REVIEW

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Recent perspectives in the design of antiasthmatic agents

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Asthma is a common respiratory disorder. It can no longer be viewed as a reversible airway obstruction but should instead be considered primarily as an inflammatory illness that has bronchial hyperreactivity and bronchospasm as its result. There are several potential benefits as well as limitations of the currently available antiasthmatic agents such as anticholinergies, β_2-selective agonists, methylxanthines, corticosteroids, or mast cell stabilizers. Recent trends in the design of new antiasthmatic agents include isozyme selective phosphodiesterase inhibitors, inhibitors of the biosynthesis of interleukin-4 and IL-4 antagonists, lipoxygenase and leukotriene inhibitors, thromboxane A_2 receptor antagonists, potassium channel openers and monoclonal antibodies.

1. Introduction

Asthma is a common inflammatory disease of the respiratory tract, accounting for 1–3% of all office visits, 500,000 hospital admissions per year and more pediatric hospital admissions than any other single illness. Annually, more than 5000 children and adults die of asthma attacks in the United States [1].

Asthma can no longer be viewed simply as a reversible airway obstruction. It should instead be considered primarily as an inflammatory illness that has bronchial hyperactivity and bronchospasm as its result. Allergen specific immunoglobulin E (IgE) is bound to the mast cells via Fc receptors. It is a fragment obtained by papain digestion of immunoglobulin molecules and contains most of the antigenic determinants. When an allergen comes into contact with IgE, the mast cells are activated and release a number of inflammatory mediators, which include granule contents like histamine, proteases, heparin, and tumor necrosis factor (TNF), a variety of lipid membrane derived molecules like prostaglandins, leukotrienes and platelet activating factor (PAF), and a number of cytokines like interleukin (IL)-1, 3, 4, 5, 6 and 8. An enormous variety of mediators are released which have more than one potent effect on airway inflammation.

As a result of vasodilation, increased vasopermeability and increased endothelial adhesiveness towards leukocytes further leads to an influx of inflammatory cells like lymphocytes, eosinophils and macrophages from blood circulation into the tissues. This in turn leads to the release of mediators which have further inflammatory effects [1].

Thus it can be understood that drugs affecting a single mediator are unlikely to be of substantial benefit. Unfortunately, the available antiasthmatics are of limited clinical use and some are only suitable for symptomatic relief.

As asthma is one of the major diseases affecting mankind, there is a need to develop drugs which can affect a wide range of mediators. This has posed a challenge to researchers to develop innovative strategies. This article is an attempt to summarize the potential benefits and limitations of available antiasthmatics and to give an overview of the emerging trends in the treatment of asthma.

2. Overview of available antiasthmatics

Currently anticholinergics, selective β_2-adrenergic agonists, methylxanthines, antihistamines, mast cell stabilizers and corticosteroids are used in the treatment of asthma.

2.1. Anticholinergics

The scientific basis for using anticholinergics as bronchodilators is that vagal fibre synapses activate nicotinic and M_3-muscarinic receptors in parasympathetic ganglia located in the airway wall. The submucosal glands are innervated by parasympathetic neurons which have M_3-receptors. Short postganglionic fibres release acetylcholine which acts on M_3-muscarinic receptors in the airway smooth muscles and submucosal glands [1].

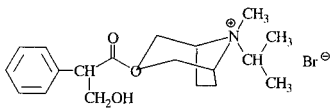
Anticholinergics have been widely used since the 1920s. They suffer from the disadvantage of slow onset and short duration of action. This was overcome by the introduction of ipratropium bromide, a quarternary anticholinergic agent with a better pharmacokinetic profile than the earlier agents of its class [1]. Ipratropium bromide (**1**) is a potent bronchodilator whose action is induced on the level of mucosa of the upper airways [2]. When combined with β_2-adrenergic agonists it shows further clinical benefits, mainly an intense and prolonged bronchodilatory effect.

2.2. β_2-Selective adrenergic agonists

The use of β_2-agonists is based on the fact that bronchial muscles are controlled by β_2-receptors, whose stimulation causes bronchodilation. Epidemiological studies have suggested that episodes of increased asthma mortality in the 1940s were accompanied by the introduction of ephedrine (**2**) and epinephrine (**3**) as antiastmatics. As they were nonselective β-adrenergic agonists, they had side effects like tachycardia due to a stimulation of β_1-receptors. Vasoconstriction attributed to the stimulation of α-receptors and increased release of histamine.

Efforts were made to induce specificity towards β_2-receptors. This resulted in the introduction of isoprenaline (isoproteranol, **4**), a derivative with a bulkier isopropyl group at the nitrogen. Its action on α-receptors was nullified but tachycardial effects remained. It has a rapid onset and a short duration of action. However, its indiscriminate use increased mortality due to asthma until the 1970s when people were educated and warned about its potential side effects.

Attempts made to minimize the tachycardial effects and to further improve selectivity towards β_2-receptors resulted in terbutaline sulphate (**5**), metaproterenol (**6**) and salbutamol (**7**) which became some of the most widely used antiasthmatics [1]. Recently (1990), two more drugs, bambuterol (**8**) and salmeterol (**9**) were introduced as compounds with



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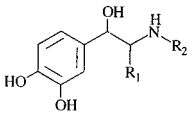
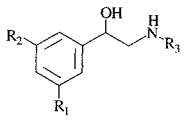
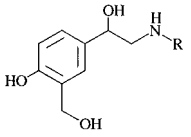


	R_1	R_2
(2) Epinephrine	H	Me
(3) Ephedrine	Me	Me
(4) Isoprenaline	H	HC(Me)Me



	R_1	R_2	R_3
(5) Terbutaline	OH	OH	$-C(Me)_3$
(6) Metaproterenol	OH	OH	$-CH(Me)_2$
(8) Bambuterol	OCON(Me)	OCON(Me)	$-C(Me)_3$



(7)

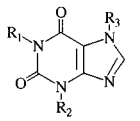
(9) $-(CH_2)_6-O-(CH_2)_4-Ph$

a duration of action longer than the earlier drugs. Bambuterol (**8**) as a prodrug is slowly converted to terbutaline (**5**) by hydrolysis in the lung tissue, generating long acting bronchodilation with comparable side effects [3]. Salmeterol (**9**) has an equally intense but four times longer lasting bronchodilatory activity than salbutamol (**7**) in equivalent doses. It is reported to be the first bronchodilator with significant anti-inflammatory activity and hence could complement prophylactic corticosteroid therapy [3, 4].

However, administration of β_2-adrenergic agonists either orally or by inhalation does not reduce bronchial hyperresponsiveness. Thus other approaches for the treatment of chronic symptoms are preferred [1].

2.3. Methylxanthines

The xanthine derivatives caffeine (**10**), theobromine (**11**) and theophylline (**12**) are closely related alkaloids isolated from various plant sources. Classical pharmacological studies, mainly with **10** during the first half of the century revealed that methylxanthines possess important pharmacological activities including bronchodilation. Theophylline (**12**) is a potent bronchodilator. The pharmacological actions of xanthines are based on multiple biochemical



	R_1	R_2	R_3
(10) Caffeine	Me	Me	Me
(11) Theobromine	H	Me	Me
(12) Theophylline	Me	Me	H
(30) Enprophylline	H	C_3H_7	H
(31) Denbufylline	$-(CH_2)_3CH_3$	$-(CH_2)_3CH_3$	$-CH_2COCH_3$
(32) Doxofylline	Me	Me	1,3-dioxalone-2-yl methyl

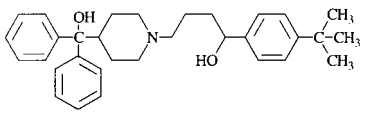
pathways, which include inhibition of phosphodiesterase enzyme (PDE), thereby increasing intracellular c-AMP levels; direct and indirect effects on the intracellular calcium concentration; increase in uncoupling of intracellular calcium with muscle contractile elements, and antagonism of adenosine receptors [5].

However, **12** has side effects like CNS stimulation, cardiac arrhythmias, hypotension and convulsions which have been attributed to its adenosine receptor antagonism [6]. Studies indicated that prolonged treatment with **12** results in hypokalemia [7]. In general, the drug has a narrow therapeutic index. It is not more effective than β_2-agonists but needs to be taken orally only once or twice a day so that the patient can be comforted by a night's sleep. This is important because asthma often increases in severity late at night and early in the morning. For a faster systemic absorption it is often used as 2 : 1 complex with ethylenediamine (aminophylline).

Further efforts were made to increase PDE inhibitory activity and to reduce adenosine receptor antagonism which has resulted in some potent PDE inhibitors which are discussed separately.

2.4. Antihistamines

Antihistamines have been available since the 1930's and have been used since the early 1940's in the treatment of allergic rhinitis and urticaria. However they were disappointing in the treatment of asthma as they possessed relatively weak antihistaminic as well as sedative and anticholinergic effects. In contrast, the newer nonsedating, more potent H_1-receptor antagonists appear to achieve effective histamine blockade in patients with asthma [8]. Terfenadine (**13**) and astemizole (**14**) inhibit bronchoconstriction induced by inhaled allergens by 50% in early asthmatic reactions [9]. Azelastine (**15**), a pthalazinone derivative, inhibited allergen-induced late asthmatic reactions in a double blind study of 11 atopic patients with asthma, possibly by suppressing the release of additional inflammatory mediators [10]. Cetirizine (**16**), a potent antihistamine has been found to reduce eosinophil and neutrophil late phase infiltration and prostaglandin D_2 release [11]. In 1990 and 1993, epinastine hydrochloride (**17**) and emedastine difumarate (**18**) were introduced for clinical use. Epinastine (**17**) is a potent non-sedating antihistaminic agent with anti-PAF and anti-LT activity. It has strong inhibitory effects on bronchoconstriction induced by histamine and bradykinin but not by other chemical mediators [12]. Emedastine (**18**) exerts its antiallergic effects via inhibition of P-induced histamine release which is mediated by the inhibition of calcium ion release from extracellular stores and of Ca^{++} influx into mast cells. In clinical trials in bronchial asthma, it improved asthmatic symptoms in 55.3% of the patients [13].



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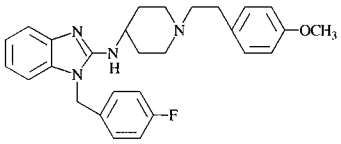

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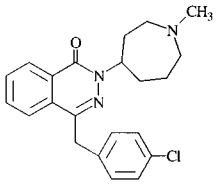

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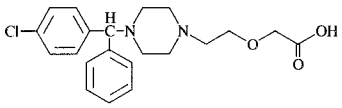

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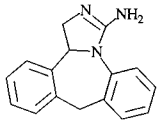

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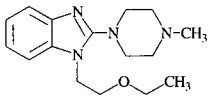

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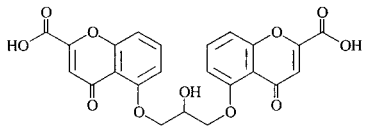

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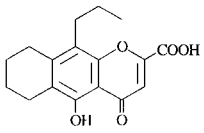

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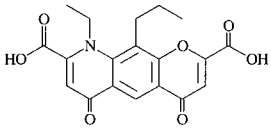

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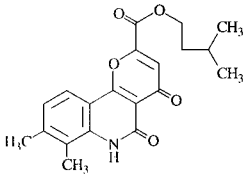

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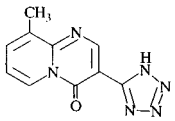

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There are relatively few clinical studies to date, but there is some evidence that treatment with newer antihistamines produces both subjective and objective improvement in younger patients. Further investigations and modifications may lead to drugs with better activity.

2.5. Mast cell stabilizers

Mast cell stabilizers are otherwise classified as interleukin-4 (IL-4) blockers. Chromolyn (**19**), a benzopyrone derivative (introduced in the 1960s by Fison) which was the result of an attempt to improve the bronchodilator activity of khellen, a chromone derived from the plant *Amni visnaga* [4]. It is now found to partially block IL-4 induced IgE production in the concentration range 10 nM–1 μM which is one hundred to one thousand times more potent than its inhibitory effect on degranulatory response in mast cells [14]. As it was ineffective orally, the Fison group developed an orally effective chromolyn derivative, proxycromil (**20**). However, potential carcinogenicity was revealed in clinical trials [4]. Further attempts led to another analogue, nedocromil (**21**) which is a potent IL-4 blocker [15]. In the years 1987 and 1991, reprinast (**22**) and pemirolast potassium (**23**) were introduced. Pemirolast potassium (**23**) is a potent antiallergic mast cell stabilizer with similar pharmacological properties to **19**. Reprinast (**22**) is 17 times more potent than chromolyn (**19**) in inhibiting histamine release due to antigen-antibody reactions [16, 17].

2.6. Corticosteroids

Several glucocorticoids are useful in the clinical management of asthma as they exhibit potent antiinflammatory actions. They stabilise the cellular lysozomal membrane. They supress immune responses and reduce antibody synthesis and impair the release of histamine and other mediators involved in bronchoconstriction [18]. Airway inflammation and bronchial hyperresponsiveness are controlled by corticosteroids. They block the uptake mechanism and potentiate the action of endogenous catecholamines and exogenous sympathomimetic bronchodilating agents. Inhaled corticosteroids reduce the severity of bronchial hyperresponsiveness in asthma but oral theophylline (**12**) does not. However they have no effect on bronchoconstriction [19]. The use of corticosteroids is limited by undesirable side effects, especially in prolonged administration (Table).

3. Current trends

3.1. Isozyme selective phosphodiesterase (PDE) inhibitors

The scientific basis for targeting isozyme selective PDE rests on two fundamental principles. Firstly, the inhibition of PDE increases the cellular content of two key messengers, c-AMP and c-GMP. This increase in messengers activates specific protein phosphorylation cascades which elicit a variety of functional responses and also suppress a broad array of functions in inflammatory and immune cells [20–22]. Moreover both c-AMP and c-GMP mediate bronchodilation [23, 24].

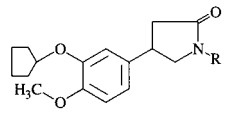
Table: Some currently available antiasthmatic agents

Drugs	Dose	Dosage form
Anticholinergics		
Ipratropium bromide	20 μg/Puff	200 metered dose
β_2-Adrenergic agonists		
Terbutaline	2.5–5 mg	Tab/syrup
	0.25–0.50 mg	Aerosol
Salbutamol	2–4 mg	Tab/syrup
	100–200 mg	Aerosol
Isoprenaline	400–800 mg	Metered dosage form
	20 mg	Tab
	2 mg	Injection
Ephedrine	20 mg	Tab
Salmeterol	50–100 mg	Metered dosage form
Mast cell stabilizers		
Sodium chromoglycate	400 dose unit	Metered dosage form
	20 mg	Capsule
Methyl xanthines		
Theophylline	100 mg	Tab
	300–600 mg	Sustianed Release Tab
Corticosteroids		
Beclomethazone	50–100 mg	Metered dosage form
Antihistamines		
Ketotifen	1 mg	Tab
Terfenadine	60–120 mg	Tab
Astemizole	10 mg	Tab
Cetirizine	10 mg	Tab
Epinastine	10, 20 mg	Tab
Emedastine	1,2 mg	Capsules

While these activities are attractive from a therapeutic standpoint, the ubiquitous distribution of cyclic nucleotides and PDEs makes the side effect profile of standard nonselective PDE inhibitors unacceptable. Thus there is a need to target the isozyme selective [PDE-IV] phosphodiesterase enzyme.

PDE-IV inhibitors can be classified essentially into three broad structural classes: catechol ethers, heterobicyclics and xanthine derivatives. In catechol ethers, archetypical members are rolipram (**24**; $IC_{50} = 1$ μM) and R020-17424 (**25**; $IC_{50} = 5$ μM). SAR studies have shown that the *S*-isomer of rolipram is 400 times more potent than the *R*-isomer. The replacement of the pyrrolidinone ring in **24** by benzamides has resulted in RP-73401 (**26**) which has shown exceptional potency in all tests and has been selected for clinical investigations [25]. Currently it is also undergoing evaluation for antiarthritic activity [26]. Further modifications carried out based upon independent molecular modeling of 24 have resulted in tibenelast (**27**), a potent competitive inhibitor of PDE-IV (isolated from guinea pig peritonial mononuclear cells). However, preliminary clinical studies showed that although, it slightly improved pulmonary function in asthmatics, this effect was not statistically significant [27].

In the heterobicyclic class of compounds. SAR studies were carried out on nitraquazone (**28**), a quinazolinedione derivative, with an enzyme mixture from rat brain cortex, in which the nitro group was replaced by ester linkage, a further benzene by pyridine, pyrimidine by pyridazine etc. which resulted in a number of potent compounds. An isosteric replacement of the benzene ring with a pyridine nucleus has resulted in a potent compound RS-25344 (**29**). It is a more potent bronchorelaxant and tends to



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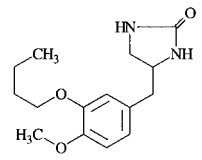

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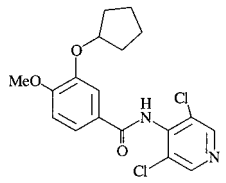

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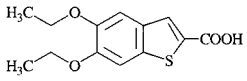

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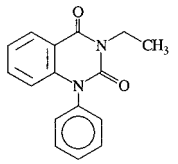

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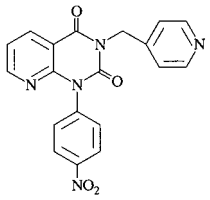

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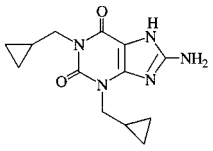
have higher affinity for the binding site. Further studies are in progress [28].

The xanthine derivatives enprophylline (**30**) [29], denbufylline (**31**) and doxofylline (**32**) [30] were found to be potent and selective for PDE-IV equivalent to **24** and lacked the adenosine receptor activity, common to most of alkylxanthines. However derivatization of N-7 and C-8 sites of the selective PDE-IV inhibitor, BRL-61083 (**33**) provided PDE-IV inhibitors with varying degrees of PDE-V and adenosine receptor activity [31, 32].

Recent reports indicate that the imidazo[4,5-*c*]quinolin-4(5*H*)-one derivative, KF-15570 (**34**, $ED_{50} = 0.42$ mg/kg, i.v., aminophylline, $ED_{50} = 7–8$ mg/kg, i.v.] is a potent bronchodilator [33] with weak adenosine receptor activity. However further investigations are in progress to develop this, as the compound has shown fewer CNS side effects than theophylline [34]. In connection with this some 6-aryl benzimidazo[1,2-*c*]quinazolines (**35**), benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones and their thio-analogues (**36**) were recently tested for bronchodilator activity. However the results were not very promising [35–37]. Advances in molecular and genetic biology have shown that



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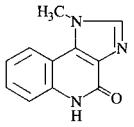

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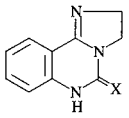

X = O, S

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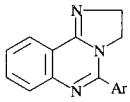

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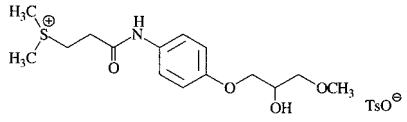

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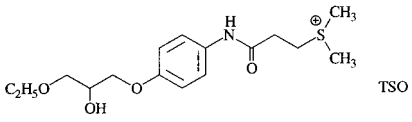

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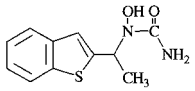

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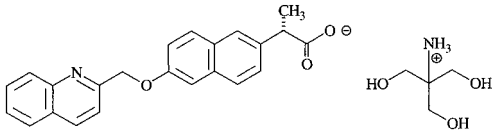

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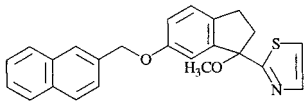

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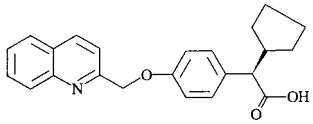

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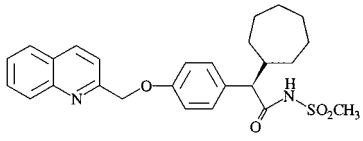

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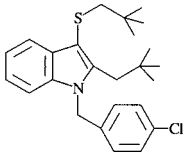

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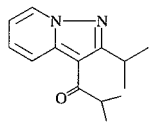


(46)

multiple subsites exist within each isozyme family. for example cDNAs encoding, at least four subtypes of PDE-IV have been cloned and two have been expressed. This information combined with experimental data suggests that PDE-IV subtypes have differential cellular and tissue distributions which raises the possibility of designing inhibitors that are subtype-specific, thereby achieving a greater degree of cellular selectivity than that afforded by current isozyme selective inhibitors in a new generation of drugs [38].

3.2. Lymphocyte derived cytokines

Immunoglobulin E is a probable cause of human atopic diseases, so inhibition of IgE production is an appropriate target for antiasthmatic drugs. Recent advances in immunology and molecular biology have shown that both T-cells and T-cell derived cytokines (interlukins 3 and 4) are required for IgE synthesis.

Interlukin-4 (IL-4) is a B-cell and T-cell stimulating factor, that is synthesized by Th-2 cells, mast cells and basophils. IL-4 is a key mediator that initiates IgE synthesis in human lymphocytes. It is also involved in expression of vascular cell adhesion molecules on endothelial cells, promoting migration of blood eosinophils into pulmonary tissues. Overexpression of IL-4 in Th-2 cells has been postulated to be the cause of elevated serum IgE in asthmatic patients.

Agents blocking the biosynthesis of IL-4 itself could be a better target than IL-4 blockers (which are covered under mast cell stabilizers). Research carried out on this assumption resulted in intron-a and IPD-1151T (**37**). In a case study a patient showed an improvement in symptoms (eczema) and a decrease in serum IgE after 1.5–5 weeks treatment with Intron-a, supporting its potential usefulness [15]. Compound **37** inhibits allergen mediated IL-4 production from helper T-cells. A phase III clinical trial showed that the serum levels of total and allergen specific IgE were significantly reduced by compound **37** (300 mg/day for 6–13 weeks) [39].

In 1995, suplatast tosylate (**38**) was introduced. Its action was found to be due to the inhibition of IL4 and IL6 production by T-cells at the gene level. In allergic patients it improved clinical symptoms markedly which correlated with a significant decrease in serum IgE antibody level [40].

3.3. Lipoxygenase and leukotrienes

Asthma has been characterized as a disease associated with chronic inflammation in which leukotrienes are found to play a significant role. Leukotrienes are the products of arachidonic acid metabolism along the lipoxygenase pathway (Fig.). They are important mediators of a variety of pathological processes in mammalian organisms [41]. Leukotriene-B_4 (LTB_4) which is mainly formed in neutrophils, is a proinflammatory mediator. It predominantly mediates chemotaxis by activating the b-leukotriene receptor (BLT) [42]. The cysteinyl leukotrienes LTC_4, LTD_4 and LTE_4 are produced in eosinophils and mast cells. Cysteinyl leukotrienes exert their actions mainly through cy-

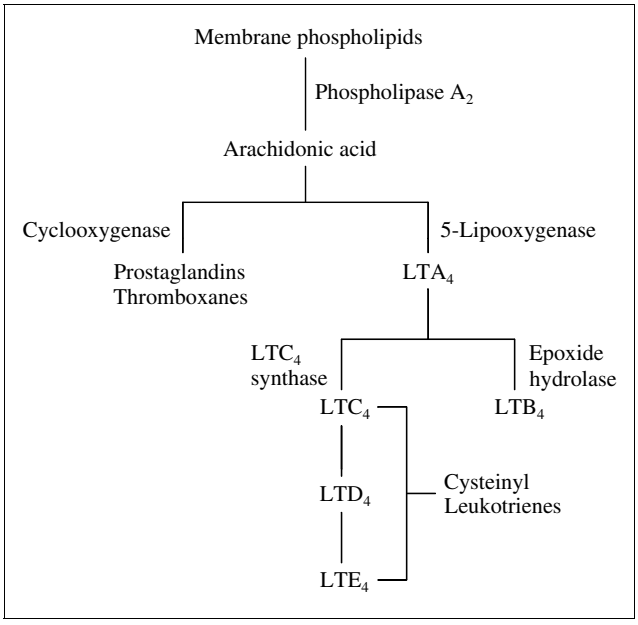


Fig. Biosynthesis of leukotrienes

steinyl leukotriene receptor-1 ($cysLT_1$) and to a lesser extent through $cysLT_2$ [43, 44]. These actions include contraction of human airway smooth muscle, chemotaxis and increased vasopermeability [45, 46]. Thus they are much involved in the pathophysiology of asthma. 5-Lipoxygenase [5-LO], a key group of enzymes involved in leukotriene formation and leukotrienes itself has been targeted with the hope of better activity. Hence, inhibition of lipoxygenase would represent a reasonable approach for the treatment of asthma.

In a double blind randomised study of the 5-LO inhibitor, zileuton (A 64077; **39**) in asthmatic males, airway reactivity to hyperventilation of cold dry air was reduced following oral administration of the drug. Allergen induced nasal congestion was reduced in human volunteers suggesting the potential therapeutic importance of 5-LO inhibition in allergic rhinitis [47]. It also reduced the number of inflammatory cells recovered in bronchoalveolar-lavage fluid from patients with late asthmatic response after bronchopulmonary segmental allergen challenge [48]. Further QSAR and modeling studies resulted in tromethamine (**40**) which elicited a dose dependent inhibition of bronchoconstriction when given orally [49]. One more compound ICI-216800 (**41**) exemplifies the first chemical series to show stereospecific interaction in the inhibition of 5-LO. The (+)-isomer inhibited LTB_4 in human blood with IC_{50} of 0.54 μM compared to >40 μM for the (−)-isomer [50].

Further BAY X 1005 (**42**), which was identified as a potent, orally active leukotriene synthesis inhibitor has shown that a good correlation exists between binding to the high affinity binding site and the potency of LTB_4 inhibition in polymorphonuclear leukocytes [51]. It significantly reduced bronchoconstriction during the early asthmatic response and partially attenuated it during the early hours of the late asthmatic response [52]. The structural modification of 42 by amidation of the carboxylic group to a methyl sulphonamido group, increase in the size of the cycloalkyl ring and enantiomeric separation of the *R*-isomer resulted in the most active compound of the series BAY Y 1015 (**43**) [53]. MK-886 (**44**), a leukotriene biosynthesis inhibitor was examined in atopic subjects with documented early and late asthmatic reaction and subsequent increase in airway responsiveness to histamine. Given orally, it inhibited antigen-induced early asthmatic reactions and delayed the late asthmatic reactions but did not afford protection against increase in airway responsiveness [54].

In 1987 and 1989, two drugs, amelexanox (**45**, Takeda) and ibudilast (**46**, Kyorin) were introduced for treatment of asthma whose activity is attributed to leukotriene D_4 receptor antagonism. Compound **45** is an orally active antiasthmatic used in the treatment of bronchial asthma and allergy related sinus disorders [55]. Ibudilast (**46**) antagonizes LT-D_4 contractions of guinea pig ileum and tracheal muscles *in vitro* and inhibits eosinophil accumulation *in vivo* [56].

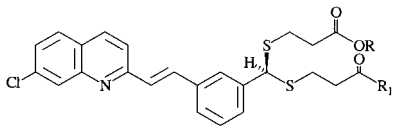
One of the first leukotriene antagonists used was FPL-55712. It has a distinctive taste and produces transient discomfort in the throat after administration. It has been found to be the least potent and least effective drug of this class [57]. In a placebo controlled trial, the potent LTD_4 receptor antagonist, MK-571 (**47**), attenuated exercise-induced bronchoconstriction in subjects with stable asthma. The *R*(+)-isomer ($pK_b = 9.0$) was slightly more potent than the *S*(−)-isomer ($pK_b = 8.7$), but the (−)-isomer achieved higher levels of concentrations at all time points and was cleared less rapidly than the (+)-isomer [58]. Four weeks of oral treatment with compound **47** has been shown to be effective in reducing symptoms, β_2-agonist and spirometry [59]. Introduction of a bicyclic ring nucleus and modification of this compound led to a more potent compound, ICI-204219 (Zafirlukast, **48**) whose preclinical and clinical pharmacology has been reported [60]. A double-blind, randomized, placebo-controlled study of **48** showed significant improvement in morning peak flow rates, night time wakening and daytime symptoms [61]. Further studies by the same group of workers showed promising results and the compound has now been marketed under the trade name Accolate® [62]. Further evaluation led to a potent benzopyran derivative GCP-45715 (**49**) which has potency comparable to **48** with a duration of action greater than 24 h [63]. The search of a better leukotriene antagonist has led to the development of two more potent compounds, montelukast [64] and pranlukast (**50**) [65].

3.4. Thromboxane A_2 receptor antagonists

Thromboxane A_2 (TXA_2) is a metabolite of the arachidonate cascade. It is involved in several cardiovascular and respiratory diseases through its potent biological effects on platelet aggregation and constriction of vascular and respiratory smooth muscles. Preliminary clinical studies of TXA_2 receptor antagonists and thromboxane synthetase inhibitors (TXSI) have been reviewed concluding that TXA_2 blockers offer greater clinical potential than TXSI (**51**) [66]. In 1995, serotradast (**52**), a benzoquinone derivative was introduced which is a potent inhibitor of platelet aggregation and bronchoconstriction induced by a TXA_2 mimic and by a variety of spasmogenic prostanoids including $PGF_{2\alpha}$, PGD_2, 9α, 11β-PGF_2. Serotradast (**52**) shows excellent efficacy in asthma and has been reported to be potentially useful in hyperresponsive disorders. The *R*-(+)-isomer is the active compound [67].

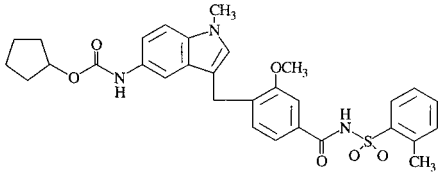
3.5. Potassium channel openers (PCO)

The 1970s and 1980s were considered to be the eras of sodium and calcium channels respectively whereas the 1990s is the era of potassium channels. There has been an



(47)

R	R_1
NMe_2	OH [R(-) isomer]
OH	NMe_2 [(S(+) isomer]



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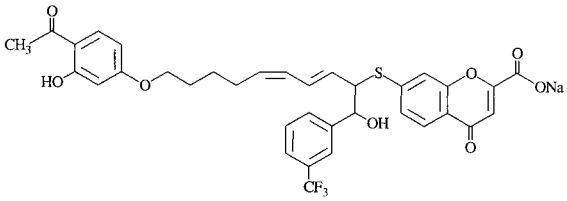

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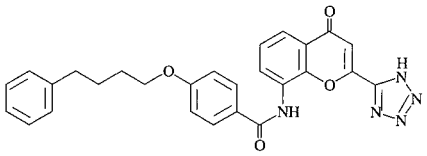

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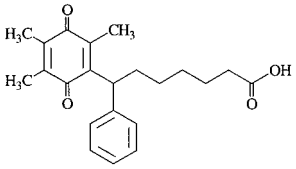

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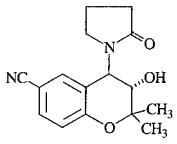

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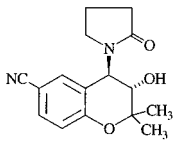

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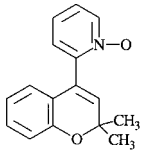

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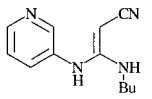

(55)

enormous growth of interest, since the elucidation of the mechanism of action of cromakalim (**53**) which involves enhancing the movements of potassium ions through smooth muscle cell membranes like vascular smooth muscles, cardiac tissues, bronchial smooth muscles, GI smooth muscles, uterine, ureter and detrusor smooth muscles etc. This is of potential benefit in the treatment of hypertension, angina and asthma [68]. Cromakalim (**53**) relaxed spontaneous tone or tone induced by a range of spasmogens including histamine, PGE_2, 5-HT, LTD_4 in guinea pig isolated trachea or human bronchial smooth muscles [69, 70]. Bronchodilator activity was also demonstrated in *in vivo* models of respiratory distress at doses lacking cardiovascular effects [70, 71].

Orally administered cromakalim was also reported to protect asthmatic patients against nocturnal bronchoconstriction [72]. Mechanistic studies indicate that the relaxant properties of PCOs are not the result of an effect on cyclic nucleotides, but their influence on Ca^{++} stores may be important. Although **53** inhibited cholinergic and adrenergic nerve mediated bronchospasm both *in vitro* and *in vivo*, it displayed greater potency in inhibiting non-adrenergic non-cholinergic nerve mediated bronchospasm [73, 74].

A more potent (3*S*,4*R*)-isomer of cromakalin (**53**), lemakalim (**54**) is being developed clinically [75]. Novel compounds R031-6930 (**55**) and P1060 (**56**) have been developed and a comparative study of four PCOs in relaxing guinea pig trachea was carried out. P1060 was found to be 4 times more potent than cromakalim [76].

3.6. Monoclonal antibody therapy

Better understanding of the mechanism of airway inflammation and recognition of the relationship between inflammation and bronchial hyperreactivity has led to the utilization of monoclonal antibody therapy as an alternative method of treatment for asthma. Targeting an ellergen-specific immunoglobulin, IgE by humanised murine monoclonal IgG_1 antibody has reduced free IgE and blocked both the early and late phase response to allergen challenge [77]. Intracellular adhesion molecule-1 (ICAM-1) plays a key role in the movement of inflammatory cells from vascular space to the airways [78, 79]. Some investigators have attempted to interfere with this process in a monkey model of asthma, by targeting ICAM-1 with a monoclonal antibody. It blocked both the eosinophil influx and bronchial hyperreactivity that occurred after repeated antigen challenge [80]. Further studies are needed to confirm its efficacy.

4. Conclusion

Current asthma therapy involves relaxation of airway smooth muscle and inhibition of the underlying pulmonary inflammatory events. However, current clinical agents, produce both these pharmacological effects inadequately. Beta adrenoceptor agonists elevate cAMP levels in smooth muscle cells promoting muscle relaxation and bronchodilation. These agents provide only moderate antiinflammatory actions. Conversely the glucocorticoids possess antiinflammatory properties but their administration over prolonged periods is often not well-tolerated. The benefits of the dual antiinflammatory and bronchodilator, theophylline, which is both a nonselective PDE inhibitor and a nonselective adenosine receptor antagonist, are limited due to its dose limiting side effects. Attempts have been made to increase selectivity towards PDE-IV by modifying the

basic theophylline ring system which has resulted in several drugs such as denbuphylline, doxophylline and enprophylline. The current trends is towards designing xanthine-based, nonxanthine analogs like imidazoquinazolines. This has shown promising results.

The IL-4 blockers like nedocromyl, and reprinast and IL-4 biosynthesis inhibitors like suplatast have attracted interest more recently. Leukotriene D4 inhibitors like ibudilast, zileuton and ameloxenox have been introduced into therapy recently. Several new leukotriene inhibitors are undergoing extensive trials. The thromboxane A receptor antagonist serotradast has been used in asthma treatment. Similarly PCOs have created enormous interest in the treatment of asthma, angina and hypertension. Cromakalim, hemakalim and their modified forms such as R 1060 are very promising. Further studies of monoclonal antibody therapy are needed. Although PDEIs and PCOs have shown some promising results, the paradigms are only now advancing from the stage of concept validation to that of technology refinement. Medicinal chemists have shown that much can be done to alter their structure, activity and properties to obtain effective molecules. Targetting of selective inhibitors of PDE isozyme subtypes may achieve increased tissue selectivity and reduced potential for side effects. Determination of the ultimate utility of this and other novel strategies currently being evaluated for asthma will require additional clinical investigations.

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