Kirk-Othmer Encyclopedia of Chemical Technology.

ANTIASTHMATIC AGENTS

Asthma is an extremely complex condition characterized by variable and reversible airways obstruction combined with nonspecific bronchial hypersensitivity (1–3). The cause of asthma, which is not always readily diagnosed (4), remains unknown. Days, if not weeks, are needed to document the spontaneous reversal of the airways obstruction in some patients. Asthmatics experience both an immediate hypersensitivity response and a delayed late-phase reaction, each mediated by a different pathway. Chronic asthma has come to be viewed as an inflammatory disease (5). The late-phase reaction plays a key role in inducing and maintaining the inflammatory state which in turn is thought to induce the bronchial hyperresponsiveness (6). The airways obstruction results from both contraction of airways smooth muscle and excessive bronchial edema. Edema, a characteristic of inflammatory states, is accompanied, in this case, by the formation of a viscous mucus which can completely block the small airways.

Asthma affects 3–5% of the population and is one of the most common chronic illnesses (7–9). Both the frequency and severity of asthma appear to be increasing (10–13). Acute, severe asthma has the potential to be fatal. The disease may first appear in childhood and individuals so affected can suffer recurrent episodes throughout their lives or they may "outgrow" the condition at puberty. On the other hand, there is also adult-onset asthma. These people show no symptoms as children or as young adults, but suddenly develop symptoms later in life. There have been many reports of bronchial infections preceding the appearance of asthma. However it is not known whether these infections contributed to the development of the disease or whether individuals who are already predisposed to asthma are more likely to experience bronchospasms as a result of a bronchial infection (14).

Clinically, there are several ways of classifying asthma and treatment varies depending upon the classification. Extrinsic asthma, also called allergic asthma, is experienced by adults and, most commonly, by children. In extrinsic asthma it is possible to demonstrate specific causal agents, usually antigens, eg, animal danders, foods, drugs, house dust, pollens, or mold spores. Atopic extrinsic asthmatics usually have elevated levels of circulating immunoglobulin E (IgE), have a family history of inherited allergies (atopy), and commonly show other allergic symptoms such as rhinitis, or have a history of eczema (15). However, especially in occupation-induced asthma, irritants may act as the allergenic agent and IgE does not appear to be involved in some nonatopic extrinsic asthmatics.

Intrinsic asthma, also called idiopathic asthma, usually develops in adulthood. In intrinsic asthma allergic factors are not demonstrable. Episodes of intrinsic asthma may be triggered by a variety of stimuli, eg, emotional state, exposure to cold air, or inert dusts. Both intrinsic and extrinsic asthmatics can be prone to exercise-induced attacks. Individuals who experience a combination of extrinsic and intrinsic asthmatic reactions have mixed asthma. Status asthmaticus refers to an especially acute life-threatening asthma attack which is resistant to normal treatments and which may require hospitalization in order to stabilize the patient.

Current asthma treatments are not curative and historically have relied on pharmacologic intervention with bronchodilators (Fig. 1) (16) to prevent or relieve the symptoms of asthma. More recently the focal points of both treatment and research efforts have shifted from bronchodilators to agents which reduce the underlying inflammatory state (5, 6, 17). Management of extrinsic asthma usually includes manipulation of the

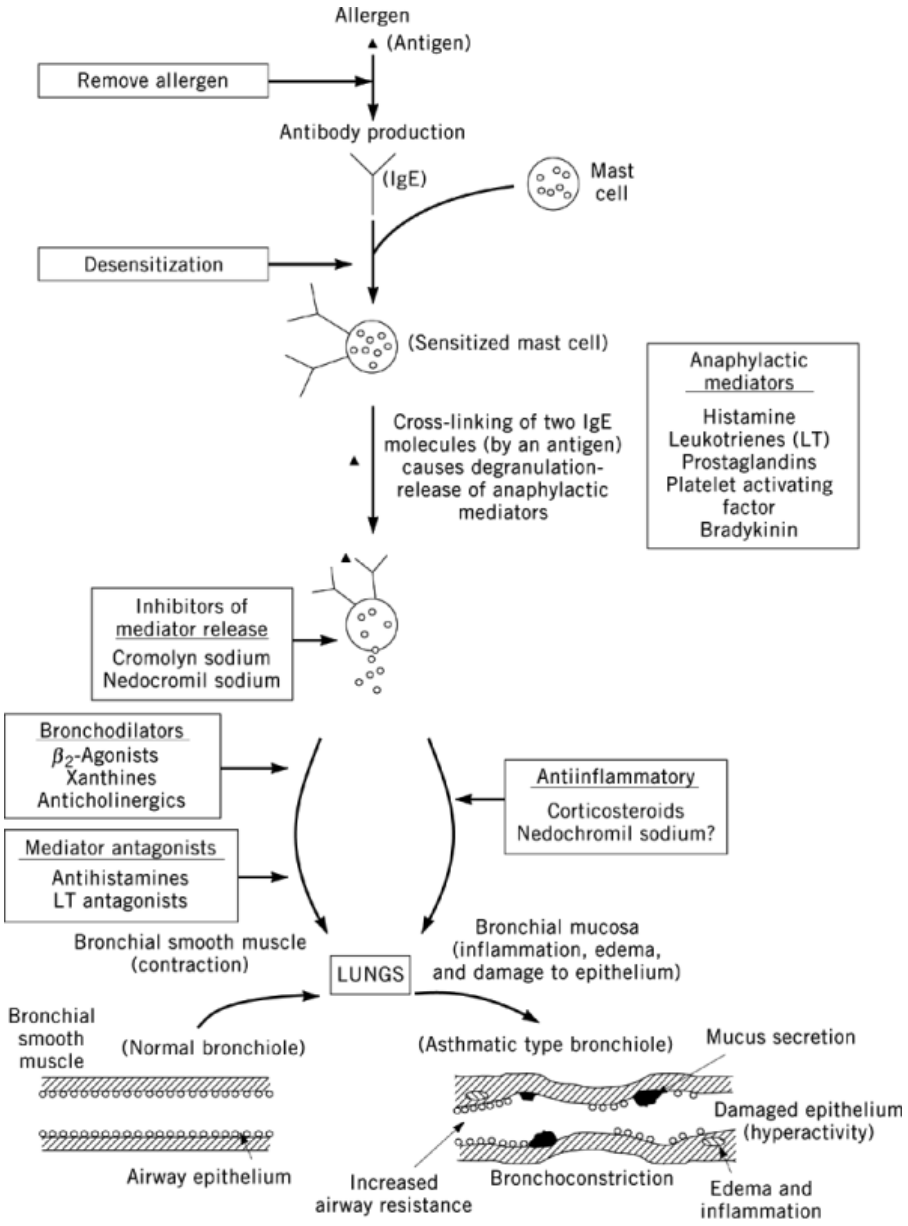


Fig. 1. Schematic diagram showing possible sites of action of antiasthmatic drugs.

patient's environment to minimize or completely eliminate the causal agent. This can be especially beneficial in occupationally induced asthma. Treatment of extrinsic asthmatics may also include hyposensitization, or desensitization, by exposure to small and increasing amounts of the known antigen. Although hyposensitization is widely used by allergists for the treatment of allergic rhinitis, its use and potential benefit in the treatment of strictly defined asthma remains controversial (18–20). The cascade of events involved in the asthmatic response and potential points for pharmacologic intervention are shown in Figure 1.

Table 1. Order of Preference for First Choice Antiasthmatic Agent Maintenance Therapy

	Order of preference		
	U.S.[b]	UK[c]	1989 U.S. market share, %[a]
oral xanthines	1	4	~27
inhaled β_2-agonist	2	1	~26
oral β_2-agonist	3		~18
inhaled steroid	4	2	~18
inhaled inhibitor of mediator release	5	3	~5

[a] Ref. 25. (Courtesy of IMS International, a company of Dun & Bradstreet Corporation.)
[b] Ref. 21.
[c] Ref. 22.

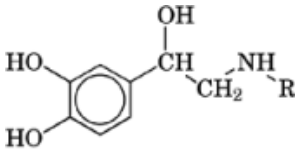
The order of preference of drug treatment varies from country to country (21, 22) (Table 1). In part this difference reflects the lack of a "magic bullet" for the treatment of asthma. However, this difference may also be explained by differences in marketing approval. Some agents are not yet available in the United States and the exposure of U.S. physicians to some of the newer inhalation formulations has been limited. However, the use of inhaled, rather than oral, agents has begun to increase in the United States (23, 24) as indicated by the changes in the market for prescription antiasthmatic drugs. In the period from 1984 to 1989 the share of new prescriptions for inhaled β_2-agonists increased from 18% to 26%, whereas that for oral xanthines dropped from 39% to 27% (25).

Improvements in asthma treatment include the development of more effective, safer formulations of known drugs. The aerosol administration of β_2-agonists or corticosteroids results in a decrease in side effects. Also, the use of reliable sustained release formulations has revolutionized the use of oral xanthines which have a very narrow therapeutic index (see Controlled release technology). For many individuals, asthma symptoms tend to worsen at night and the inhaled bronchodilators do not usually last through an entire night's sleep (26, 27).

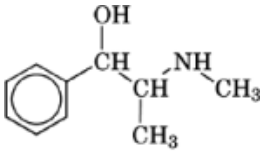
1. β-Adrenergic Stimulants

β_2-Agonists are widely used in the symptomatic treatment of asthma. Although both oral and aerosol formulations of these bronchodilators have been available for many years, advances have occurred in delivery technology with the development of dry powder aerosols (qv) (see Drug delivery systems) (28). The ease of usage of these breath-activated systems has improved patient compliance and therapeutic response. There are several detailed reviews on β_2-agonist therapy of bronchial asthma (29–31), and on the structure-activity relationships of this class of drugs (32).

The modern usage of β_2-agonists for the treatment of asthma dates to 1903 when the effect of injected epinephrine [51-43-4] (adrenaline) $C_9H_{13}NO_3$, (**1** R = CH_3) was investigated (see Epinephrine and norepinephrine) (33). As in some other modern treatments, eg, xanthines and anticholinergics, the roots of β_2-agonist therapy for asthma can be found in historical records which document the use of herbal extracts containing ephedrine [299-42-3], $C_{10}H_{15}NO$, (**2**) as bronchodilators. Epinephrine and ephedrine are structurally related to the catecholamine norepinephrine [51-41-2], $C_8H_{11}NO_3$, (**1**, R = H), a neurotransmitter of the adrenergic nervous system (see Neuroregulators).



(1)



(2)

Endogenous catecholamines have an extremely short half-life and reuptake into sympathetic nerve storage vesicules is the main mechanism for removing norepinephrine from circulation. To some degree reuptake also occurs with epinephrine. This process is relatively selective, however, and does not readily take place with nonnaturally occurring catecholamines. Catecholamines that escape reuptake are rapidly catabolized by two widely distributed enzymes, catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). The former transfers a methyl group to the 3-hydroxy of catecholamines. The resultant 3-methoxy compounds have no adrenergic agonist activity and in some cases may be adrenergic antagonists. MAO is less descriminatory, cleaving the carbon–nitrogen bond of primary and secondary amines with concommitant oxidation of the carbon atom.

Ephedrine, which is not a catecholamine, has weak oral activity as a bronchodilator and although it has some direct action at adrenergic receptors, its predominant mode of action is by displacing norepinephrine from storage vesicules. β_2-Agonists which are in use or are under investigation are the result of quests for improved selectivity, retention of potency, oral activity, and longer duration of action.

The adrenergic nervous system is one of the two main branches of the autonomic nervous system (34), which regulates the so-called automatic functions of the body, eg, the actions of various organs such as the lungs and heart. The other main branch of the autonomic nervous system is called the cholinergic nervous system and it has acetylcholine [51-84-3], $CH_3COO(CH_2)_2N(CH_3)^+{}_3$, (see Choline; ENZYME INHIBITION) as a neurotransmitter. More recently, a third branch to the autonomic nervous system has been identified in human (35) and animal airways (36, 37). In this nonadrenergic, noncholinergic nervous system both the neurotransmitter and the importance in lung function are in dispute (38). The adrenergic and cholinergic nervous systems often act in opposition to one another (34).

Division of the receptors in the adrenergic nervous system into two classes (α and β) was proposed in 1948 (39) when a difference in the rank order of potency of epinephrine (**1**, R = CH_3), norephinephrine (**1**, R = H), and isoproterenol [7683-59-2], $C_{11}H_{17}NO_3$, (**1**, R = $CH(CH_3)_2$) was noted to depend on the organ examined. Further subdivision into groups β_1 and β_2 was proposed in 1967 (40). Both types of β-adrenoceptors are found throughout the body. One of the more significant roles for β_1-receptors is in cardiac tissues where they mediate contraction. Although the effect of triggering β_2-receptors is tissue-dependent, stimulating those found in bronchial and vascular smooth muscle induces relaxation (Fig. 2). Stimulating the adrenergic receptor results in activation of adenylate cyclase which in turn catalyzes production of cyclic-3′,5′-adenosine monophosphate (cyclic AMP). The cyclic AMP then acts as a second messenger activating a protein kinase which selectively phosphorylates myosin kinase resulting in inhibition of calcium-dependent smooth muscle contraction. Also, activation of β_2-adrenoceptors results in the inhibition of cholinergic neurotransmission in human airways (41) and this too should cause smooth muscle relaxation.

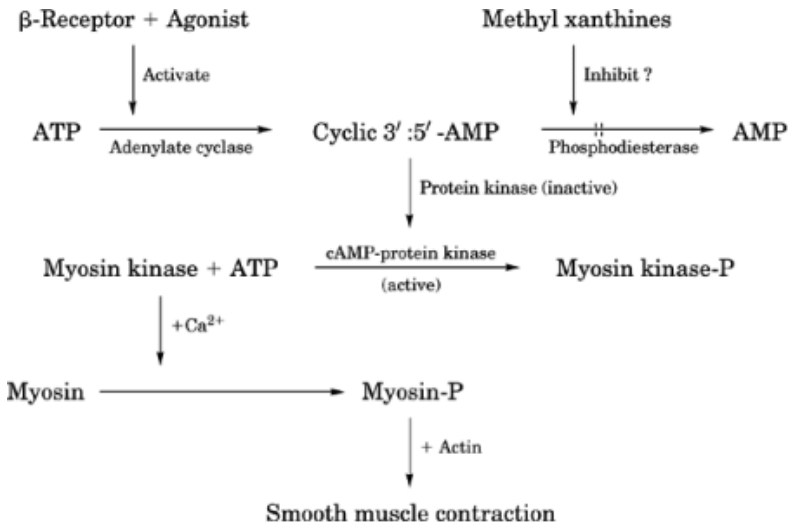


Fig. 2. Proposed mechanism of inbition of smooth muscle contraction by β_2-agonists, where AMP is adenosine monophosphate, cAMP is cyclic-3:5′ adenosine monophosphate, ATP is adenosine triphosphate, and -P is an attached phosphate.

Elevation of cyclic AMP levels is also known to inhibit the release of inflammatory and contractile mediators from mast cells (42). The good clinical efficacy of β_2-agonists may be related to this action because some members of this class of drugs inhibit mediator release at the same concentrations at which they relax smooth muscle (43). In contrast to their effectiveness against immediate bronchoconstriction, β_2-agonists do not inhibit the late asthmatic response or reverse bronchial hyperreactivity (44, 45).

Because of the widespread nature of adrenoceptors, nonselective β-agonists can produce many undesirable side effects. Therefore, before adrenergic agonists could become widely used in the treatment of asthma, some selectivity in action was needed. Whereas epinephrine and ephedrine have significant agonist activity at both α and β adrenoceptors, isoproterenol is a selective agonist at the β-receptor (39). However, isoproterenol does not distinguish between the β_1 and β_2 receptors and it is not active orally.

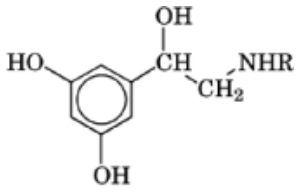
Aerosol administration of isoproterenol produces a prompt (2–5 minutes) intense bronchodilatation of relatively short (1 h) duration. The lack of β_2-selectivity leads, in many cases, to tachycardia and blood pressure elevation. Also, use of isoproterenol, like all other known β-agonists, results in a down-regulation, or desensitization, of β-adrenergic receptors. This desensitization is only partial, and after time (depending on dose, patient, and agent), a stable, less responsive state is achieved in which β-agonists remain effective. Isoproterenol has been widely used for many years.

A significant advance in β-agonist therapy occurred with the discovery of metaproterenol [586-06-1], $C_{11}H_{17}NO_3$, (**3** R = $CH(CH_3)_2$). Replacing the catechol subgroup with a resorcinol unit results in a compound which is no longer susceptible to metabolism by COMT and therefore has a longer (4 h) duration of action. Metaproterenol has a selectivity profile that is similar to that of isoproterenol, but it is 10–40 times less potent *in vitro* (46). However, metaproterenol is active if given orally and, therapeutically, it is administered either orally or by aerosol. Better selectivity of action is achieved by the aerosol route, although large or frequently repeated aerosol doses may also cause side effects.

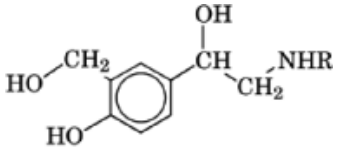
Changing the *N*-substituent of metaproterenol to a *tert*-butyl group gives rise to terbutaline [23031-25-6], $C_{12}H_{19}NO_3$, (**3** R = $C(CH_3)_3$) (47), an orally active agent having a duration of action of from 6–7 h. The presence of a tertiary carbon alpha to the amine protects against the action of MAO. Also, it had been shown earlier for catecholamines that increasing the steric bulk around the nitrogen results in improved β_2-selectivity (32).

This finding carries over to the resorcinol series: terbutaline stimulates β_2-receptors to a significantly greater extent than β_1-receptors.

Terbutaline has about six times the selectivity of isoproterenol and is claimed to produce fewer side effects. Terbutaline inhibits the release of mediators from sensitized human lungs at clinically relevant concentrations (31), and has been shown to have a prophylactic effect in bronchial challenge studies in addition to being a bronchodilator. Also, nasal administration of fenoterol [13392-18-2], $C_{17}H_{21}NO_4$, (**3**, R = $CH(CH_3)CH_2C_6H_4OH$), a closely related β_2-agonist, in clinical studies on the treatment of allergic rhinitis has clearly shown inhibition of release of allergic mediators (48, 49). Both aerosol and oral formulations of terbutaline are in use, although examination of an oral slow-release formulation for use in nocturnal asthma revealed that patients preferred long-acting theophylline preparations because of the incidence of undesired side effects (50).



(**3**)



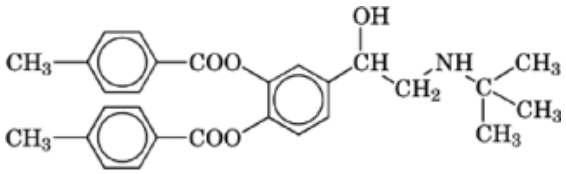
(**4**)

Variation of the substituents on the aromatic ring led to the discovery that the 3-hydroxy could be replaced with a variety of groups, eg, CH_2OH, $NHCH_3$, $NHCONH_2$, $NHS(O)_2CH_3$, that successfully mimic the electron donating and hydrogen bonding properties of the hydroxide moiety at the adrenergic receptor. The 3-CH_2OH analogue has been the most studied in this series of compounds. Albuterol [18559-94-9], $C_{13}H_{21}NO_3$, (**4** R = $C(CH_3)_3$) also called salbutamol (51), is the most widely prescribed β_2-agonist for either aerosol or oral administration both in the United States and worldwide.

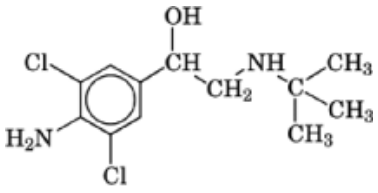
Replacement of the hydroxy with CH_2OH results in resistance to both COMT and conjugation. Also, because the *tert*-butyl group confers resistance to MAO, albuterol is metabolically quite stable and animal studies have shown that it is excreted unchanged and as the phenolic glucuronide (31). *In vitro,* albuterol has been shown to inhibit mediator release and to have about 59 times the β_2/β_1-selectivity of isproterenol (32). In contrast, clinical studies using po albuterol reveal only a seven- to tenfold improvement in selectivity as compared to isoproterenol (52). Studies using aerosol administration show that albuterol has fewer side effects, more rapid onset, and at least the same duration of action (5 h) as the immediate release oral formulations. It is believed that the cardiac responses following oral administration result from an indirect reflex stimulation of cardiac output. This reflex results from the lowering in blood pressure that the β_2-agonist induced relaxation of vascular smooth muscle produces. Because of this finding the preferred mode of administration of β_2-agonists is by aerosol even with newer, more selective agents.

More recent research efforts have focused on the development of longer acting β-agonists which could be administered less frequently and be more efficacious in controlling nocturnal asthma. There are several agents currently under clinical evaluation. Bitolterol [30392-40-6], $C_{28}H_{31}NO_5$, (**5**) represents one approach

to extending duration of action. It is a prodrug having no direct effect at adrenergic receptors; it must be hydrolized by esterases to the active phenolic agent. Bitolterol, presumably because of differential rates of hydrolysis, gives unpredictable bronchodilation if given orally (53). However it is hydrolyzed efficiently in the lung and an aerosol formulation of it has been compared, albeit unfavorably, with sustained release theophylline for control of nocturnal asthma (27).



(**5**)



(**6**)

Clenbuterol [37148-27-9], $C_{12}H_{18}Cl_2N_2O$, (**6**) (54), a nonphenolic analogue of terbutaline, is not susceptible to COMT or to conjugation. It has a long plasma half-life (20 h), but does not seem to differ in pharmacological half-life from albuterol (55).

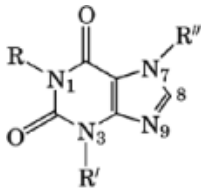
Salmeterol [89365-50-4], $C_{25}H_{37}NO_4$, (**4**, R = $(CH_2)_6O(CH_2)_4C_6H_5$) (56), is a long-acting analogue of albuterol in which the amine substituent is a long lipophilic chain. Although the plasma half-life of salmeterol is the same as that of albuterol, salmeterol has a much longer (12 h) duration of action following aerosol administration and tests to determine its efficacy in nocturnal asthma are underway (55). *In vitro,* salmeterol is about five times as potent as salbutamol and also shows an unusually extended duration of action (57) which might result from exo-receptor binding (56).

Although β_2-agonists are useful in the treatment of asthma, the profiles would be improved if the bronchodilating effects could be further separated from the side effects. It is not clear how this could be accomplished, but it has been shown that a β_3-receptor exists in humans and other uncharacterized subclasses of receptors have also been postulated (58). The investigation of these other β-receptors could lead to more selective agents.

2. Xanthine Derivatives

For many years oral xanthines, shown in Table 2, were the preferred first-line treatment for asthma in the United States, and if the aerosol and oral formulations of β_2-agonists are considered separately, as they are in Table 1, this was still the case in 1989. Within this class of compounds theophylline (**8**), or one of its various salt forms, such as aminophylline [317-34-0] (theophylline: ethylenediamine::2:1), have been the predominant agents. Theophylline, 1,3-dimethylxanthine [58-55-9], is but one member of a class of naturally occurring alkaloids. Two more common alkaloids are theobromine (**9**), isomeric with theophylline and the principal alkaloid in cacao beans, and caffeine, (**10**), 1,3,7-Trimethylxanthine [58-08-2], found in coffee and tea.

Table 2. Xanthine and Xanthine Derivatives Used as Oral Antiasthmatic Agents



Compound	CAS Registry Number	Molecular formula	Structure number	R	R′	R″
xanthine	[69-89-6]	$C_5H_4N_4O_2$	(**7**)	H	H	H
theophylline	[58-55-9]	$C_7H_8N_4O_2$	(**8**)	CH_3	CH_3	H
theobromine	[83-67-0]	$C_7H_8N_4O_2$	(**9**)	H	CH_3	CH_3
caffeine	[58-08-2]	$C_8H_{10}N_4O_2$	(**10**)	CH_3	CH_3	CH_3
enprofylline	[41078-02-8]	$C_8H_{10}N_4O_2$	(**11**)	H	n-C_3H_7	H

The bronchodilating effect of caffeine has been recognized for hundreds of years. In the western world the first description of a caffeine preparation for asthma was made in 1859 (59) by a Scottish physician who recommended strong black coffee as a bronchodilator. In many parts of the world, however, use of xanthines is less frequent than in the United States.

Historically, the use of xanthines has been hampered by poor aqueous solubility, rapid but highly variable metabolism, and the existance of a low therapeutic index. Solubility problems were partially solved by the preparation of various salt forms, eg, aminophylline. However, it was since recognized that the added base in aminophylline only increases solubility by increasing pH and thus does not affect the rate of absorption from the gut (65). Thus, in more recent medical practice, theophylline is commonly dispensed in anhydrous form and aminophylline is only recommended for iv administration.

The development of easy-to-use assays for determining theophylline blood levels afforded a handle on maintenance of effective but nontoxic levels. The relatively good availability of such assays in the United States probably contributed to the historical preference for theophylline treatment by U.S. physicians. Careful titration of the dose must be done on a patient-by-patient basis because individual rates of metabolism vary widely. Most ($\sim$85%) of an oral dose of theophylline is metabolized by liver microsomal enzymes. As a result many drugs, eg, cimetidine [51481-61-9], anticonvulsants, or conditions, eg, fever, cigarette smoking, liver disease, which affect liver function alter theophylline blood levels.

Common side effects of theophylline therapy include headache, dyspepsia, and nausea. More serious side effects such as lethal seizures or cardiac arrythmias can occur if blood levels are too high. Many derivatives of theophylline have been prepared in an effort to discover an analogue without these limitations (60, 61). However, the most universal solution has resulted from the development of reliable sustained release formulations. This technology limits the peaks and valleys in serum blood levels that occur with frequent dosing of immediate release formulations. Controlled release addresses the problems inherent in a drug which is rapidly metabolized but which is toxic at levels (>20 γg/mL) that are only slightly higher than the therapeutically efficacious ones (10–20 μg/mL). Furthermore, such once-a-day formulations taken just before bedtime have proven especially beneficial in the control of nocturnal asthma (27, 50, 62).

The effectiveness of theophylline in the treatment of asthma seems to result from a combination of biological properties which are not clearly understood (63). Detailed discussions of the possible role of xanthines in asthma may be found in references (64–66).

The effects of xanthine alkyl substitution on bronchodilation have been summarized as follows (60, 61): N_1 alkylation is essential for adenosine antagonism, bronchodilator and toxic potency may increase; N_3 alkylation is essential for increased bronchodilator potency, toxicity may increase; N_7 alkylation results in decreased bronchodilator and toxic potency; C_8 alkylation has no effect on bronchodilator potency, but toxic potency and adenosine antagonism may increase; and N_9 alkylation results in general loss of potency.

Theophylline's predominant mode of action appears to be bronchodilation. However, it has also been shown that prophylactic administration of theophylline provides some protection from asthma attacks and suppresses the late-phase response (67, 68). Some researchers believe that at therapeutic serum concentrations theophylline may inhibit the development of airway inflammation (69). There are conflicting reports on the effect of theophylline on allergen-induced bronchial hyperresponsiveness: some clinical studies report a reduction in hyper-responsiveness, others do not (69, 70). Theophylline clearly does not reverse the general bronchial hyperresponsiveness over the course of long-term therapy (71). Because of the relationship between hyperresponsiveness and inflammation (Fig. 1), these findings argue against theophylline having a significant antiinflammatory component.

Initially, it was believed that the ability of xanthines phosphodiesterase (PDE) led to bronchodilation (Fig. 2). One significant flaw in this proposal is that the concentration of theophylline needed to significantly inhibit PDE *in vitro* is higher than the therapeutically useful serum values (72). It is possible that concentration of theophylline in airways smooth muscle occurs, but there is no support for this idea from tissue distribution studies. Furthermore, other potent PDE inhibitors such as dipyridamole [58-32-2] are not bronchodilators (73). Finally, although clinical studies have shown that neither po nor continuous iv theophylline has a direct effect on circulating cyclic AMP levels (74, 75), one study has shown that iv theophylline significant potentiates the increase in cyclic AMP levels induced by isoproterenol (74).

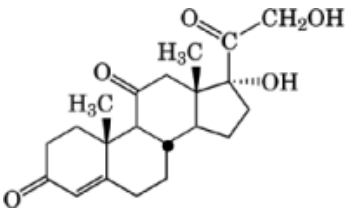
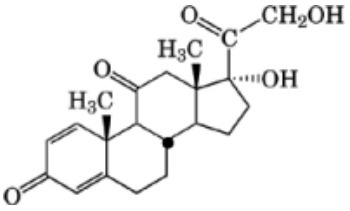
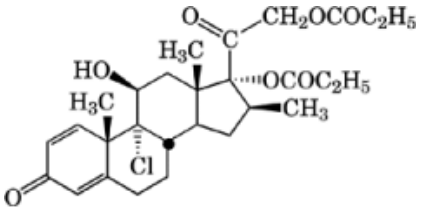
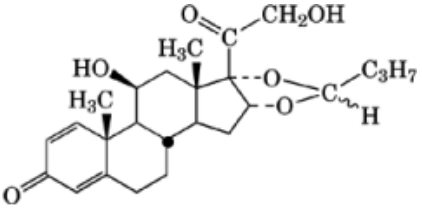
An alternative mechanism which has more recently been suggested is antagonism by theophylline of adenosine receptors. This is a well-documented effect which has been blamed for causing many of the theophylline side effects. Adenosine has a bronchoconstrictor effect when given by inhalation to asthmatics but not when given to controls (76). Also, asthmatics release adenosine into the circulation following antigen-induced bronchoconstriction (77). Therefore, it may be relevant that theophylline is an antagonist of adenosine at therapeutically useful concentrations (78). Arguing against this theory is the fact that enprofylline (3-propylxanthine [41078-02-8]), (**11**) is simultaneously claimed as a more potent bronchodilator than theophylline and not being an adenosine antagonist (67, 79, 80). Furthermore, theophylline relaxes airways smooth muscle *in vitro* probably independently of adenosine antagonism because significant concentrations of adenosine should not be present under *in vitro* conditions.

Although the benefit of theophylline treatment in asthma is without question, its use is decreasing as a result of the introduction of other effective drugs which do not have the same potential for serious side effects. It is as yet unclear whether enprofylline is a better agent or whether better drug design will require a better understanding of theophylline's mechanism of action. A theophyllinelike agent, lacking the side effects profile, would clearly be advantageous in the treatment of asthma.

3. Steroids

Steroids are widely used for the preventative treatment of asthma. Especially useful in the management of severe cases, their usage appears to be increasing. However, they have had a checkered history in asthma treatment. Shortly after the first synthetic corticosteroids became available, po cortisone (**12**) (Table 3) was tried as an antiasthmatic agent and showed remarkable success (81). However, within a few years the number and severity of side effects reported from the systemic administration of nonselective corticosteroids was deemed unacceptable (82–84). In an effort to reduce systemic side effects, treatment of asthmatics with inhaled cortisone was explored (85). Although this therapy was successful, steroid-induced side effects such as adrenal

Table 3. Steroids Used as Antiasthmatic Agents

Name	CAS Registry Number	Molecular formula	Structure number	Structure
cortisone	[53-06-5]	$C_{21}H_{28}O_5$	(**12**)	
prednisone	[53-03-2]	$C_{21}H_{26}O_5$	(**13**)	
beclomethasone diproprionate	[5534-09-8]	$C_{22}H_{29}ClO_5$	(**14**)	
budesonide	[51333-22-3]	$C_{25}H_{34}O_6$	(**15**)	

suppression and retention of both sodium and water still occurred, resulting in the long held view that whereas corticosteroids are effective antiasthmatic agents, they should only be used when all other therapy fails to control the disease.

Resurgent interest in the use of steroids for the treatment of asthma has been prompted by several developments. First, came the discovery of steroids such as prednisone (**13**), beclomethasone dipropionate (**14**), and budesonide (**15**). These newer, more selective, compounds successfully separate glucocorticoid (anti-inflammatory) and mineralocorticoid (electrolyte regulation) activities and do not suppress serum hydrocortisone. Both beclomethasone dipropionate and budesonide were initially developed as topical agents for derma-

tological indications. Later they were reformulated using aerosol delivery systems to produce antiasthmatic agents having good efficacy which do not produce most of the side effects found with oral steroids (86–88). In part, the selectivity of both of these agents derives from the ability to get into the circulatory system where they are rapidly converted into less active metabolites that do not behave as systemic glucocorticoids. Steroid usage has increased because of the identification of asthma as an inflammatory disease. Thus aerosolized antiinflammatory steroids are often used for first-line asthma treatment (5, 6).

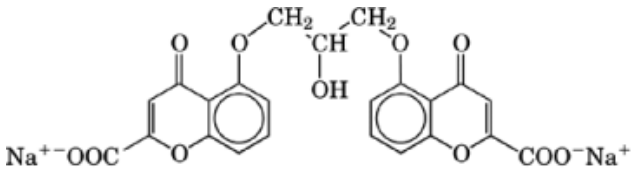
Although the mechanism of glucocorticosteriod action in bronchial asthma is not fully understood, various possibilities have been discussed in depth (89, 90). The time course of action of steroids is slower than that of β_2-agonists or theophylline and therefore steroids are not considered to be bronchodilators. It is known that steroids bind to cytosolic receptors. The steroid-receptor complex then enters the cell nucleus where the complex acts at specific sites and affects protein synthesis. The effect is to reduce the inflammatory response as well as the concentration of bronchoconstricting mediators. In addition, glucocorticoid treatment is known to reverse β_2-agonist induced adrenergic subsensitivity and to increase the number of β_2-adrenergic receptors in lung cells (91). The resultant increase in sensitivity to the natural circulating levels of norepinephrine could help induce bronchorelaxation.

Single dose or short-term treatment with aerosolized steroids inhibits both the late asthmatic response and allergen-induced bronchial hyperresponsiveness (45, 92). However it does not affect the early asthmatic response nor does it induce bronchodilation (45, 92). Long-term treatment with steroids protects against both the early and late asthmatic responses and also reduces bronchial hyperresponsiveness (44, 71, 86, 93). Over time, the airways relax (dilate) and measures of airway function, such as forced expiratory volume in one second (FEV_1), gradually return to almost normal levels.

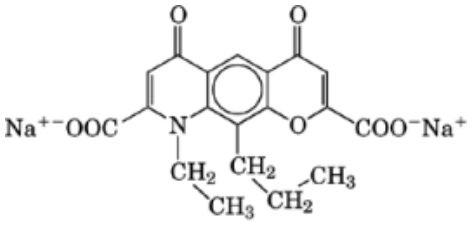
Aerosolized steroids clearly play an important role in the present-day management of asthma (87). They are reasonably safe and work best when taken prophylactically. Patient compliance, however, remains a significant problem. In part this problem is typical of any aerosolized agent. But in the case of steroids, the problem is exacerbated because a patient needs to take the steroids (especially prednisone) are the antiasthmatic agents of last resort and are widely used to treat status asthmaticus. An agent that could mimic the actions of steroids but which would work faster and/or without side effects might be the ideal antiasthmatic agent.

4. Inhibitors of Mediator Release

Whereas disodium chromoglycate [15826-37-6] (DSCG), $C_{23}H_{14}Na_2O_{11}$, (**16**) enjoys some modest success as a preventative antiasthmatic agent, it has never achieved the same level of popularity in the United States as it has in other markets, such as in the United Kingdom. Its properties have been covered in detail in several reviews (94, 95). DSCG was discovered by testing by an allergic man without the support of animal models (94, 96). This uncommon approach is now viewed as unacceptable. DSCG has been unique in its class for many years, partly because early tests designed to determine the mode of action showed that DSCG is not an antagonist of any of the known mediators of asthma nor does it induce bronchodilation (95).



(**16**)



(**17**)

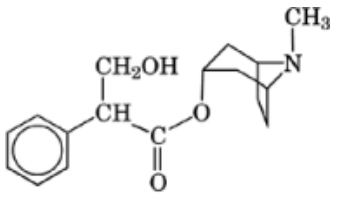
To aid in both the understanding of DSCG's effective mechanism and the discovery of an active analogue, animal models were developed (97). It was believed that DSCG's mode of action is by stabilization of mast cells and inhibition of mediators' release (42, 98). The tremendous effort expended by the pharmaceutical industry initially resulted in failure. These investigations have been reviewed in depth (97), and it is now believed that improper disease models were employed (99, 100). These early models measured the stabilizing effect of the test agents on connective tissue mast cells. Newer models have focused on mucosal (lung) mast cells and a more recent proposal is that DSCG and a related compound, nedocromil sodium [69049-74-7], $C_{19}H_{15}NNa_2O_7$, (**17**), both inhibit the effect of sensory nerve activation, thereby interfering with bronchoconstriction (101).

DSCG is very poorly absorbed following oral dosing and is therefore administered by aerosol inhalation, four times a day (94, 95). Metabolism is minimal: DSCG is excreted mostly as unchanged drug. Thus, although it is considered one of the safest available antiasthmatic agents, it is not a cure-all and seems to work best as an adjunct to other therapy, allowing a reduction in the dosage of the other agents (94). Clinical studies show that DSCG offers no protection if administered following antigen challenge (94, 95), but if administered prophylactically, it protects both extrinsic and intrinsic asthmatics (94, 102, 103). DSCG is uniquely effective against both the early and late-phase asthmatic responses; it also protects against exercise-induced asthma (45, 104, 105). The effect of DSCG on nonspecific bronchial hyperreactivity is not at all clear; clinical studies have produced conflicting reports (45, 104–106).

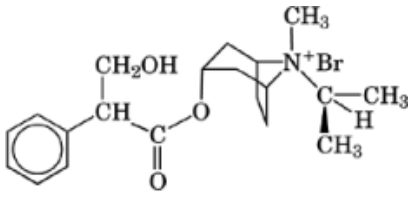
With the shift in preference to aerosolized agents, nedocromil sodium (**17**) has been introduced as a follow-up agent to DSCG (**16**) (107–109). Nedocromil sodium, structurally distinct from DSCG, is significantly more potent in humans, and can be administered twice daily. Like DSCG, it is administered only via an aerosol, is not significantly metabolized, and is excreted as unchanged drug. The rate limiting step for the duration of action seems to be absorption. A clinical trial has shown that, if given four times a day at 4 mg per dose, nedocromil sodium is comparable with, and equivalent to, inhaled beclomethasone dipropionate (**14**) in nearly all parameters (110).

5. Anticholinergic Agents

At this writing anticholinergic agents are not widely used for the symptomatic treatment of asthma, although compounds such as atropine [51-55-8], $C_{17}H_{23}NO_3$, (**18**) have been used for centuries (111). Inhalation of the smoke produced by burning herbal mixtures, such as *Datura Stramonium*, provided bronchodilation and relief from some of the symptoms of asthma. The major active component in these preparations was atropine or other closely related alkaloids (qv).



(**18**)



(**19**)

The beneficial effect of anticholinergics in asthma relies upon bronchial smooth muscle exhibiting a cholinergically mediated tone (resting state tension) (112, 113). Receptors in the cholinergic nervous system are divided into two main classes, muscarinic (M) and nicotinic (113). Anticholinergic agents exert their bronchodilating effect by blocking the muscarinic-receptors found in bronchial smooth muscle. This blockade inhibits the normal cholinergic-induced tone. In addition, it has been shown that cholinergic receptor stimulation results in inhibition of adenylate cyclase, thereby reducing cyclic AMP levels (114). Blockade of this effect should result in indirect bronchodilatation (Fig. 2). Although atropine is effective in preventing exercise-induced asthma (103), it and other anticholinergic agents have no effect on bronchial hyperesponsiveness, the release of other mediators, or on the inflammatory process (115, 116). Significant dose related side-effects such as blurred vision, dry mouth, and inhibition of gastric motility occur. These side effects result from systematic distribution of the drugs, including penetration into the central nervous system and their widespread antagonism of other muscarinic receptors.

Ipratropium bromide [22254-24-6], $C_{20}H_{30}BrNO_3$, (**19**) (115) is an example of a newer anticholinergic agent. This isopropyl quarternary salt derivative of atropine is not lipid soluble or well-absorbed through the gut, nor does it readily cross the blood-brain barrier. Using aerosol administration, this agent has a much lower incidence of side effects. Ipratropium bromide has gained limited acceptance as an antiasthmatic agent and seems to be more useful in patient populations that show limited response to B_2-adrenergic agonists (117). Clinical studies suggest that a synergistic effect may result from the co-administration of a B_2-agonist and an anticholinergic agent (117, 118).

Research efforts on anticholinergic agents have been influenced by the finding that muscarinic-receptors can be divided into subtypes: M_1, M_2, and M_3 (119–121). It has been suggested that all three muscarinic-receptor subtypes may play a role in asthma etiology (119). Neither atropine nor ipratropium bromide successfully differentiates between subtypes (120). Because of the possibility that indiscriminate blockade of muscarinic receptors may increase release of acetylcholine via a feedback mechanism, it seems possible that agents which selectively block the smooth muscle receptors (M_3) may have better profiles than present drugs (120). However, more than half the cholinergic receptors in human lung are of the M_1 subtype, so this view may represent an oversimplification (119).

6. Agents Undergoing Clinical Evaluation

6.1. Antihistamines

Antihistamines are not recommended for the symptomatic treatment of asthma, although recent studies have shown that histamine (**20**) (Table 4) released from mast cells may account for 50% of the immediate asthmatic response (see Histamine and histamine antagonists) (122). Reviews on antihistamines in asthma therapy may be found in references (124–127). The possible role of histamine in the anaphylactic response was first recognized in the early 1900s (123). Almost 40 years passed before compounds became available which were sufficiently nontoxic to be tried in clinical studies. These early agents, tested as therapeutic agents for allergic rhinitis and asthma (128), were only weakly active as antihistamines. They were not specific for histamine receptors and activity at muscarinic (cholinergic) and adrenergic receptors contributed both to bronchodilating actions and to a wide variety of side effects which limited use.

The discovery that histamine receptors, just like adrenergic and cholinergic receptors, may be divided into subtypes H_1 and H_2, combined with the recognition that the bronchial receptors were of the H_1 type, set the stage for a newer generation of antihistamines. Clinical investigation in the late 1970s of the H_1-antihistamines clemastine (**21**) (129) and chlorpheniramine (**22**) (130, 131), shown in Table 4, revealed that these agents had a bronchodilating effect and provided some protection against exercise-induced asthma. But the side effects, induced at H_1-receptors in the central nervous system which produced sedation and at cholinergic receptors, limited the maximal doses that could be given. These drugs were not useful as antiasthmatic agents.

Two newer potent selective H_1-antagonists, terfenadine (**23**) (132) and astemizole (**24**) (133), have been developed which have neither the sedative nor the anticholinergic liabilities of the earlier agents. Both of these compounds have proven efficacious in the treatment of hay fever and produce very few side effects, prompting a re-evaluation of the role of antihistamines in asthma treatment.

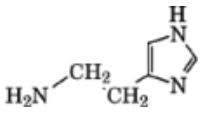
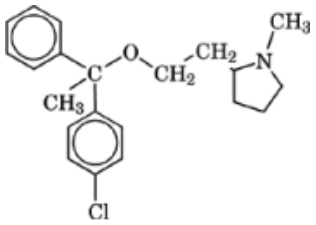
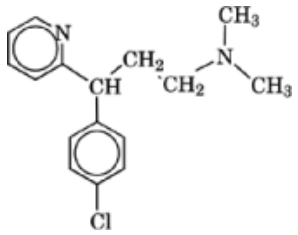
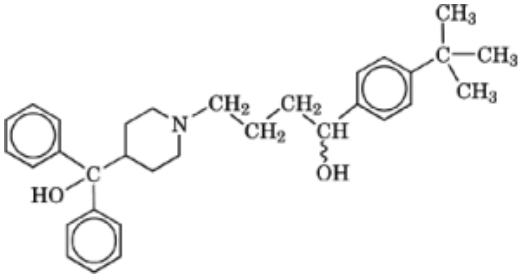
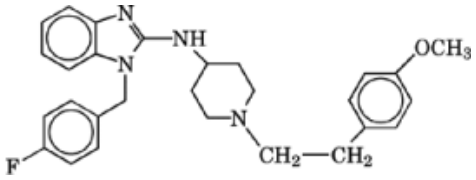
Astemizole has very unusual pharmacokinetic parameters. It shows delayed onset both *in vitro* and *in vivo* (126) and also has a very long duration of action. *In vivo* formation of the desmethyl metabolite, equiactive to astemizole as an H_1-antagonist, occurs. This metabolite is cleared at only 1/10th the rate of astemizole. Clinically, it may take two days following a dose of astemizole for symptom alleviation to occur in the treatment of hay fever (134). However, the effect is very long lasting: after a single 10-mg tablet, significant antihistaminic activity can be demonstrated in volunteers for about 20 days (135). Astemizole seems to delay the onset of exercise-induced asthma but not affect the severity of the bronchoconstriction (136, 137). Also, prolonged astemizole treatment offers some protection from the symptoms of seasonal asthma with significant attenuation of the early component of bronchoconstriction but little effect on the late-phase response (138).

Oral terfenadine has a relatively rapid onset (134), and a sufficiently long duration of action that it needs to be dosed only once or twice a day. Clinical studies show: it effectively blocks histamine-induced bronchospasm (124); it causes modest bronchodilation (139, 140); and it provides limited protection against either exercise-induced asthma (140, 141) or challenge using nebullized water (139). The bronchodilatory response to 120-mg oral terfenadine has been shown to approach that of 200-μg of inhaled albuterol (**4**, R = $C(CH_3)_3$) (142). Terfenadine, however, has no effect on the dose of methacholine needed to cause a 20% fall in FEV_1 (143). Also, it has only a very modest protective effect against antigen-induced asthma, that effect being partial blockade of the immediate bronchoconstrictor response (144). Studies on its use in the treatment of seasonal atopic asthmatics have shown minor, but statistically significant, effects which have correlated with a reduction in the need to use other bronchodilators (125, 145).

6.2. Leukotriene Antagonists

Over 50 years ago a second component, besides histamine, of the immediate type hypersensitivity reaction was identified (146). This discovery was named the slow reacting substance of anaphylaxis (SRS-A). Because it was

Table 4. Histamine and Antihistamines

Name	CAS Registry Number	Molecular formula	Structure number	Structure
histamine	[51-45-6]	$C_5H_9N_3$	(**20**)	
clemastine	[15686-51-8]	$C_{21}H_{26}ClNO$	(**21**)	
chloro-pheniramine	[132-22-9]	$C_{16}H_{19}N_2Cl$	(**22**)	
terfenadine	[50679-08-8]	$C_{20}H_{41}NO_2$	(**23**)	
astemizole	[68844-77-9]	$C_{28}H_{31}N_4FO$	(**24**)	

believed that SRS-A played a primary role in the etiology of asthma and other diseases, the discovery generated a great deal of interest. However, determination of SRS-A structure and development of either antagonists or biosynthesis inhibitors was severely hampered by the limited availability of SRS-A from biological sources and chemical and biological instability (147). In 1980 it was shown that SRS-A was made up of a mixture of leukotrienes (148), which were products of the 5-lipoxygenase pathway of arachidonic acid metabolism (see Prostaglandins). Tests showed that the pure leukotrienes are 100 to 1000 times as potent as histamine in terms of bronchial spasmogens both *in vitro* and in clinical studies, prompting a resurgence of interest in the development of leukotriene antagonists and biosynthesis inhibitors. At this writing, only work in receptor antagonists has progressed far enough to show promise in the clinic. The leukotrienes are listed in Table 5 as are some antagonists.

The first SRS-A antagonist, FPL-55712 (**26**) (149), was discovered before the structures of the leukotrienes were determined. Although this compound is relatively weak as an antagonist and suffers from a very short half-life *in vivo,* it played an important role both in leukotriene structure elucidation and as a model for later antagonists. In work structurally related to FPL-55712, LY-171883 was developed (**27**) (150). LY-171883 was evaluated in several clinical trials before development was stopped. Orally administered, LY-171883 blocked slightly the response to aerosol LTD_4, improved pulmonary function (FEV_1) in mild asthmatics (151), decreased the sensitivity of asthmatics to cold air-induced bronchoconstriction (152), and significantly reduced the bronchoconstrictor response to inhaled antigen (153). However, in all these studies the beneficial effects were minimal.

Many structurally diverse newer leukotriene antagonists that are at varying stages of development have since been discovered (154, 155). Two compounds which are especially potent and which seemed most promising as potential antiasthmatic agents are MK-571 (formerly L-660711) (**28**) (156), and ICI-204219 (**29**) (157). Both of these agents advanced to the clinic but the development of MK-571 has since been discontinued. However, studies show that two hours after a single 40-mg po dose, ICI–204219 caused a greater than 100-fold shift in the dose-response curve to aerosol LTD_4 (158), and caused a greater than tenfold shift in the dose-response to inhaled antigen (159).

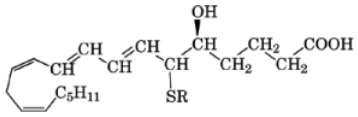
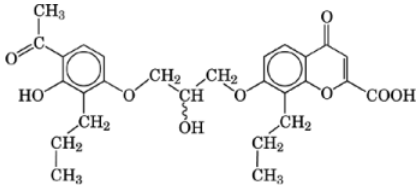
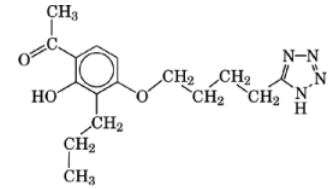
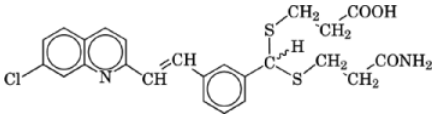
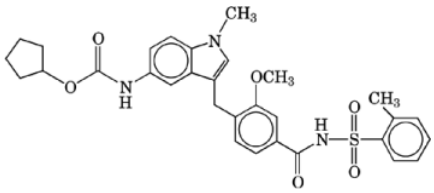
6.3. Other Drugs

In addition to the drugs already discussed, a wide variety of other agents have been investigated for antiasthmatic potential. For example, a large but unsuccessful effort went into the search for a prostaglandin-type bronchodilator in the 1970s. Within this general area the uncertain role of thromboxane as a mediator in asthma has prompted limited interest in the exploration of thromboxane A_2 synthesis inhibitors and/or antagonists (160, 161).

In 1990 5-lipoxygenase inhibitors, ie, leukotriene biosynthesis inhibitors, began undergoing clinical evaluation (161, 162). Also, rapidly approaching clinical evaluation are a structurally diverse group of platelet-activating factor (PAF) antagonists (162). In humans, PAF is a potent bronchospastic agent that also induces bronchial hyperreactivity. There is significant effort being expended to discover and develop potent PAF antagonists as antiasthmatic agents (163, 164).

The key to a cure for asthma is presumably to be found in a better understanding of its etiology. Until then, there are many approaches being utilized (165). As an example, there is interest in discovering a drug which would specifically affect calcium ions in airway smooth muscle and cause bronchodilation. Similarly, if selective potassium channel openers can be found, they should act as bronchodilators. Alternatively, a selective inhibitor of the correct phosphodiesterase isozyme should mimic the bronchodilating effects of the β_2-agonists without inducing the side effects. Formation of both the prostanoid and leukotriene bronchoconstrictors as well as platelet activating factor should theoretically be inhibited, if a selective phospholipase A_2 inhibitor can be discovered. Finally, the roles of the nonadrenergic, noncholinergic nervous system (38) and the neuropeptides, eg, tachykinins, in asthma have only begun to be explored.

Table 5. Leukotrienes and Leukotriene Antagonists

Name	CAS Registry Number	Molecular formula	Structure number	Structure
			Leukotrienes	
leukotriene C_4 leukotriene D_4 leukotriene E_4	[72025-60-6][73836-78-9][75715-89-8]	$C_{30}H_{47}N_3O_9S$ $C_{25}H_{40}N_2O_6S$ $C_{23}H_{37}NO_5S$	(**25**, RSH = glutathione)(**25**, RSH = cysteinylglycine)(**25**, RSH = cysteine)	
			Leukotriene antagonists	
FPL-55712	[40786-08-1]	$C_{27}H_{30}O_9$	(**26**)	
LY-171883	[88107-10-2]	$C_{16}H_{22}N_4O_3$	(**27**)	
MK-571 (formerly L-660711)	[115104-28-4]	$C_{24}H_{23}N_2O_3ClS_2$	(**28**)	
ICI-204219	[107753-78-6]	$C_{31}H_{33}N_3O_6S$	(**29**)	

7. Economic Aspects

Total sales of prescription bronchodilators and antiasthma products in 1989 were approximately $1.2 and $3.3 billion in the North American and world markets, respectively (166). The three largest shares of the world market were held by: Glaxo Holdings plc, Schering-Plough Corporation, and Boehringer Ingelheim Corporation.

In 1989 β_2-agonists were the largest class of prescription bronchodilators and antiasthma agents. Total sales reached approximately $1.2 billion. Albuterol (**4**, R = $C(CH_3)_3$) was the best-selling (ranked by dollar value) antiasthmatic agent (167). Most of the remaining β_2-agonist sales were for terbutaline (**3**, R = $C(CH_3)_3$) and metaproterenol (**3**, R = $CH(CH_3)_2$). Inhaled corticoids were the next largest class. Corticoid sales, which reached approximately $400 million, were predominantly accounted for by beclomethasone diproprionate (**14**) and budenoside (**15**). Sales of nonprescription, over-the-counter, antiasthma products are only a small fraction of the prescription market.

BIBLIOGRAPHY

"Antiasthmatic Agents" in *ECT,* 3rd ed., pp. 758–782, by D. D. Miller, Ohio State University.

Cited Publications

1. M. E. Gershwin, ed., *Bronchial Asthma,* Grune & Stratton, Orlando, Fla., 1986.
2. D. R. Buckle and H. Smith, eds., *Development of Anti-Asthma Drugs,* Butterworths, London, UK, 1984.
3. E. B. Weiss, M. S. Segal, and M. Stein, eds., *Bronchial Asthma: Mechanism and Therapeutics,* 2nd ed., Little, Brown and Co., Toronto, Canada, 1985.
4. Committee on Diagnostic Standards, American Thoracic Society, *Am. Rev. Respir. Dis.* **85,** 762 (1962).
5. Editorial, *Ann. Allergy* **62,** 481 (1989).
6. F. E. Hargreave, *J. Allergy Clin. Immunol.* **83,** 525 (1989).
7. D. M. Fleming and D. L. Crombie, *Br. Med. J.* **294,** 279 (1987).
8. A. J. Woolcock, *Chest* (suppl.) **90,** 40S (1986).
9. R. R. Dodge and B. Burrows, *Am. Rev. Resp. Dis.* **122,** 567 (1980).
10. S. R. Benatar, *N. Engl. J. Med.* **314,** 423 (1986).
11. P. G. J. Burney, *Lancet* **2,** 323 (1986).
12. E. D. Robin, *Chest* **93,** 614 (1988).
13. R. M. Sly, *Ann. Allergy* **53,** 20 (1984).
14. Ref. 3, p. 18.
15. J. W. Gerrard, C. G. Ko, P. Vickers, and C. D. Gerrard, *Ann. Allergy* **36,** 10 (1976).
16. C. G. A. Persson, *Trends in Pharmacol. Sci.* **3,** 312 (1982).
17. P. J. Barnes, *J. Allergy Clin. Immunol.* **83,** 1013 (1989).
18. D. W. Moran and A. W. Wheeler in Ref. 2, 349–390.
19. R. W. Fox and R. F. Lockey in Ref. 1, 371–392.
20. P. S. Creticos, *J. Allergy Clin. Immunol.* **83,** 554 (1989).
21. J. E. Hodgkin, *Chest* (Suppl.) **90,** 62S (1986).
22. T. J. H. Clark, *Chest* (Suppl.) **90,** 67S (1986).
23. A. F. Barker, *West. J. Med.* **150,** 303 (1989).
24. M. T. Newhouse and M. B. Dolovich, *N. Engl. J. Med.* **315,** 870 (1986).
25. *National Prescription Audits 1984–1989.* IMS International, a Company of the Dun & Bradstreet Corporation, 1989.
26. Editorial, "Asthma at Night," *Lancet* **1,** 220 (1983).
27. C. W. Zwillich and co-workers, *Am. Rev. Respir. Dis.* **139,** 470 (1989).
28. S. P. Newman, in J. A. Bristal, ed., *Annual Reports in Medicinal Chemistry,* Vol. 25, Academic Press, New York, 1990, 178–189.
29. H. S. Nelson, *J. Allergy Clin. Immunol.* **77,** 771 (1986).
30. C. E. Reed, *J. Allergy Clin. Immunol.* **76,** 335 (1985).
31. L. E. Martin, J. C. Hobson, J. A. Page, and C. Harrison, *Eur. J. Pharmacol.* **14,** 183 (1971).
32. C. Kaiser in D. L. Temple Jr., ed., *Drugs Affecting the Respiratory System, ACS Symp. Ser.* **118,** 251 (1980).
33. J. G. M. Bullowa and D. M. Kaplan, *Med. News* **83,** 787 (1903).

34. S. E. Meyer in A. G. Goodman, L. S. Goodman, and A. Gilman, eds., *The Pharmacological Basis of Therapeutics,* 6th ed., MacMillan, New York, 1980, p. 56.
35. J. B. Richardson and J. Beland, *J. Appl. Physiol.* **41,** 764 (1976).
36. J. B. Richardson, *J. Allergy Clin. Immunol.* **56,** 473 (1975).
37. J. F. Souhrada, E. Melzer, and P. Grantham, *Respir. Physiol.* **40,** 199 (1980).
38. J. B. Richardson in Ref. 3, 123–126.
39. R. P. Alquist, *Am. J. Physiol.* **153,** 586 (1948).
40. A. M. Lands and co-workers, *Nature (London)* **214,** 597 (1967).
41. K. J. Rhoden, L. A. Meldrum, and P. J. Barnes, *J. Appl. Physiol.* **65,** 700 (1988).
42. F. L. Pearce and J. Clements, *Biochem. Pharmacol.* **31,** 2247 (1982).
43. I. F. Skidmore in A. B. Kay, ed., *Asthma: Clinical Pharmacology and Therapeutic Progress,* Blackwell Scientific, Oxford, UK, 1986, p. 171.
44. K. F. Kerrebijn, E. E. M. van Essen-Zandvliet, and H. J. Neijens, *J. Allergy Clin. Immunol.* **79,** 653 (1987).
45. D. W. Cockcroft and K. Y. Murdock, *J. Allergy Clin. Immunol.* **79,** 734 (1987).
46. J. D. S. McEvoy, A. Vall-Spinosa, and J. W. Paterson, *Am. Rev. Respir. Dis.* **108,** 490 (1973).
47. J. J. McPhillips in M. E. Goldberg, ed., *Pharmacological and Biochemical Properties of Drug Substances,* Vol. 1, American Pharmaceutical Association, Washington, D.C., 1977, p. 311. A review on terbutaline.
48. M. J. Schumacher, *J. Allergy Clin. Immunol.* **66,** 33 (1980).
49. P. Borum and N. Mygind, *J. Allergy Clin. Immunol.* **66,** 25 (1980).
50. M. Heins and co-workers, *Eur. Respir. J.* **1,** 306 (1988).
51. R. T. Brittain and D. M. Harris in Ref. 45, p. 257. A review on albuterol.
52. J. W. Paterson, R. J. Courtney-Evans, and F. J. Prime, *Br. J. Dis. Chest* **65,** 21 (1971).
53. I. Kass and T. S. Mingo, *Chest* **78,** 283 (1980).
54. *Arzneim.-Forsch.* **26,** 1403 (1976). A series of articles on the properties of clenbuterol.
55. A. Ullman and N. Svedmyr, *Thorax* **43,** 674 (1988).
56. J. Bradshaw and co-workers, *Br. J. Pharmacol.* **92,** 590P (1987).
57. D. I. Ball and co-workers, *Br. J. Pharmacol.* **92,** 591P (1987).
58. L. J. Emorine and co-workers, *Sciences,* **245,** 1118 (1989).
59. H. Salter, *Edinburgh Med. J.,* 1109 (1859).
60. C. G. A. Persson, *Agents and Actions* (Suppl.) **13,** 115 (1983). A review on Theophylline structure-activity relationships.
61. C. G. A. Persson, *Trends in Pharmacol. Sci.* **3,** 312 (1982). A review on Theophylline structure-activity relationships.
62. W. W. Arkinstall, M. E. Atkins, D. Harrison, and J. H. Stewart, *Am. Rev. Respir. Dis.* **135,** 316 (1987).
63. C. G. A. Persson, *J. Allergy Clin. Immunol.* **78,** 780 (1986).
64. N. Cushley and S. T. Holgate in Ref. 2, 205–223.
65. M. Weinberger and L. Hendeles in Ref. 3, 646–674.
66. For a review on "Recent Innovations in Theophylline-Like Bronchodilator Drugs" see R. J. Seidehamel and D. L. Temple, Jr., in D. L. Temple, Jr., ed., *Drugs Affecting the Respiratory System, ACS Symp. Ser.* **118,** 285 (1980).
67. R. Pauwels and co-workers, *J. Allergy Clin. Immunol.* **76,** 583 (1985).
68. S. Godfrey, *J. Allergy Clin. Immunol.* **65,** 97 (1980).
69. R. A. Pauwels, *J. Allergy Clin. Immunol.* **83,** 548 (1989).
70. D. W. Cockcroft and co-workers, *J. Allergy Clin. Immunol.* **83,** 913 (1989).
71. J. I. Dutoit, C. M. Salome, and A. J. Woolcock, *Am. Rev. Respir. Dis.* **136,** 1174 (1987).
72. J. B. Polson, J. J. Krzanowski, A. L. Goodman, and A. Szentivanyi, *J. Clin. Exp. Pharmacol. Physiol.* **5,** 535 (1978).
73. R. E. Ruffin and M. T. Newhouse, *Eur. J. Respir. Dis.* **62,** 123 (1981).
74. P. W. Trembath and J. Shaw, *Br. J. Clin. Pharmacol.* **6,** 499 (1978).
75. F. H. Parrott and co-workers, *Am. Rev. Respir. Dis.* **113,** 156 (1976).
76. M. J. Cushley, A. E. Tattersfield, and S. T. Holgate, *Br. J. Clin. Pharmacol.* **15,** 161 (1983).
77. J. S. Mann, A. G. Renwick, and S. T. Holgate, *Clin. Sci.* **65,** 22P (1983).
78. B. B. Fredholm, *Eur. J. Respir. Dis.* **61** (suppl. **109**), 29 (1980).
79. K. R. Chapman and co-workers, *Am. Rev. Respir. Dis.* **139,** 688 (1989).
80. C. G. A. Persson, I. Erjefalt, and J. A. Karlsson, *Acta Pharmacol. et Toxicol.* **49,** 317 (1981).
81. H. M. Carryer and co-workers, *J. of Allergy* **21,** 282 (1950).

82. H. Arnoldsson, *Acta Allergol.* **6,** 1 (1958).
83. M. McAllen, *Respiration* (suppl.) **27,** 250 (1970).
84. H. C. Smyllie and C. K. Connolly, *Thorax* **23,** 571 (1968).
85. M. L. Gelfand, *N. Eng. J. Med.* **245,** 293 (1951).
86. J. M. Henriksen, *Br. Med. J.* **291,** 248 (1985).
87. J. H. Toogood, B. Jennings, and J. C. Baskerville in Ref. 3, 698–713.
88. E. O. Meltzer, J. P. Kemp, M. J. Welch, and H. A. Orgel, *Am. Rev. Respir. Dis.* **131,** 732 (1985).
89. M. Kaliner, *J. Allergy Clin. Immunol.* **76,** 321 (1985).
90. Supplement: "Corticosteroids: Their Biological Mechanisms and Application to the Treatment of Asthma", *Am. Rev. Respir. Dis.* **141,** S1 (1990).
91. C. M. Fraser and J. C. Venter, *Biochem. Biophys. Res. Commun.* **94,** 390 (1989).
92. R. Dahl, J. M. Henriksen, S-A. Johansson, and P. Venge in A. B. Kay, ed., *Asthma: Clinical Pharmacology and Therapeutic Progress,* Blackwell Scientific, Oxford, UK, 1986, p. 331.
93. A. J. Woolcock, K. Yan, and C. M. Salome, *Clin. Allergy* **18,** 165 (1988).
94. R. N. Brogden, T. M. Speight, and G. S. Avery, *Drugs* **7,** 164 (1974).
95. J. S. G. Cox and co-workers, *Adv. in Drug Res.* **5,** 115 (1970).
96. R. E. C. Altounyan, *Acta Allergol.* **22,** 487 (1967).
97. J. L. Suschitzky and P. Sheard in G. P. Ellis and G. B. West, eds., *Progress in Medicinal Chemistry,* Elsevier Science, B.V., **21,** 1 (1984).
98. J. S. G. Cox, *Nature (London)* **216,** 1328 (1967).
99. T. C. Stokes and J. Morley, *Br. J. Dis. Chest* **75,** 1 (1981).
100. T. S. C. Orr, *Drugs* **37** (Suppl. 1), 113 (1989).
101. C. M. S. Dixon and P. J. Barnes, *Br. J. Clin. Pharmacol.* **27,** 831 (1989).
102. Brompton Hospital/Medical Research Council Collaborative Trial, *Br. Med. J.* **4,** 383 (1972).
103. S. Godfrey and P. Koenig, *Pediatrics* **56,** 930 (1975).
104. U. G. Svendsen, *J. Allergy Clin. Immunol.* **80,** 68 (1987).
105. I. L. Bernstein, *J. Allergy Clin. Immunol.* **76,** 381 (1987).
106. P. Haber, G. Keyer, and C. O. Burghuber, *Respiration* **55,** 44 (1989).
107. T. S. C. Orr and co-workers, in A. B. Kay, ed., *Asthma: Clinical Pharmacology and Therapeutic Progress,* Blackwell Scientific, Oxford, UK, 1986, p. 265.
108. J. P. Gonzalez and R. N. Brogden, *Drugs* **34,** 560 (1987).
109. S. Lal, S. Malhotra, D. Gribben, and D. Hodder, *Thorax* **39,** 809 (1984).
110. K. C. Bergmann, C. P. Bauer, and A. Overlack, *Curr. Med. Res. Opin.* **11,** 533 (1989).
111. B. Gandevia, *Postgrad. Med. J.* **51** (suppl. 7), 12 (1985).
112. G. E. Pakes in Ref. 2, p. 159.
113. P. Taylor in A. G. Goodman, L. S. Goodman, and A. Gilman, eds., *The Pharmacological Basis of Therapeutics,* 6th ed., MacMillan, New York, 1980, p. 211.
114. C. A. Jones, J. M. Madison, M. Tom-moy, and J. K. Brown, *Am. J. Physiol.* **253,** C97 (1987).
115. R. Bauer and co-workers in M. E. Goldberg, ed., *Pharmacological and Biochemical Properties of Drug Substances,* Vol. 2, American Pharmaceutical Association, Washington, D.C., 1979, p. 489. A general review on ipratropium bromide.
116. P. H. Howarth and co-workers, *Am. Rev. Respir. Dis.* **132,** 986 (1985).
117. F. E. R. Simons, *J. Allergy Clin. Immunol.* **80,** 239 (1987).
118. A. S. Rebuck and co-workers, *Am. J. Med.* **82,** 59 (1987).
119. J. Maclagan and P. J. Barnes, *Trends Pharmacol. Sci.* (Suppl. 1) **10,** 88 (1989).
120. P. J. Barnes, P. A. Minette, and J. Macalagan, *Trends Pharmacol. Sci.* **9,** 412 (1988).
121. R. B. Barlow, K. N. Burston, and A. Vis, *Proceed. Br. Pharm. Soc.* 141P (1979).
122. P. Rafferty, R. Beasley, and S. T. Holgate, *Am. Rev. Respir. Dis.* **136,** 369 (1987).
123. H. H. Dale and P. P. Laidlaw, *J. Physiol.* **41,** 318 (1910).
124. P. Rafferty, *Ann. Allergy* **63,** 389 (1989).
125. S. T. Holgate and J. P. Finnerty, *J. Allergy Clin. Immunol.* **83,** 537 (1989).
126. P. Rafferty and S. T. Holgate, *J. Allergy Clin. Immunol.* **84,** 144 (1989).
127. W. E. Pierson and F. S. Virant, *Ann. Allergy* **63,** 601 (1989).

128. C. H. Eyermann, *J. Allergy* **17,** 210 (1946).
129. J. P. R. Hartley and S. G. Nogrady, *Aust. and N.Z. J. Med.* **11,** 106 (1981).
130. V. T. Popa, *J. Allergy Clin. Immunol.* **59,** 54 (1977).
131. R. C. Groggins, A. D. Milner, and G. M. Stokes, *Br. J. Dis. Chest* **73,** 297 (1979).
132. B. L. Martz, J. P. Mumford, J. T. Burke, and J. L. R. Barlow, *Arzneim. Forsch.* **32,** 1153 (1982).
133. P. M. Laduron, P. F. M. Janssen, W. Gommeren, and J. E. Leysen, *Mol. Pharmacol.* **21,** 294 (1982).
134. J. P. Girard, D. Sommacal-Schopf, P. Bigliardi, and S. A. Henauer, *J. Int. Med. Res.* **13,** 102 (1985).
135. J. Callier and co-workers, *Curr. Ther. Res.* **29,** 24 (1981).
136. V. Backer and co-workers, *Allergy* **44,** 209 (1989).
137. M. D. Clee, C. G. Ingram, P. C. Reid, and A. S. Robertson, *Br. J. Dis. Chest* **78,** 180 (1984).
138. S. T. Holgate, M. B. Emanuel, and P. H. Howarth, *J. Allergy Clin. Immunol.* **76,** 375 (1985).
139. R. G. Townley, R. J. Hopp, A. K. Bewtra, and M. Nabe, *Ann. Allergy* **63,** 455 (1989).
140. W. E. Pierson and co-workers, *Ann. Allergy* **63,** 461 (1989).
141. K. R. Patel, *Br. Med. J.* **288,** 1496 (1984).
142. W. O. C. M. Cookson, *Br. J. Clin. Pharmacol.* **24,** 120 (1987).
143. K. R. Patel, *J. Allergy Clin. Immunol.* **79,** 355 (1987).
144. T. B. Chan, D. M. Shelton, and N. M. Eiser, **Br. J. Dis. Chest 80,** 375 (1986).
145. A. Taytard and co-workers, *Br. J. Clin. Pharmacol.* **24,** 743 (1987).
146. C. H. Kellaway and W. R. Trethewie, *Q. J. Exp. Physiol. Cog. Med. Sci.* **30,** 121 (1940).
147. L. W. Chakrin and D. M. Bailey, eds., *The Leukotrienes, Chemistry and Biology,* Academic Press, New York, 1984. A review on the leukotrienes.
148. S. Hammarstrom and co-workers, *Biochem. Biophys. Res. Commun.* **91,** 1266 (1979).
149. J. Augstein and co-workers, *Nat. New Biol.* **245,** 215 (1973).
150. J. H. Fleisch, *J. Pharmacol. Exp. Ther.* **233,** 148 (1985).
151. M. L. Cloud and co-workers, *Am. Rev. Respir. Dis.* **140,** 1336 (1989).
152. E. Israel and co-workers, *Am. Rev. Respir. Dis.* **140,** 1348 (1989).
153. R. W. Fuller, P. N. Black, and C. T. Dollery, *J. Allergy Clin. Immunol.* **83,** 939 (1989).
154. D. W. Snyder and J. H. Fleisch, *Annu. Rev. Pharmacol. Toxicol.* **29,** 123 (1989).
155. A. Shaw and R. D. Krell, *J. Med. Chem.* in press (1990).
156. J. C. Kips and co-workers, *Am. Rev. Resp. Dis.* **139,** A63 (1989).
157. R. D. Krell and co-workers, *Am. Acad. Allergy Immunol.* **81,** 276 (1988).
158. L. J. Smith and co-workers, *Am. Rev. Respir. Dis.* **141,** 987 (1990).
159. S. R. Findlay, C. Easley, J. M. Barden, and M. Glass, *J. Allergy Clin. Immunol.* **85,** 197 (1990).
160. E. W. Collington and H. Finch in J. A. Bristol, ed., *Annual Reports in Medicinal Chemistry,* Vol. 25, Academic Press, New York, 1990, 99–108.
161. A. Shaw in J. A. Bristol, ed., in Ref. 160, 61–70.
162. J. H. Musser, *J. Med. Chem.* **34** (1991).
163. C. P. Page, D. N. Robertson, and A. J. Coyle "New Anti-Asthma Drugs", in S. O. Donnell and C. Persson, eds., *Agents and Actions Suppl. 23,* Birkhauser Verlag, Basel, Switzerland, 1988, 173–185.
164. C. Page and A. Abbott, *Trends in Pharm. Sci.* **10**(7) (1989).
165. P. J. Barnes, ed., *New Drugs for Asthma,* IBC Technical Services, London, 1989.
166. *The Pharmaceutical Market, World Review 1989,* IMS International, a Company of the Dun & Bradstreet Corporation.
167. *Annual Report and Accounts 1990* Glaxo Holdings plc, London, 1990, p. 13.

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