Asthma remains one of the most common respiratory diseases encountered in the clinical practice. It is a chronic inflammatory disorder of the airways with a wide range of presentations from intermittent but mild symptoms to persistent symptoms with chronicity. The pharmacological arsenal for asthma is fast growing and according to Global Initiative for Asthma (GINA) report, it is now estimated that approximately 5% of the global population or 1 in 20 persons is suffering from asthma.\textsuperscript{1-6} Asthma is characterized by recurrent episodes of wheezing, breathlessness, chest tightness and cough, reversible airway obstruction and bronchial hyperresponsiveness to a variety of specific and nonspecific stimuli including allergens, histamines, chemical irritants, cold air and exercise.\textsuperscript{7-13}

With the understanding about the pathophysiology of asthma, it is now described as a complex multifactorial disease, characterized by inflammatory phenomena, which includes denudation of the airway epithelium, edema of the submucosa, smooth muscle hypertrophy, and the infiltration or activation of inflammatory cells.\textsuperscript{9}

**PATHOPHYSIOLOGY OF ASTHMA**

Asthma is a chronic disease mediated by reaginic (IgE) antibodies bound to mast cells in the airway mucosa. On reexposure to an antigen, antigen-antibody interaction takes place on the surface of mast cells, triggering both the release of mediators stored in cell’s granules and the synthesis and release of other mediators,\textsuperscript{2} which exert many inflammatory effects on the airways.\textsuperscript{13} The features of the inflammatory process in asthma are complex, involving interplay of events leading to hyperresponsiveness of the airways.

Immunological and nonimmunological mechanisms leading to asthma are depicted in figure 1.\textsuperscript{14} The immediate pulmonary response following exposure to allergens is bronchoconstriction, which generally develops due to the activation of mast cells by
specific antigens through cell-bound IgE\(^5\) resulting in the release of histamines and synthesis of cysteinyl-leukotrienes (cysLTs). Acute phase mediators cause airflow obstruction by increasing airway tone. Mast cells also release proteases (tryptase, stromolysin and chymase) and many pro-inflammatory cytokines [e.g., tumor necrosis factor-alpha (TNF-\(\alpha\)), gran macrophage colony-stimulating factor (GM-CSF), interleukins IL-13 and chemokines], which contribute to airway inflammation and airway hyperresponsiveness (Figure 1).\(^5,14,15\)

**Fig. 1: Pathophysiology of asthma**

Thus on activation, epithelial cells, mast cells, eosinophils, neutrophils, macrophages and fibroblasts release a wide range of inflammatory mediators including histamine, proteases, growth factors, platelet activating factors and cytokines and leukotrienes, which leads to bronchospasm, airway smooth muscle hypertrophy, hyperresponsiveness, airway smooth muscle hypertrophy, denudation of basement membrane, mucus hypersecretion and activation of sensory nerves, all of which contribute to the pathophysiology of asthma.\(^16\)
MANAGEMENT OF ASTHMA

The main approaches towards the management of asthma are mainly based on both the pharmacologic and non-pharmacologic prevention. Avoidance of exposure to allergens\textsuperscript{13} and other triggers of acute exacerbations are the major component of non-pharmacologic management whereas the pharmacological management of asthma is by use of drugs.\textsuperscript{17} Although the available drugs for asthma are effective and well tolerated in majority of patients but still there is a need for safer, effective and orally active bronchodilators and anti-inflammatory agents.\textsuperscript{2-5,9,17-19}

Bronchodilators relax airway smooth muscles and end an episode of asthma.\textsuperscript{20} However these agents do not have an effect on airway inflammation. Until recently asthma therapy has principally emphasized the use of bronchodilators but a greater understanding of the central role of inflammation in the pathogenesis of asthma has led to a reevaluation of the use of anti-inflammatory agents in the management of asthma.

ANTIASTHMATIC AGENTS

Antiasthmatic agents have been categorized under various heads as follows:

- Corticosteroids
- Leukotriene synthesis (5-lipoxygenase) inhibitors
- Leukotriene receptor antagonists
- Cromolyn sodium and other mediator release inhibitors
- Phosphodiesterase inhibitors
- Adenosine receptor modulators
- Long acting \( \beta_2 \) agonists (LABAs)
- Anticholinergic agents
- Antihistaminic agents
- Miscellaneous agents
  - Platelet activating factor antagonists
Various types of antiasthmatic agents along with their mechanism and site of action have been depicted in figure 2.14

**Fig. 2: Various classes of antiasthmatic agents along with their mechanism and site of action**

**Corticosteroids**

Shortly after their discovery corticosteroids became the cornerstones of asthma treatment. Steroids have been associated with treatment of asthma since 1949, when patients were first treated with adrenocorticotropic hormone (ACTH).18 These are the most potent and effective agents available for the treatment of asthma because of their excellent anti-inflammatory profile.19 Development of steroidal molecules with increased selectivity for the glucocorticoid receptor...
to the development of orally active anti-inflammatory glucocorticoids. These drugs are still in use today particularly in patients with severe asthma. However, therapeutic doses of oral glucocorticoids are associated with a range of adverse reactions which prevent steroids from being the ideal therapy for allergic asthma.

Therefore inhalation glucocorticoids have been developed in an attempt to reduce systemic side effects. The introduction of inhaled preparations and the revelation of asthma as an inflammatory disease make this class of drugs the most suitable for treatment of asthmatic patients. The anti-inflammatory activity of hydrocortisone (1), cortisone (2) and corticosterone (3), isolated from adrenal glands, was demonstrated way back in 1930's and 1940's. The major drawback of these agents was systemic side effects, which include adrenocortical suppression, bone thinning, muscle wasting, thinning of skin, cataracts, decreased growth in children, facial
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rounding, fluid retention, decreased glucose tolerance, increased blood pressure and acne. It was established that the key structural features required for the anti-inflammatory activity include the 3-keto group, double bond between 4,5-position and presence of 11-hydroxyl, 17α-hydroxyl and 21-hydroxyl groups.

Numbers of attempts were made to synthesize numerous analogs of cortisone possessing anti-inflammatory activity with improved therapeutic index\(^{19,24}\) and initial breakthrough came with the introduction of 1,2-double bond in A ring of steroid nucleus giving prednisone (4) and prednisolone (5). These were four times more potent as anti-inflammatory agents than hydrocortisone along with lower mineralocorticoid properties.

Introduction of 6α-methyl and 9α-fluoro group in 5 gave the compounds methylprednisolone (6) and triamcinolone (7), respectively\(^{25,26}\). These agents provided further separation of the anti-inflammatory and mineralocorticoid properties.
Replacement of 16α-OH group with 16α-methyl group afforded dexamethasone (8), its 16β-isomer betamethasone (9) was found to be a potent anti-inflammatory agent devoid of mineralocorticoid properties.\textsuperscript{21,24}

Further the replacement of 9α-fluoro group in 9 with 9α-chloro gave the compound beclomethasone (10).\textsuperscript{27}

Still the separation of anti-inflammatory activity from other side effects was not completely achieved and the use of topically active steroids via inhalation to reduce completely the systemic side effects was investigated. It eventually became the breakthrough therapy for asthma.

As far back as in 1950s inhaled hydrocortisone (1) and cortisone (2) were tried but the initial trials for the management of asthma were made with betamethasone (9) valerate and beclomethasone (10) dipropionate.\textsuperscript{27} The response observed with these inhaled topical steroids was better than that with inhaled hydrocortisone.
Further research in this area led to the development of fluocinolone acetonide (11), flunisolide (12) and fluocortin butyl ester (13) as anti-inflammatory agents.

Nasal spray of flunisolide is effective in allergic rhinitis in clinical use. Their protective effect in patients with bronchial asthma has been studied.\textsuperscript{1,24,28}

Success in the latter approach has been reported for androstane 17-thioketals (tipredane)\textsuperscript{29} (14) and 17\textbeta-carboxyandrostane esters.\textsuperscript{30-32}

The newer compounds like budesonide (15) and fluticasone propionate (16) are the most recently introduced glucocorticoids for
inhalation use in asthma. These agents are also being developed with the advantage of lower systemic side effects because the dose used for inhalation is much less to produce side effects.

Recently, nasal spray of mometasone furoate (17) has been marketed by the United States Food and Drug Administration for use in asthma. All these drugs differ markedly in their affinity for the glucocorticoid receptor with fluticasone and budesonide having much higher affinity than beclomethasone.

**Molecular mechanism of steroid action**

Corticosteroids alleviate major symptoms of asthma by reducing airway reactivity while restoring the integrity of the airways. However the mechanism of action used to achieve these effects is not fully understood (Figure 3). In the past decades, great progress has been made in understanding the cellular biology and antiallergic and anti-inflammatory mechanisms of corticosteroids. Corticosteroids enter the cell via passive diffusion through the plasma membrane where it bind to soluble class specific glucocorticoid receptors (GRs) which are present in cytoplasm of respiratory cells and only on binding of the glucocorticoid does it move into the nuclear compartment.

Glucocorticoid receptors are expressed in all cell types but predominantly in airway epithelium and endothelium of bronchial vessels. Corticosteroids may be effective in controlling asthma by
inhibiting several aspects of the inflammatory process through increasing or decreasing gene transcription. Although it is not yet possible to be certain of the most critical aspects of steroid action in asthma, it is likely that steroids decrease the accumulation and activation of inflammatory cells in asthmatic lung probably via cytokine associated mechanisms.

![Control of gene expression through the glucocorticoid receptors signalling pathway](image)

**Fig. 3: Control of gene expression through the glucocorticoid receptors signalling pathway**

Corticosteroids may decrease the number of inflammatory cells, including mast cells, lymphocytes and eosinophils in the bronchial wall and also downregulate migration of eosinophils, block neutrophil adherence, microphage function and diminish microvascular leakage. These effects are associated with the inhibition of cytokine production. Corticosteroids also have been shown to inhibit the production of IL-1α, IL-8, tumor necrosis factor alpha (TNF-α), granulocyte-monocyte colony-stimulating factor (GM-CSF), gamma-interferon and fibroblast growth factors.

**Leukotriene synthesis (5-lipoxygenase) inhibitors**

Inhibition of leukotriene biosynthesis has been extensively studied as a potential area for the development of novel therapies for asthma. The
key enzyme in this process, 5-lipoxygenase, transforms arachidonic acid in a two step process to first 5-hydroperoxyeicosatetraenoic acid (5-HPETE), and then through a dehydration step to leukotriene A₄ (LTA₄), an unstable intermediate converted via specific enzymes to LTB₄, LTC₄, LTD₄, LTE₄, mediators in asthma.⁴⁶

Four distinct classes of compounds have been identified to inhibit the key enzyme 5-lipoxygenase.

**Redox inhibitors**
Experience over the past two decades with redox inhibitors has been disappointing. Although a number of potent compounds have been identified, they have often been associated with ancilliary toxicity and non-specificity. Examples of this group include phenothiazine analogs L-615919 (18)⁴⁷ and L-651392 (19).⁴⁸

**Iron chelator inhibitors**
These compounds were designed basically with the expectation that the functional groups might chelate iron and inhibit the enzyme. The most successful efforts have been in the area of hydroxamic acids and related $N$-hydroxy ureas.

Zileuton (20), an $N$-hydroxy urea was introduced in 1996, as first agent of this new class of antileukotriene drugs⁴⁹ for the treatment of chronic asthma. It exhibits some degree of bronchodilatory, anti-inflammatory,
steroid sparing effects and variety of adverse effects. A number of more potent analogs of zileuton are in clinical trial stages.

**Competitive reversible inhibitors of 5-lipoxygenase**

Compounds of the series methoxyalkylthiazoles and methoxytetrahydropyrans series were found to be potent in this class. Lignan derivative, justicidin E has also been found to be a moderately potent inhibitor of this series. However, extensive metabolism of pyran ring in their hybrids has complicated their development.

**Inhibitors of 5-lipoxygenase activating protein (FLAP)**

FLAP has been indicated as a necessary factor facilitating the transfer of arachidonic acid to 5-lipoxygenase in cells. MK-886 (21), an indole inhibitor was found to inhibit leukotriene biosynthesis incompletely by blocking this transfer. Its significantly potent analog MK-0591 (22), was found to be clinically effective, but its development was suspended in favor of LTD₄ receptor antagonist montelukast.

Another quinoline compound, BAY-X-1005 (23), is in clinical trials as an antiasthmatic. It is apparent from clinical trials of MK-0591 (22) and
BAY-X-1005 (23) that leukotriene biosynthesis inhibition could provide useful therapy in asthma but no clear advantage of 5-lipoxygenase inhibitors has been demonstrated relative to LTD$_4$ antagonists.\textsuperscript{46}

**Leukotriene receptor antagonists**

Leukotriene receptor antagonists constitute the first new class of drugs developed for asthma therapy in twenty years.\textsuperscript{64} The two types of leukotriene receptors, LTB$_4$ and cysteinyl LT$_1$ receptors are known to mediate asthma pathophysiology.\textsuperscript{47,65}

Leukotriene receptor antagonists function by blocking the interaction of cysteinyl leukotrienes with cysteinyl LT$_1$ receptors, thereby blocking end organ response of airway obstruction\textsuperscript{2}. From the historical and structural point of view, cysteinyl leukotriene antagonists have been grouped under different heads.

**First generation**

Hydroxyacetophenone antagonists

The first peptidyl leukotriene antagonists FPL-55712 (24) predated the elucidation of the structure of leukotriene. The early peptidyl leukotriene antagonists were structural analogs of 24 containing a common hydroxyacetophenone moiety linked through flexible spacer to an acidic group.\textsuperscript{66} The best studied member of this class of
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antagonists is tomelukast (25)\textsuperscript{67,68} with additional activity as a thromboxane antagonists and PDE inhibitor,\textsuperscript{69} whose development was discontinued due to toxic reactions.\textsuperscript{70}

**Second generation**

LTD\textsubscript{4} analogs

Several antagonists, analogs of LTD\textsubscript{4}, were designed without the information of natural agonist/antagonist. The two antagonists, pobilukast\textsuperscript{71} (26)

and sulukast (27) retaining natural LTD\textsubscript{4} configuration about thioether linkage and hydroxyl group were plagued with low oral bioavailability.

Improved oral bioavailability could be achieved by removal of hydroxyl group, but with decrease in potency.\textsuperscript{72}
**Quinoline antagonists**

In mid 1980’s, REV-5901 (28) was discovered as FLAP inhibitor with a weak LTD₄ receptor antagonistic activity leading to the synthesis of many other quinoline containing compounds such as ritolukast (29) and RG 12525 advancing to clinical trials. MK-571 (30) was developed with a quinoline template and a thioacetal unit. It displayed affinity for LTD₄ receptor comparable to the natural ligand LTD₄ but was withdrawn from clinical development due to liver function abnormalities.

Continued optimization of early members led to a second generation antagonist, MK-476 (31), montelukast, providing the most potent and long lasting blockade of LTD₄ induced bronchoconstriction.
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Its use in chronic asthmatics has led to a significant improvement in lung function, quality of life and reduced β-agonist use.\textsuperscript{79}

**Miscellaneous**

Pranlukast (32) was the first LTD\textsubscript{4} antagonist to be marketed.\textsuperscript{80,81} It was shown to attenuate bronchoconstriction response to asthma challenges and also to reduce β-agonist usage.\textsuperscript{82}

Zafirlukast (33) has the structural components of FPL-55712 (24) and LTD\textsubscript{4}.\textsuperscript{83,84} The \{[(cyclopentyloxy)carboxyl]amino\}indole was replacement for the hydroxyacetophenone portion of FPL-55712 and \(N\)-(4-methyl benzoyl)-arylsulfonamide served as the surrogate for triene system of LTD\textsubscript{4}. It has provided greatest benefit in patients with more severe asthma along with significant inhibition of antigen, LTD\textsubscript{4} and exercise induced bronchoconstriction following both oral and aerosol administration.\textsuperscript{85-87}

**Cromolyn sodium and other mediator release inhibitors**

Cromolyn was synthesized in 1965 as a part of an attempt to improve the bronchodilatory properties of khellin (34), a chromone
(benzopyrone), from plant *Ammi visnaga* (fam. Umbelliferae), used by ancient Egyptians as an antispasmodic.88

Cromolyn sodium (35) was chosen for development as an antiasthmatic from a series of bischromone dicarboxylate modification of khellin.89 A second generation, pyranoquinoline derivative, nedocromil sodium (36) was later developed in an effort to overcome some limitations of cromolyn sodium.90 These are mast cell stabilizers,91,92 which prevent antigen induced release of histamine and other mediators from sensitized mast cells.93

These agents are primarily used prophylactically in the treatment of mild to moderate bronchial asthma. Some additional mediator release inhibitors developed for asthma treatment are picumast hydrochloride, tazanolast, repirinast, amoxanox and
Pemilorast potassium. All of these acts through mast cell stabilization like sodium cromoglycate.94-97.

**Phosphodiesterase inhibitors**

In the last few years selective phosphodiesterase inhibitors have received considerable attention as molecular targets for the development of antiasthmatic agents.98-100 Phosphodiesterases 3, 4 and 5 are particularly important with respect to targets for the development of novel antiasthmatic agents.101 Phosphodiesterase type 4 (PDE4) plays a major role in modulating the activity of virtually all cells involved in the inflammatory processes.102 Therefore, much of the emphasis on selective phosphodiesterase inhibitors for asthma therapy has been focused on PDE4 inhibitors.19,103 Inhibition of cyclic phosphodiesterase isoenzyme resulting in increased intracellular accumulation of cyclic adenosine monophosphate (cAMP) is the hypothesis, which explains the ability of PDE4 inhibitors to cause bronchodilation.104-110 Structurally, PDE4 inhibitors are mainly classified as catechol ethers, quinazolinediones and xanthine related compounds.

**Catechol ethers**

Rolipram (37), originally developed as an antidepressant, is the most studied of all selective PDE4 inhibitors. SAR studies of a series of rolipram analogues as PDE4 inhibitors have been published.100,103 In fact, rolipram, since its discovery as a potent and selective PDE4 inhibitor has represented a useful pharmacological tool for the characterization of this isoenzyme in different tissues, a reference drug in evaluating novel inhibitors, as well as the main template for
the synthesis of novel inhibitors. Rolipram has been found to bind to a high affinity site on PDE4, distinct from the catalytic site resulting in undesirable side effects including nausea and vomiting. The bronchodilatory effects of several PDE4 inhibitors correlate better with displacement of rolipram binding than with the PDE4 inhibition. To combine nanomolar inhibitory potency with strongly reduced affinity for Rolipram High Affinity Binding Site (RHABS) in order to improve the therapeutic index is a challenge in this class of PDE4 inhibitors.

Catechol ethers are characterized by the presence of substructure 38 in which R is generally a methyl and R' is a cyclopentyl group, alternatively highly lipophilic groups are present as R'.

Piclamilast (RP 73401) (39), an N-4-pyridylbenzamide, is a potent PDE4 inhibitor. But it shows no-selectivity for inhibiting PDE4 (catalytic site) over the displacement of rolipram from its binding site and is therefore not free from side effects.

Phenylpentoxy derivative 40 was found to exhibit potent PDE4 inhibitory activity and possessed ~400 times weaker activity than rolipram.
for \(^{(3H)}\) rolipram binding site and demonstrated a significant decrease in emetic side effects.

Cilomilast (Ariflo\textsuperscript{TM}) (41) developed by Glaxo Smithkline Beecham\textsuperscript{118} has been marketed for treatment of COPD and asthma in 2003, despite an earlier decision by the FDA advisory panel (2002) to reject approval due to its poor results in clinical studies, even though it has a large therapeutic potential and a decreased potential for side effects as compared to rolipram.\textsuperscript{119}

**Quinazolinediones and related compounds**

The quinazolinedione moiety of the lead molecule, nitraquazone (42) has been extensively manipulated to afford a variety of structure-derived compounds.\textsuperscript{19} SAR studies demonstrated that 3'-NO\textsubscript{2} group has been successfully replaced by different non-protic, electron withdrawing groups like -Cl, -Br and -COOCH\textsubscript{3}.\textsuperscript{120} Benzene-pyridine

![Chemical structures](image)

isosteric replacement, as well as introduction of more space filling groups at \(N_3\) afforded the Pfizer compound CP 77059 (43) and Roche (earlier syntax) RS 25344 (44).
Further simplification of the structure led to quinoline RS 14203 (45), one of the most potent inhibitor of PDE4. Replacement of 3’-nitro phenyl group of 45 by benzotriazole resulted in 46. The naftridinones 47 and 48 result from a lesser structural simplification of nitraquzone. Based on these observations, it has been concluded that nitraquzone like inhibitors are based on an almost flat heteroaromatic area, generally formed by 6-6 condensed system in which, one (hetero) aromatic or a cycloalkyl system is connected to flat portion through a methylene spacer and another aromatic system bearing an electron withdrawing substituent at meta position is directly attached.

This represents the best pharmacophoric model 49 for this class of PDE4 inhibitor. From the common pharmacophore for
nitraquazone related compounds, several novel heteroaromatic compounds have been designed, synthesized and evaluated as PDE4 inhibitors.\textsuperscript{115}

![Chemical Structure](image)

\(X = N, C\)  
\(Y = NO_2, Br, Cl, COOCH_3\)

**Xanthines and related compounds**

The oldest and most popular compound displaying non-specific PDE4 inhibitory activity is theophylline, a xanthine derivative widely prescribed world-wide for treatment in asthma. It is suggested as an additional bronchodilator when moderate to high doses of inhaled steroids fail to completely control asthma symptoms. The usefulness of theophylline is due in part to the oral activity and its ability to control nocturnal asthma.

This class of antiasthmatic agents has been discussed in details under the heading ‘xanthine derivatives’ in the later part of this section.

**Adenosine receptor modulators**

It is now well established that the role of adenosine in the pathogenesis of asthma is due to its \textit{in vivo} release following provocation of the airways.\textsuperscript{2} This emphasizes the importance of adenosine as a central therapeutic target and advocates the principle that modulating adenosine receptor signalling could translate into clinical benefit for patients with chronic airway diseases.

Adenosine is an omnipresent, endogenous nucleoside-signaling molecule, which by acting on extracellular adenosine
receptors (G-protein coupled: \(A_1\), \(A_{2A}\), \(A_{2B}\) and \(A_3\)) play a number of physiological and pathophysiological effects in the body including bronchoconstriction and inflammation. These receptors are widely distributed throughout the body, with their presence on basically every cell making them an interesting target for the pharmacological intervention in many pathophysiological situations linked to an increase of adenosine levels (Figure 4).

**Fig. 4: Novel disease targets for selective adenosine receptor ligands**

All the four subtypes are members of the super family of protein-coupled receptors (GPCRs), and are most closely related to the receptors for biogenic amines. Extracellular adenosine levels are quite variable, depending on the tissue and the degree of tissue oxygenation, and so the basal levels of stimulation of adenosine receptors vary enormously. Adenosine itself is rapidly metabolized by adenosine kinase and, to a small degree, adenosine deaminase to AMP and inosine, respectively.
both of which are less active than adenosine at the adenosine receptors (ARs).\textsuperscript{124}

The development of potent and selective synthetic agonists and antagonists of ARs has been the subject of medicinal chemistry research for more than three decades. The action of adenosine receptors might also be modulated not only by direct-acting ligands, but by inhibition of the metabolism of extracellular adenosine or its cellular uptake. The basic science suggests that selective adenosine modulators have promise for numerous therapeutic applications, including cardiovascular, inflammatory and neurodegenerative diseases, in practice this goal has been elusive. One reason for this is the ubiquity of ARs and the possibility of side effects. In addition, species differences in the affinity of putatively selective ligands complicate preclinical testing in animal models.\textsuperscript{123}

Adenosine receptor subtypes are expressed in the lung and in inflammatory cells involved in asthma, and selective agonists or antagonists to these receptor subtypes are being exploited by the pharmaceutical industry in an attempt to generate novel therapies for asthma and chronic obstructive pulmonary disease (COPD) (Table 1).\textsuperscript{2,125}

Table 1: Comparison of Adenosine Receptor (AR) subtypes for asthma therapy

<table>
<thead>
<tr>
<th>Adenosine Receptors (AR)</th>
<th>G-Protein</th>
<th>Signal transduction</th>
<th>Affinity for adenosine</th>
<th>Potential effects in asthmatics</th>
<th>Clinical Developments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Gi</td>
<td>cAMP</td>
<td>High</td>
<td>Bronchodilation; Anti-inflammatory; Inhibition of mucus Hypersecretion; Block angiogenesis</td>
<td>Doxophylline, Theophylline (Launched)</td>
</tr>
<tr>
<td>A&lt;sub&gt;2A&lt;/sub&gt;</td>
<td>Gs</td>
<td>cAMP</td>
<td>High</td>
<td>Bronchodilation; Anti-inflammatory</td>
<td>UK 430297 (Phase II)</td>
</tr>
<tr>
<td>A&lt;sub&gt;2B&lt;/sub&gt;</td>
<td>Gs</td>
<td>cAMP</td>
<td>Low</td>
<td>Anti-inflammatory; Inhibit airway remodeling</td>
<td>CVT-6883 (Phase I)</td>
</tr>
<tr>
<td>A&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Gi</td>
<td>cAMP</td>
<td>Low</td>
<td>Bronchodilation; Anti-inflammatory; Inhibit mucus hyperplasia</td>
<td>CF 101 (Phase II) Agonist QAF 805 (Phase Ib) Antagonist</td>
</tr>
</tbody>
</table>
A₁ and A₂A adenosine receptors are stimulate adenosine concentration, while higher adenosine levels are for activation of A₂B and A₃ receptors as shown in figure 5.

**Fig. 5: Bronchconstriction at different levels of intracellular adenosine.**

Among the four adenosine receptor subtypes, A₂B adenosine seems to play a more prominent role in mediating the bronchoconstrictor effect of adenosine in the lung. The initial evidence of an A₂B receptor role in asthma came from pharmacological studies of enprofylline (50), a methylxanthine structurally closely related to 1. It was shown that enprofylline is a selective antagonist for the A₂B receptor.
whereas theophylline has similar binding affinities for A1, A2A and A2B receptors. Importantly, the therapeutic concentrations of theophylline and enprofylline are in the range of their affinities for A2B receptors.\(^{126,127}\)

Thus, it was proposed that A2B receptor might be the therapeutic target for the long-term clinical benefit achieved with relatively low doses of theophylline and enprofylline. Selective A2B receptor antagonists are of interest for the treatment of asthma and chronic obstructive pulmonary disease. On the basis of structural approach, the adenosine receptor modulators used for asthma may be classified into two classes of compounds, \textit{xanthine} and \textit{non-xanthine} derivatives.

**Xanthines**

The adenosine receptor antagonist family consists of a number of classes of heterocycles, among which the xanthine derivatives showed high affinity and selectivity at these receptors. The xanthine derivatives caffeine and theophylline are considered classic nonselective antagonists for adenosine receptors. Following further structural exploration of the xanthine moiety, the 8-aryl-xanthines such as 8-phenyl and 8-pyrazolyl derivatives appeared to be very potent and selective adenosine receptor antagonists. This class of antiasthmatic agents has been discussed in details under the heading ‘\textit{xanthine derivatives}’ in the later part of this section.

**Non-xanthines**

Due to non specific effects of xanthines, there has been considerable effort directed at identifying non-xanthine adenosine antagonists. A variety of heterocycles including pyrazolopyridines, thiazolopyrimidines, imidazopyridines, and benzimidazoles have been found to modulate the effects at adenosine receptors.\(^{128}\)

FK-453 (51), a non-xanthine derivative, containing pyrazolo[1,5-a]pyridine nucleus has potent and selective adenosine
A₁ antagonistic activity as demonstrated in radioligand binding study ($K_i = 18 \text{ nM}$).\(^{129}\)

Recently, OSIP-339391 (52), a potent compound of pyrrolopyrimidines series reported by OSI Pharmaceuticals Inc. displayed 70-fold selectivity for A₂B adenosine receptors ($K_i = 0.5 \text{ nM}$) over the other human adenosine receptor subtypes.\(^{130,131}\)

Jacobson et al. used the 1,4-dihydropyridine nucleus as a template for probing the SAR profile at the A₃ adenosine receptor subtype, which showed that the sterically bulky groups are well tolerated at 4-, 5- and 6-positions. The combination led to the discovery of MRS-1097 (53), as the first A₃ adenosine receptor antagonist ($K_i = 108 \text{ nM}$) based on 1,4-dihydropyridine scaffold.\(^{132-135}\)
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The pyrazolo-triazolo-pyrimidine nucleus is a prototypical template for adenosine receptor antagonist in the past decade. One such compound MRE-3008-F20 (54), is an adenosine receptor ligand which showed very high affinity towards A3 adenosine receptor subtype ($K_i = 0.82$ nM).

Table 2 enlists some non-xanthine derivatives, synthesized by several medicinal chemistry research groups, having affinity and selectivity towards various adenosine receptor subtypes.

Table 2: Molecular structures and binding affinities of various non-xanthines as selective adenosine receptor antagonists

<table>
<thead>
<tr>
<th>C. No.</th>
<th>AR antagonists</th>
<th>Structure</th>
<th>$K_i$ values for ARs (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A1</td>
<td>A2A</td>
<td>A2B</td>
</tr>
<tr>
<td>A1 antagonists</td>
<td></td>
<td></td>
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<td>56</td>
<td>WRC-0571$^{138}$</td>
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### C. AR No. antagonists Structure

#### Kᵢ values for ARs (nM)

<table>
<thead>
<tr>
<th></th>
<th>A₁</th>
<th>A₂A</th>
<th>A₂B</th>
<th>A₃</th>
</tr>
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<tbody>
<tr>
<td>57</td>
<td>17</td>
<td>1000</td>
<td>&gt;2500</td>
<td>&gt;1000</td>
</tr>
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</table>

#### A₂B antagonist

![Structure of LAS-38096](image)

#### A₃ antagonists

<table>
<thead>
<tr>
<th></th>
<th>A₁</th>
<th>A₂A</th>
<th>A₂B</th>
<th>A₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>58</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>-</td>
<td>2.69</td>
</tr>
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### Long acting β₂-adrenoceptor agonists (LABA)

Long acting β₂-adrenoceptor agonists belong to a highly precedent drug class, which is used for the treatment of asthma and chronic obstructive pulmonary disease (COPD). They are preferred both for rapid relief of symptoms and for the level of bronchodilation achieved in patients with bronchial asthma. These drugs produce their effects through stimulation of specific β₂-adrenergic receptors.
located in plasma membrane resulting in alterations in adenyl cyclase and elevations in intracellular cyclic adenosine monophosphate (cAMP), which is responsible for the bronchodilatory response.145

Inhalation of β-adrenergic agonists is the preferred therapy for bronchoconstriction.146 The history of development started with epinephrine (61) (α- and β-receptor agonist) to isoproterenol (62) (β-agonist) to almost pure β2-adrenoceptor agonists, salbutamol (63) and fenoterol (64), the currently preferred agents.19,147

Since the discovery of naturally occurring epinephrine, the search for improved bronchodilator agents has centered on compounds possessing β2-selective agonist activity due to cardiac stimulating potential of β1-receptors.148 Salbutamol (63) inhalation was found to possess several times greater bronchodilatory activity with weaker cardiovascular effects than isoproterenol.149

Once the problem of direct cardiac side effects had been minimized, many additional drugs were investigated as
bronchodilators that were less active as vasodilators or in producing muscle tremors. Some examples of compounds brought to various stages of development are soterenol (65) and carbuterol (66).150,151

![Chemical structures]

Recent developments of β2-adrenoceptor agonists have been focused on increased duration of action leading to less frequent administration of bronchodilators. The two long acting medications are formoterol (67) and salmeterol (68) with enhanced duration of action due to increased size of nitrogen substituent.152-154

**Anticholinergic agents**

The current interest in anticholinergic bronchodilators for respiratory therapy has been increased by demonstration of the importance of vagus nerves in bronchospastic responses.155 These agents competitively inhibit post synaptic muscarinic receptors and block the
actions of acetylcholine at vagal nerve endings leading to bronchodilation and decrease in airway resistance.² ⁸

Atropine (69) is the prototype anticholinergic but is rarely used due to the systemic side effects of mydriasis, tachycardia and decrease in gastric and salivary secretions.¹⁵⁶ Interest in anticholinergics was rekindled by development of ipratropium bromide (70), a quaternary salt derivative of atropine with limited side effects due to less lipid solubility and a new long acting anticholinergic agent, e.g.; tiotropium bromide.¹⁵⁷–¹⁵⁹

Several additional compounds with anticholinergic properties have been studied clinically but were eventually discontinued.¹⁶⁰ Revatropate (71) is a new antimuscarinic agent with marked selectivity for M₁ and M₃ receptor subtypes.¹⁶¹ These anticholinergic
agents are less effective as bronchodilators than $\beta_2$-agonists but are useful in patients intolerance to side effects of $\beta_2$-agonists.\textsuperscript{47}

Cholinergic mechanism cannot account for all aspects of bronchospasm and thus anticholinergic drugs demonstrated variable efficacy towards bronchoconstriction triggered by different irritants and chemical mediators.\textsuperscript{19}

**Antihistaminic agents**

Histamine is produced from mast cells in asthmatic airways and exerts many effects that are relevant to the pathophysiological mechanisms of asthma, including bronchoconstriction, plasma exudation and mucus secretion.\textsuperscript{162-164} It mediates most of its effects on airway function via $H_1$ receptors suggesting therapeutic effects of $H_1$ antagonists in airway diseases. Antihistaminics block the actions of histamine and produce bronchodilation.\textsuperscript{165} $H_1$ antihistaminics may be classified as:

**First generation antihistaminics**

This group includes various compounds of arylether, ethylenediamine, aminoethylether and aminopropylether classes.\textsuperscript{166-169} Chlorpheniramine (72)

produces potent, long lasting $H_1$ antagonistic activity. It is a moderate
bronchodilator but is not therapeutically useful for this indication and minor effects shown by other antihistamines in the treatment of chronic asthma were also not found to be clinically important. These first generation compounds penetrate the blood brain barrier and also possess anticholinergic properties leading to various side effects.

**Second generation antihistaminics**

The ideal antihistamine should have a rapid onset of action, long duration of action, be orally active and free from side effects. This led to the development of second generation nonsedating H\textsubscript{1} antagonists such as terfenadine (73) and astemizole. Both terfenadine and astemizole cause inhibition of immediate response to allergens but has no effect on the late response of asthma. Chronic administration of terfenadine has a small clinical effect among patients with mild and moderate asthma but is far less effective than other antiasthma therapies and thus is not recommended for routine management of asthma.
Some new antihistamines, cetirizine (74) and azilastine have been shown to have beneficial effects in asthma, which may be unrelated to its H₁ antagonistic effects. Overall, H₁ antagonists have been disappointing in asthma therapy and this suggests that re-evaluation of the role of this class of drugs in the treatment of mild to moderate asthma is needed.

\[ N,N'-\text{Disubstituted piperazine, a moiety with potent antihistaminic properties, have been linked with theophylline at 7-position with the aim of discovering novel } N-7 \text{ substituted theophyllines exhibiting high potency as bronchodilators as well as antihistaminics.} \]

The piperazine [flufylline (Sgd 195/78)] (75) and piperidine (fluprophylline (Sgd 144/80)] (76) derivatives of theophylline, possess bronchodilator and hypotensive properties with low toxicity, respectively.
Review of Literature

Miscellaneous agents

Platelet activating factor antagonists

Platelet activating factor (PAF), an endogenous lipid mediator found in a variety of inflammatory cell types has been long implicated in the pathophysiological mechanisms of asthma.\textsuperscript{179} The action of PAF is indirect and involves a complex interaction with mediators from lipoxygenase pathway as well as various cytokines ultimately leading to airways epithelial damage and prolonged increase in airway hyperactivity.\textsuperscript{180} This has led to search for specific, potent PAF antagonists as potential therapeutic agents in asthma. A very large number of chemically diverse antagonists of PAF have been identified with many having progressed to clinical trials. Most of reported PAF antagonists arose from the ones-

Structurally related to PAF

These non constrained structural analogs of PAF were the first PAF antagonists reported, e.g., CV 6209 (77), SRI 63-441, BN 52111 (78).\textsuperscript{181}

Structurally unrelated to PAF

Reports of weak PAF antagonist activity in the calcium channel blockers, diltiazem and verapamil, resulted in study of dihydropyridine
derivatives for asthma. From these evolved PAF antagonist UK 74,505 (79), proceeding to clinical trials.\(^{182}\)

\[
\text{(79)}
\]

Screening of psychotropic triazolo-benzodiazepines as PAF antagonists resulted in a thieno-triazolodiazepines derivative, WEB 2086 (80), with no CNS activity but effective suppression of late phase inflammatory events in allergen challenges.\(^{183}\)

\[
\text{(80)}
\]

**Natural sources**
A unique group of natural PAF antagonists termed as ‘ginkgolides’, was isolated from *Ginkgo biloba* tree. Ginkgolide B, one of the most potent PAF antagonists of the series has undergone extensive pharmacological and clinical investigation.\(^{184}\) Extensive modification of structure of kadsurenone, from *Piper futokadsure*, yielded tetrahydrofuran derivative MK-287 (81) exhibiting effect in early or late phase response to antigen challenge.\(^{185}\) Although no PAF
antagonist has progressed to approved drug status, new chemical series with PAF antagonistic activity continue to be reported.

**Thromboxane A\(_2\) inhibitors**

There is considerable amount of evidence supporting TXA\(_2\) involvement in the asthmatic response. Inhibition of biological effects of TXA\(_2\) can be achieved with:

**TXA\(_2\) antagonists**

Seratrodast, a TXA\(_2\) antagonist was launched in Japan in 1995 for the treatment of asthma. Two other TXA\(_2\) antagonists, ramatroban (82) and domitroban calcium hydrate have reached phase III clinical trials.\(^{186,187}\)

**TXA\(_2\) synthase inhibitor**

Ozagrel hydrochloride, a TXA\(_2\) synthase inhibitor was launched in Japan in 1992 for the asthma therapy. Imitrodast sodium (83), a potent
TXA\textsubscript{2} synthase inhibitor has also been evaluated in asthma therapy.\textsuperscript{188}

\begin{center}
\includegraphics[width=0.4\textwidth]{TXA2_inhibitor}
\end{center}

**Tryptase inhibitors**
Tryptase, a serine protease, is released from activated mast cells and has been shown to cause bronchconstriction when inhaled. There is evidence of efficacy of antitryptase agent, APC-366 (84) in improving bronchial hyperresponsiveness.\textsuperscript{189,190} There may be a role for this form of therapy in the future but more needs to be known about its effectiveness *in vivo.*

\begin{center}
\includegraphics[width=0.4\textwidth]{tryptase_inhibitor}
\end{center}

**Interleukin-4 modulators (IL-4)**
Interleukin-4 is a B and T cell stimulatory factor synthesized by T-helper-2 (Th-2) cells, mast cells, basophils. It is a key mediator in IgE synthesis. A drug that interferes with the action and biosynthesis of interleukin-4 may be potentially useful for the treatment of asthma. Cromolyn and nedocronil, inhaled antiasthmatic drugs partially block
interleukin-4 induced IgE production. IFN-γ and non T-cell derived proteins such as vasoactive intestinal peptide, somatostatin and IL-8 are also blockers of interleukin-4 response. No small molecules have been shown to antagonize interleukin-4 receptors. Suplatast tosylate (IPD-1151T) (85) has been shown to inhibit allergen-mediated interleukin-4 production in phase III clinical studies.¹⁹¹

**Tachykinin antagonists**

Substance P and structurally related peptides neurokinin A (NKA) and neurokinin B (NKB) belong to a family of biologically active neurotransmitter peptides known as tachykinins. These are potent constrictors of airway smooth muscles, stimulate mucus secretions, activate several inflammatory and immune cells in respiratory tissue.

The biological effects of the tachykinins are mediated through distinct G protein-coupled receptors (NK1, NK2, and NK3), which are found in mammalian lung. Although all the endogenous tachykinins are known to interact with all three receptor subtypes, there is a rank order of potency with substance P having the highest affinity for the tachykinin NK1 receptor, Neurokinin A for the tachykinin NK2 receptor, and neurokinin B for the tachykinin NK3 receptor. Substance P has been shown to be involved in asthma, which is considered to be produced at least in part by the neurogenic inflammation mechanism.¹⁹²

There is mounting evidence that neurokinins play an important role in airway disease induction and progression via the activation of NK1 and NK2 receptors. Novel dipeptide neurokinin NK1 antagonist,
FK-888 (86) has been discovered and selected for further evaluation.\textsuperscript{193}

\begin{center}
\includegraphics[width=0.5\textwidth]{FK-888.png}
\end{center}

Saredutant (SR-48,968) (87) and GR-159,897 (88), is non peptide NK-2 receptor antagonist, reported to reduce bronchoconstriction of the airways, which may make them potentially useful for the treatment of asthma.\textsuperscript{194}

\begin{center}
\includegraphics[width=0.5\textwidth]{Saredutant.png}
\end{center}

\begin{center}
\includegraphics[width=0.5\textwidth]{GR-159897.png}
\end{center}

SCH 206272 (89) is a potent human
tachykinin NK1, NK2, and NK3 receptor antagonist that is orally active in a variety of animal models that involve tachykinin pathophysiology.\textsuperscript{195}

Osanetant (SR-142,801) \textsuperscript{90} is a neurokinin 3 receptor antagonist, synthesized by Schering–Plough laboratories and marketed by Sanofi-Synthelabo.\textsuperscript{196}

Anti-immunoglobulin E therapy
New treatments aimed at reducing immunoglobulin E (IgE) production in allergen induced asthma, or by reducing the clinical effects brought about by activation of IgE antibodies have been proposed. In animal models anti IgE antibodies reduce serum IgE, cytokine production and pulmonary eosinophil infiltration.\textsuperscript{197} Small molecules TEI-1338 \textsuperscript{91} and KSU-2178 \textsuperscript{92} have been shown to prevent allergen dependent production \textit{in vitro} and \textit{in vivo}. Specific
IgE binds to high affinity IgE receptor (FceRI) on mast cells and elicits cell degranulation and the release of a broad spectrum of inflammatory mediators. FceRI expression on mast cells is directly correlated with IgE concentrations.\textsuperscript{198}

Omalizumab is a humanized monoclonal anti-IgE antibody registered for the treatment of moderate allergic asthma. It does not bind to IgE already bound by FceRI on mast cells and basophils, thus not mimicking the effects of cross-linking by allergen. Treatment with omalizumab effectively reduced serum free IgE levels accompanied by a significant reduction in the number and frequency of exacerbations and improvements for total symptoms.\textsuperscript{199}

**Antioxidants**

Oxidative stress, defined as exposure to excessive oxidants and/or reduced antioxidant capacity, is directly or indirectly implicated in the pathogenesis of asthma. It is known to play a prominent role in the pathogenesis of various airway disorders such as adult respiratory distress syndrome, cystic fibrosis, idiopathic fibrosis, and chronic obstructive pulmonary disease. Oxidative stress occurs also in many
allergic and immunologic disorders including bronchial asthma. The two most widely used antioxidants are N-acetyl-L-cysteine (NAC) (93) and L-2-oxothiazolidine-4-carboxylic acid (OTC) (94), which show beneficial effects to reduce airway inflammation and hyper-responsiveness of asthma.200

Several studies have shown that reactive oxygen species (ROS) play a key role in initiation as well as amplification of inflammation in asthmatic airways. Excessive ROS production in asthma leads to alteration in key enzymatic as well as nonenzymatic antioxidants such as glutathione, vitamins C and E, beta-carotene, uric acid, thioredoxin, superoxide dismutases, catalase, and glutathione peroxidases leading to oxidant–antioxidant imbalance in airways.201 Oxidant–antioxidant imbalance leads to pathophysiological effects associated with asthma such as vascular permeability, mucus hypersecretion, smooth muscle contraction, and epithelial shedding.202,203

Modulation of these events by enhancing antioxidant levels offers unique opportunities for therapeutic prevention or inhibition of inflammation.204 Before this approach becomes reality, additional research is needed to better understand not only the molecular events involved in the pathogenesis of asthmatic inflammation, but also the complex actions and interplay between antioxidants and ROS in both the healthy and the asthmatic lung.205

**Anti-TNF-α Therapy**

TNF-α is the most widely studied cytokine member of Tumour Necrosis Factor (TNF) super family. It is produced by several pro-
inflammatory cells (mainly macrophages, but also monocytes, dendritic cells, B-cells, CD4+ cells, neutrophils, mast cells and eosinophils) and structural cells (fibroblasts, epithelial cells and smooth muscle cells) known to be crucial in orchestrating and perpetuating inflammation in asthma, COPD, cystic fibrosis, acute respiratory distress syndrome and pulmonary fibrosis. The biological function of TNF-α can be achieved by the modulation of TNF-α receptors, inhibiting signal transduction or preventing cytokine gene transcription.206 The commercially available TNF-α blockers translated into clinical application include- infliximab (Remicade), etanercept (Enbrel) and adalimumab (Humira).

In summary, TNF-α is a potentially important cytokine in refractory asthma, and preliminary studies on small numbers of patients have demonstrated an improvement in lung function, airway hyperresponsiveness, asthma quality-of-life and exacerbation rate following treatment with anti-TNF-α therapy.207

**XANTHINE DERIVATIVES**

One of the earliest report on the efficacy of methylxanthines in asthma was published in the Edinburgh Medical journal in 1859 where, Henry Hyde Salter, himself an asthmatic, described his experience that one of the commonest and best reputed remedies of asthma is strong coffee208,209 and theophylline was isolated in 1888 by Kossel.210 The plants containing methylxanthines were discovered throughout the world and beverages were prepared from these plants. The basis for the popularity of all the methylxanthine containing beverages has been the ancient belief that these beverages had stimulant and antisoporific actions,211 which elevated mood, decreased fatigue, increased capacity for work and helped people to be awake for prayers all through the night.212

At least half of the population of the world consumes tea prepared from the leaves of *Thea sinensis* (L: camellia, the link), a
bush belongs to family Ternstroemiaceae, native to southern China and now extensively cultivated in India, Sri Lanka, Japan and other countries. Tea contains caffeine as a major component (1-5%) and small proportions of theophylline and theobromine. From the seeds of *Theobroma cacao* (Fam. Sterculiaceae), cocoa and chocolate are obtained which contain theobromine as the major component and small amounts of caffeine and different volatile components responsible for aroma.\textsuperscript{213} Cocoa has nutrient, stimulant and diuretic properties. Coffee, the most important source of caffeine in the American diet, is extracted from the fruits of *Coffea arabica* (Fam. Rubiaceae) and other related species. It contains caffeine (1-1.3%), tannins, caffeotannic acid, fats, sugars etc. Kola seeds (gooroo nuts) (cocoa, cola seed, kolanut) are obtained from various species of cola tree (e.g. *Cola acuminata*, *Cola nitida*) found in West Africa, West Indies, Brazil and Java. Kola seeds contain caffeine (1-2.5%) and a little theobromine. Hence the cola flavoured drinks contain considerable amounts of caffeine.\textsuperscript{212}

The naturally occurring methylxanthines namely caffeine (95), theobromine (96), and theophylline (97) belongs to the category of

![Purine and Xanthine structures](image)

the purine alkaloids and share in common several pharmacological actions of therapeutic interest.\textsuperscript{214,215} They stimulate central nervous system...
system and cardiac muscle, relax various smooth muscles, notably bronchial muscle and act on kidney to produce diuresis. Caffeine stimulates central nervous system and has a weak diuretic action, whereas theobromine is a weak central nervous system stimulant but has powerful diuretic action.\textsuperscript{216,217} Theophylline has more powerful diuretic action than caffeine. It also relaxes involuntary muscles more effectively than either theobromine or caffeine. All methylxanthines are related to theophylline, the prototype drug of this class used to manage asthma and apnea.

Theophylline (97), 1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione; has been considered to be the most effective non-corticosteroid prophylactic agent for the control of symptoms of chronic asthma. It is present in small amounts in tea and is produced by total synthesis. It was first isolated by Kossel\textsuperscript{210} from the leaves of tea and was identified and synthesized in 1895.

**Pharmacological actions**

Several pharmacological actions of theophylline are of therapeutic interest. It is the most effective methylated xanthine which causes smooth muscle relaxation in bronchi, especially in bronchospastic conditions.\textsuperscript{215} Theophylline is a potent central nervous system stimulant and produces potentially more dangerous actions than caffeine if used at higher therapeutic range.\textsuperscript{218-221} Theophylline has the capacity to decrease peripheral resistance and stimulate heart, to increase perfusion of most organs.\textsuperscript{222,223} Theophylline stimulates myocardium and produces modest decrease in peripheral resistance of vascular system and venous pressure and causes diuresis probably because of both renal vasodilation and direct effect on the tubules. These properties formerly were used in the treatment of congestive heart failure (CHF), angina pectoris and as diuretic. However, the use of more effective agents are now preferred.

When plasma theophylline levels exceed 40 \( \mu \text{g/ml} \), generalized convulsions\textsuperscript{219} and serious cardiac arrhythmias may
occur. The increased dose of theophylline may produce insomnia, anxiety, restlessness, nervousness, tremors and hyperesthesia. At therapeutic range and in overdose, theophylline can precipitate sinus tachycardia and supraventricular and ventricular premature contractions. Drug interactions of theophylline have also been observed with a number of drugs. Allopurinol, erythromycin, cimetidine, propranolol, methotrexate, oral contraceptives etc., precipitate toxicity of theophylline by decreasing the metabolism and renal clearance of theophylline, while tobacco, phenytoin, albuterol, barbiturates increase the renal clearance of theophylline possibly by increasing metabolism of theophylline.

Theophylline is rapidly, consistently and completely absorbed when given as solution, uncoated tablet and capsules. Food significantly affects the rate of absorption of theophylline whereas the extent of absorption is unaffected. Once it is absorbed, it rapidly distributes throughout extracellular and to a lesser extent, intracellular body water. It also crosses the placenta and passes in the milk freely. Theophylline is extensively metabolized by demethylation in the liver to uric acid derivatives; 1-methyluric acid, 1,3-dimethyluric acid, 3-methylxanthine and 3-methylxanthinic acid. The principal metabolites are excreted in the urine.

Theophylline is primarily a bronchodilator which may possess some degree of antiinflammatory activity. The use of theophylline has been limited by its potential for serious toxicity but has regained an important position in the treatment of asthma with the development of the knowledge about its antiinflammatory action.

Theophylline and theophylline containing preparations are mainly indicated to produce bronchodilation, to relax the smooth muscles of bronchi in the symptomatic treatment of mild to moderate or acute bronchial asthma, reversible bronchospasm associated with bronchitis, emphysema and other obstructive pulmonary diseases in children and adults. It improves pulmonary functions and
relieves shortness of breath, wheezing and dyspnea. Caffeine and theophylline may increase diaphragmatic contractility and reduce diaphragmatic fatigue\textsuperscript{247} in patients with chronic obstructive pulmonary diseases.\textsuperscript{248} These effects may cause an improvement in ventilatory function.\textsuperscript{249} Theophylline may be tried in chronic obstructive bronchitis which is not controlled by other therapies.\textsuperscript{250-252} Oral xanthines are recommended in patients with nocturnal symptoms.\textsuperscript{253-255}

The precise mechanism underlying xanthine-induced antiasthmatic effects is not clearly understood.\textsuperscript{215,249,256-259} One of the proposed mechanisms (Figure 6) is the inhibition of cyclic phosphodiesterase isoenzyme resulting in increased intracellular accumulation of cyclic adenosine monophosphate (cAMP),\textsuperscript{260-262} the hypothesis to explain the ability of theophylline to cause bronchodilation.\textsuperscript{263-265}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{phosphodiesterase.png}
\caption{Inhibition of phosphodiesterase by theophylline to cause bronchodilation}
\end{figure}
**Phosphodiesterase 4 inhibitors (PDE4)**

Many 7-alkylated derivatives of theophylline such as dyphylline (98), doxophylline (99), thio-analog of doxophylline (100), proxyphylline (101), acephylline (102) and etiophylline (103) have been synthesized and studied. Among these, dyphylline (98), was approved for the asthma therapy and has been marketed in U.S.

Cipamphylline (BRL 60063, 104) is the prototype of a series of potent PDE4 inhibitors reported from this class and has been synthesized by Smithkline Beecham.

The compounds VII294 A (105) and RPR 132703 (106), hybrid structures of xanthine system and rolipram have progressed into...
phase II clinical trials for asthma. LAS31025 (107) is a compound which has further advanced in phase III clinical trials.

Adenosine receptor modulators
Alkylxanthines constitute the best-known class of compounds characterised by adenosine receptor antagonists. They inhibit both forms of the extract

Adenosine receptor sites namely high affinity $A_1$, which inhibit adenylate cyclase and low affinity $A_2$, which is found in human lung mast and basophils and activate adenyl cyclase as shown in figure 7.2.
Interestingly arophylline (108), a xanthine derivative, developed by Almirall for oral asthma therapy\textsuperscript{97} is a weak but selective PDE4 inhibitor, but shows affinity for adenosine $A_1$ and $A_2$ receptors. It is 25-30 fold less emetic as compared to rolipram and also lacks central stimulant effects\textsuperscript{109} raising doubts regarding PDE4 inhibitory activity of xanthines as a sole criterion for antiasthmatic activity.

Bamifylline (109), has been reported to produce $A_1$ receptor antagonism and is approved for the treatment of respiratory diseases.\textsuperscript{19}

The ability of theophylline and its derivatives to block the adenosine receptors has attracted much attention.\textsuperscript{266-274} Theophylline, which has 9 $\mu$M affinity for the $A_{2B}$ receptors, displays no selectivity against the other adenosine receptor subtypes.

Further structural exploration of the xanthine scaffold by several research groups was made in an effort to increase the potency and
selectivity at adenosine receptors. This led to the discovery of 8-phenylxanthines as selective $A_{2B}$ adenosine receptor antagonists. 8-$(p$-Hydroxyphenyl)theophylline (110) and its propylated derivative 111 have emerged as highly potent antagonists of $A_1$- and $A_2$-adenosine receptors in earlier studies on 8-phenylxanthines$^{275}$ and were chosen as suitable lead compounds in an effort to develop potent and selective functionalized congeners as antagonists for adenosine receptors.

![Chemical structure of 8-phenylxanthine derivatives](image)

The carboxamide derivative 112 of compound 111 has high affinity and is 8-fold more potent at adenosine $A_1$ receptors than at $A_2$ receptors. SAR of 8-phenyl-1,3-di-(n-propyl)xanthine derivatives in binding to recombinant human $A_{2B}$ adenosine receptors and at other adenosine receptor subtypes were further explored and various amide derivatives of 8-[4-{(carboxymethyl)oxy}phenyl]-1,3-di-(n-propyl)xanthine (113) were synthesized.$^{276,277}$
Among these compounds, highly potent and selective A$_{2B}$ antagonists were $p$-aminoacetophenone (114) and $p$-cyanoanilide (MRS 1754, 115) derivatives. Compound 115 is the first selective A$_{2B}$ antagonist with the K$_i$ value of 1.9 nM at human A$_{2B}$ adenosine receptors and high selectivity versus the other human adenosine receptor subtypes.$^{276}$

![Chemical Structure of 115](image1.png)

To address the metabolic stability of compound 115 in human liver microsomal enzymes, Zablocki et al. synthesized compound (CVT-5440, 116) that contains a bioisostere of the metabolically labile amide group present in 115 and demonstrated good affinity for the A$_{2B}$ adenosine receptor (K$_i$ = 50 nM) and selectivity over the other adenosine receptors.$^{278}$

![Chemical Structure of 116](image2.png)

Improved *in vitro* metabolic stability was also observed but still has a very low systemic exposure in rats when dosed orally, presumably due to low solubility as compared to 115.

Water soluble adenosine antagonists (117, 118) were prepared by introducing polar substituents at *para*-position of 8-phenyl
theophyllines and it was observed that \( p \)-sulfonyl substituents reduce the potency of 8-phenyltheophylline, but are 2-5 fold more potent than theophylline at adenosine receptors.\(^{279}\) The water soluble 8-(\( p \)-sulfo-phenyl) (117) and 8-(\( p \)-carboxyphenyl)-1,3-dipropylxanthine (118) no longer exhibit marked selectivity but both compounds were much more potent as adenosine antagonists than theophylline.

\[
\begin{align*}
R_1 & \quad R_2 & \quad R_3 \\
(117) & \text{CH}_2\text{CH}_2\text{CH}_3 & \text{CH}_2\text{CH}_2\text{CH}_3 & \text{SO}_3\text{H} \\
(118) & \text{CH}_2\text{CH}_2\text{CH}_3 & \text{CH}_2\text{CH}_2\text{CH}_3 & \text{COOH}
\end{align*}
\]

Various 8-substituted cycloalkyl derivatives have been reported as potent adenosine A\(_1\) antagonists.\(^{280-282}\) The most striking examples are 8-cyclopentyl (119) and 8-cyclohexyl-1,3-dipropylxanthine (120), which were both very potent and 10-fold more selective for A\(_1\) receptors versus A\(_2\) adenosine receptors.\(^{283}\)

Recently, in a series of 8-(substituted-phenyl)xanthines (121), the effects of varying the positions of 8-phenyl substituents on affinity
Review of Literature

and selectivity at A₁ and A₂A adenosine receptor subtypes have been studied by Bansal et al. It was observed that substitution pattern on 8-phenyl group greatly affects the affinity and selectivity at adenosine receptors with A₂A tolerating bulkier substituents than did A₁ receptors.

Another xanthine derivative GW 328267X (122), a specific A₂A AR agonist, did not block allergen-induced early and late asthmatic responses or inflammation but was used as an inhalational treatment.

GlaxoSmithKline discontinued the clinical development of this A₂A AR
agonist because of its low therapeutic index. However another molecule of the same series, CGS 21680 (123) decreased airway inflammation in an allergic animal model of asthma and displayed 144-fold selectivity for $A_{2A}$ AR over $A_1$ AR.$^{125,286}$

Introduction of the (E)-3,4-dimethoxystyryl or (E)-3,4,5-trimethoxy styryl group (124) at 8-position of 1,3-dialkyl-7-methylxanthine was found to enhance $A_2$ antagonism.$^{287}$

![Structure of Compound 124](image)

A new series of $N$-3 substituted xanthine derivatives was synthesized and tested for affinity and apparent irreversible binding at the $A_1$ and $A_{2A}$ adenosine receptors. Compound 125 appears to be the most advantageous as an apparent irreversible ligand for $A_1$ adenosine receptors.$^{288}$

![Structure of Compound 125](image)

Some of the important new molecules obtained by substitution at various positions of xanthine scaffold to produce various selective adenosine modulators are summarized in table 3.
Table 3: Molecular structures and binding affinities of various xanthine based selective adenosine receptor modulators

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>AR Modulators</th>
<th>Structure</th>
<th>Kᵢ values for ARs (nM)</th>
<th>A₁</th>
<th>A₂A</th>
<th>A₂B</th>
<th>A₃</th>
</tr>
</thead>
<tbody>
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<td>A₁, antagonists</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>126</td>
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<td>Comp. No.</td>
<td>AR Modulators</td>
<td>Structure</td>
<td>K&lt;sub&gt;v&lt;/sub&gt; values for ARs (nM)</td>
<td></td>
<td></td>
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<tr>
<td>128</td>
<td>L-97-1&lt;sup&gt;290&lt;/sup&gt;</td>
<td><img src="image128.png" alt="Structure 128" /></td>
<td>A&lt;sub&gt;1&lt;/sub&gt; 580 &gt;10000 &gt;10000 -</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>A&lt;sub&gt;2A&lt;/sub&gt; agonists</td>
<td><img src="imageA2A.png" alt="Structure A2A agonists" /></td>
<td>- -</td>
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<tr>
<td>129</td>
<td>UK-371104&lt;sup&gt;291&lt;/sup&gt;</td>
<td><img src="image129.png" alt="Structure 129" /></td>
<td>- 65 -</td>
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</tbody>
</table>
### Compounds and AR Modulators

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Modulators</th>
<th>Structure</th>
<th>Kᵢ values for ARs (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>130</td>
<td>CVT-7124²⁹²</td>
<td><img src="image" alt="Structure 130" /></td>
<td>A₁ &gt;6000, A₂A &gt;5000, A₂B 6, A₃ &gt;9000</td>
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<tr>
<td>131</td>
<td>CVT-6694²⁹³</td>
<td><img src="image" alt="Structure 131" /></td>
<td>A₁ &gt;6000, A₂A &gt;5000, A₂B 7, A₃ &gt;9000</td>
</tr>
<tr>
<td>132</td>
<td>MRE-2029-F20²⁹⁴²⁹⁵</td>
<td><img src="image" alt="Structure 132" /></td>
<td>A₁ &gt;1000, A₂A &gt;1000, A₂B 5.5, A₃ &gt;1000</td>
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</tbody>
</table>

*Note: A₂B antagonists*
<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>AR Modulators</th>
<th>Structure</th>
<th>L2B'2A &amp; A3 antagonists</th>
<th>K&lt;sub&gt;i&lt;/sub&gt; values for ARs (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>133</td>
<td>PSB-10&lt;sup&gt;350&lt;/sup&gt;</td>
<td><img src="image1.png" alt="Structure 133" /></td>
<td><img src="image2.png" alt="Structure 134" /></td>
<td>1700 2700 1800 470 620 0.20</td>
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</tbody>
</table>
| 134      | KF-26777<sup>357</sup> | ![Structure 134](image2.png) |  | }
<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>AR Modulators</th>
<th>Structure</th>
<th>$K_i$ values for ARs (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>135</td>
<td>7-Benzyl-2-methyl-5-propyl-1H,7H-1,3a,5,7,8-pentaaza-cyclopenta[a]indene-4,6-dione</td>
<td><img src="image" alt="Structure" /></td>
<td>$&gt;1000$ $&gt;1000$ $&gt;1000$ $0.80$</td>
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<tr>
<td>136</td>
<td>OT-7999$^{299}$</td>
<td><img src="image" alt="Structure" /></td>
<td>$&gt;10000$ $&gt;10000$ $&gt;10000$ $0.95$</td>
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</tbody>
</table>
Conclusions
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 bronchodilatory and anti-inflammatory agents with improve therapeutic index. This precludes a rational approach for the discovery of new and more efficient therapeutic agents for the management of asthma. 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.

Xanthines are effective in the treatment of asthma, but their mechanism of action remains unclear. Pulmonary effects of xanthines, exhibiting a range of potencies as cyclic nucleotide phosphodiesterase (PDE) inhibitors and as adenosine antagonists, were investigated in anesthetized and ventilated guinea pigs. The bronchodilator effects of xanthines, determined from reversal of bronchoconstriction induced by aerosols of histamine and carbachol, correlated with their relative potencies as cyclic AMP-PDE inhibitors. The hypotensive effects of xanthines at bronchodilator doses were also consistent with PDE inhibition. Prophylactic effects of xanthines against bronchoconstriction induced by an aerosol of ovalbumin in sensitized guinea pigs, or by aerosols of leukotriene and platelet-activating factor (PAF) in normal guinea pigs, occurred by a mechanism unrelated to bronchodilation and could not be readily attributed to PDE inhibition or adenosine A₁/A₂ receptor antagonism. These results indicate that the bronchodilator, antiallergic and anti-inflammatory effects of xanthines occur through multiple molecular mechanisms of action, including at least one unknown mechanism. Xanthine molecule has been substituted at several positions to produce derivatives that quantitatively and qualitatively differ from theophylline. Furthermore, 8-phenyltheophylline derivatives produce
these prophylactic effects at a dose that does not produce the cardiovascular or emetic side effects associated with xanthines, thereby exhibiting unique characteristics of potential therapeutic importance.

The above survey of literature highlights the significance of substituting different positions of the xanthine nucleus to develop potent antiasthmatic drugs. These observations encouraged the present investigator to design and synthesize new more potential xanthine derivatives, which may address not only asthmatic bronchoconstriction but also underlying bronchial inflammation. A series of substitutions have been made by the investigator at 8-position of theophylline with the aim to get new 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.