LITERATURE REVIEW

Despite the latest significant advancements in the understanding of the disease, the ultimate mechanisms underlying its onset and development remain intangible. This precludes a rationale for the discovery of new and more efficient therapeutic agents for the management of this disease.\textsuperscript{125} Although, the existing therapies for asthma are effective and well tolerated in majority of the patients but the challenge still exists in the pharmaceutical industry to develop safer, effective and orally active bronchodilator and anti-inflammatory agents with improved therapeutic index. The main challenge for a medicinal chemist is to develop a compound that should be potent as well as free from undesirable effects. To combine various desirable properties into a single compound is a tedious job.

Few decades back on the basis of experimental evidences, role of adenosine in asthmatic patients has been proved.\textsuperscript{126} In addition, adenosine also induces bronchospasm in the form of adenosine monophosphate (AMP) in asthmatics but not in healthy individuals.\textsuperscript{127} Theophylline (1, 3-dimethylxanthine), a xanthine derivative has well established role in the management of asthma by blocking selectively the AMP-induced bronchoconstriction. The bronchodilating effect of theophylline and its structural analogues has been recently attributed to a selective, although small, $A_{2B}$-adenosine receptor antagonism. This outcome further prompted several research groups to design, synthesize and screen large number of xanthine derivatives, in the search of new more potent $A_{2B}$-selective ligands.

Xanthines are effective in the treatment of asthma, but their mechanism of action remains unclear till date. The bronchodilator and pulmonary effects of xanthines, exhibits range of potencies as cyclic nucleotide phosphodiesterase (PDE) inhibitors and as adenosine antagonists, were investigated. Xanthine molecule has been substituted at several positions to produce derivatives that quantitatively and qualitatively differ from theophylline.
The present literature highlights the significance of substitution at different positions of the xanthine nucleus to develop potent antiasthmatic drugs. Series of substitutions have been made by the various research groups at 1-, 3- and 8-positions of theophylline. This includes the lengthening of alkyl chain at position 1- and 3-, addition of a carboxamide chain, introduction of alkyl chain between xanthine nucleus and phenyl ring, substitution of phenyl ring using various sulphonamides with the aim to get new more potent and selective theophylline derivatives as antiasthmatic agents. The present literature describes the different synthetic routes for the preparation of various 8-substituted xanthine derivatives.

MRS-1754 (6), 8-phenylxanthinecarboxylic acid congener, proved to be the most potent and selective A$_{2B}$ antagonist ever reported. This has further led the investigators in the synthesis and characterization of the tritium-labeled form of MRS-1754, which is the first radioligand for the A$_{2B}$-receptor subtype.$^{128}$

![Molecule Structure](image)

A series of 8-substituted xanthines containing oxadiazole ring has been evaluated as A$_{2B}$ adenosine receptor antagonist. Depending on the attachment of the oxadiazole ring to phenyl ring, two series of compounds such as 3-phenyl-1, 2, 4-oxadiazole and 5-phenyl-1, 2, 4-oxadiazole were developed. CVT-5440 (7), a compound of series 5-phenyl-1, 2, 4-oxadiazole has been found to prove comparable affinity and selectivity to MRS-1754.$^{129}$
PSB-1115 (1-Propyl-8-p-sulfophenylxanthine, 8), a 3-unsubstituted 1-alkyl-8-phenyl xanthine derivative has been revealed by Yan et al. as potent and selective A<sub>2B</sub> adenosine receptor antagonist.

![Chemical structure of PSB-1115](8)

Sulfonate group in this compound was considered to enhance hydrophobicity but it decreases adenosine receptor affinity. This derivative was further converted into its sulfonamide type 9 compounds, with broad variation of the substitution pattern at the sulfonamide nitrogen, to enhance affinity and selectivity on the receptors.\textsuperscript{130}

Esteve et al. reported a number of pyrrolo-pyrimidine derivatives of type 10 as potent A<sub>2B</sub>-adenosine receptor antagonists and selective versus A<sub>1</sub> and A<sub>3</sub> adenosine receptors with improved physicochemical properties containing a metabolically stable benzene-sulfonamide group. The introduction of a basic ionizable function at the sulfonamide moiety was found to increase solubility and to achieve the oral bioavailability. Among these derivatives, the (4-benzylpiperazin-1-yl)-sulfonyl derivative (11) come out be one of the most promising groups both in terms of potency and selectivity.

![Chemical structures of PSB-109120 and PSB-0788](10, 11)

PSB-09120 (12) and PSB-0788 (13) are 1-alkyl-8-(piperazine-1-sulfonyl)-phenyl xanthines derivatives and found to be most potent compounds in terms of
affinity and selectivity as $A_{2B}$-receptor antagonists. The 1-ethyl- and 1-propyl-substituted xanthines showed very similar affinities for the $A_{2B}$ adenosine receptor. The variation of the spacer and the aromatic residue at position-8 of the xanthine core with benzyl-piperazinyl and phenyl-piperazinyl residues appeared to be the best tolerated modification for the $A_{2B}$ adenosine receptor. The introduction of basic nitrogen atoms as spacer was done to improve the low water solubility and limited peroral bioavailability.

8-(Substituted-phenyl)-xanthines found to possess high affinity and selectivity towards $A_1$ and $A_{2A}$ adenosine receptor antagonism. Among the various synthesized xanthine derivatives, morpholinoethoxy (14) and diethylaminoethoxy (15) were emerged to be the most active and selective compounds at $A_{2A}$ adenosine receptor subtype.

The substitution pattern and type of substituents on 8-phenyl group greatly affects the affinity and selectivity of xanthine derivatives at adenosine receptors. As in (14), the methoxy substituent ortho to a polar side chain and at 4-position of
phenyl ring resulted in increased selectivity for A\textsubscript{2} over A\textsubscript{1} adenosine receptors. While in (15), the polar side chain at 3-position of 8-phenyl ring without any methoxy group also resulted in equal selectivity for both subtypes of receptors. Thus selection of substituent and its proper positioning at aryl ring may lead to the development of potent and selective xanthine based adenosine receptor antagonists.\textsuperscript{133}

In continuation to this, Yadav et al. reported number of 8-(p-substituted-phenyl/benzyl)-xanthines containing various polar dialkylaminoethoxy substituents at \textit{para} position of 8-phenyl ring of xanthine.

The chloropropoxy phenyl substituted xanthine (16) was found to be highly selective as compared to amino substituted xanthines. The imidazolyl substituted xanthine (17) was found to be the most potent compound for A\textsubscript{2A} adenosine receptor in terms of affinity and selectivity.\textsuperscript{134} 1\textit{H}-Imidazole found to induce selectivity for adenosine receptors and also results in the synergistic effects.

KW-6002 (18), a well characterized A\textsubscript{2A} receptor antagonist, is currently under clinical trial for the treatment of motor symptoms associated with
Parkinson’s disease. A structural analogue of KW-6002, (E)-8-(3-chlorostyryl)-caffeine (CSC, 19), A\textsubscript{2A} receptor antagonist has also been reported as a potent reversible inhibitor of monoamine oxidase-B.\textsuperscript{135}

The 9-deazaxanthine derivatives of 19 were found to be as dual inhibitors i.e. A\textsubscript{2A} receptor antagonist and inhibition of monoamine oxidase-B. Among the synthesized derivatives, (E)-6-(4-chlorostyryl)-1, 3, 5-trimethyl-1H-pyrrolo [3, 2-d] pyrimidine-2, 4-(3H, 5H)-dione (20) was the most potent and could be considered as a new lead in the field of antiparkinsonism’s.\textsuperscript{136}

The 8-substituted benzamido-phenylxanthine derivatives reported as neuroprotectants to treat motor symptoms of Parkinson’s by inhibiting MAO-B. The targeted compound (21) with no substitution in benzamide region showed 42-fold higher MAO-B inhibitory activity than the earlier reported KW-6002 and CSC. The compounds with caffeine structure and smaller substituted groups tend to be more potent MAO-B inhibitors as small substituent can fit easily in active sites of MAO-B.\textsuperscript{137}

\[ \text{Xanthine scaffold also reported to be effective in type-2 diabetes by inhibition of DPP-4. The structural modifications of purine nucleus at } N-1, N-7 \text{ and C-8 led to the discovery of BI1356 (22), a highly potent, selective, long acting and orally active DPP-4 inhibitor showing considerable blood glucose lowering in different animal species.}\textsuperscript{138} \text{It is in phase IIb clinical trials and holds potential for once daily treatment.}

The highly potent but modestly selective N-(2-amino-4-methoxybenzothiazol-7-yl)-N-ethyl-acetamide derivative (23) reported as novel adenosine A\textsubscript{2B} receptor antagonist. Due to its excellent potency, good drug-like properties, it resulted in the designing of a compound with excellent potency with improved
selectivity against both $A_{2A}$ and $A_1$ receptors. The compound (24) was designed to contain a non aromatic spacer (piperidine), followed by a sulfonyl linker which connects the core aminobenzothiazole to $m$-trifluoromethylphenyl moiety required for potency at $A_{2B}$ along with $A_{2A}$ versus $A_1$ selectivity.  

Jin Xie et al. reported aminopyridinecarboxamide-based inhaled IKK-2 inhibitors (25) for asthma and COPD. The 8-(5-chloro-2-(4-methylpiperazin-1-yl)isonicotinamido)-1-(4-fluorophenyl)-4,5-dihydro-1$H$-benzo[g]-indazole-3-carboxamide (PHA-767408 or PHA-408) series containing tricyclic pyrazole showed good selectivity for IKK-2 than other kinases. The SAR of PHA-408 was explored to improve potency, cellular activity; pharmacokinetics and duration of action keeping the core structure same for selectivity.  

The variation of substituents at 2$^{nd}$ and 5$^{th}$ position of the pyrimidine ring gave a very potent, orally bioavailable VLA-4 inhibitor (26) effective orally in sheep asthma model.
Synthetic route to a series of 8-(cyclopentyloxy)-phenyl substituted xanthine derivatives as adenosine A$_{2A}$ ligands has been reported.$^{142}$ The effects of moving the cyclopentyloxy substituent with or without an ortho methoxy group on the various positions of the 8-phenyl ring has been studied. The vanilloid based xanthes 8-[4-(cyclopentyloxy)-3-methoxyphenyl]-1,3-dimethylxanthine (27) and 8-[(4-cyclopentyloxy)-3-methoxyphenyl]-3-methyl-1-propylxanthine (28) displayed the highest affinity at A$_{2A}$ receptors as well as over 1000 fold selectivity over the A$_1$ adenosine receptor subtype.

ZI-n-91, a selective phosphodiesterase-4 inhibitor (29) has been reported to reduce the inflammation and improves lung function in the rat model for COPD.$^{143}$ The ZI-n-91 at various dosages results in decreases of inflammatory cell in bronchoalveolar lavage fluid (BALF), showed inhibition in PDE4 action and also decreased MMP-9 level in lungs as compared with vehicle treatment.

The structure-activity relationships of a series of 2-amino-5-benzoyl-4-phenylthiazole derivatives were investigated in order to develop compounds with high affinity and subtype selectivity for AdoA$_1$R with the goal to obtain potent and A$_1$-selective antagonists. 2-Benzoylamino-5-$p$-methylbenzoyl-4-phenylthiazole
(30) was reported to be most potent among the series, showing a $K_i$ value of 4.83 nM at rat and 57.4 nM at human $A_1$ receptors with high selectivity versus other adenosine receptor subtypes.\(^{144}\)

\[ \text{Chemical structure of compound 30} \]

Dilip K. Tosh et al. reported 2-Dialkynyl derivatives of (N)-methanocarba nucleoside 5'-uronamides (31) as potent and selective $A_3$ adenosine receptor (AR) agonists.\(^{145}\) The most potent and selective novel compound was 1-adamantyl derivative having $K_i$ 6.5 nM.

The oligo(ethylene glycol)-alkene substituted theophylline derivatives at position 7\(^{th}\) and 8\(^{th}\) had been synthesized and studied as adenosine receptor antagonists.\(^{146}\) Compound 32 showed high affinity for human $A_{2B}$ adenosine receptor with a selectivity $K_iA_{2A}/K_iA_{2B}$ of 24.1 and water solubility of 1 mM. As theophylline derivatives influence neuronal activities they are immobilized on silicon substrate surfaces and a vinyl group was added as handle to form Si-C bonds with hydrogen-terminated silicon surfaces and an oligo-(ethylene glycol) spacer used to connect the theophylline moiety with the handles.

4-Substituted-7-N-alkyl-N-acetyl-2-aminobenzothiazole amides\(^{147}\) are described herewith as drug-like and non-xanthine based $A_{2B}$ adenosine receptor antagonists. By SAR exploration of 7-N-Acetamide-4-methoxy-2-aminobenzothiazole 4-fluorobenzamide (33), modifications done at 7-N-acetamide group, substitution of the 4-methoxy group by halogens and
replacement of the p-flourobenzamide side chain resulting in compound **34** with excellent \( A_{2B} \) potency and modest selectivity versus \( A_{2A} \) and \( A_{1} \) adenosine receptors.

![Image of molecules](image_url)

**Novel xanthines bearing substituents at 1-, 3-, 7-, and 8-position were prepared and evaluated for their binding affinity to the human adenosine receptor \( A_{1} \), \( A_{2A} \), \( A_{2B} \) and \( A_{3} \) subtypes.**\(^{148}\) The structural variations includes alkyl substituent at position-1; alkyl, aryl or heteroaryl substituent at position-3; unsubstituted or methyl substituent at position-7 and aryl or heteroaryl substituent at position-8 of the xanthine nucleus. The most active compound 1-ethyl-8-((furan-2-yl)-methyl)-7-methyl-3-((thiophen-2-yl)-methyl)-1H-purine-2,6(3H,7H)-dione (35) having a pK\(_i\) of 7.57 nM for \( hA_{2B} \) receptors and a selectivity over \( hA_{2A} \) receptors of 8.1-fold and \( hA_{1} \) receptors of 3.7-fold.

![Image of molecule](image_url)

The novel tetrahydroisoquinoline amides reported as bronchorelaxants because of their ability to relax LTD4 contracted isolated human small airways ex-vivo. A series of (hetero)-aromatic amide derivatives were synthesized by various substitutions on 4,7-dichloro-5,6-dihydroxy–tetrahydro–isoquinoline core structure containing cinnamide to vary the length and flexibility of linker.\(^{149}\) The cinnamide (36) displayed highly efficacious bronchorelaxing properties thus
constitutes a promising candidate for broncho-pulmonary disorders. The EC50 for cinnamamide determined to be 2.27 µm and the maximum functional efficacy of 98 % in the ex-vivo assay. It has moderate aqueous solubility, plasma stability but undergoes phase II metabolism.

Further, the synthesis of N-(5, 6-diarylpyridin-2-yl)-amide derivatives gave potent and selective A2B adenosine receptor antagonists. The C-5 pyrimidine and C-6 furan substitution on pyridine core ring (37) resulted in the best balance of potency and selectivity. The compound showed good selectivity at A2B adenosine receptor versus other adenosine receptors. The oral pharmacokinetic studies in rats resulted in rapid absorption and good bioavailability of 37 over the others derivatives synthesized in the series.\textsuperscript{150}

The pyrimidinone derivative (38) discovered to be as a effective A2A/A1 receptor antagonist \textit{in vitro}, with excellent activity for the treatment of Parkinson’s disease.\textsuperscript{151}
Jens Carlsson et al. reported the molecular docking studies with the aim to discover novel A\textsubscript{2A} adenosine receptor ligands.\textsuperscript{152} The A\textsubscript{2A} AR signals in both the periphery and the CNS, with agonists explored as anti-inflammatory drugs and antagonists explored for neurodegenerative disease such as Parkinson’s. The two most potent ligands were (39) and (40) whereas 39 found to be more specific with over 50-fold higher affinity at the A\textsubscript{2A} AR versus the related A\textsubscript{1} and A\textsubscript{3} subtypes. Despite this, numbers of new ligands were found to be novel, dissimilar from the known ligands, providing new lead structures for alteration of this medically important target.

8-Bromo-9-alkyl adenines were prepared and characterized in radioligand binding assays or functional cyclase experiments in respect to their interaction with adenosine receptor subtypes. The bromination of 9-ethyladenine (41) resulted in 40-fold increase in AA\textsubscript{2A}R affinity and also promotes interaction with the adenosine receptors, particularly A\textsubscript{2A} subtype. The study also indicates that adenine derivatives could be a good starting point to obtain selective adenosine A\textsubscript{2B} receptor antagonists as they showed good activity at AA\textsubscript{2B}R.\textsuperscript{153}

A number of ligands were obtained by modifying substituent at 2-, 6- and 9- positions of purine and 8-azapurine nucleus and assayed by Irene Giorgi et al. towards their affinity for A\textsubscript{1}, A\textsubscript{2A} and A\textsubscript{3} receptors.\textsuperscript{154} The synthesized compounds bearing an alkyl or cycloalkyl group (42), or phenyl containing (43) or substituted phenyl (44) bound to the carbonyl carbon position possess a very interesting
affinity and good selectivity properties towards $A_1$ receptors with respect to $A_{2A}$ and $A_3$ receptors.

The $L$-nucleoside, $L$-3’-amino-3’-deoxy-$N^6$-dimethyladenosine ($L$-3’-ADMdA) (45) was synthesized and evaluated in an ischemia/reperfusion model on Langendorff perfused mouse heart as cardio protective agent. It was found to enhance functional recovery from ischemia, an increase the time to onset of ischemic contracture and decreased infarction area as compared to adenosine. Being adenosine analog, its activity was speculated may be due to its agonistic action on $A_1$ and/or $A_3$AR subtypes. It is found to be the first $L$-nucleoside that shows biological activity besides antiviral or anticancer effect as it interacts with animal enzymes other than kinases. The nature of $L$-nucleosides is likely to endow potential candidates with favorable features such as lower toxicity and higher metabolic stability than their $D$-counterparts.

A series of $N^6$-substituted-4’-thioadenosine-5’-uronamides were designed and synthesized (46) as potent and selective human $A_3$ adenosine receptor agonists. Modifications on adenosine nucleus resulted in the synthesis of IB-MECA ($N^6$-(3-iodo-benzyl)-9-(5’-methylamino carbonyl-$\beta$-D-ribofuranosyl)-adenine). The 4’-thio analogue of IB-MECA showed extremely high binding affinity ($K_i = 0.25$ nM) at the human $A_3$AR and was even more potent than IB-MECA ($K_i = 1.4$ nM). (47)
1,8-disubstituted-3-(3-methoxypropyl)-xanthines were prepared and evaluated for their binding affinity at recombinant human adenosine A\textsubscript{2A} and A\textsubscript{2B} receptors. The derivatives of 1-ethyl-3-(3-methoxypropyl)-8-aryl substituted xanthines showed moderate-to-high affinity at human A\textsubscript{2B} receptors. Among this series, 8-{4-[(4-Bromophenylcarbamoyl)-methoxy]-phenyl}-1-ethyl-3-(3-methoxy propyl)-1\textit{H}-purine-2,6-(3\textit{H}, 7\textit{H})-dione (47) showed 34 fold more A\textsubscript{2B} selectivity over the other adenosine receptors.\textsuperscript{157}

![Chemical Structures](image)

New class of xanthine based thienopyrimidine derivatives as human A\textsubscript{2B} antagonists were reported and optimized to give derivatives for conditions associated with this receptor such as nociception, diabetes, asthma, COPD and also showed activity in Parkinson’s disease.\textsuperscript{158} The methylamino derivative (48) displayed both single-digit nanomolar antagonist efficacy and an almost 300-fold difference in functional activity at the A\textsubscript{2A} and A\textsubscript{2B} receptor subtypes with strong antagonism at A\textsubscript{2B}. The limited solubility of this compound was an issue which resulted in the synthesis of a racemic mixture whose (S)-isomer (49) displayed good selectivity at A\textsubscript{1} and A\textsubscript{3} receptor subtypes along with antagonism at A\textsubscript{2B}, improved solubility, good cellular permeability.
1- and 8-Substituted-3-furfuryl xanthines were synthesized and reported as adenosine receptor antagonists at rat A₁ and human A₂A, A₂B and A₃ receptor subtypes. The 3-furfuryl-7-methylxanthines showed affinity for human A₂B receptors among which 1-ethyl and 8-thiophen-2-yl substituted derivative (50) showed maximum binding affinity of $K_i$ 8.13 nm at hA₂B receptor along with selectivity at rA₁ and hA₂A subtypes.¹⁵⁹

Number of 1, 3-dialkyl-9-deazaxanthenes (9-dAXs), containing $N$-substituted benzyloxycarbonylamino substituents at position 8, were synthesized and evaluated for their binding affinity at recombinant human adenosine receptors (hARs), mainly hA₂B and hA₂A AR subtypes. The derivatives showed excellent binding affinity at hA₂B receptor but low selectivity versus hA₂A and hA₁. Among all derivatives, 1,3-dimethyl-$N$-3'-thienyl carbamate (51) found to be most potent ligand at hA₂B, with a low selectivity versus hA₂A and hA₁ and a higher selectivity versus hA₃. In in vitro functional assays, 51 exhibited high antagonist activity and efficacy at both the A₂A and A₂B receptor subtypes.¹⁶⁰

Adenosine A₂A (A₂AR) and dopamine D₂ (D₂R) receptors mediate the antagonism between adenosinergic and dopaminergic transmission at GABANergic neurons thus acts as pharmacological targets for the treatment of Parkinson’s disease. Keeping in view, a library of heterobivalent ligands (54) containing a D₂R agonist (52) and an A₂AR antagonist (53) linked through spacer of variable size were designed and synthesized to study A₂AR-D₂R heteromers.

¹⁶¹
2-Substituted AMP derivatives were synthesized in the form of nucleoside-5'-monophosphate prodrugs of adenosine $A_{2A}$ receptor agonists which are activated by ecto-5'-nucleotidase. As ecto-5'-nucleotidase shows up regulation in inflammatory cells only so these prodrugs are expected to be released at the site of inflammation. Ecto-5'-nucleotidase convert these 2-substituted AMP derivatives into their corresponding 2-substituted adenosine derivatives. The various derivates synthesized were 2-hexylthio-AMP, 2-cyclopentythio-AMP, 2-cyclohexylmethylthio-AMP, and 2-cyclohexylethylthioAMP. Among the synthesized derivates, 2-cyclohexylethylthio substitution (55) proved to be best compromise between requirements of the ecto-5'-nucleotidaes and the $A_{2A}$ adenosine receptors.\cite{162}
MSX-2, a xanthine derivative (56) was found to be one of the most potent and selective adenosine A\textsubscript{2A} receptor antagonists. It is used in trituated form ([N\textsuperscript{7}-methyl-\textsuperscript{3}H] MSX-2) as a radioligand for the labeling of A\textsubscript{2A} receptors. But this high affinity A2A antagonist is associated with major problem of low solubility thus limiting its usefulness in \textit{in-vivo} studies.

To increase the water solubility, phosphate prodrug of MSX-2 was developed which was found to be highly stable in aqueous solution at pH7. Due to high water solubility of MSX-3, it is found to be useful pharmacological tool for parenteral application in aqueous form and can be easily cleaved by phosphatases to liberate MSX-2. As prodrugs can be absorbed easily, it may release drug before absorption so amino acid ester prodrug approach was applied. MSX-4 (57) was synthesized and found to be relatively more stable than phosphate prodrug.\textsuperscript{163}

Andras \textit{et al.} studied the effect of local and systemic administration of subtype selective adenosine receptor antagonists on inflammation and
inflammatory hyperalgesia. PSB-1115 (58), selective antagonist of A_{2B} receptor found to be effective in reducing edema at high doses while attenuating it at low dose. MSX-3 (59), A_{2A} receptor antagonist found effective in totally eliminating inflammatory hyperalgesia. In contrast to A_1 antagonist, the selective antagonists of A_{2A}, A_{2B}, and A_3 receptors were also found effective on local administration. Thus blockade of selective adenosine receptors decreases inflammation where A_{2A} antagonists may be useful for the treatment of inflammatory hyperalgesia, while A_{2B} antagonists have potential as analgesic drugs for the treatment of inflammatory pain.¹⁶⁴

The effect of different substitutions on 1-, 3-, and 8-positions of xanthine core was evaluated in order to improve potency and hydrophilicity resulting in the synthesis of a series of 1-benzyl-3-propyl-1\(H\),8\(H\)-imidazo[2,1-\(f\])purine-2,4-diones (60) as selective A_3 adenosine receptor antagonists.¹⁶⁵ Among the new reported compounds, two derivatives (61) and (62) confirmed high A_3 adenosine receptor binding affinity along with relevant selectivity in comparison to reference compound (60).

\(N\)-1 monosubstituted 8-pyrazolyl xanthines were synthesized and reported to be effective at adenosine receptors. The 8-pyrazolyl derivate of xanthines have been synthesized and evaluated for their affinity towards adenosine receptor subtypes. Among the series only two compounds, CVT-7124 (63) and CVT-6694 (64) displayed good affinity at A_{2B} adenosine receptor subtype and also greater selectivity for all human adenosine receptor subtypes (A_1, A_{2A} and A_3). CVT-6694 also found to block the release of interleukin-6 (IL-6)
and monocyte chemotactic protein-1 from bronchial smooth muscle cells (BSMC) whose release is due to the activation of A\(_{2B}\) adenosine receptors. Thus they acted as selective antagonists of A\(_{2B}\).\(^{166}\)

A number of synthesized 1, 3-dialkyl-8-(hetero) aryl-9-OH-9-deazaxanthines were evaluated as ligands of recombinant human adenosine receptors (hARs). A comparison of 1, 3-dipropyl derivatives of 7-OH, 7, 9-unsubstituted deazaxanthine and 9-OH-9-deazaxanthines revealed that 9-OH-9-deazaxanthines are more potent ligands of A\(_{2B}\) receptor with lower partition coefficients and higher water solubility. The \textit{para}-substituent of the 8-phenyl ring of 9-OH-9-deazaxanthines led to the discovery of compound (65) with outstanding affinity at hA\(_{2B}\), excellent antagonist potency on rat A\(_{2B}\) and good selectivity over hA\(_{2A}\), hA\(_1\) and hA\(_3\).\(^{167}\)

1,3-dipropyl-8-(1-phenylacetamide-1H-pyrazol-3-yl)-xanthine derivatives evaluated for their binding affinities for human A2B, A1, A2A and A3 adenosine receptors and found as potent antagonists of A\(_{2B}\) adenosine receptors. The N-(4-chloro-phenyl)-2-[3-(2, 6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1H-purin-8-yl)-5-methyl-pyrazol-1-yl] (66) showed high affinity for the human A\(_{2B}\) adenosine receptor.\(^{168}\)
Various conventional and multiple parallel syntheses method were used to synthesize a large series of piperazine, piperidine and tetrahydroisoquinolinamides of 4-(1, 3-dialkyl-9-deazaxanthin-8-yl)-phenoxyacetic acid. These derivatives were evaluated for their binding affinity at recombinant human adenosine receptors mainly at hA$_{2B}$ and hA$_{2A}$ subtypes. Among the different series, chloro (67) and trifluoro (68) substituted piperazinamide derivatives and piperidinamide derivative (69) found to be highly potent at hA$_{2B}$ and selective towards hA$_{2A}$, hA$_3$ and hA$_1$.

Further studies on structure–affinity and structure–selectivity relationships revealed that increasing lipophilicity of substituent at N-4 of piperazinamides and
orth-CH$_3$ substituent at 8-phenyl ring and larger alkyl group at N-1 then N-3 in 9-deazaxanthine ring strongly enhances hA$_{2A}$/hA$_{2B}$ selectivity.

The molecular modeling approach was applied to study various binding modes at A$_{2B}$ adenosine receptors of the derivatives of adenosine and its 5'-N-methyluronamide with substituent at 2- and N-6 positions. On the basis of modeling results obtained, four novel analogues of adenosine (70-73) were synthesized with elongated and bulky substitutions at N-6 and/or 2 position and evaluated biologically for binding affinity at A$_{2B}$ adenosine receptors.
All the analogues were found to be potent and full agonists at the $A_{2B}$ AR in adenylate cyclase studies. The results indicated that bulky substitutions at 2 and $N$-6 position have no effect on the activation of $A_{2B}$ AR.

A series of 1, 3-symmetrically ($R_1=R_3$) substituted xanthines found to have high affinity and selectivity for human adenosine $A_{2B}$ receptors but also with poor pharmacokinetic profile. Thus differential alkyl substitutions were made at the $N$-1 and $N$-3 positions and their effect on $A_{2B}$ receptor affinity and selectivity was studied. This resulted in the discovery of a compound (74) with high affinity and selectivity for the $A_{2B}$ adenosine receptor along with enhanced oral bioavailability. This compound also reported to have no serious adverse effects and was well tolerated in a single ascending dose phase I clinical study.\(^{171}\)

A new series of $N^6$-[(hetero)aryl/(cyclo)alkyl-carbamoyl-methoxy-phenyl]-(2-chloro)-5'-N-ethylcarboxamido-adenosines were synthesized and tested for their binding affinity at $hA_1$, $hA_2A$ and $hA_3$ adenosine receptors and in a functional assay at the $hA_{2B}$ subtype. The compounds found to posses high potency in activating $A_{2B}$ receptors with good selectivity. The introduction of an unsubstituted 4-[(phenylcarbamoyl)-methoxy]-phenyl chain at the $N^6$ position of 5'-N-ethylcarboxamido-adenosine led to the discovery of a compound (75) displaying highest efficacy and full agonistic activity in the low nanomolar range.\(^{172}\)
A number of groups significantly contributed towards the investigation of aromatic heterocycle-based DPP-IV inhibitors. Xanthine based DPP-IV inhibitors were analogues of purine with varying degree of arrangement of nitrogen atoms in core structure such as uracils, imidazoles, pyrimidines, pyridines etc. Among xanthine derived DPP-IV inhibitors, SYR-322 (76) reported to be in Phase III clinical trials for type 2 diabetes mellitus. Further SAR studies revealed the importance of nitrogen atom proximal to xanthine core and different substitutions at N-1, C-2 and N-3 for potent DPP-IV inhibitory activity resulting in a series of DPP-IV inhibitors (77, 78, and 79).

A series of potent and selective A1 adenosine receptor agonists reported as dual acting antioxidants including the incorporation of a functionalized linker with antioxidant moiety. Among the series, N6-(2, 2, 5, 5-tetramethylpyrrolidin-1-yloxyl-3-ylmethyl)-adenosine (VCP28, 80) found to possess high affinity and good selectivity for the A1 adenosine receptor while N6-[4-[2-[1, 1, 3, 3-tetramethylisoindolin-2-yloxyl-5-amido] ethyl] phenyl] adenosine (VCP102, 81) possesses higher binding affinity but lower selectivity. All the compounds found to
have weak binding affinity to A\textsubscript{2A} and A\textsubscript{2B} receptors. The dual acting A\textsubscript{1} agonists with antioxidant activity also found effective as cardioprotective.\textsuperscript{174}

A new series of indole based long acting \(\beta_2\)-adrenoceptor agonists were described by Alan Brown \textit{et al}. The initial indole analogues were synthesized as a mixture of diastereoisomers among which the potent di-methoxybenzyl amide analogue separated to obtain single diastereoisomers and studied for the effect of \(\alpha\)-methyl stereocentre on their potency towards \(\beta_2\)-adrenoceptor. The \((R)\)-configuration of the \(\alpha\)-methyl stereocentre \textbf{(82)} found to be 100-fold greater active than the \((S)\)-configuration. The indole based analogues were evaluated \textit{in vitro} by guinea pig trachea tissue model. The model demonstrates that analogues within this series have salmeterol-like duration of action with potential for long duration of action in humans.\textsuperscript{175}

A series of \((E)\)-8-styrylcaffeines and \((E)\)-2-styrylbenzimidazoles found to be potent and competitive inhibitors of monoamine oxidase B (MAO-B) among which \((E)\)-8-(3-chlorostyryl) caffeine (CSC) found to be most potent. To further improve the inhibition profile of MAO-B, additional analogues of caffeine and benzimidazole were prepared. The most potent inhibitor among the caffeine analogues was \((E)\)-8-(3,4-dichlorostyryl)caffeine \textbf{(83)} approximately 3.5 times more potent than CSC while among the benzimidazole analogues was \((E)\)-2-(4-trifluoromethylstyryl)-1-methylbenzimidazole \textbf{(84)}. An SAR profile indicated that
among analogues of benzimidazole, the inhibition potency of MAO-B depends on the steric hindrance by C-4 substituents of styryl phenyl ring where large degree of steric hindrance appears to enhance inhibition potency. The MAO-B inhibition by (E)-8-styrylcaffeines and (E)-2-styrylbenzimidazoles is based on simultaneous binding to both the entrance and substrate cavities for which presence of styryl side chain is mandatory.  

The lack of molecules with selective and potent agonistic activity toward the hA2B adenosine receptors has limited the studies towards this target. Pier Giovanni et al. designed and reported the synthesis of the first potent and selective hA2B adenosine receptor antagonists containing 1-deoxy-1-[6-[(hetero) aryl carbonyl] hydrazino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide derivatives. The effect of substituent at N6 of the purine nucleus was studied and effective substitutions found were ((hetero)-arylcarbonyl)-hydrazino function and 2-chloro substitution. Among the whole series, 1-deoxy-1-{6-[N'-(furan-2-carbonyl) hydrazino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide (85) found to be most potent and full agonist in a functional assay to modulate cAMP levels in CHO cells expressing the hA2B receptor. 

Based on features of earlier reported pyrimidine and purine derivatives, a refined model for antagonists of the human adenosine A1 receptor was developed and a series of 1-deazapurines were synthesized. The 1-deazapurines, also known as 3H-imidazo [4,5-b]pyridines, were substituted at their 2- and 6-positions, yielding a series of derivatives. The most potent among these, LUF 5978 (86) displayed more than 300 fold affinity at the human adenosine A1 receptor with and 45-fold selectivity toward A2A and A3 receptors while LUF 5981 (87) appeared to have the best overall selectivity with respect to adenosine A2A (>200-fold) and A3 (700-fold) receptors.
A new series of $N^6$-methoxy-2-alkynyladenosine derivatives were synthesized with the aim to study their binding affinity and selectivity at the human recombinant A<sub>3</sub> adenosine receptors. The compounds having an $N$-methylcarboxamido substituent (88) in the 4'-position found to possess highest affinity and selectivity at A<sub>3</sub>. In particular, the $N^6$-methoxy-2-pacetylphenylethynyl, MECA (89) reported to be one of the most potent and selective agonists at the human A<sub>3</sub> adenosine receptors. The functional assay, performed with selected new compounds, revealed that the presence of an alkylcarboxamido group in the 4'-position seems to be essential to obtain full agonistic action at the A<sub>3</sub> subtype.\textsuperscript{179}
The derivatives of adenosine were synthesized by possible substitution at 2, $N^6$, and 5'-positions starting from the alkylation of 2-oxypurine nucleosides leading to 2-arylalkylether derivatives. Among them, 2-(3-(Indolyl)-ethyloxy)-adenosine (90) was found to be a potent agonist against binding affinity studies at human $A_{2B}$ adenosine receptor and also in cAMP assays. Further simplification and mimicking of the 90 failed to maintain $A_{2B}$ AR potency. The introduction of $N^6$-ethyl or $N^6$-guanidino substitution favored $A_{2B}$ AR potency but no enhancement was seen in the potency of 2-(3-(indolyl)-ethyloxy) adenosine series. Indole 5''-or 6''-halo substitution was favored and 2-(3''-(6''-Bromoindolyl)-ethyloxy)-adenosine (91) found to be more potent full agonist at $A_{2B}$ and A2A ARs and a low efficacy partial agonist at $A_1$ and $A_3$ ARs than the parent compound 90.\(^{180}\)

A number of structural modifications have been done at the $N^6$-position and 4'-hydroxymethyl group of natural mediator adenosine in the search of potent
ligands at $A_3$ adenosine receptors. A series of $N^\beta$-substituted-$D$-$4'$-thionucleosides had been synthesized by condensation of a glycosyl donor obtained from $D$-mannose with 2, 6-dichloropurine. The derivatization and optimization of truncated $D$-$4'$-thioadenosine derivatives, which lack 4'-hydroxymethylene moiety, resulted in a series of final nucleosides. The binding assays of final nucleosides showed that 3-chlorobenzyl derivative (92) possess highest binding affinity at $hA_3$ adenosine receptors while low affinity at $h1$ and $h2A$ adenosine receptors. Thus 3-substitution on aromatic ring was preferred than 2-, 4-, or 2,5-disubstitution.

The $A_{2A}$ adenosine receptors had emerged as new targets for the treatment of Parkinson’s disease (PD). Several studies had reported that $A_{2A}$ antagonists are also the inhibitors of enzyme monoamine oxidase (MAO-B). Among various inhibitors of MAO, (E)-8-(3-chlorostyryl) caffeine (CSC) found effective also in examining in vivo pharmacological effects of $A_{2A}$ antagonists. MAO-B inhibitors are also effective as antiparkinson’s drugs thus CSC possess dual properties of blocking MAO-B and $A_{2A}$ receptors in the treatment of PD. A series of analogues of CSC (93) were prepared and their structural features were examined. The results showed that potency of MAO-B inhibition by (E)-8-styrylcaffeinyl analogues depends upon the electronic characteristics of the substituent attached to C-3 of the phenyl ring of the styryl moiety where electronic withdrawing groups (93) are potent inhibitors that unsubstituted and electronic donating groups and also with the size of substituent attached to C-4 (94) where bulky groups found to be more potent.

The development of potent and selective adenosine receptor ligands as potential drugs represents an active area of research among which xanthine analogues are of prime importance. A series of 1- and 3-[1-(2-hydroxy-3-
phenoxypyropyl)] xanthine derivatives were synthesized from 5-substituted-2-amino-2-oxazoline as a synthon. The structural modifications were done at 1- and 3-positions by selective introduction of a large, functionalized and β-adrenergic 2-hydroxy-3-phenoxypyropyl pharmacophore. The synthesized derivatives were evaluated as adenosine A\textsubscript{1}, A\textsubscript{2A} and A\textsubscript{3} receptor ligands in radioligand binding studies. The 2-hydroxy-3-phenoxypyropyl moiety was well tolerated in the 3-position of the xanthine core, while its introduction in the 1-position of the xanthine moiety led to a large decrease in adenosine receptor affinity. 1,7-Dimethyl-3-[1-(2-chloro-3-phenoxypyropyl)]-8-(3,4,5-trimethoxystyryl)xanthine (95) was the most potent and selective A\textsubscript{2A} adenosine antagonist of the present series while 1-Propyl-3-[1-(2-hydroxy-3-phenoxypyropyl)]-8-noradamantylxanthine (96) was identified as a potent and highly selective adenosine A\textsubscript{1} receptor antagonist.\textsuperscript{183}

A series of new 1,3-dipropyl-8-(1-heteroarylmethyl-1\textsubscript{H}-pyrazol-4-yl)-xanthine derivatives have been synthesized as A\textsubscript{2B} adenosine receptor antagonists and evaluated for their binding affinities at A\textsubscript{2B}, A\textsubscript{1}, A\textsubscript{2A} and A\textsubscript{3} adenosine receptors. 8-(1-((3-phenyl-1,2,4-oxadiazo-5-yl)methyl)-1\textsubscript{H}-pyrazol-4-yl)-1,3-dipropyl-1\textsubscript{H}-purine-2,6(3\textsubscript{H},7\textsubscript{H})-dione (97) displayed high affinity and selectivity for the A\textsubscript{2B} adenosine receptor versus A\textsubscript{1}, A\textsubscript{2A} and A\textsubscript{3} adenosine receptors.\textsuperscript{184}

Based on the hypothesis that a selective, high-affinity A\textsubscript{2B} adenosine receptor antagonist may provide therapeutic benefit in the treatment of asthma, a
series of 8-(C-4-pyrazolyl) xanthines had been synthesized. Among them 8-(1H-pyrazol-4-yl)-1,3-dipropyl xanthine (98), a N-1 unsubstituted pyrazole derivative possess favorable binding affinity for the A2B adenosine receptors, but it is only 2-fold selective versus the A1 adenosine receptors. The introduction of a benzyl group at the N-1 pyrazole position resulted in 99 with moderate selectivity. Further synthesis involved preparation of substituted benzyl derivatives of 99 where the preferred substitution on the phenyl ring contains an electron-withdrawing group, specifically F (100) or CF3 (101) at the m-position which increases the selectivity while retaining the affinity for the A2B adenosine receptors. Exploring disubstitution on the phenyl ring of derivatives 100 and 101 led to the 2-chloro-5-trifluoromethylphenyl derivative (102), which retained the A2B AdoR affinity but enhanced the selectivity relative to36. After optimization of the substitution on the 8-pyrazole xanthine, 1,3-disubstitution of the xanthine core was explored with methyl, ethyl, butyl, and isobutyl groups. In comparison to the corresponding dipropyl analogues, the smaller 1,3-dialkyl groups (methyl and ethyl) increased the A2B adenosine binding selectivity of the xanthine derivatives while retaining the affinity. However, the larger 1,3-dialkyl groups (isobutyl and butyl) resulted in a decrease in both A2B adenosine receptor affinity and selectivity. This final SAR optimization led to the discovery of 1,3-dimethyl derivative 103, 8-(1-(3-(trifluoromethyl) benzyl)-1H-pyrazol-4-yl)-1,3-dimethyl xanthine, a high-affinity A2B adenosine receptor antagonist with high selectivity for the human A1, A2A and A3 adenosine receptors.\textsuperscript{185}

A radial approach was applied by Maykel Pe´rez Gonzá´lez et al. to predict A2B agonist effect of adenosine analogues.\textsuperscript{186} 5’-N-ethylcarboxamidoadenosine (NECA, 104) a high affinity ligand at all adenosine receptors, is one of more potent agonist on this subtype with an EC_{50} in the low micromolar range. A total of 89 adenosine analogues were studied and evaluated for parameters such as the cyclic AMP (cAMP) production, in Chinese Hamster Ovary cells (CHO) expressing human A2B receptors as percentage of the production by 100\mu M NECA.
Many of the known antagonists of purinergic (P) receptors are anionic molecules bearing one or several phenylsulfonate groups.

Among the P₁ (adenosine) receptor antagonists, the xanthine phenyl-sulfonates are a potent class of compounds. But they being negatively charged at physiologic pH due to their high acidity are not able to penetrate cell membranes. So the lipophilic, perorally bioavailable prodrugs of sulfonates were developed by
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converting them into chemically stable nitrophenyl esters. The studies showed that m-nitrophenyl esters were stable over a wide pH range, while the ortho and para isomers were less stable under strongly acidic or basic conditions. The nitrophenyl esters of sulfophenylxanthines were additionally investigated for their adenosine receptor affinities. They showed high affinity at $A_1$, $A_{2A}$ and $A_{2B}$, but not at $A_3$ adenosine receptors. One of the most potent compounds was 1-propyl-8-[4-[[p-nitrophenoxy]sulfonyl]-phenyl]xanthine ($105$), a mixed $A_1/A_{2B}$ antagonist.$^{187}$

![Image of molecule](image)

(105)

The synthesis of new high affinity and selective $A_3$-adenosine receptor agonists was described. The introduction of a methyl group at the N$^6$-position of the $A_{2A}$ adenosine selective 2-pyrazolyl adenosine analogues resulted in an increase in the $A_3$-adenosine receptor binding affinity and selectivity. While the N$^6$-desmethyl analogues $106$ and $107$ were inactive at the $A_3$ adenosine receptors their corresponding N$^6$-methyl analogues $108$ and $109$ showed good binding affinity at the $A_3$ adenosine receptors. The further replacement of the carboxamide group in $108$ with different heteroaryl groups resulted in analogues with high affinities and selectivity. (2$R$, 3$S$, 4$R$)-tetrahydro-2-(hydroxymethyl)-5-(6-(methylamino)-2-(4-(pyridin-2-yl)-1H-pyrazol-1-yl)-9H-purin-9-yl) furan-3,4-diol ($110$) displayed high selectivity for the $A_3$-adenosine receptors versus $A_1$- and $A_{2A}$-adenosine receptors.$^{188}$
A new series of 1-deoxy-1-[(6-(4-(substituted-aminosulfonyl)phenyl)amino) carbonylamino-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamides have been synthesized and evaluated for their affinity and selectivity at the human A3 adenosine receptor subtype. Most of the derivatives displayed affinity versus good selectivity at A1 and A3 adenosine receptor subtype thus confirms the positive affect of p-sulfonamido moiety on the activity of the molecules. The substituents best described for the sulfonamido nucleus were found to be small alkyl groups, like methyl, isopropyl, ethyl, or allyl moieties (111-115), whereas
monosubstitution of the amino group found to be associated with a decrease in A₃ affinity values. The selectivity and affinity at A₁ adenosine receptor subtype is increased when the amino group in the sulfonamido core is replaced by heterocyclic ring like piperidine, morpholine, or pyrroline.¹⁸⁹

The development of SCH58261 (116) by Pier Giovanni group had emerged as a first potent and selective adenosine A₂A antagonist. Based on that compound, substitutions were done on pyrazole ring of pyrazolotriazolopyrimidine series to study the influence of substitution. The
substituents chosen were based on their ability to improve water solubility while retaining high affinity and selectivity at the human $A_{2A}$ adenosine receptor subtype. Some of the structural characteristics such as tricyclic system, free amino group at 5-position, furan ring and substituent at 7-position of pyrazole were retained and main focus was on the nature of phenyl ring substituent to improve water solubility. Based on this the new compounds were synthesized and evaluated for their affinity and selectivity at $A_{2A}$ adenosine receptors. The new compounds with varying substitutions on nitrogen atom of phenyl ring, 117-120 found to posses high affinity and selectivity at $A_{2A}$ while they have no significant interaction with either $A_{2B}$ or $A_3$ receptor subtypes.

With the aim to search selective $A_{2B}$ adenosine receptor antagonists, 3-unsubstituted xanthine derivatives bearing a cyclopentyl or a phenyl residue in the 8-position were synthesized. 1-Alkyl-8-phenylxanthine derivatives were also found to exhibit high affinity for $A_{2B}$ adenosine receptors and were equi- or more potent than 1,3,8-trisubstituted xanthines at $A_{2B}$ adenosine receptors, but generally less potent at $A_1$ and $A_{2A}$, and much less potent at $A_3$ adenosine receptors. Thus, the new compounds exhibited increased $A_{2B}$ selectivity versus all other adenosine receptor subtypes. 9-Deazaxanthines (pyrrolo-[2,3-d]-pyrimidindiones) appeared to be less potent at $A_{2B}$ adenosine receptors than the corresponding xanthine derivatives. 1-Propyl-8-p-sulfophenylxanthine (121) was
found to be the most selective compound at human $A_{2B}$ adenosine receptors. The compound is highly water-soluble due to its sulfonate function.

Similarly, 1-Butyl-8-$p$-carboxyphenylxanthine (122), another polar analogue bearing a carboxylate function, also found to be selective at $A_{2B}$ than $A_{2A}$ and $A_3$. 8-[4-(2-Hydroxyethylamino)-2-oxoethoxy)-phenyl]-1-propylxanthine (123) and 1-butyl-8-[4-(4-benzyl)-piperazino-2-oxoethoxy)-phenyl]-xanthine (124) were among the most potent $A_{2B}$ antagonists.$^{191}$

A series of 8-substituted xanthines were synthesized by Giovannella Strappagheti et al. and evaluated in vitro by radioligand receptor binding assays towards their affinity for $A_1$ and $A_{2A}$ adenosine receptors.
The compounds showed great affinity and selectivity towards $A_1$ adenosine receptors than theophylline. The compounds containing propyl group at 1-position of xanthine nucleus and $p$-chloro substituted pyridazinone ring at 8-position linked by a chain of two carbon atoms (125) or four carbon atoms (126) showed highest selectivity and affinity.\(^{192}\) The introduction of phenyl substituent (127) at 8-pyridazinone ring also found to be effective.

The above survey of literature highlights the significance of substituting different positions of the xanthine nucleus to develop potent drugs for the management of asthma. The reported findings from various research groups encouraged us to design and synthesize some more new potential xanthine derivatives. Number of substitutions have been made by the investigator at 8\textsuperscript{th}-position of theophylline to get more potent and selective theophylline derivatives as antiasthmatic agents.

The work carried out has been described in RESUMÉ AND DISCUSSION section followed by the EXPERIMENTAL WORK details.