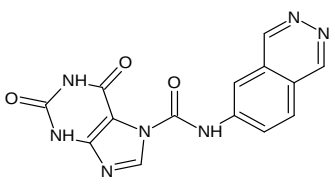
Purine 2,6 dione analogues are designed for anti-asthmatic activity and they are showed in the table 3.1.

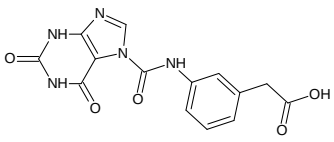
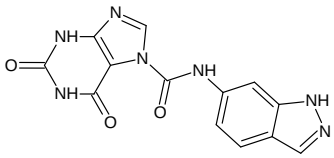
Table 3.1. IUPAC names and SMILES notations of Proposed Ligand

SL .NO.	PROPOSED LIGANDS	IUPAC NAME	SMILES
1.		*N*-(1-benzothiophen-2-yl)-2,6-dioxo-1,2,3,6,8,9-hexahydro-7*H*-purine-7-carboxamide	O=C1NC(=O)NC=2NCN(C1=2)C(=O)Nc1cc2ccccc2s1
2.		2,6-dioxo-*N*-(pyrazin-2-yl)-1,2,3,6,8,9-hexahydro-7*H*-purine-7-carboxamide	O=C1NC(=O)NC=2NCN(C1=2)C(=O)Nc1cnccn1
3.		N-(5,6-dihydro-1H-pyrrolo[2,3-b]pyridin-3-yl)-2,6-dioxo-8,9-dihydro-3H-purine-7-carboxamide	O=C1NC(=O)NC=2NCN(C1=2)C(=O)NC1=CNC2=NCCC=C21
4.		2,6-dioxo-*N*-(10*H*-phenothiazin-10-yl)-1,2,3,6,8,9-hexahydro-7*H*-purine-7-carboxamide	O=C1NC(=O)NC=2NCN(C1=2)C(=O)NN1c2ccccc2Sc2ccccc12

5.		2,6-dioxo-*N*-(piperidin-3-yl)-1,2,3,6,8,9-hexahydro-7*H*-purine-7-carboxamide	O=C1NC(=O)NC=2NCN(C1=2)C(=O)NC1CCCNC1
6.		*N*-(1,3-benzothiazol-5-yl)-2,6-dioxo-1,2,3,6,8,9-hexahydro-7*H*-purine-7-carboxamide	O=C1NC(=O)NC=2NCN(C1=2)C(=O)Nc1cc2ncsc2cc1
7.		*N*-(1,2-oxazol-4-yl)-2,6-dioxo-1,2,3,6,8,9-hexahydro-7*H*-purine-7-carboxamide	O=C(Nc1conc1)N1CNC=2NC(=O)NC(=O)C1=2
8.		2,6-dioxo-*N*-(4-oxopiperidin-3-yl)-1,2,3,6,8,9-hexahydro-7*H*-purine-7-carboxamide	O=C1CCNCC1NC(=O)N1CNC=2NC(=O)NC(=O)C=21

9.		*N*-(1-benzyl-1*H*-indol-3-yl)-2,6-dioxo-1,2,3,6,8,9-hexahydro-7*H*-purine-7-carboxamide	O=C1NC(=O)NC=2NCN(C1=2)C(=O)Nc1cn(Cc2ccccc2)c2ccccc21
10.		*N*-(1-benzofuran-2-yl)-2,6-dioxo-1,2,3,6,8,9-hexahydro-7*H*-purine-7-carboxamide	O=C1NC(=O)NC=2NCN(C1=2)C(=O)Nc1cc2ccccc2o1
11.		*N*-(1*H*-1,3-benzimidazol-5-yl)-2,6-dioxo-1,2,3,6,8,9-hexahydro-7*H*-purine-7-carboxamide	O=C1NC(=O)NC=2NCN(C1=2)C(=O)Nc1ccc2[NH]cnc2c1
12.		*N*-(1*H*-indol-3-yl)-2,6-dioxo-1,2,3,6,8,9-hexahydro-7*H*-purine-7-carboxamide	O=C1NC(=O)NC=2NCN(C1=2)C(=O)Nc1c[NH]c2ccccc21

13.		2,6-dioxo-N-(2-oxo-3H-1,3-benzothiazol-5-yl)-8,9-dihydro-3H-purine-7-carboxamide	O=C1NC(=O)NC=2NCN(C1=2)C(=O)Nc1cc2NC(=O)Sc2cc1
14.		*N*-(1,3-benzoxazol-4-yl)-2,6-dioxo-1,2,3,6,8,9-hexahydro-7*H*-purine-7-carboxamide	O=C1NC(=O)NC=2NCN(C1=2)C(=O)Nc1cccc2ocnc12
15.		7-(pyrrolidine-3-carbonyl)-3,7,8,9-tetrahydro-1*H*-purine-2,6-dione	O=C1NC(=O)NC=2NCN(C1=2)C(=O)C1CCNC1 16
16.		7-(2-oxo-1,3-oxazolidine-5-carbonyl)-3,7,8,9-tetrahydro-1*H*-purine-2,6-dione	O=C1NCC(O1)C(=O)N1CNC=2NC(=O)NC(=O)C1=2
17.		7-(2-oxopyrrolidine-3-carbonyl)-3,7,8,9-tetrahydro-1*H*-purine-2,6-dione	O=C1NCCC1C(=O)N1CNC=2NC(=O)NC(=O)C=21
18.		2,6-dioxo-*N*-(phthalazin-6-yl)-1,2,3,6-tetrahydro-7*H*-purine-7-carboxamide	O=C1NC(=O)Nc2ncn(c12)C(=O)Nc1cc2cnncc2cc1

19.		{3-[(2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purine-7-carbonyl)amino]phenyl} acetic acid	O=C(O)Cc1cc(ccc1)NC(=O)n1cnc2NC(=O)NC(=O)c21
20.		*N*-(1*H*-indazol-6-yl)-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purine-7-carboxamide	O=C1NC(=O)Nc2ncn(c12)C(=O)Nc1ccc2cn[NH]c2c1

All the proposed derivatives were drawn by using ACD Chemsketch. The IUPAC naming and the smiles notations were considered for obtaining the molinspiration.

MOLINSPIRATION VALUES

The molinspiration values depicts whether the molecule follows the Lipinski rule of five. The drug likeness properties of proposed ligands were shown in table 3.2.

Table 3.2. Molinspiration values of the standard & designed ligands

COMPOUNDS	Log P	Mol Wt	n.HDO	n.HA	n.rotb	nViolations
Theophylline	-0.01	180.17	1	6	0	0
1	1.62	329.34	4	8	0	0
2	-1.05	275.23	4	10	1	0
3	-0.41	315.29	5	10	1	0
4	2.57	394.42	4	9	1	0
5	-1.34	280.29	5	9	1	0
6	0.94	330.33	4	9	1	0
7	-1.06	264.20	4	10	1	0
8	-2.44	294.27	5	10	1	0
9	2.34	402.41	4	9	3	0
10	0.98	313.27	4	9	1	0
11	-0.00	313.28	5	10	1	0
12	0.68	312.29	5	9	1	0
13	0.39	346.33	5	10	1	0
14	0.27	314.26	4	10	1	0
15	-1.21	251.25	4	8	1	0
16	-2.01	267.20	4	10	1	0
17	-1.89	265.23	4	9	1	0
18	-0.73	323.27	3	10	1	0
19	-0.27	329.27	4	10	3	0
20	0.17	313.28	5	10	1	0

nHDO- number of hydrogen bond donor, nHA- number of hydrogen bond acceptors,

nrotb - number of rotational bonds

All the proposed derivatives were undergone Lipinski's rule analysis and no one exhibit variations. Thus, concluded that all the proposed ligands are suitable to be a drug.

Table 3.3. Molinspiration bioactivity scores of the standard & designed ligands

Proposed Ligand	GPCR ligand	Ion channel modulator	Kinase Inhibitor	Nuclear receptor ligand	Protease Inhibitor	Enzyme inhibitor
1	-0.19	-0.48	0.14	-0.59	-0.60	0.10
2	-0.12	-0.36	0.17	-0.74	-0.63	0.19
3	-0.13	-0.62	-0.35	-0.80	-0.67	0.03
4	-0.13	-0.51	-0.14	-0.49	-0.41	0.05
5	0.01	-0.26	-0.19	-0.66	-0.29	0.13
6	-0.24	-0.49	0.15	-0.54	-0.54	0.04
7	-0.15	-0.41	-0.20	-0.68	-0.80	0.06
8	0.03	-0.45	-0.34	-0.62	-0.17	0.23
9	-0.06	-0.49	0.03	-0.33	-0.50	0.01
10	-0.04	-0.27	0.15	-0.67	-0.52	0.17
11	0.03	-0.47	-0.12	-0.52	-0.67	0.03
12	-0.14	-0.45	0.04	-0.62	-0.65	-0.10
13	-0.16	-0.59	-0.06	-0.64	-0.80	-0.07
14	0.00	-0.32	-0.07	-0.41	-0.42	0.22
15	-0.15	-0.28	-0.28	-0.93	-0.37	0.27
16	-0.38	-0.35	-0.69	-0.56	-0.40	0.12
17	-0.33	-0.56	-0.38	-0.94	-0.50	0.09
18	0.17	-0.34	0.20	-1.18	-0.45	0.33
19	0.25	-0.40	-0.04	-0.68	-0.25	0.40
20	0.26	-0.13	0.44	-0.97	-0.36	0.35
Theophylline	-0.40	-0.79	-1.24	-2.56	-1.46	-0.12

GPCR- G protein coupled receptor

The drug likeness properties like G- protein coupled receptors ligand score, Ion channel modulator, Kinase inhibitors, Nuclear receptor ligand, Protease inhibitors and enzyme inhibitor scores were analysed by Molinspiration calculator.

PASS VALUES

The significance of these PASS values is to predict the probability of whether the molecule possess biological activity at its binding site or not. It also enables us to evaluate the contribution of each atom in the structure to its biological activity. The PASS value of the proposed derivatives were shown in the table 3.4.

Table 3.4. PASS Values of the standard & designed ligands

COMPOUNDS	PASS VALUES	
	Pa	**Pi**
Theophylline	0.941	0.003
1	0.198	0.129
2	0.192	0.148
3	0.202	0.120
4	0.201	0.122
5	0.185	0.171
6	0.190	0.154
7	0.187	0.167
8	0.183	0.179
9	0.226	0.069
10	0.210	0.098
11	0.359	0.006
12	0.206	0.109
13	0.186	0.167
14	0.189	0.158
15	0.101	0.019
16	0.205	0.111
17	0.114	0.014
18	0.285	0.018
19	0.309	0.012
20	0.273	0.023

The 2D proposed derivatives of Purine2,6 diones shows the PASS value which indicate the proposed ligands having probability to be active PDE receptor inhibitors. From these values, the activity of the derivatives were predicted and these were subjected to docking studies.

DOCKING

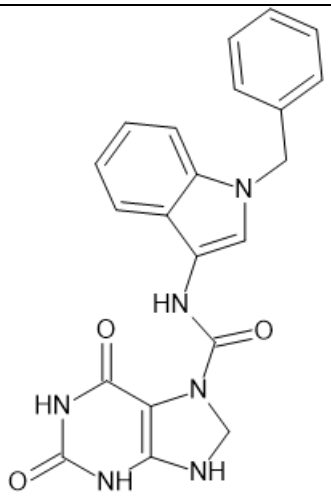
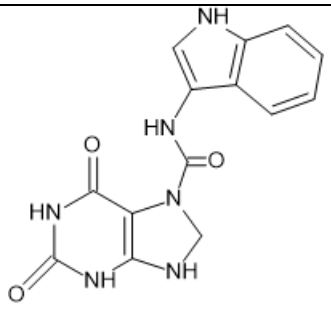
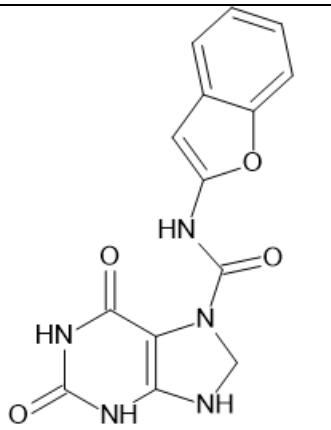
Designed Ligands docked with the protein 1Y2B. The docking score of analogues indicates its binding affinity towards the receptor. The docking scores of the ligands are shown in table 3.5.

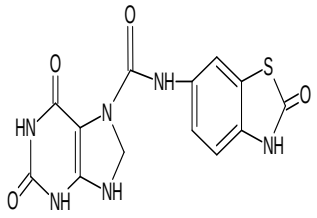
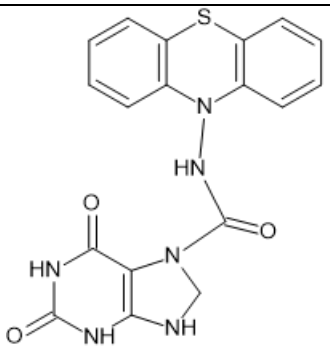
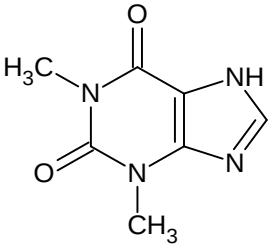
Table 3.5. Docking score of standard & designed ligands with 1Y2B

SL NO	Compound	Docking score
1	1	-8.9
2	2	-7.7
3	3	-8.1
4	4	-9.0
5	5	-7.8
6	6	-8.6
7	7	-8.0
8	8	-7.5
9	9	-9.2
10	10	-9.0
11	11	-8.6
12	12	-9.1
13	13	-9.0
14	14	-8.1
15	15	-7.1
16	16	-7.8
17	17	-8.2
18	18	-8.7
19	19	-8.2
20	20	-7.3
Standard	Theophylline	-6.0

Based on the Docking score of the designed ligands and upon comparing with the score of the standard drug Theophylline, 5 ligands with better docking scores were selected for further In-silico design and wet lab synthesis. The selected ligands with their scores are depicted in the table 3.

Table 3.6. Selected ligands and their docking scores

Sl.NO	CODE	STRUCTURE	SCORE
1	9		-9.2
2	12		-9.1
3	10		-9.0

4	13		-9.0
5	4		-9.0
THEOPHYLLINE			-6.0

Docking images of the selected analogues

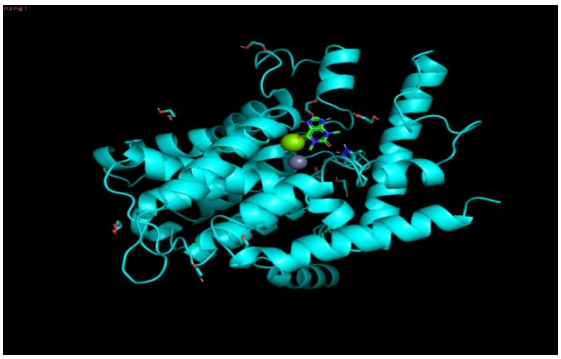


Fig 5.1 Standard with 1Y2B

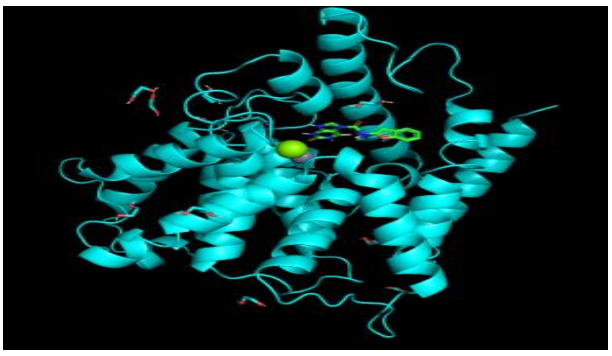


Fig 5.2. Compound 10 with 1Y2B

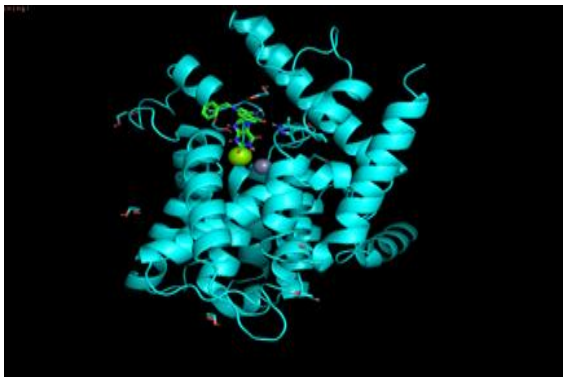


Fig.5.3 Compound 9 with 1Y2B

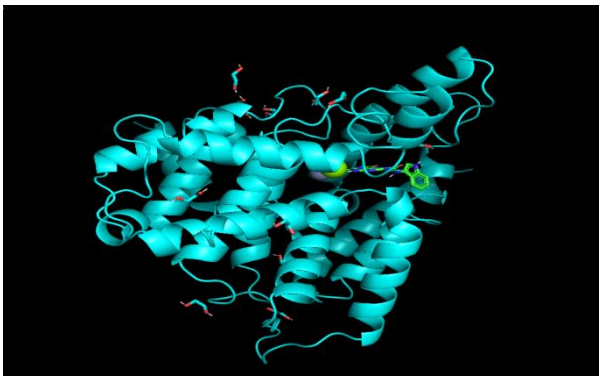


Fig 5.4. Compound 13 with 1Y2B

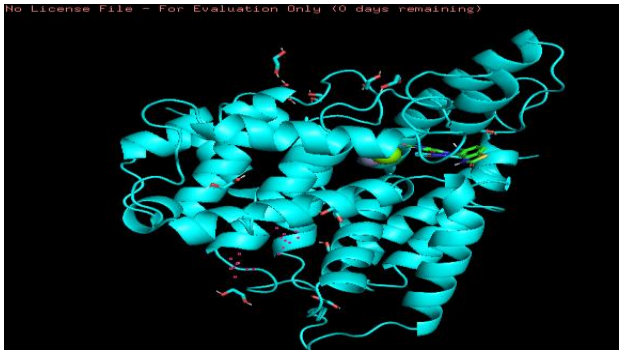


Fig.5.5. Compound 12 with 1Y2B

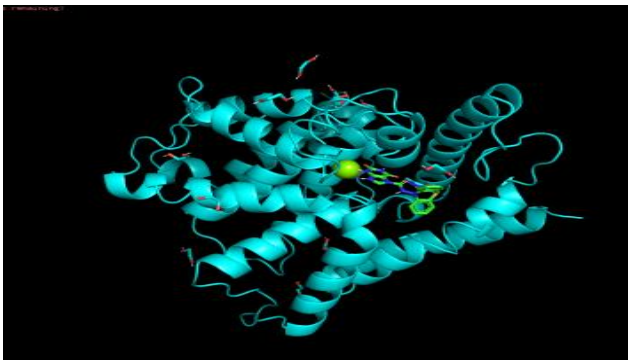


Fig. 5.6. Compound 4 with 1Y2B

CONCLUSION

The protein 1Y2B of the Phoshphodiesterase enzyme binds with the derivatives attached in N7 position of the nucleus to produce its inhibitory action. This inhibition produces an increase in intracellular concentrations of cyclic AMP, which thereby leads to bronchodilation and decreases the production of inflammatory cells. The xanthine nucleus was incorporated with diversified heterocyclic and aromatic compounds by means of an amide group to enhance its drug action.

The selected ligands having the heterocyclic ring and they are more electronegative because of the inductive, field and mesomeric effect. The electronegativity facilitate the binding interaction with the receptor. Here, the linker used is NH-C=O group which links the basic

nucleus with the derivative. This linker help for binding affinity towards the bonding pockets residing in receptor. In these compounds, the use of an oxygen atom as a bioisosteric linker which has smaller bond angle and greater electronegativity results in analogs in increased potency. The difference in the force field energy of the analogues varies the binding score of proposed ligands.

Thereby the work concluded that the selected ligands are promising antiasthmatic s Phosphodiesterase enzyme inhibitors.

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Author's contributions

The work was done under the guidance of Sreeja S. and Vani V. The molecular studies were done by Akhila A. and Rizwan Bin Nizar M, the docking studies were done by Anakha S. Anil and Sapna Sivanthie Suresh Kumar.

Conflict of interests

None

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