Selective Phosphodiesterase 4 Inhibitors — Emerging Trends in Asthma Therapy (Antiasthmatics-3)
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Considerable interest has been generated in the potential utility of isozyme selective inhibitors of phosphodiesterases in the treatment of asthma and other inflammatory disorders. Heterogeneity in tissue distribution as well as their different functional roles make these enzymes very attractive targets for medicinal chemists. To date at least 11 different families of PDE isozymes are known, among which PDE 4 plays a major role in modulating the activity of virtually all cells involved in the inflammatory process. Inhibitors of this enzyme family display impressive antiasthmatic activity by reducing the bronchial smooth muscle tone and considerable anti-inflammatory activity. The review details the various classes of PDE 4 inhibitors structurally related to rolipram, nitraquazone and xanthines, which appear to be very attractive models for synthesis of novel selective PDE 4 inhibitors potentially useful for the treatment of asthma and chronic obstructive pulmonary diseases. Rationale for the use of PDE4 inhibitors in the treatment of asthma is also discussed.

Key words: Phosphodiesterase 4 inhibitors, Asthma therapy, Antiasthmatics, Isozyme, Rolipram, Nitraquazone, Xanthines.

Introduction
There has been growing interest in recent years in the utility of selective phosphodiesterase (PDE) inhibitors as novel targets for drug discovery. Phosphodiesterases comprise a heterogenous group of isozymes which differ nevertheless in their kinetic and physical characteristics, substrate (cAMP or cGMP) selectivities, sensitivity to endogenous activators, susceptibility and response to phosphorylation by protein kinase, tissue distribution and subcellular localization1-3. These isozymes hydrolyse the 3'-phosphodiester bond of cyclic messengers cAMP or cGMP to their inactive 5'-nucleotide forms. cAMP and cGMP are ubiquitous intracellular second messengers which play a prominent role in the regulation of important cellular functions such as secretion, contraction, metabolism and growth. The elevation of their intracellular levels by PDE inhibitors represents a useful strategy for eliciting a variety of pharmacological effects.

Phosphodiesterase Superfamily
At least eleven different families of PDE isozymes are known based on their substrate specificity (cAMP or cGMP) kinetics, and their responsiveness to allosterics modulator and endogenous or exogenous regulators1-9 (Table 1).

Each PDE family includes subfamilies that are encoded by distinct genes but have 70-80 per cent homology with one another and finally contain several members. The families of PDEs are referred by Arabic numerals (1-10), subfamilies by capital letters (A-D) and members by Arabic numerals (1-3). Nearly all these different PDEs have unique primary sequence in their catalytic or regulatory domains and they are often selectively expressed. This implies that it may be possible to modulate individual isozymes using specific drugs. The differing distribution of PDEs between cell types, the large diversity in structure, function and regulation among PDE isozymes makes it possible to develop selective and possibly therapeutically useful inhibitors and activators of individual isozymes, which will be devoid of unnecessary side effects. A number of inhibitors of phosphodiesterase isozymes have been described9. They can be used as cardiotonics,
antithrombotic agents, vascular and airway smooth muscle relaxants, anti-inflammatory agents and antidepressants. The knowledge that – (a) multiple distinct PDE isozymes exist, (b) Isozymes differ in their cellular distribution and synthesis of a variety of inhibitors possessing marked degree of selectivity for one isozyme over other, raises the possibility that the unfavourable side effects profile of nonselective PDE inhibitors can be reduced by synthesizing compounds that are targeted specifically for the isozymes that predominates in the particular tissue or the cell of interest.

Recently, selective phosphodiesterase inhibitors have received considerable attention as molecular targets for the development of antiasthmatic agents. Several comprehensive reviews have been published recently on the use of PDE 4 inhibitors in the treatment of asthma.

**Phosphodiesterase Inhibitors in Asthma**

Bronchial asthma is a noninfectious respiratory pathology involving the concerted actions of multiple inflammatory cells, spasmodgens, inflammatory mediators, cytokines and growth factors. Acute airway obstruction, bronchial hyperresponsiveness and inflammatory state of bronchial mucosa with increased level of inflammatory mediators characterise this pathology. Eosinophils also play a prominent role in asthma suggesting it to be an inflammatory disorder. Today asthma is affecting over 5 per cent of the adult population and perhaps up to 10 per cent of children. It is rising in prevalence, severity and mortality in the developing countries despite substantial increase in number of newer antiasthmatic agents. Many classes of drugs like leukotriene receptor antagonists, 5-lipoxygenase inhibitors, adenosine antagonists, anticholinergics, beta-agonists, glucocorticoids and antihistamines are also used as effective bronchodilators. Beta-Adrenergic agonists are widely used in asthma therapy and on inhalation produce instant bronchodilation. They however have little effect on underlying inflammation and because of this reason their regular and long term use has been debated. Systemic side effects such as tachycardia, palpitation and headache are observed with inhaled beta-adrenergic agonists and also the self-administration of inhaled drugs may be difficult for old and disabled persons. Glucocorticoids on the other hand have well documented anti-inflammatory properties and can reduce airway hyperresponsiveness but lack immediate bronchodilatory action. Chronic administration of glucocorticoids can cause significant suppression of hypothalamus pituitary adrenal (HPA) axis and of bone growth in children. It may also affect disease progression. Two detailed reviews have been published by Jindal et al. on beta-adrenergic agonists and methylxanthines as antiasthmatics.

Novel orally active antiasthmatic drugs which display both bronchodilatory and anti-inflammatory profile with reduced side effects and also which can substitute the combined therapy of inhaled beta-receptor agonists (bronchodilators) and corticosteroids (anti-inflammatory) is the need of hour. One class of drugs, which we can look forward for effective asthma therapy with both bronchodilatory and glucocorticoid like anti-inflammatory property can be selective phosphodiesterase inhibitors. Phosphodiesterase (PDE) inhibitors result in enhanced intracellular levels of second messengers cAMP and cGMP, which are generally associated with dampening
effects on airway smooth muscle. cAMP suppresses the activation and mediator release from inflammatory cells \(^{12,18,19}\) (Figure 1). These mediate the functional responses of cells to a multitude of hormones, neurotransmitters and autacoids with respect to the regulatory function of cells involved in pathophysiology of asthma. So PDE inhibitors have a theoretical advantage over the use of other antiasthmatic agents that inhibit the formation or antagonize the action of individual mediators.

Phosphodiesterases 3, 4 and 5 are particularly important with respect to targets for the development of novel antiasthmatic agents.\(^\text{5,20}\) The mixed anti-inflammatory and bronchodilatory profile of PDE inhibitors could allow the discovery of new agents able to compete and replace corticosteroids and \(\beta_2\) agonists, which so far represent the basis of therapeutic management of asthma\(^\text{8}\). All five (1-5) major types of isozymes are found in human airways. The role of PDE 1 and PDE 2 isozymes have not been clarified due to lack of potent and selective inhibitors of these two isozymes. Much of the emphasis on selective PDE inhibitors for asthma therapy has been focused on PDE 4, which is a cAMP specific isozyme with a \(K_m\) of 3 \(\mu\)M for cAMP and more than 3,000 \(\mu\)M for cGMP\(^\text{21}\). There are at least two main reasons for the basis of growing interest in the chemical, pharmacological and biochemical research in the area of selective phosphodiesterase 4 inhibitors. First, there is general conviction that the dual anti-inflammatory and bronchodilatory profile of PDE 4 inhibitors could lead to the discovery of new agents able to compete and perhaps to replace corticosteroids (anti-inflammatory) and \(\beta_2\) agonists (bronchodilators), the basic therapeutic agents for the management of asthma and second, new and promising therapeutic applications of PDE 4 inhibitors in certain autoimmune diseases, e.g., rheumatoid arthritis, multiple sclerosis and type 2 diabetes\(^\text{8,22}\).

**Selective PDE 4 Inhibitors as Antiasthmatic Agents**

Inhibitors of low \(K_m\), cAMP-specific type 4 isozymes in particular are attractive targets as potential antiasthmatic agents. This isozyme exerts a key role in regulation of inflammatory cells implicated in the pathology of the disease\(^\text{4,10}\) because of its tissue distribution. PDE 4 is also an important enzyme in human bronchi\(^\text{23}\). They inhibit superoxide generation in monocytes, macrophages, neutrophils and eosinophils, reduction of TNF\(\alpha\) release in monocytes and macrophages and suppression of chemotaxis and phagocytosis\(^\text{15,24}\). Inhibition of mediator synthesis or release from mast cells, basophils, eosinophils, neutrophils, macrophages and

![Figure 1](image-url)
T-lymphocytes have also been demonstrated. PDE 4 inhibitors have the ability to reduce the bronchospasm induced by histamine, leukotriene D4 (LTD4), carbachol and methacholine. Selective inhibitors of PDE 4 may address not only asthmatic bronchoconstriction but also underlying bronchial inflammation. Thus the profile of selective PDE 4 inhibitors seems to fulfill the requirements for a unique therapy for asthma.

From a structural point of view, selective PDE 4 inhibitors can be divided into 4 classes.
1. Catechol ethers: Structural analogues of rolipram (1).
2. Heterocyclics and analogues: Structural analogues of nitratazone (2).
3. Xanthines and related compounds: Structural analogues of theophylline (3).
4. Miscellaneous Selective PDE 4 Inhibitors

Catechol Ethers

Rolipram (1) is the prototype of this class of selective PDE 4 inhibitors. Rolipram originally developed, as an antidepressant is now the most studied of all selective PDE 4 inhibitors. SAR studies of a series of rolipram analogues as PDE inhibitors have been published. Rolipram has been found to bind to a high affinity site on PDE 4, distinct from catalytic site. While high affinity rolipram binding site do not appear to be present in all tissues that contain PDE 4, this activity is coexpressed with human recombinant PDE 4 activity. The bronchodilatory effect of several PDE 4 inhibitors correlate better with displacement of rolipram binding than with PDE 4 inhibition. In addition to having desirable inhibitory effects on inflammatory, anaphylaxis and smooth muscle contraction, selective PDE 4 inhibitors also produce undesirable side effects including nausea and vomiting. PDE 4 inhibitors also potentially displace [3H]rolipram from a high affinity binding site which is proposed to be an allosteric binding site on PDE 4 enzyme. Emetic potency of PDE 4 inhibitors is correlated with affinity for rolipram binding site in brain rather than potency of inhibiting PDE 4 enzyme activity. The most obvious concern regarding the PDE 4 inhibitors stems from their antidepressant activity resulting from their inhibition of PDE 4 in the brain. Efforts have been made to eliminate the emetic potential of PDE 4 inhibitors by developing compounds with decreased [3H]rolipram binding affinity while retaining PDE 4 potency.

Rolipram Binding Site

The high affinity rolipram binding site is an intriguing factor in the puzzle of PDE 4 activity regulation. It has been reported that high affinity binding sites in the rat brain membrane are labeled by [3H]rolipram in a stereospecific and stereoselective and saturable manner. It has also been disclosed that a monocyte derived recombinant PDE 4 has a binding site with an affinity for rolipram approximately 100 times that of catalytic site. Studies with other PDE inhibitors that bind to catalytic domain indicated the distinction of rolipram binding site. Recently, evidence indicating that rolipram binding site may not be allosteric but a part of a different conformer of PDE 4 has appeared.

Rolipram has frequently been used as a basis for design of new and subtype specific PDE 4 inhibitors. RO 20-1724, (4) is another potent compound containing the catechol ether moiety found in rolipram.
Several N-heterocyclic benzamide derivatives 5, designed from rolipram have been demonstrated to show exceptional potency in histamine induced bronchospasm and PDE 4 inhibition. RP73401 (6) is a potent benzamide PDE 4 inhibitor. It shows nonselectivity for inhibiting PDE 4 (catalytic site) over the displacement of rolipram from its binding site.

\[
\begin{align*}
\text{R} &= \text{Cyclopentyl} \\
\text{Het} &= 3,5\text{-dichloro-pyrid-4-yl}
\end{align*}
\]

\(5\)

Bacher et al. synthesized highly potent N-phenyl rolipram derivative 7 with a hydrophilic substitution in 5 position of central phenyl ring.

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{CONH} \\
\text{R} & \quad \text{Het}
\end{align*}
\]

\(7\)

Another group replaced 3-methoxy-4-cyclohexyloxy or catechol like moiety with indole producing compounds that potently inhibited the activation of inflammatory cells \textit{in vitro}. A series of conformationally constrained quaternary substituted oxindole derivative of CDP-840, a potent and selective PDE 4 inhibitor, was also synthesized by this group. Bioavailable and efficacious 2-methoxy-benzimidazole based PDE 4 inhibitors has also been evaluated by Regan et al.

In a series of 5-(catechol ethers)-2-imidazolidinones, comprising structural features of both rolipram (1) and RO 20-1724 (4), the substituents on catechol-3-oxygen was primarily modified to get compound 8 and 9 (ref. 20).

\[
\begin{align*}
\text{R} &= \text{Cyclopentyl} \\
\text{Het} &= 3,5\text{-dichloro-pyrid-4-yl}
\end{align*}
\]

\(6\)

\[
\begin{align*}
\text{R}_1 &= 0 \\
\text{R}_2 &= -\text{NH} \\
\text{H}_3\text{CO} & \quad \text{CONH} \\
\text{R}_1 & \quad \text{Het}
\end{align*}
\]

\(8\)

\[
\begin{align*}
\text{R}_1 &= \text{Cyclopentyl} \\
\text{R}_2 &= \text{CH}_3 \\
\text{H}_3\text{CO} & \quad \text{CONH} \\
\text{R}_1 & \quad \text{Het}
\end{align*}
\]

\(9\)

\[
\begin{align*}
\text{R}_1 &= \text{Cyclopentyl} \\
\text{R}_2 &= \text{CH}_3 \\
\text{H}_3\text{CO} & \quad \text{CONH} \\
\text{R}_1 & \quad \text{Het}
\end{align*}
\]

\(10\)

\[
\begin{align*}
\text{R}_1 &= \text{Cyclopentyl} \\
\text{R}_2 &= \text{CH}_3 \\
\text{H}_3\text{CO} & \quad \text{CONH} \\
\text{R}_1 & \quad \text{Het}
\end{align*}
\]

\(11\)

Another series containing bi, tri and tetracyclic hydrocarbons at 3-alkoxy position of the same parent structure has also been studied; Compound 10 and 11 were the most potent inhibitors in this series.

Tetrahydro-pyrimidinone 12 was also prepared and was observed that two enantiomers were equipotent. PDA-641 (13) was equipotent to rolipram as an inhibitor of dog trachealis PDE 4.

\[
\begin{align*}
\text{R}_1 &= \text{Cyclopentyl} \\
\text{R}_2 &= \text{CH}_3 \\
\text{H}_3\text{CO} & \quad \text{CONH} \\
\text{R}_1 & \quad \text{Het}
\end{align*}
\]

\(12\)
A novel series of 4-(3-alkoxy-4-methoxyphenyl)benzoic acids and their corresponding carboxamides have been prepared and evaluated in an effort to reduce emetic side effects. Phenylpentoxy derivative (14) was found to exhibit potent PDE 4 inhibitory activity and possessed approximately 400 times weaker activity than rolipram for [\(^3\)H] rolipram binding site and demonstrated a significant reduction in emetic side effects.

A series of rolipram derivatives differently substituted either at the pyrrolidinone or at aromatic ring have been synthesized and reported, AWD-12-281 (Loteprednol), a 5-hydroxyindole derivative which has been developed by Celltech has also been evaluated in passively sensitized human airways and prevented contraction in reducing allergen challenge in sensitized guinea pig and Brown Norway rats.

Piclamilast, (PDE 4 inhibitor) acts by down regulating-tumour necrosis factor and has shown potent anti-inflammatory activity in vitro studies using novel human whole blood assay.

Similar strategy led to the development of a potent second generation inhibitor of PDE 4 with a decreased potential for side effects. SB, 207499 (4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-cyclohexane-1-carboxylic acid), Ariflo (15) developed by Smithkline Beecham, is presently undergoing phase II and III clinical trials with respect to paediatric patients with asthma and patients with chronic obstructive pulmonary disease, respectively. It has a large therapeutic potential and a decreased potential for side effects as compared to rolipram. It has been suggested that agents displaying potent catalytic site activity with a reduced activity at HARBS (high affinity rolipram binding site) would have good anti-inflammatory property with decreased potential to induce side effects and it has been established that Ariflo displays potent selective affinities for PDE 4 catalytic site (IC\(_{50}\) = 95 nm) and for HARBS (IC\(_{50}\) = 120 nm) compared to rolipram which showed (IC\(_{50}\) value of 300 and 5 nm respectively for PDE 4 and HARBS), suggesting it to display an improved therapeutic activity with low incidence of side effects as compared to rolipram.

PDE 4 inhibitors have been described. This structurally unique class of PDE 4 inhibitors has conformationally constrained indan ring linker and led to the identification of inhibitors with nanomolar potency, no emetic and oral activity.
Heterocycles and Analogues

This class of PDE 4 inhibitors is exemplified by nitraquazone (2). The archetypal quinazolindione moiety of compound 2 has been extensively manipulated to afford a variety of structure derived compounds. 3'-NO₂ group of compound 2 has been replaced by different nonprotic, electron-withdrawing functionalities like -Cl, -Br, -COOCH₃ to study SAR. Corresponding acid and N-methyl amide produced a substantial and complete loss in potency respectively.

Pyridopyrimidinedione analogues have also been prepared. Although benzene-pyridine isosteric replacement led to decrease in potency in case of compound 17 as compared to compound 18 but introduction of bulkier groups at N₃ afforded 19-21 with substantially increased potency. The corresponding 4-pyridyl derivative 22 has proved to be four times potent inhibitor of PDE 4 with respect to prototype 17. Compounds of the type 23 containing pyridopyrimidazole nucleus are nanomolar selective inhibitors of PDE 4. The concomitant increase in side effects limited their development. Attempts were made to reduce these adverse effects and compounds were synthesized by replacing pyridine with a series of heterocyclic systems like pyrrole, pyrazole, 1,2-dihydropyridine and thiophene.

These compounds showed significantly better balance between PDE 4 inhibition and emetic side effects. Further simplification led to quinoline derivative RS 14203 (24) which is one of the most potent PDE 4 inhibitor.

Replacement of 3' nitrophenyl group of compound 24 by benzotriazole resulted in formation of compound 25.

Naftiridinones 26 and compound 27 (ref. 8 and 44) result from a lesser structural simplification of nitraquazone. Heterocyclic fused 3[2/1]-4 pyridazinones 28 have been synthesized and reported to have potent selective PDE 4 inhibitory activity and
greatly attenuated affinity for rolipram high affinity binding site\(^{43}\).

\[
\begin{align*}
\text{(26) } & \\
\text{(27) } & \\
\text{(28) } & \\
\text{(29) } & \\
\end{align*}
\]

Nicotinamide ethers 29, ring opened variants of pyridopyridindiones have recently aroused renewed interest in inhibition of PDE 4. They also have reduced emetic side effects. These compounds were earlier reported in 1991\(^{45}\). A variety of substituents \( Z = -F, -Cl, -OCH_3, -CN, -CF_3 \) have been prepared. Meta and para positions were found to be favourable but ortho was not favoured\(^{45}\). Recently, PDE 4 inhibitors based on pyrido[2,3-\(d\)]pyrazino 30 backbone have been disclosed\(^{46,47}\).

\[
\begin{align*}
\text{(30) } & \\
\text{(31) } & \\
\text{(32) } & \\
\end{align*}
\]

A novel class of inhibitors like compound 31 and 32 based on same quinoline, quinolone and naftiridinone template but also with the presence of carboxamido or sulfonamido groups have been reported\(^{48,49}\).

\[
\begin{align*}
\text{(33) } & \\
\end{align*}
\]

Nitraquazone like inhibitors based on an almost flat heteroaromatic area generally formed by 6-6 condensed system; One (hetero) aromatic or a cycloalkyl systems connected to flat portion through a methylene spacer with an electron withdrawing substituent\(^8\) represents the best pharmacophore model 33. Challenge in this class of PDE 4 inhibitors is to have the selective PDE 4 inhibitory activity in nanomolar potency with strongly reduced affinity for high affinity rolipram binding site to improve the therapeutic index.
A new type of bronchodilator agents, bi- and tri-cyclic nitrogen bridgehead compounds with a pyrimidine-4(3H)-one ring have been synthesized and evaluated for bronchodilatory activity. One of the compounds was found as a potent bronchodilator.

A series of novel tricyclic heterocycles imidazo[4,5-c] [1,8] napthyridin-4-(5H)-ones have been designed and synthesized. Compound 34 relaxed spontaneous guinea pig isolated tracheal preparation with 4-16 fold greater potency than aminophylline. It also inhibited PDE 4.

New heterocyclic compounds 3H-imidazo[4,5-c]quinoxaline-4(5H)-ones 35 have been designed by Suzuki et al. This tricyclic heterocyclic can be regarded as a fusion compound of a benzene ring to the bond between 2 and 3 position of 7-substituted xanthine. 5-Ethyl-3-methyl derivative was found to be 5-fold more active than theophylline for their protective effect against antigen induced contraction of guinea pig trachea.

Similarly, 7,5-disubstituted 1H-imidazo[4,5-c]quinolin-4(5H)-ones (36) were synthesized and were tested as potent and active bronchodilators. The most potent compound of this series showed weak PDE 4 inhibition which could not account for its potent bronchodilation.

From the common pharmacophore for nitaquazone related compounds, a series of novel heteroaromatic compounds have been designed, synthesized and evaluated as PDE 4 inhibitors. Thienopyrimidin (37) was selected as a lead compound and a number of compounds with various lipophilic and aromatic groups in both C-2 and C-4 position were synthesized. These compounds showed a good balance of PDE 4 activity and displacement of [3H]rolipram from its binding site.

Order of reactivity of pteridine carbon atoms towards secondary amines have been elucidated and alkylamino substituted pteridines 38 free of positional isomers have been prepared.

6,8-Disubstituted-1,7-naphthyridines (NVP-ABE 171, 39 ), a new class of selective phosphodiesterase inhibitors has recently been reported. 39 Has been found about 40-times more potent as compared to Ariflo (15). A series of 1-aryl-2,3-di(hydroxymethyl) naphthalene lignan have been synthesized and
evaluated for their ability to selectively inhibit PDE 4 in isolated pig tracheal strip. Replacement of 1-phenyl ring by a pyridone ring led to marked improvement of their selectivity for PDE 4 over PDE 3. Compound 40 was chosen as candidate for further pharmacological evaluation.

A new approach to improve therapeutic window of PDE 4 inhibitors is aimed at the identification of the specific targets for emesis and efficacy. An emetic, efficacious and competitive PDE 4 inhibitor 41 capable of covalently tagging its biological targets upon photoactivation has been synthesized. Highly emetic and efficacious PDE 4 photoaffinity probe has been reported. This probe would be highly useful for identification of respective targets through which PDE 4 specific inhibitors cause emesis and also produce their efficacy.

![Image of compound 40 and 41]

Xanthine and Related Compounds

Theophylline represents this class of selective PDE 4 inhibitors. Xanthines have long been known to cause a variety of physiological effects. The CNS stimulatory properties of caffeine have been utilized for centuries. Tachycardia and bronchodilation are other responses elicited by xanthines. Inhibition of phosphodiesterase in heart, brain and lungs may be the mechanism by which xanthines exert their effects. Theophylline preparations have found continuous use as bronchodilators in the treatment of asthma for almost a century. It is a weak non-selective phosphodiesterase inhibitor, but it is believed that PDE inhibitory activity may contribute to both its bronchodilatory and anti-inflammatory activities. Although theophylline is useful in the treatment of asthma, the value of theophylline is limited to a narrow therapeutic index due to wide range of gastrointestinal, CNS and cardiovascular side effects. The drugs that couple the efficacy of theophylline with an improved side effects profile and an increased therapeutic index would be an important advance in the treatment of asthma. Attempts have been made to improve therapeutic profile by synthesizing new xanthine analogues without specifically focusing on PDE inhibitory activity but so far these efforts have not been successful.

An alternative approach towards developing an 'improved theophylline' has emerged recently. Using xanthine skeleton, attempts have been made to design and synthesize novel compounds which are selective PDE 4 inhibitors and also retain the therapeutic efficacy of theophylline. Xanthine nucleus present in theophylline is also present in the PDE substrate and will bind to and block highly conserved enzyme catalytic site. Miyamoto et al. studied SAR of this class and reported an interesting series of heterocyclic fused xanthines.

A series of xanthines with varied substituents at the 1,3 and 8 positions have been prepared in order to understand the SAR for alkyl xanthines as inhibitors of phosphodiesterase.

Many 7-alkylated derivatives of theophylline such as dyphylline (42), doxophylline (43), thioanalogue of doxophylline (44), proxphylline (45), bamiphylline (46), acephylline (47) and etophylline (48) have been synthesized and studied. Among the therapeutically useful synthetic xanthine analogues, dyphylline (42) has been approved and has appeared in the US market as an antiasthmatic drug. Bamiphylline (46) and...
Doxophylline (43) have been marketed in Europe\textsuperscript{5,62}. These derivatives are generally less active and exhibit low or moderate PDE 4 inhibitory activity than theophylline but are stable in solution and in vivo. These possess same side effects as theophylline.

\[
\text{(42) CH}_2\text{CH(OH)CH}_2\text{OH} \quad \text{R}_1 \quad \text{R}_2 \\
\text{(43) CH}_2\text{-} \quad \text{H} \\
\text{(44) CH}_2\text{-} \quad \text{H} \\
\text{(45) CH}_2\text{CH(OH)CH}_3 \quad \text{H} \\
\text{(46) (CH}_2)_2\text{-N(C}_2\text{H}_5)\text{-}(\text{CH}_2)_2\text{OH} \quad \text{CH}_2\text{-} \\
\text{(47) CH}_2\text{COOH} \quad \text{H} \\
\text{(48) CH}_2\text{CH}_2\text{OH} \quad \text{H}
\]

Denbufylline (49) is a selective PDE 4 inhibitor showing low adenosine receptor affinity\textsuperscript{8,64}, but the development of compound was discontinued because of poor pharmacokinetics.

Aroffylline (50) is in phase III clinical trials for oral asthma therapy\textsuperscript{65}. It is a weak but selective inhibitor of PDE 4 as compared to theophylline.

\[
\text{(49) CH}_3 \\
\text{(50) pClC}_6\text{H}_4 \quad \text{H} \quad \text{C}_2\text{H}_5
\]

It is 25-30 fold less emetic as compared to rolipram. Aroffylline demonstrated significant improvement of pulmonary function, as well as safe profile. Structural analogues of aroffylline have been reported by a chirosience group. The compounds showed improved ratio for PDE 4 inhibitory activity versus emetic side effects. Cipamphylline (51) (BRL 60063) was the prototype of a series of potent PDE 4 inhibitors reported and has been synthesized by Smithkline Beecham\textsuperscript{66}. Sulfonation of cipamphylline at 7- and 8-positions increased potency against PDE 5A as compared to PDE 4 isozymes. 8-substituted piperazine derivatives have been reported by Ragnier et al.\textsuperscript{67} having a combination of antiallergic and antihistaminic properties. They also displayed a potent bronchodilatory activity with enhanced duration of action. Among these, 1-methyl-3-isobutyl-8-(4-benzhydrylpiperazinoyl) xanthine S9795 (52) exhibited inhibitory action on mast cell degranulation and phosphodiesterase enzyme\textsuperscript{8,67}.

\[
\text{(51)}
\]

A series of benzoseparated compounds purines, isoguanidines and thioxanthines which inhibit PDE 4 from bovine tracheal smooth muscle have been synthesized and reported\textsuperscript{68}. Depending upon the substituents at C-7, C-8 or C-1 positions, these
benzoseparated linear derivatives of 3-isobutyl-1-methylxanthine 53 show PDE inhibiting activity.

One of the xanthine analogue, Ibudilast (54), marketed as an orally acting antiasthmatic drug in Japan\(^8,\)\(^9\) has been found to be a nonspecific and moderately potent PDE 4 inhibitor.

SCA 40 (55)\(^7\)\(^0\) is an effective bronchodilator in human bronchus precontracted with different spasmogens. The presence of bromine on position 6 and an amino (alkylamino) group on position 8 plays a critical role in the activity. It also shows PDE inhibitory activity in micromolar range. ICI-63197 (55) is another reported compound which is a weak selective inhibitor of PDE 4\(^7\)\(^1\).

Efforts have been made to prepare hybrid structures of xanthine skeleton and rolipram. V11294

A (57)\(^7\)\(^2\) and RPR 132703 (58)\(^7\)\(^3\) are the most interesting examples.

These compounds have progressed into phase II clinical trials for asthma.

**Miscellaneous Selective PDE 4 Inhibitors**

PDE 4 inhibitors based on benzofuran (59) and benzopyran (60) nucleus have been reported\(^6\). (61) Showed PDE 4 inhibitory activity in the nanomolar range\(^5\). Indazole (62)\(^7\)\(^4\) and pyrazolo[3,4-c]pyridine (63) represent various other PDE 4 inhibitors synthesized by Pfizer Labs\(^7\)\(^5\).
Conclusions

With the development of selective PDE 4 inhibitors, interest and excitement has been generated to discover new classes of drugs for the treatment of asthma. Clinical experience with the use of isozymes selective PDE 4 inhibitors for the treatment of asthma is limited. Determination of the utility of this novel strategy currently being evaluated for asthma require additional clinical studies. Although mechanism of action, safety and continuous efficacy of PDE 4 inhibitors on chronic use is still questionable, it seems to be reasonable isozyme for continued evaluation as novel bronchodilators. Evidence is also mounting in support of PDE 4 as a target for anti-inflammatory agents. Combining PDE 4 inhibitory activity with PDE 3 or PDE 5 inhibitory activity within a single molecule could lead to a very effective bronchodilator with anti-inflammatory activity, although there will also be increase in side effects.

No selective PDE 4 inhibitor is currently marketed. Some of the selective PDE 4 inhibitors are in phase II and III clinical trials as antiasthmatic agents. The recent discovery of two PDE 4 conformers HPDE4 and LPDE4 with their unique tissue distribution and activity has further contributed to design of new and specific inhibitors with decreased side effects. It has been accepted that high affinity for HARBS is associated with more propensity to induce side effects. Thus high potency at catalytic site and reduced affinity for HARBS with selectivity for PDE 4 may afford the ideal physiological and toxicological profile for drugs with clinical efficacy in asthma. One such compound is SB207499 (Arifio™) which is in the final stages of clinical trials. Several PDE 4 inhibitors based on the modification of theophylline, rolipram or nitraquazone are currently undergoing evaluation and show much promise for future therapy of asthma.

Although the PDE 4 inhibitory effect of therapeutically useful antiasthmatic drugs, methylxanthines was initially considered as an important mechanism in their antiasthmatic activity, but they generally display lower or moderate potency at the catalytic site e.g. arofylline, a PDE 4 inhibitor, is one of the most advanced drugs in clinical evaluation. The mechanism remains controversial and
data suggest that for clinical efficacy in asthma potency at catalytic site of PDE 4 inhibitors is not an essential requirement. To prove this, further, development of many potent PDE 4 inhibitors have been discontinued as antiasthmatic agents in recent years. Still there is much promise remaining in the research in the field.

Theophylline nucleus may be very useful for designing new antiasthmatic drugs with inherent antiasthmatic properties of this old drug and decreased cardiovascular and CNS side effects. On the whole, selective PDE 4 inhibitors, particularly xanthines open a very interesting prospective of a breakthrough in this area of research for medicinal chemists. The rational design of PDE 4 inhibitors has taken on new meaning and vitality and now selective PDE 4 inhibitors could be designed with a specific therapeutic endpoint for optimum clinical benefit.

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References


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64 Nicholson C D, Jackman S A & Wilke R. The ability of dipyridostigmine to inhibit cyclic nucleotide phosphodiesterase and its affinity for adenosine receptors and the adenosine re-uptake site, Br J Pharmacol, 97 (1989) 889.


71 Davies G E, Antibronchoconstriction activity of two new phosphodiesterase inhibitors, a triazolopyrazine (ICI 58301) and triazolopyrimidine (ICI 63197), J Pharm Pharmacol, 25 (1973) 681.


