INTRODUCTION

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. Despite advancements in the treatment, asthma is rising in prevalence, severity and mortality affecting approximately 10% of children and 5% of adults worldwide.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.7-13 With the understanding about the pathophysiology of asthma, the original belief that asthma is associated with isolated acute episodes of bronchospasm resulting from wide variations in resistance to flow in the airways has changed and it is now recognized as an inflammatory disorder.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,2 which exert many inflammatory effects on the airways.13 The features of the inflammatory process in asthma are complex, involving an interplay of events leading to hyperresponsiveness of the airways. Immunological and nonimmunological mechanisms leading to asthma are depicted in Figure 1.14 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 IgE5 resulting in the release of histamines and synthesis of
cysteinyl-leukotrienes (cys LTs). These acute phase mediators cause airflow obstruction by directly increasing airway tone. Mast cells also release proteases (e.g. tryptase, stromolysin and chymase) and many pro-inflammatory cytokines [e.g., tumor necrosis factor-alpha (TNF-α), granulocyte macrophage colony-stimulating factor (GM-CSF), interleukins IL-3-5, IL-13 and chemokines] which contribute to airway inflammation and airway hyperresponsiveness\(^5\)\(^{,\,14,\,15}\) (Figure 1). 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, cytokines and leukotrienes, which leads to bronchospasm, airway hyperresponsiveness, airway smooth muscle hypertrophy, denudation of basement membrane, mucus hypersecretion and

![Figure 1: Pathogenesis of asthma](image-url)
activation of sensory nerves, all of which contribute to the pathophysiology of asthma.\textsuperscript{16}

Depending upon the etiology asthma can be of four types. \textbf{Extrinsic} asthma is associated with specific allergic reactions due to allergens such as environmental pollutants, modern urban living, domestic pets, coloring and flavoring agents, chemical and physical stimuli and possibly with the production of precipitating antibodies.\textsuperscript{7} Avoidance of exposure to allergens and possibly, hyposensitisation are particularly relevant to this type of asthma, in addition to the other drug therapies. \textbf{Intrinsic} asthma is not attributable to any specific allergic reaction and avoidance and hyposensitisation have no place in the therapy of this type of asthma. \textbf{Exercise-induced} asthma occurs in some patients who develop wheeze that regularly follows within the few minutes of exercise and \textbf{asthma associated with chronic obstructive lung disease} is common in number of patients who exhibit considerable variation in airways resistance which leads to dyspnea.\textsuperscript{8}

\textbf{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 antiinflammatory 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 antiinflammatory agents in the management of asthma.

**ANTIASTHMATIC AGENTS**

The various classes of antiasthmatic agents are:

**Antiinflammatory agents**
- Corticosteroids
- Leukotriene synthesis (5-Lipoxygenase) inhibitors
- Leukotriene receptor antagonists
- Cromolyn sodium and other mediator release inhibitors
- Phosphodiesterase 4 inhibitors.

**Bronchodilators**
- $\beta_2$-Agonists
- Anticholinergic agents
- Antihistaminic agents

**New approaches**
- Platelet activating factor antagonists
- Thromboxane $A_2$ inhibitors
- Antitryptase therapy
- Interleukin-4 modulators
- Neurokinin antagonists
- Anti-immunoglobulin E therapy

**Xanthine derivatives**

Various types of antiasthmatic agents along with their mechanism and site of action are shown in Figure 214.
INTRODUCTION

Mast cells Bronchial smooth muscle cells
Phosphodiesterase Inducers β2-agonists cAMP
β-cAMP Xanthines
β2-agonists Anticholinergics
Xanthines Acetylcholine
β2-agonists Antihistaminics
Corticosteroids Leukotriene receptor
Cromoglycate Antagonists
Inflammatory mediators Bronchodilators

Figure 2: Various classes of antiasthmatic agents along with their mechanism and site of action

ANTIINFLAMMATORY AGENTS

Corticosteroids

Corticosteroids remain the mainstay in the management of all types of asthma as these are the most potent and effective antiinflammatory agents available so far. A detailed review on the use of corticosteroids for the treatment of asthma has been published recently by Gupta et al.14 These agents reduce morbidity during severe attacks, reduce inflammation and aid the restoration of pulmonary function. Mechanism-Corticosteroids interact with intracellular glucocorticoid receptors and thus inhibit the release of inflammatory mediators resulting in decrease in airway inflammation and bronchial hyperactivity with increased responsiveness to adrenergic agents.14,21

Shortly after their discovery corticosteroids became the cornerstone of asthma treatment. The antiinflammatory activity of hydrocortisone (1), cortisone (2) and corticosterone (3), isolated
from adrenal glands, was demonstrated way back in 1930’s and 1940’s.¹⁹

The major drawback of this therapy was systemic side effects of glucocorticoids, which include adrenocortical suppression, bone thinning, muscle wasting, thinning of skin, cataracts, decreased growth in children, facial rounding, fluid retention, decreased glucose tolerance, increased blood pressure and acne.²,²² It was established that the key structural features required for the antiinflammatory activity include the 3–keto group, double bond between 4,5–position and presence of 11–hydroxy, 17α–hydroxy and 21–hydroxy groups. Numbers of attempts were made to synthesize numerous analogs of cortisone (2) possessing antiinflammatory activity with improved therapeutic index and initial breakthrough came with the introduction of 1,2-double bond in A
ring of steroid nucleus giving prednisone (4) and prednisolone (5) with lower mineralocorticoid properties.\textsuperscript{14,19} Methylprednisolone\textsuperscript{23} (6) and triamcinolone\textsuperscript{24} (7) provided further separation of the antiinflammatory and mineralocorticoid properties. Betamethasone (8), 9α-flouro, 16β-methyl analog and dexamethasone (9), 9α-flouro, 16α-methyl analogs were developed as potent anti-inflammatory agents devoid of mineralocorticoid properties.\textsuperscript{25,26}

Still the separation of antiinflammatory activity from other side effects was not completely achieved and the use of topically active steroids, betamethasone valerate (10) and beclomethasone dipropionate (11),\textsuperscript{27,28} through inhalation eventually became a breakthrough therapy for asthma.

The newer highly potent glucocorticoids like budesonide (12)\textsuperscript{14,29,30} and fluticasone propionate (13)\textsuperscript{29,31,32} have been
developed with advantage of lower systemic side effects by having better ratio of topical to systemic potency in the treatment of asthma.

The clinical effectiveness of inhaled corticosteroids and increased awareness of inflammatory component of asthma\textsuperscript{33} has made them the first line therapy for asthma.\textsuperscript{34}

**Leukotriene synthesis inhibitors**

Inhibition of leukotriene biosynthesis has been extensively studied as a potential area for the development of novel therapies for asthma.\textsuperscript{35,36}

**Mechanism**—The key enzyme in this process, 5-lipoxygenase, transforms arachidonic acid in a two step process to first 5-hydroperoxyeicosatetraenoic acid (5-HPETE), and thence through a dehydration step to leukotriene A\textsubscript{4} (LTA\textsubscript{4}), an unstable intermediate converted via specific enzymes to LTB\textsubscript{4}, LTC\textsubscript{4}, LTD\textsubscript{4}, LTE\textsubscript{4}, mediators in asthma.

Many compounds have been identified which inhibit the key enzyme 5-lipoxygenase. Four distinct classes of compounds identified are:

**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 nonspecificity. Examples of this group include, phenothiazine analogs L-615919 (14)$^{36}$ and L-651392 (15)$^{37}$.

**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 (16), an $N$-hydroxy urea was introduced in 1996, as first agent of this new class of antileukotriene drugs$^{38}$ for the treatment of chronic asthma. It exhibits some degree of bronchodilatory, antiinflammatory, steroid sparing effects$^{39}$ and variety of adverse effects.$^{40}$ A number of more potent analogs of zileuton are in clinical trial stages.$^{41,42}$

**Competitive reversible inhibitors of 5-lipoxygenase**

The multiple toxicities and difficulties encountered in developing redox inhibitors of 5-lipoxygenase has led to research in this area of competitive non redox inhibitors of 5-lipoxygenase.

Compounds of the series of methoxyalkylthiazoles$^{43}$ and methoxytetrahydropyrans$^{44}$ were found to be potent in this class.$^{45}$
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.46

**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.36

![Chemical structure of MK-0591](image)

MK-886, an indole inhibitor47,48 was found to inhibit leukotriene biosynthesis incompletely49 by blocking this transfer. Its significantly potent analog MK-0591 (17),50,51 was found to be clinically effective, but its development was suspended in favor of LTD₄ receptor antagonist montelukast.52

Another quinoline compound, BAY-X-1005, is in clinical trials as an antiasthmatic.53 It is apparent from clinical trials of MK-0591 (17) and BAYx 1005 that leukotriene biosynthesis inhibition could provide useful therapy in asthma but no clear advantage of 5-lipoxygenase inhibitors has been demonstrated relative to LTD₄ antagonists.36

**Leukotriene receptor antagonists**

Leukotriene receptor antagonists is the first new class of drugs developed for asthma therapy in twenty years.54 The two types of leukotriene receptors, LTB₄ and cysteinyl LT₁ receptors are known to mediate asthma pathophysiology.55
Only preliminary reports on clinical evaluation of LTB₄ antagonists has appeared showing modulation of inflammation amplification phenomenon of these, while numerous clinical studies have convincingly established the therapeutic potential of cysteinyl leukotriene antagonists in asthma.⁵⁶,⁵⁷

Mechanism- Leukotriene receptor antagonists function by blocking the interaction of cysteinyl leukotrienes with cysteinyl LT₁ receptors, thereby blocking end organ response of airway obstruction.²

Various classes of cysteinyl leukotriene antagonists have been described as below:

*Hydroxyacetophenone antagonists*

The first peptidyl leukotriene antagonists FPL-55712 (18) predated the elucidation of the structure of leukotriene. The early peptidyl leukotriene antagonists were structural analogs of 18 containing a common hydroxyacetophenone moiety linked through flexible spacer to an acidic group.⁵⁸ The best studied member of
this class of antagonists is tomelukast (19)\textsuperscript{59,60} with additional activity as a thromboxane antagonists and PDE inhibitor\textsuperscript{51} whose development was discontinued due to toxic reactions.\textsuperscript{62}

**LTD\textsubscript{4} analogs**

Several antagonists, analogs of LTD\textsubscript{4}, were designed without the information of natural agonist/antagonist. The two antagonists, poblukast (20)\textsuperscript{63} and sulukast (21) 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{64}

**Quinoline antagonists**

In mid 1980's, REV-5901 (22) was discovered as FLAP inhibitor with a weak LTD\textsubscript{4} receptor antagonistic activity\textsuperscript{65} leading
to the synthesis of many other quinoline containing compounds such as ritolukast (23) and RG 12525 advancing to clinical trials. MK-571 (24) 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 (25), montelukast, providing the most potent and long lasting blockade of LTD₄ induced bronchoconstriction. Its use in chronic asthmatics has led to a significant improvement in lung function, quality of life and reduced β-agonist use.

**Miscellaneous**

Pranlukast (26) was first LTD₄ antagonist to be marketed. It was shown to attenuate bronchoconstrictor response to asthma.
challenges\textsuperscript{73} and also to reduce $\beta$-agonist usage.\textsuperscript{74} Zafirlukast (27)\textsuperscript{75,76} has the structural components of FPL-55712 (18) and LTD$_4$. The [[[cyclopentyloxy]carboxyl]amino]indole was replacement for the hydroxyacetophenone portion of FPL-55712 and $N$-(4-methylbenzoyl)arylsulfonamide served as the surrogate for triene system of LTD$_4$. It has provided greatest benefit in patients with more severe asthma along with significant inhibition of antigen, LTD$_4$ and exercise induced bronchoconstriction following both oral and aerosol administration.\textsuperscript{77-79}

**Cromolyn sodium and other mediator release inhibitors**

Cromolyn was synthesized in 1965 as part of an attempt to improve the bronchodilatory properties of khellin (28), a chromone
(benzopyrone), derived from plant *Ammi visnaga* (fam. Umbelliferae), used by ancient Egyptians as an antispasmodic.\(^{80}\)

![Chemical structure of sodium cromoglycate](image)

Cromolyn sodium (29) was chosen for development as an antiasthmatic from a series of bischromone dicarboxylate modification of khellin.\(^{81}\) A second generation, pyranoquinoline derivative, nedocromil sodium (30) was developed in an effort to overcome some limitations of cromolyn sodium.\(^{82}\)

**Mechanism-** These are mast cell stabilizers\(^{83,84}\) and prevent antigen induced release of histamine and other mediators from sensitized mast cells.\(^{85}\) These 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,\(^{86}\) tazanolast,\(^{87}\) repirinast,\(^{88}\) amoxanox\(^{89}\) and pemilorast potassium.\(^{90}\) All of these act through mast cell stabilization like sodium cromoglycate.

**Phosphodiesterase 4 inhibitors**

In the last few years selective phosphodiesterase inhibitors have received considerable attention as molecular targets for the development of antiasthmatic agents.\(^{91,92}\)
**Mechanism**—These inhibitors inhibit the hydrolysis of 3'-phosphodiester bond of cyclic messengers cAMP to their inactive 5'-nucleotide forms. cAMP is a ubiquitous intracellular second messenger playing a prominent role in bronchodilation and inhibition of release of inflammatory mediators.\(^{92-95}\)

Phosphodiesterases 3, 4 and 5 are particularly important with respect to targets for the development of novel antiasthmatic agents.\(^{96}\) Much of the emphasis on selective PDE inhibitors for asthma therapy has been focused on selective PDE 4 or mixed PDE 3/4 inhibitors. Structurally, PDE 4 inhibitors are classified as catechol ethers, quinazolinediones and xanthines and related compounds\(^{97}\).

**Catechol ethers**

Rolipram\(^{98}\) (31), originally developed as an antidepressant, is the most studied of all selective PDE 4 inhibitors. Structure-activity relationship studies of a series of rolipram analogs as PDE 4 inhibitors have been published.\(^{99,100}\)

![Catechol Ether](image)

In addition to having desirable inhibitory effects on inflammation and smooth muscle contraction, rolipram shows undesirable effects of nausea and vomiting. The side effects displayed by this compound are related with its ability to bind with nanomolar affinity to a binding site, which for a long time was considered distinct from catalytic site of PDE 4.\(^{97}\) Rolipram has frequently been used as a basis for design of new and subtype specific PDE4 inhibitors. These agents are characterized by the presence of substructure

16
in which \( R_1 \) is generally a methyl and \( R_2 \) a cyclopentyl group, alternatively highly lipophilic groups are present at \( R_2 \).

Ariflo™ (33)\(^{101} \) developed by Smithkline Beecham, is presently undergoing phase II and III clinical trials with respect to paediatric patients with asthma. It exhibits decreased side effects as compared to rolipram.

**Quinazolinediones**

This class comprises of structural analogs of nitraquazone (34). Challenge in this class of inhibitors is to have selective PDE 4 inhibitory activity in nanomolar potency with strongly reduced affinity for high affinity rolipram binding site. Research has led to the development of RS 14203 (35), a quinoline derivative and one of the most potent PDE4 inhibitor.\(^{102} \) Naftiridinones result from structural modification of 34.\(^{103} \) Attempts to reduce emetic side effects of PDE 4 inhibitors have been made using many heterocyclic ring systems like fused 3[2H]-4-pyridazinones\(^{104} \) and
ni}ocinamide ethers etc. Bi and tricyclic nitrogen bridge head compounds with pyrimidine-4(3H)-one ring have also been found to be potent bronchodilators.

**Xanthines and related compounds**

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

Some interesting hybrid molecules combining the xanthine system with other selective PDE 4 inhibitors such as rolipram and piclamilast has been reported as quite potent selective PDE 4 inhibitors with IC$_{50}$ values in the range of 200-300 nM. Of these

V11294 A (36)$^{107}$ and RPR 132703 (37)$^{108}$ have progressed into phase II of clinical trials for asthma.

**BRONCHODILATORS**

**β$_2$-Adrenoceptor agonists**

β$_2$-Adrenergic agonists is the most prescribed class of drugs for asthma treatment. They are preferred both for rapid relief of symptoms and for the level of bronchodilation achieved in patients with bronchial asthma.$^{109}$
Mechanism- These drugs produce their effects through stimulation of specific \( \beta_2 \)-adrenergic receptors located in plasma membrane resulting in alterations in adenylyl cyclase and elevations in intracellular cyclic adenosine monophosphate (cAMP). cAMP is responsible for the physiologic response of bronchodilation.\(^{110}\)

Inhalation of \( \beta \)-adrenergic agonists is the preferred therapy of bronchoconstriction.\(^{111}\) The history of development started with epinephrine\(^{112}\) (38) (\( \alpha \)- and \( \beta \)-receptor agonist) to isoproterenol (39) (\( \beta \)-agonist) to almost pure \( \beta_2 \)-adrenoceptor agonists, salbutamol (40) and fenoterol (41), the currently preferred agents.\(^{19}\)

Since the discovery of naturally occurring epinephrine, the search for improved bronchodilator agents has centered on compounds possessing \( \beta_2 \) selective agonist activity due to cardiac stimulating potential of \( \beta_1 \) receptors.\(^{113}\) Salbutamol (40) inhalation was found to possess several times greater bronchodilatory activity with weaker cardiovascular effects than isoproterenol.\(^{114}\)
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 (42)\textsuperscript{115} and carbuterol (43).\textsuperscript{116}

Recent developments with respect to \(\beta_2\)-adrenoceptor agonists has been focused on increased duration of action leading to less frequent administration of bronchodilators. The two long acting medications are formoterol (44) and salmeterol (45), with enhanced duration of action due to increased size of nitrogen substituent.\textsuperscript{117,118}
Development of $\beta_2$-adrenoceptor agonists as antiasthmatics has been reviewed extensively by Jindal et al.\textsuperscript{119}

**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.\textsuperscript{120}

*Mechanism*- These agents competitively inhibit post synaptic muscarinic receptors\textsuperscript{8} and block the actions of acetylcholine at vagal nerve endings leading to bronchodilation and decrease in airway resistance.\textsuperscript{2}

Atropine (46) is the prototype anticholinergic but is rarely used due to the systemic side effects of mydriasis, tachycardia and decrease in gastric and salivary secretions.\textsuperscript{121} Interest in anticholinergics was rekindled by development of ipratropium bromide (47), a quaternary salt derivative of atropine with limited side effects due to less lipid solubility\textsuperscript{122,123} and a new long acting anticholinergic agent tiotropium bromide.\textsuperscript{124} Several additional compounds with anticholinergic properties have been studied clinically but were eventually discontinued.\textsuperscript{125}

Revatropate (48) is a new antimuscarinic agent with marked selectivity for $M_1$ and $M_3$ receptor subtypes.\textsuperscript{126} These
anticholinergic agents are less effective as bronchodilators than \( \beta_2 \)-agonists but are useful in patients intolerant to side effects of \( \beta_2 \)-agonists.\(^5\) 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.\(^1\)\(^9\)

**Antihistaminic agents**

Histamine is produced from mast cells in asthmatic airways\(^1\)\(^2\)\(^7\) and exerts many effects that are relevant to the pathophysiological mechanisms of asthma, including bronchoconstriction,\(^1\)\(^2\)\(^6\) plasma exudation and mucus secretion.\(^1\)\(^2\)\(^9\)

**Mechanism-** Histamine 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.\(^1\)\(^3\)\(^0\)

\( H_1 \) Antihistamincs can be classified as:

**First generation antihistaminics**

This group includes various compounds of arylether,\(^1\)\(^3\)\(^1\) ethylenediamine,\(^1\)\(^3\)\(^2\) aminoethylether\(^1\)\(^3\)\(^3\) and aminopropylether classes.\(^1\)\(^3\)\(^4\) Chlorpheniramine (49) 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.\textsuperscript{135} These first generation compounds penetrate the blood brain barrier and also possess anticholinergic properties leading to various side effects.\textsuperscript{136}

**Second generation antihistaminics**

The ideal antihistamine should have a rapid onset of action, a long duration of action, be orally active and free from side effects. This led to the development of second generation non-sedating H\textsubscript{1} antagonists such as terfenadine (50)\textsuperscript{137} and astemizole.\textsuperscript{138} Both terfenadine and astemizole cause inhibition of immediate response to allergen 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\textsuperscript{139} but is far less effective than other antiasthma therapies\textsuperscript{140} and thus is not recommended for routine management of asthma. Some new antihistamines, cetirizine (51) and azilastine...
INTRODUCTION

have been shown to have beneficial effects in asthma, which may be unrelated to its H₁ antagonistic effects.\textsuperscript{141}

![Chemical Structure](image)

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.

NEW APPROACHES

**Platelet activating factor antagonists**

Plate 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{142}

Mechanism- The action of PAF is indirect and involves a complex interaction with mediators from lipoxigenase pathway as well as various cytokines ultimately leading to airways epithelial damage and prolonged increase in airway hyperactivity.\textsuperscript{143}

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 –
Chemical manipulation of core PAF structure.

These nonconstrained structural analogs of PAF were the first PAF antagonists reported, e.g., CV 6209 (52), SRI 63-441, BN 52111 (53).

Novel synthetic compounds structurally unrelated to PAF

Reports of weak PAF antagonist activity in the calcium channel blockers, diltiazem and verapamil, resulted also in study of dihydropyridine derivatives. From these evolved PAF antagonist UK 74,505 (54), proceeding to clinical trials.
INTRODUCTION

Screening of psychotropic triazolobenzodiazepines as PAF antagonists resulted in a thienotriazolodiazepines derivative WEB 2086\textsuperscript{146} (55) with no CNS activity but effective in suppressing late phase inflammatory events in allergen challenges.

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.\textsuperscript{147}

Extensive modification of structure of kadsurenone, from *Piper futokadsure*, yielded tetrahydrofuran derivative MK-287 (56)

\begin{center}
\begin{tabular}{c}
\includegraphics[width=0.5\textwidth]{55.png}
\end{tabular}
\end{center}

exhibiting effect in early or late phase response to antigen challenge.\textsuperscript{148}

Although no PAF antagonist has progressed to approved drug status, new chemical series with PAF antagonistic activity continue to be reported.
**Thromboxane A₂ inhibitors**

There is considerable amount of evidence supporting TXA₂ involvement in the asthmatic response. Inhibition of biological effects of TXA₂ can be achieved with –

**TXA₂ Antagonists**

Seratrodast, a TXA₂ antagonist was launched in Japan in 1995 for the treatment of asthma. Two other TXA₂ antagonists, ramatroban (57)¹⁴⁹ and domitroban¹⁵⁰ calcium hydrate have reached phase III clinical trials.

**TXA₂ Synthase inhibitor**

Ozagrel hydrochloride, a TXA₂ synthase inhibitor was launched in Japan in 1992 for the asthma therapy¹⁵¹. Imitrodast sodium¹⁵² (58), a potent TXA₂ synthase inhibitor has also been evaluated in asthma therapy.

**Antitryptase therapy (Tryptase inhibitor)**

Tryptase 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 (59) in improving bronchial hyperresponsiveness.\textsuperscript{153}

There may be a role for this form of therapy in the future but more needs to be known about its effectiveness \textit{in vivo}.

\textbf{Interleukin-4 modulators}

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-\(\gamma\) 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 (60) has been shown to inhibit allergen-mediated interleukin-4 production in phase III clinical studies.\(^{154}\)

Interleukin-13 and interleukin-4 have also exhibited role in the pathogenesis of asthma but need to be further studied.

**Neurokinin antagonists**

Substance P and structurally related peptides neurokinin A and neurokinin B belong to a family of biologically active peptides known as tachykinins. 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.\(^{155}\) A novel dipeptide neurokinin NK\(_1\) antagonist, FK-888 (61) has been discovered and selected for further evaluation.\(^{156}\)

Many more tachykinin receptor antagonists are available but need further evaluation to determine their therapeutic effect.

**Anti-immunoglobulin E therapies**

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. Studies
to date show that this treatment may be useful in atopic asthma and clinical trials exhibit that they reduce early and late phase bronchoconstriction responses. Small molecules TEI-1338 (62) and KSU-2178 (63) have been shown to prevent allergen dependent production \textit{in vitro} and \textit{in vivo}.

Much work still needs to be done on this novel approach to modulate the allergic responses.

Since the current research project involves synthesis of newer xanthine derivatives, therefore literature pertaining to xanthines has been extensively reviewed.
INTRODUCTION

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, describe his experience that one of the commonest and best reputed remedies of asthma is strong coffee\(^{158,159}\) and theophylline was isolated in 1888 by Kossel.\(^{160}\) 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,\(^{2}\) which elevated mood, decreased fatigue, increased capacity for work and helped people to be awake for prayers all through the night.\(^{161}\)

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.\(^{162}\) Cocoa has nutrient, stimulant and diuretic properties. Coffee, the most important source of caffeine in the American diet, is extracted from the fruits of *Coffee arabica* (Fam. Rubiaceae) and other related species. It contains caffeine (1-1.3%), tannins, caffeotannic acid, fats, sugars etc. Kola seeds (gooroo nuts) (colacola 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
INTRODUCTION

Caffeine (1-2.5%) and a little theobromine. Hence the cola flavoured drinks contain considerable amounts of caffeine.\textsuperscript{161}

The well known examples of purine alkaloids are caffeine (64), theobromine (65), and theophylline (66) which are methylated xanthines and share in common several pharmacological actions of therapeutic interest.\textsuperscript{163,164} They stimulate central nervous 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{165,166} 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 (66), 1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione; 1,3-dimethylxanthine, has been considered to be the most effective noncorticosteroid 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{160} 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{164} Theophylline is a potent central nervous system stimulant and produces potentially more dangerous actions than caffeine if used at higher therapeutic range.\textsuperscript{167-170} Theophylline has the capacity to decrease peripheral resistance and stimulate heart,\textsuperscript{171,172} to increase perfusion of most organs. 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 $\mu$g/ml, generalized convulsions\textsuperscript{168} 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,\textsuperscript{173-176} theophylline can precipitate sinus tachycardia and supraventricular and ventricular premature contractions.\textsuperscript{177} Overdose also cause multifocal atrial tachycardia.\textsuperscript{178} 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.\textsuperscript{6}

Theophylline (66) is rapidly, consistently and completely absorbed when given as solution, uncoated tablet and capsules.\textsuperscript{179,180} Food significantly affects the rate of absorption of theophylline whereas the extent of absorption is unaffected.\textsuperscript{181} Once it is absorbed, it rapidly distributes\textsuperscript{182-184} 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\textsuperscript{185,186} to uric acid derivatives; 1-methyluric acid, 1,3-dimethyluric acid, 3-methylxanthine and 3-methylxanthinic acid.\textsuperscript{187} The principal metabolites are excreted in the urine.\textsuperscript{188-190} 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\textsuperscript{191} and other obstructive pulmonary diseases in children and adults.\textsuperscript{192-194} It improves pulmonary functions and relieves shortness of breath, wheezing and dyspnea. Caffeine and theophylline may increase diaphragmatic contractility and reduce diaphragmatic fatigue\textsuperscript{195} in patients with chronic obstructive pulmonary diseases.\textsuperscript{196} These effects may cause an improvement in ventilatory function.\textsuperscript{197} Theophylline may be tried in chronic obstructive bronchitis which is not controlled by other therapies.\textsuperscript{198-200} Oral xanthines are recommended in patients with nocturnal symptoms.\textsuperscript{201-203}
MECHANISM OF ACTION

The precise mechanism underlying xanthine-induced antiasthmatic effects is not clearly understood.\textsuperscript{164,197,204-207} One of the proposed mechanisms is the inhibition of cyclic phosphodiesterase isoenzyme resulting in increased intracellular accumulation of cyclic adenosine monophosphate (cAMP).\textsuperscript{208-210}

\begin{center}
\begin{tikzpicture}
  \node (ATP) {ATP};
  \node (cAMP) [right of=ATP] {cAMP};
  \node (Phosphodiesterase) [right of=cAMP] {Phosphodiesterase};
  \node (5-AMP) [right of=Phosphodiesterase] {5'-AMP};
  \draw[->] (ATP) -- (cAMP);
  \draw[->] (cAMP) -- (Phosphodiesterase);
  \draw[->] (Phosphodiesterase) -- (5-AMP);
  \node at (cAMP) [above] {Bronchodilation};
  \node at (cAMP) [below] {Vasodilation};
  \node at (cAMP) [left] {Inhibition of mediator release};
  \node at (5-AMP) {Theophylline inhibits};
\end{tikzpicture}
\end{center}

\textbf{Figure 3: Inhibition of phosphodiesterase by theophylline to cause bronchodilation.}

the hypothesis to explain the ability of theophylline to cause bronchodilation\textsuperscript{211-213} (Figure 3). Theophylline is a poor phosphodiesterase inhibitor to cause significant changes in plasma cAMP concentrations. The ability of theophylline to block the adenosine receptors has attracted much attention.\textsuperscript{160,214-218} Both caffeine and theophylline are best known competitive antagonists of adenosine receptors, suggesting that adenosine might be playing significant role in the pathophysiology of human asthma\textsuperscript{219}. Adenosine receptors can be divided into four types, termed $A_1$, $A_{2A}$, $A_{2B}$ and
INTRODUCTION

A3, A1 and A2A adenosine receptors are stimulated by low adenosine concentration, while higher adenosine levels are required for activation of A2B and A3 receptors. Selective A2B receptor antagonists are of interest for asthma and chronic obstructive pulmonary disease.

Figure 4: Role of adenosine in pathophysiology of asthma.

Methylxanthines inhibit both forms of the extracellular adenosine receptor sites namely high affinity A1, which inhibit adenyl cyclase and low affinity A2, which is found in human lung mast cells and basophils, activate adenyl cyclase.160,214,215,219,220 (Figure 4). The bronchodilator effects of theophylline may not be related to the adenosine receptor antagonism because it has been found that enrofylline, which is 4-5 time more potent as bronchodilator than theophylline both in vitro and in vivo221-228 is devoid of adenosine antagonism.221,224,225,230 Therefore, antagonism of theophylline on the adenosine receptor may not be the sole mechanism of action of theophylline160,226 as an antiasthmatic agent.

The dual bronchodilatory and anti-inflammatory potential of xanthines place this class of drugs in a better position in the
management of asthma. Theophylline (66) has been widely used in the therapy\textsuperscript{231,232} of bronchospastic diseases including acute asthma attacks, chronic bronchitis and emphysema,\textsuperscript{233} but several drawbacks\textsuperscript{234} such as narrow margin of safety,\textsuperscript{235,236} powerful effects in cardiovascular system,\textsuperscript{237} central nervous system stimulation,\textsuperscript{18} effect on the gastrointestinal tract\textsuperscript{197} limits their usefulness. Therefore much efforts have been made with the aim of designing new more potent and selective theophylline derivatives with larger margin of safety, longer duration of action and lacking undesirable effects. Xanthine molecule has been substituted at several positions to produce derivatives that quantitatively and qualitatively differ from theophylline (66).\textsuperscript{238-242}

**SUBSTITUTED XANTHININES**

7-Substituted derivatives

A series of substitutions made at position-7 of the theophylline (66) with hydroalkyl-, haloalkyl- or aminoalkyl- groups have been reported in the literature and compounds were evaluated for their antiasthmatic activity by using Herxheimer’s anaphylactic microshock and Fribeln methods.\textsuperscript{243} One of these compounds, 7-(3-hydroxypropyl)theophylline (67) showed the true synergism.

\[ \text{CH}_3 \text{CH}_2 \text{CH}_2 \text{OH} \]

\[ \text{(67)} \]

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

antihistaminics. The compound 68 (RS 49014 or LN 2974), 3,7-
dihydro-1,3-dimethyl-7-[3-[4-[3-(phenylthio)propyl]piperazin-1-
yl]-2-hydroxypropyl]-1H-purine-2,6-dione, was selected for clinical
trials on the basis of its potent pharmacological activity.244

Some more piperazine and piperidine derivatives of theo-
phylline, flufylline (Sgd 19578) (69) and fluprophylline (Sgd 14480)

(70) possess bronchodilator and hypotensive properties with low
toxicity.245

A number of 7-alkylated derivatives of theophylline such as
dyphylline (71),246,247 doxophylline (72),248 thioanalogue of
doxophylline (73),249 proxphylline (74),250 bamiphylline (75),251
acephylline (76)222,253 and etophylline (77)254 were prepared. These
derivatives are generally less active than theophylline, but are
stable in solution and in vivo but possess same side effects as of
theophylline. Compound 73, 7-(1,3-dithiolan-2-ylmethyl)theophylline,
exhibited an antihistaminic, anti-bronchospastic action in the guinea-
pig tracheal test and increased production of tracheo-bronchial mucus in the rabbit.

Synthesis and bronchodilator activities of various 7-[(2-naphthyloxy)-
alkyl]theophylline and 7-[(4-coumaryloxy)alkyl]theophylline derivatives have also been described. \(^\text{255}\) (4-Coumaryloxy)alkyl
derivative 78 was more potent than naphthyloxy analogue 79.
Benzhydryl moiety, an essential structural component of many drugs, was joined by two or three-membered amino alkyl group with theophylline. Of the series, compound 80 showed good muscle relaxant activity.\textsuperscript{256}

Numerous slow release preparations of theophylline have been developed to eliminate the undesired effects\textsuperscript{257-259} and to increase the plasma half life. Some 7-acyl theophylline derivatives were prepared and dissolution rates were determined.\textsuperscript{260} One of these derivatives, 7,7'-succinylditheophylline (81) afforded slow release or controlled release prodrug of theophylline.

Another 7-substituted xanthine derivative 82 with 3-\textit{n}-propyl group has been shown to possess more antiallergic/bronchodilator activity as compared to theophylline indicating the significance of
3-n-propyl group in xanthine skeleton for bronchodilatory activity.\textsuperscript{261}

\begin{center}
\includegraphics[width=0.5\textwidth]{structure_82.png}
\end{center}

Lots of research has been carried out to synthesize selective bronchodilators\textsuperscript{9,222,262,263} and in the process a novel series of 1-, 3- and 7-trialkylxanthines was developed.\textsuperscript{264} Structure-activity relationship studies revealed that the substitution at 1-position is more important than the 3-position for bronchoselectivity, while the 3-substitution increased tracheal smooth muscle relaxant action. The substitution at 1- and 7-positions was significant for tracheal relaxation and decrease heart stimulation.

In another series of 3-n-propylxanthines substituted at 1- or 7-position, 1-(2'-ethoxyethyl)-3-propylxanthine (83) was reported to be a good bronchodilator without drawbacks of theophylline.\textsuperscript{265}

\begin{center}
\includegraphics[width=0.5\textwidth]{structure_83.png}
\end{center}

\textbf{8-Substituted derivatives}

8-Aminoalkyl substituted xanthines bearing a diphenyl methyl piperazino group, which confer antiallergic-antihistaminic properties, were prepared by Regnier et al. with the aim of designing new more
potent theophylline analogues having a larger margin of safety and a longer duration of action. Among them, 1-methyl-3-isobutyl-8-(4-benzhydryl piperazinoethyl)xanthine (S 9795) (84) demonstrated longer duration of action and inhibiting action on mast cell degranulation and phosphodiesterase activity and was selected for clinical trials in asthmatic patients.

In another series of 8-substituted xanthines, isobutyl moiety was introduced at various positions to observe the effect on bronchodilation. Among these compounds, (1,3-diisobutyl-8-methyl)xanthine (85) displayed a potency of about 250 and 14-fold that of theophylline in the tracheal relaxation test and in the bronchospasm inhibition assay, respectively.

8-(p-Hydroxyphenyl)theophylline (86) and 1,3-dipropyl-8-(p-hydroxyphenyl)theophylline (87) have emerged as highly potent antagonists of \( \text{A}_1 \) and \( \text{A}_2 \) adenosine receptors in earlier studies.
INTRODUCTION

on 8-phenylxanthines as adenosine receptor antagonists.\textsuperscript{268} Compound 86 is 280-fold more potent than theophylline in displacing $[^{3}\text{H}]$ cyclohexyl adenosine from $A_1$-adenosine receptors and is 107-fold more potent than theophylline in antagonising $A_2$-adenosine receptors and was chosen as a suitable lead compound in an effort to develop potent and selective functionalized congeners as antagonists for adenosine receptors. The replacement of 1,3-dimethyl groups of 86 with n-propyl groups yields 1,3-dipropyl-8-(p-hydroxyphenyl)xanthine (87), which is an extremely potent $A_1$-adenosine antagonist. The carboxamide derivative 88 of 87 has high affinity and is 8-fold more potent at $A_1$-receptors than at $A_2$ receptors.

Structure-activity relationships 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 (89) were synthesised.\textsuperscript{269} It was observed that electron withdrawing
INTRODUCTION

substituents at 2- or 4-position of the benzamido group are best suited for $A_{2B}$ receptor selectivity. Among these compounds, highly potent and selective $A_{2B}$ antagonists were $p$-aminoacetophenone (90) and $p$-cyanoanilide (MRS 1754, 91) derivatives. Compound 91 is first selective $A_{2B}$ antagonist with the $K_i$ value of 1.9 nM at human $A_{2B}$ adenosine receptors and selectivity versus the other human adenosine receptor subtypes. Substitution of $p$-carboxy-

methoxy group of 89 and its amide with acrylic acid decreased affinity at $A_{2B}$ receptors while increasing affinity at $A_1$ receptors.269

Various 8-substituted cycloalkyl derivatives have been reported as potent adenosine $A_1$ antagonists.270-272 The most striking examples are 8-cyclopentyl (92) and 8-cyclohexyl-1,3-dipropylxanthine (93), which were both very potent and ten fold more selective for $A_1$ receptors versus $A_2$ adenosine receptors. 8-Cycloalkylmethyl analogues were found to be ten fold less potent, but still very selective for $A_1$ receptors.270-272 It was found that 8-(2-methylcyclopropyl)-1,3-dipropylxanthine (94) was at least 1000-fold more potent as $A_1$- antagonist,272 whereas 8-{trans-4-
(acetamidomethyl)-cyclohexyl-1,3-dipropylxanthine (95) was nearly equipotent as $A_1$ and $A_2$ receptor antagonist. Noradamantyl derivative (96) was also identified as a very selective and potent $A_1$ receptor antagonist. \[R \quad (92) \quad (95) \quad (96) \quad (94)\]

A number of sulfur containing 8-substituted derivatives of xanthine were also prepared in an effort to increase selectivity and potency as antagonists at adenosine receptors.\(^{273}\) It has been observed that 2-thio-8-cycloalkylxanthines (97) were at least as $A_1$-selective as the corresponding oxygen analogues, while 2-thio-8-aryl (98) derivatives tend to be more potent at $A_2$ receptor than...
INTRODUCTION

oxygen analogues. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-dipropyl-2-thioxanthine ethyl ester was found to be 740-fold more $A_1$ selective versus $A_2$ receptors. However, another sulphur containing 8-alkylthio-6-thiotheophylline series manifested two types of activity, both CNS depression and CNS stimulation. 8-(2-$N,N$-Diethylaminoethyl)thio-6-thiotheophylline \((99)\) was the potent CNS stimulant, cause tonic clonic convulsions and death within 2 minutes.

Water soluble adenosine antagonists were prepared by introducing polar substituents at \(para\)-position of 8-phenyltheophyllines and it was observed that \(p\)-sulfonyl substituents reduce the potency of 8-phenyl theophylline, but are 2-5 fold more potent than theophylline at adenosine receptors. The water soluble 8-(\(p\)-sulfophenyl) \((100)\) and 8-(\(p\)-carboxyphenyl)-1,3-dipropylxanthine \((101)\) no longer exhibit
marked selectivity but both compounds were much more potent as adenosine antagonists than theophylline.

The striking selectivity of 1-isoamyl-3-isobutyl xanthine (102)\textsuperscript{275,276} as an $A_1$ antagonist is retained in 8-phenyl derivative but is virtually lost in 8-sulfophenyl derivative.

In a series of 3-unsubstituted 8-phenylxanthines, carboxylic acid derivatives 103-105 were coupled with amines bearing polar

![Chemical structures](image)

...groups in order to increase water solubility.\textsuperscript{277} The aminoethylamide (106) was less potent at $A_{2B}$ receptors but showed increased $A_1$ and $A_{2A}$ affinity whereas the corresponding hydroxyethylamide (107) exhibited high $A_{2B}$ affinity.

To enhance bioavailability of 8-phenylxanthines, nitrophenyl esters of sulfophenylxanthine derivatives were prepared using

![Chemical structure](image)

prodrug approach.\textsuperscript{278} Of the series, 1-propyl-8-[4-[[m-nitrophenoxy]-sulfonyl]-phenyl]xanthine (108) has been investigated as a
prototypic ester and it was observed that \textit{m}-nitrophenyl group was found to be a suitable protecting group for sulfonates in organic synthesis due to high lipophilicity and stability. 1-Butyl-8-[(\textit{p}-nitrophenoxysulfonyl)phenyl]-xanthine (109) was the most potent

\begin{center}
\begin{align*}
\text{R} & \quad \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\
(109) & \\
(110) & \quad \text{CH}_2\text{CH}_3
\end{align*}
\end{center}

and selective \textit{A}1 adenosine receptor antagonist of the present series with a \textit{K}_\text{i} of 2.6 nM at rat \textit{A}1 adenosine receptors. The corresponding propyl xanthine derivative (110) was a very potent mixed \textit{A}1/\textit{A}2B antagonist.\textsuperscript{278}

Some more sulfonamide derivatives (111) with high potency and increased aqueous solubility has been reported in an earlier study, making use of a practical quantitative structure-activity

\begin{center}
\begin{align*}
\text{R}_1 & \quad \text{SO}_2\text{NR}_3 \\
\text{R}_2 & \\
(111)
\end{align*}
\end{center}

relationship application and it has been observed that 8-phenyl sulfonamides represent novel soluble xanthines with high affinity

48
for adenosine receptors in the brain which produce functional
antagonism in the heart.\textsuperscript{279}

Introduction of the (E)-3,4-dimethoxystyryl or (E)-3,4,5-
trimethoxy styryl group (112) at 8-position of 1,3-dialkyl-7-
methylxanthine was found to enhance $A_2$ antagonism.\textsuperscript{280}

In another series of 8-aryl or 8-heteroaryl substituted

\begin{align*}
\text{(113)} & \quad \text{furanic (113) and 2-chlorophenyl (114) derivatives} \\
\text{(114)} & \quad \text{were 4 times more active than theophylline.}\textsuperscript{281}
\end{align*}

Various modifications of the xanthine structure have also
been made by incorporating various substituents at 1-, 3- and 8-
positions to understand the structure-activity relationships of
alkylxanthines as inhibitors of two different forms of phosphodiesterase, the calmodulin-sensitive form (Peak 1) and the cAMP specific form (Peak 2), which are found in most mammalian cells. It was noted that if H at position 8 is replaced by a larger group, it reduces the potency to inhibit the cAMP. Cipamphylline (BRL 60063, 115), synthesized by Smithkline Beecham, is the prototype of a series of xanthine derivatives as potent PDE 4 inhibitors. However, sulfonation of 115 at 7- and 8-positions increased potency against PDE 5a as compared to PDE 4 isoenzyme as was observed in 116.

Bronchodilation activity has also been correlated with partition parameters and/or the steric “bulk” of 1-and 3-substituents in a series of 6-thioxanthines (117) in an earlier study. It was observed that with the introduction of “bulky” substituents at both these positions, there is an increase in activity to inhibit the phosphodiesterase but the adenosine antagonistic activity remained unchanged.
Several studies indicating that 8-aza theophylline is more potent than theophylline in inhibiting the passive cutaneous anaphylactic reaction in rats have also been reported.\textsuperscript{288-290} 3-(4-Nitrobenzyl) derivative 118 exhibited maximum activity. The compound 119 (M & B 22948) has been developed as a potent antiallergic agent, which was ineffective against histamine-induced asthma but significantly reduced EIA.\textsuperscript{288-290}

Recently a new series of N-3 substituted xanthine derivatives was synthesized and tested for affinity and apparent irreversible binding at the A\textsubscript{1} and A\textsubscript{2A} adenosine receptors. Compound 120 appear to be the most advantageous as an apparent irreversible ligand for A\textsubscript{1} adenosine receptors.\textsuperscript{291}
A series of xanthine related compounds with substituted 6,7-dihydroimidazo[1,2-a]purin-9(4H)-ones (121) was also reported to optimize the bronchodilating and antiallergic effects of xanthine molecule. In this series, 2-carbonyl group of theophylline has been replaced with a 2-iminoalkylene moiety cyclized to the 1- position. These derivatives showed improved bronchodilating and antiallergic effects when compared to theophylline. A number of linear and proximal benzo-separated derivatives of 8-phenyltheophylline, 1,3-diethyl-8-phenylxanthine, 1,3-dipropylxanthine, 1,3-dibutylxanthine, 3-isobutyl-1-methylxanthine, theophylline, caffeine and isocaffeine have been synthesized. Among them, linear benzo-separated derivatives of 3-isobutyl-1-methylxanthine (122) possessing an alkyl or aralkyl substituent in the 7-position or an alkyl group in 8-position are potent inhibitors of peak 1 phosphodiesterase whereas 3-isobutyl-1-methylxanthine analogues, in which 1-methyl group is replaced by large alkyl substituents, show preferential inhibition of peak 2 phosphodiesterase.

The main challenge for a medicinal chemist is to develop a compound that should be potent as well as free from undesirable...
INTRODUCTION

effects. To combine various desirable properties into a single compound is a tedious job. The above survey of literature highlights the significance of substituting different positions of the xanthine nucleus to develop potent antiasthmatic drugs. These observations prompted the present investigator to design and synthesize new more potential xanthine derivatives, which may address not only asthmatic bronchoconstriction but also underline bronchial inflammation.

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