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Perspective

Modulators of Leukotriene Biosynthesis and Receptor Activation

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Introduction

The history of leukotriene (LT) research has been documented in numerous articles and reviews since the discovery of the LT biosynthetic pathway[1] and the delineation of the various chemical structures involved in the pathway and their total synthesis.[2] Three previous Perspective articles have provided periodic updates, the first in 1981,[3] the second 1 decade later covering LT receptor antagonists,[4] and the third in 1992 covering LT biosynthesis inhibitors.[5] With this background, the task of this Perspective is to update the status of LT intervention research by providing an overview of the leading enzyme inhibitors and receptor antagonists as well as the status of clinical trials with these agents and how the latter are influencing the development of new therapeutic modalities for the treatment of inflammation and allergy.

The clinical proof-of-concept for LT intervention has taken longer than expected considering that the biosynthesis and chemical composition of LTs were delineated by 1979. It is now clear that LT intervention therapy represents a promising new modality for the treatment of asthma. Several compounds including the 5-lipoxygenase (5-LO) inhibitor zileuton (**1**) and the cysteinyl LT antagonist zafirlukast (**2**) have completed pivotal clinical trials, while several other LT modulators are progressing to this stage. Within a few years the therapeutic potential of these new agents in asthma and other inflammatory and allergic disorders will be evident.

Leukotriene Intervention Strategies

Leukotriene Biosynthesis. Leukotrienes are biosynthesized via the 5-LO (arachidonate:oxygen 5-oxidoreductase, EC 1.13.11.34) pathway of arachidonic acid (AA) metabolism (Figure 1). The 5-LO product LTA_4 is a pivotal reactive epoxide intermediate in an important branch in the biosynthetic pathway that is further metabolized by either (i) stereoselective hydration by LTA_4 hydrolase to LTB_4 or (ii) glutathione addition by LTC_4 synthase to LTC_4. Successive amino acid cleavage steps convert LTC_4 to LTD_4 and then to LTE_4. The cysteinyl LTs (LTC_4, LTD_4, LTE_4) are the constituents of the biological substance previously known as slow-reacting substance of anaphlyaxis (SRS-A).[6] LTB_4 is a very potent neutrophil chemotactic agent, inducing neutrophil adherence to endothelial cells, degranulation, and modulation of cytokine production. The biosynthesis, release, and recovery of LTs from specific cells involved in inflammatory disorders together with the observed ability of these products to mimic aspects of disease support their involvement as mediators of inflammatory and allergic disorders.[7,8] Despite such circumstantial evidence, confirmation of the pathophysiological role of these mediators requires selective blockade of their actions.

At the outset of research efforts in the LT area, it was not entirely clear which LTs or subsequent metabolites were the predominant mediators of a particular human disorder. LTs are short-lived, being rapidly converted to inactive metabolites, and prolonged expression of activity is thus dependent on continuous biosynthesis. The enzyme 5-LO has a limited cellular distribution and has been found in neutrophils, eosinophils, monocytes, macrophages, mast cells, basophils, and B lymphocytes. These cells produce and secrete LTA_4. The branch point-processing enzymes LTA_4 hydrolase and LTC_4 synthase are more widely distributed than 5-LO. For example, erythrocytes lack 5-LO but have LTA_4 hydrolase which utilizes neutrophil-derived LTA_4 to produce LTB_4.[9] Platelets lack 5-LO but have LTC_4 synthase which converts imported LTA_4 of LTC_4. A complex

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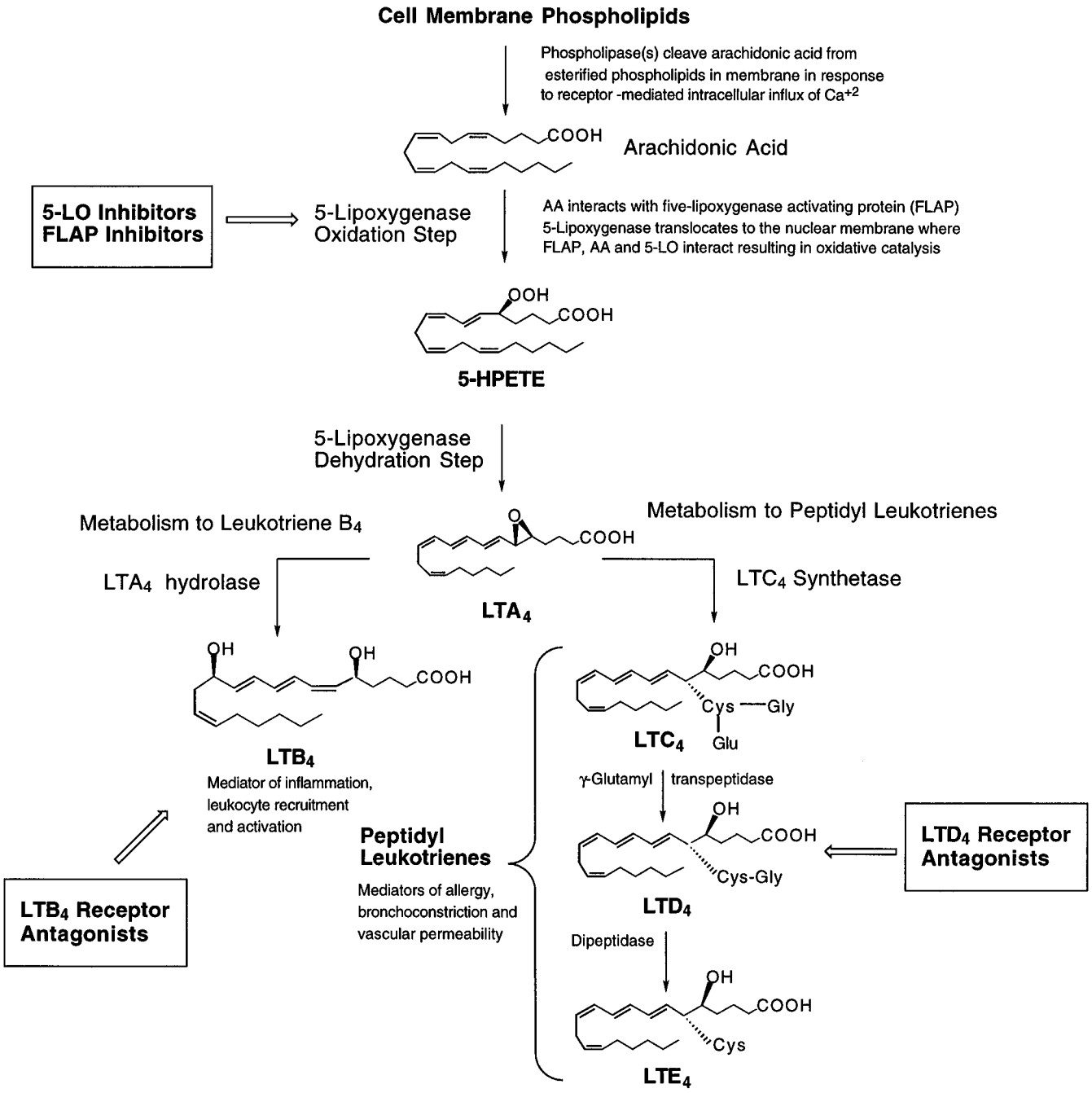


Figure 1. Leukotriene biosynthesis.

array of leukotriene-mediated biological responses and regulation phenomena occurs as a result of cellular secretion of LTA_4 and subsequent transcellular conversion to LTC_4 or LTB_4. The elucidation of cell specific export mechanisms for LTC_4 and LTB_4 and the processes for deactivating LTs will contribute to a better understanding of LT function.[7]

5-Lipoxygenase. The 5-LO enzyme has been the focus of intensive research since its discovery.[1] The instability of purified 5-LO preparations, suicide inactivation by lipid hydroperoxides, optimal activity being dependent on cellular factors such as Ca^{2+}, ATP, and phosphatidylcholine, and a complex kinetic behavior confounded initial research efforts.[10,11] 5-LO was purified from several sources with a molecular weight of 72–78 kDa.[12] Arachidonate and ATP binding sites on human 5-LO have been characterized.[13] Site-directed mutagenesis of 5-LO has led to the proposal that a single non-heme iron in the enzyme is bound by three "permanent" ligands, His-372, His-550, and Ile-673, and one "exchangeable" ligand, His-367.[14] It was further proposed that a reaction intermediate replaces the exchangeable ligand during the catalytic cycle. This type of active site model supports the possibility that compounds with affinity for the iron atom in the appropriate oxidation state could displace the "exchangeable" ligand and thus inhibit catalysis. The hydroxamate and *N*-hydroxyurea inhibitors have affinity for Fe^{3+} and might reversibly exchange with this putative "exchangeable" ligand as a possible explanation for their mechanism of reversible inhibition.

5-Lipoxygenase Inhibition as a Therapeutic Target. Since 5-LO catalyzes the first step in the LT biosynthetic pathway, inhibition of this enzyme provided a definitive target to potentially limit the effects of all LTs. An advantage of this approach was that this target

was independent of the evolving understanding of LT receptor heterogeneity, agonist/ligand specificity, and signalling pathways. However, cross-examination of this logic raised the question whether blockade of 5-LO products would result in untoward side effects—a relevant point with precedent for inhibitors of cyclooxygenase.

Although specific knowledge of any essential physiological role of LTs was not evident, this potential concern provided justification for devising more selective intervention strategies. The existence of the divergent transformations of LTA_4 to provide metabolites with different biological activities provided alternative enzyme inhibition or specific receptor targets. Broad intervention strategies, while having the potential to achieve wide ranging efficacy in LT-mediated pathology, also had the potential for side effects due to interference with essential physiological processes. A selective agent targeting partial LT intervention might offer improved safety but may have limited efficacy. Accordingly, both approaches were investigated in the clinic. More recently, mice made 5-LO deficient by gene disruption[15,16] were found to develop normally and showed no adverse health effects that could be attributed to leukotriene deficiency.

5-Lipoxygenase Inhibitors That Have Progressed to Clinical Evaluation

Early inhibitors of 5-LO were nonselective antioxidants, suffered problems of toxicity, or lacked oral bioavailability. The following discussion will emphasize the classes of LT inhibitors that have been evaluated in the clinic (Table 1).

Hydroxamic Acid 5-Lipoxygenase Inhibitors. Background. A logical starting point for the rational design of 5-LO inhibitors resulted in the evaluation of molecular entities interacting with the catalytically important iron moiety. The first validation of this hypothesis was the synthesis of arachidonohydroxamic acid as a potent *in vitro* inhibitor of 5-LO.[17] Low molecular weight, non-lipid hydroxamates were subsequently identified that were also potent *in vitro* inhibitors. This strategy of inhibitor design was elaborated using various 5-substituted-6,8,11,14-eicosatetraenoic acid (5-HETE) analogs[18,19] and 15-HETE templates.[20]

Many hydroxamate 5-LO inhibitors were identified that had impressive *in vitro* inhibitory potency. However, evaluation of these compounds in *in vivo* models led to disappointing results. The rapid *in vivo* hydrolysis of the hydroxamate pharmacophore to the corresponding inactive carboxylate was a major limitation of this class of compounds.[21] A key structural modification involving substitution of the lipophilic arylalkyl group on the hydroxylamine led to the acetylhydroxamates **3** (A-63162)[22,23] and **4** (BW A4C)[24] with improved *in vivo* activity (Scheme 1). A methyl substituent on the carbon adjacent to the hydroxamate as in **3** (Scheme 1) led to better *in vivo* activity compared to the methylene congener.[23] Although *in vivo* hydrolysis of these modified hydroxamates was reduced, oral dosing in rats and dogs revealed rapid glucuronidation of the hydroxamate function with half-lives of about 1 h for **3** and **4** in rat and dog.

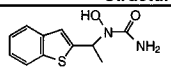
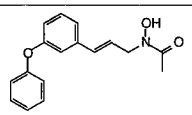
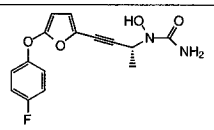
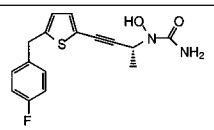
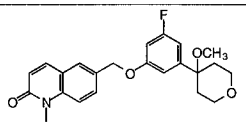
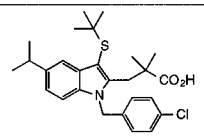
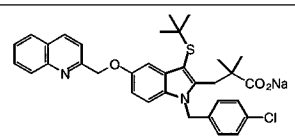
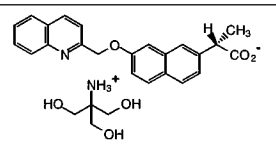
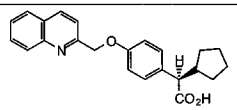
The metabolism of **4** was studied in rats and rabbits.[25] Four major metabolites were observed (Chart 1) as follows: (i) the glucuronide **5** of the hydroxamate, (ii) the propionic acid **6** (believed to result from reduction of the olefin followed by oxidation at the carbon adjacent to the hydroxamate), (iii) the benzoic acid analog **7** derived by side chain oxidation, and (iv) the amide **8** resulting from N−O bond reduction of **4**. A methyl substituent in the analog **9** (BW B218C; Scheme 1) resulted in improved plasma concentrations and duration in orally dosed rabbits, and no oxidatively derived carboxylate metabolites were detected.[25]

The predictability of these animal studies to man remained a perplexing question which was answered in a phase I clinical safety study.[26] Oral administration of 400 mg of **4** in humans resulted in an estimated plasma half-life of about 2 h which correlated with the short duration observed in rat and dog. A dosing regime of 400 mg, three times daily, resulted in prolonged inhibition of *ex vivo* stimulated LTB_4 production in blood samples taken over a 24 h period. Clinical investigation of **4** was subsequently terminated due to extensive metabolism resulting in the accumulation of metabolites. The limiting pharmacokinetic properties of hydroxamic acids in humans, as predicted by the preclinical studies, precluded their feasibility as viable, orally active clinical candidates.

First-Generation *N*-Hydroxyurea Inhibitors of 5-Lipoxygenase. The challenge in identifying alternative novel pharmacophores that might provide 5-LO inhibitors less susceptible to metabolism required extensive analysis of pharmacokinetics and *in vivo* LT inhibition for new chemical entities. This resulted in the identification of the *N*-hydroxyurea series of 5-LO inhibitors.[27,28] These analogs typically had *in vitro* 5-LO inhibitory activity comparable to their hydroxamate congeners. The advantage of significantly improved *in vivo* activity was largely due to higher plasma levels after oral administration and longer duration due to reduced glucuronidation rates. From hundreds of *N*-hydroxyureas studied, *N*-(1-benzo[*b*]thien-2-ylethyl)-*N*-hydroxyurea (**1**, zileuton; Scheme 1) was selected for clinical evaluation.[29,30] The discovery of **1** led to considerable interest in further optimization of *N*-hydroxyurea inhibitors.[31] Several previous hydroxamate leads were converted into promising *N*-hydroxyurea inhibitors like **10** (BW-B70C; Scheme 1).[32] This compound caused kidney lesions in rat, a finding that precluded clinical development.[33] Only a few compounds from the intense research efforts on hydroxamates and *N*-hydroxyureas actually progressed through phase II clinical studies.

Clinical Results with First-Generation Leukotriene Inhibitors. Clinical Measurement of Leukotriene Inhibition. The calcium ionophore A23187 can induce LTB_4 biosynthesis in whole blood which is readily measured by immunoassay.[34,35] This method was adapted to provide an *ex vivo* method for the evaluation of LT inhibition in clinical studies. This *ex vivo* LT assay provided a method to establish the level and duration of LT inhibition after a given oral dose of inhibitor, the degree of inhibition being correlated with the inhibitor plasma concentration time course and the observed therapeutic response parameters. Compound **1** was the first selective, orally active 5-LO inhibitor to demonstrate LT inhibition in man.[30] In the phase I safety evaluation of **1**, escalating single oral doses

Table 1. Leukotriene Biosynthesis Inhibitors Proceeding to Clinical Evaluation

Name	Structure	Company, Status, Route, Effective Dose	*in vitro* Inhibition IC_{50} (assay type)	*in vivo* Inhibition ED_{50}	Clinical Results
A-64077 zileuton **1**		Abbott Phase III NDA filed 7/94 oral 600 mg qid	100-500 nM (broken RBL-1); 600 nM (human PMNL); 700 nM (human whole blood)[29]	3 mg/kg rat peritoneal anaphylaxis[240]; 31 mg/kg mouse AA ear edema[29]; 18 mg/kg gp AA bronchospasm[241]; 12 mg/kg gp antigen bronchospasm[242]	Phase I oral half life of about 3 h[66] ; Asthma challenge studies:cold air 800 mg, 3 h pretreat[50] ; allergen 800 mg, 3 h pretreat[47] ; allergen 600 mg qid, 7 day pretreat[48,49] ; exercise 600 mg qid, 2 day pretreat[54] ; aspirin sensitive 600 mg qid, 7 day pretreat[57] Asthma chronic studies: 600 mg qid 4 weeks[59] ; 600 mg qid 13 weeks[60] ; 600 mg qid 13 weeks[61]; 600 mg qid 6 weeks ASA-intolerant asthmatics[58] Ulcerative Colitis: 800 mg, bid, 4 weeks[63]; 600 mg, qid, 8 weeks[64] ; 600 mg, qid, 26 weeks[65]
BW-A4C **4**		Wellcome suspended oral	100 nM (broken human PMNL) ; 40 nM (human PMNL); 100 nM (rat whole blood)[243]	10-100 mg/kg gp antigen bronchospasm[244]; 54 mg/kg rat PMNL [245]	Phase I: 400 mg oral half life about 2h[26]
A-79175 ABT-175 **12**		Abbott suspended oral	54 nM (broken RBL-1); 25 nM (human PMNL); 80 nM (human whole blood)[69]	1.5 mg/kg rat peritoneal anaphylaxis; 3 mg/kg mouse AA ear edema[69]; 2 mg/kg gp AA bronchospasm; 2.5 mg/kg gp antigen bronchospasm	Phase I: 200 mg oral half life about 7h[71]
A-85761 ABT-761 **14**		Abbott Phase II oral	23 nM (broken RBL-1); 23 nM (human PMNL); 150 nM (human whole blood)[72]	0.6 - 1.4 mg/kg rat peritoneal anaphylaxis[72]; 4 mg/kg gp antigen bronchospasm	Phase I: 200 mg oral half life about 15h; 200 mg provided >95% inhibition of *ex vivo* stimulated LTB_4 in blood up to 18h post dose[72]
ZD2138 **17**		Zeneca suspended oral	3 nM (murine macrophage); 20 nM (human whole blood)[246]	1.8 mg/kg mouse AA ear edema; 0.3 mg/kg rat zymosan-inflamed air pouch; 0.1 mg/kg gp antigen bronchospasm[246]	Phase I: 350 mg oral half life 12-16h[78] Asthma challenge studies: allergen 350 mg, 4 h pretreat[79]; aspirin sensitive 350 mg, 4 h pretreat[80]; cold air 350 and 1000 mg [81]
MK-886 **18**		Merck suspended oral	3 nM (human PMNL); 2100 nM (human whole blood); 23 nM (FLAP binding assay) [102]	0.036 mg/kg rat antigen bronchospasm; 85% inhibition at 1 mg/kg squirrel monkey antigen bronchospasm; 0.2-2.3 mg/ kg rat pleural ionophore challenge LTB_4 formation[97]	Phase I [83,247] Asthma challenge studies: allergen 500mg, 1 h pretreat & 250 mg 2h posttreat[248]
MK-0591 **19**		Merck suspended oral	6 nM (rat PMNL); 3 nM (human PMNL); 510 nM (human whole blood); 1.6 nM (FLAP binding assay) [103]	0.16-0.38 mg/kg rat antigen bronchospasm; 0.3-1 mg/kg squirrel monkey antigen bronchospasm[103]	Phase I: oral half life of 6h; 250 mg provided 90% *ex vivo* inhibition of LTB_4 formation in stimulated blood up to 12h[249]
Wy 50295 **22**		Wyeth-Ayerst suspended oral	5700 nM (broken gp peritoneal exudate cells); 160 nM (murine macrophage); 1200 nM (human PMNL); 8100 nM (rat blood); PDE-III IC_{50} = 15.8 μM; PDE-IV IC_{50} = 8.9 μM[108]; 53 nM (5-LO translocation in RBL-2H3 cells)[109]	7.3 mg/kg gp antigen bronchospasm[108]	Phase 1 suspended
BAY X 1005 **24**		Bayer Phase III oral	26 nM (rat PMNL); 220 nM (human PMNL); 11,600 nM (human whole blood)[112]	49 mg/kg mouse AA ear edema; 8-10 mg/kg rat zymosan-induced exudate[250]; 6.3 mg/kg gp antigen bronchospasm[251]	Phase I: 50 - 750 mg single doses, oral half life 4-8 hours[114] Asthma challenge studies: cold air 750 mg, 3 h pretreat[117]; allergen 750 mg, 4 h pretreat[115]; allergen 500 mg bid, 3 day pretreat[116] Chronic asthma, severe steroid dependent add on 250 mg bid, 8 days[118] Chronic asthma, inhaled steroid add on 250 mg qd, 4 weeks[119]

demonstrated an associative relationship of plasma drug levels and the degree of inhibition of *ex vivo* stimulated LTB_4 in blood samples from healthy volunteers.[36] In a multiple-dose safety evaluation of **1** given orally at 600 mg, four times daily (qid), for 14 days, greater than 70% inhibition of *ex vivo* stimulated LTB_4 formation was

Scheme 1. Hydroxamate and *N*-Hydroxyurea 5-LO Inhibitor Optimization

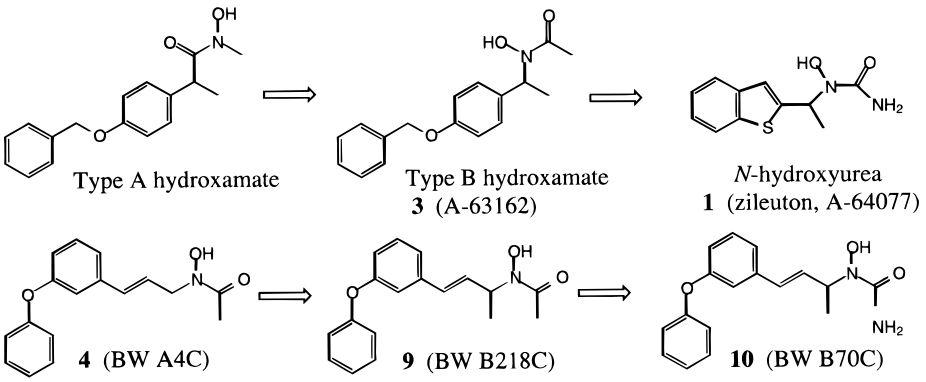
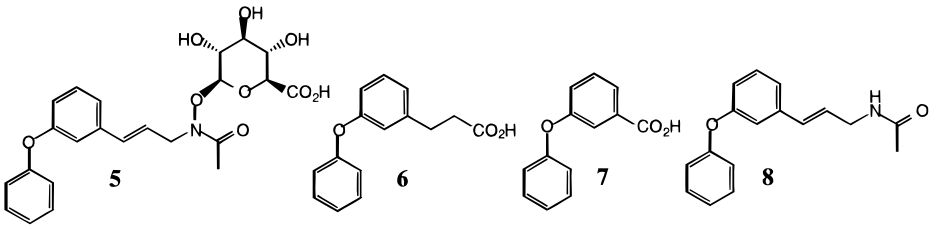


Chart 1. Metabolites of **4** (BW A4C)



maintained and the LTB_4 concentration returned to control levels after stopping the drug.[37]

There were complicating factors regarding this *ex vivo* method of monitoring LT inhibition. A23187 stimulation of blood results in the formation of several eicosanoid metabolites. The immunoassay methods used to measure LTB_4 must therefore have high selectivity to avoid underestimation of inhibition by cross-reactivity, for example, with 12-HETE and dihydroxyeicosanoids. The amount of stimulated LTB_4 formation is also dependent on species differences, ionophore concentration, and leukocyte count.[38] LT inhibitors that had high plasma protein binding exhibited attenuated potency in this assay compared to that observed in protein-free inhibition assays.

An alternative method of evaluating LT inhibition *in vivo* involves the measurement of urinary LTE_4 levels via immunoassay. Levels of LTE_4 are usually negligible in normal volunteers, while asthmatics have increased levels.[39] This method has been useful in determining effective dosing of LT inhibitors in studies involving induced asthmatic responses in patients.

Other methods used to measure inhibition of LTs at the site of the effector tissue include bronchoalveolar lavage fluid (BAL) from asthmatics,[40] nasal washings from allergic rhinitis patients,[41] extractions from psoriatic skin,[42] and rectal dialysis samples from patients with ulcerative colitis.[43] Interpretation of the LT inhibition from *in vivo* derived sources is complicated by the fact that agents which reduce the inflammatory response by blocking the influx of LT-producing cells can demonstrate decreased *in vivo* formation of LTs and yet lack activity as inhibitors of product formation.

Leukotriene Modulators in Asthma. The discovery of elevated levels of LTs in asthmatics[44] and more recently the positive results from clinical studies with LT modulators[45,46] have demonstrated that LTs are pathological mediators of asthma. Clinical trials of LT intervention treatments were typically initiated with studies designed to induce asthmatic attacks in patients in a controlled clinical setting using a variety of stimuli such as allergen, exercise, cold dry air, or aspirin.

1. Allergen Challenge. Atopic asthmatics challenged with inhaled allergen typically undergo two types of obstructed airway responses: an early asthmatic response (EAR) that resolves in a few hours but is often followed (4−8 h) by a more prolonged late asthmatic response (LAR). In an early study with **1** there was no improvement in antigen-challenged asthmatics although 5-LO inhibition was observed for *ex vivo* stimulated LTB_4 in blood (70%) and urinary LTE_4 (50%) at the single 800 mg oral dose 3 h prior to challenge.[47] More promising results were achieved with an improved pretreatment regimen in a more complex segmental antigen lung challenge study in asthmatics sensitive to ragweed pollen.[48,49] Zileuton (**1**) given 600 mg orally qid for 7 days protected against the effects of segmental allergen instillation. Eosinophil influx into bronchoalveolar lavage fluids and albumin leakage were both reduced. The increase in urinary LTE_4 upon allergen challenge was also blocked by **1** (86%). These results demonstrated the effectiveness of a LT inhibitor in reducing IgE-associated airway inflammation.

2. Cold Air Challenge. In asthmatics known to experience cold dry air-induced airway obstruction, the amount of cold dry air required to reduce the forced expiratory volume in 1 s (FEV_1) by 10−15% provided a useful clinical test. Pretreatment with a single 800 mg oral dose of **1** 3 h prior to challenge reduced the sensitivity in patients by requiring 47% more cold air to induce a 10% drop in FEV_1.[50] This level of benefit by **1** was greater than that reported for established asthma treatments that included cromolyn sodium, theophylline, and inhaled terbutaline.[51,52]

3. Exercise Challenge. Many asthmatics experience airway obstruction induced by strenuous exercise.[53] Pretreatment with **1** (600 mg qid po for 2 days) reduced the bronchoconstriction induced by exercise in asthmatics by 40%.[54]

4. Aspirin Sensitive Asthmatics. A subgroup of approximately 10% of asthmatics develop intolerance to aspirin (ASA) or other cyclooxygenase (COX) inhibitors that leads to bronchoconstriction and additional naso-ocular, gastrointestinal, or dermal reactions.[55] In ASA sensitive asthmatics, ASA ingestion results in increased urinary LTE_4 levels compared to placebo, whereas the urinary LTE_4 levels of control asthmatic subjects remain unaffected by ASA.[56] In a double-blind crossover study, **1** (600 mg qid po for 6−8 days) versus placebo was evaluated against ASA challenge in asthmatics with known sensitivity to ASA and hyperexcretion of urinary LTE_4 measured.[57] Patients on placebo when challenged by ASA suffered a decrease in FEV_1, of 18.6% from pre-ASA measurements. Treatment with **1** reduced the ASA-induced decrease in FEV_1 to 4.4% and also reduced the mean maximal urinary LTE_4 levels after ASA challenge by 68%. **1** also prevented the nasal, gastrointestinal, and dermal responses to ASA challenge observed in the placebo-treated ASA challenge phase.

In a controlled crossover study of 40 ASA intolerant asthmatics treated with glucocorticoids, add-on treatment with **1** (600 mg qid po for 6 weeks) resulted in significant chronic bronchodilation, reduced nasal symptoms, and reduced hypersensitivity to histamine, indicating that 5-LO inhibitors have additional therapeutic benefit in combination with glucocorticoids.[58]

5. Chronic Asthma. In a multicenter clinical trial with 129 mild to moderate asthmatics, **1** (600 mg qid po for 4 weeks) provided significant improvement versus placebo in mean FEV_1 (13.4%), decreased β-agonist use per day (24%), and improved symptom scores (37%).[59] Acute improvement of airway obstruction was observed with the first 600 mg dose. The mean FEV_1 improved at 30 min after dosing and continued throughout the 2 h observation time with a maximum increase of 15% 60 min postdosing. As 5-LO inhibitors like **1** are not bronchodilators acting via β-adrenoreceptors, the bronchodilation observed results from inhibition of LT biosynthesis that directly effects the base-line airway obstruction caused by ongoing LT formation, an integral component of the pathology of asthma. This pivotal clinical study provided the first validation of the therapeutic potential of a 5-LO inhibitor in chronic asthma.

Compound **1** (600 mg qid po) provided similar efficacy in a 13 week trial with 398 patients demonstrating that LT inhibition resulted in sustained improvement in lung function and overall asthma symptoms for at least 3 months.[60] Steroid use was allowed to control asthmatic attacks, and the group treated with **1** required an average of 7 bursts of steroid use compared to 22 in the placebo group. A subset of 10 asthmatics participating in this trial were evaluated by cold dry air challenge before the study, 1 day after and then 10 days after the 13 week study. Those receiving **1** demonstrated a 55% increased tolerance to cold dry air required to produce a 15% reduction in FEV_1.

In a placebo-controlled study with 401 patients with moderate asthma, **1** (600 mg qid po for 13 weeks) reduced steroid rescue by greater than 80% compared to placebo in patients with more severe asthma (FEV_1 < 50% of predicted).[61] These results further confirmed the efficacy of LT blockade in preventing asthma exacerbations.

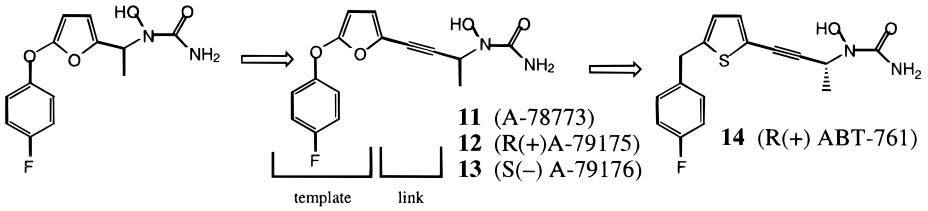
Leukotriene Inhibition in Ulcerative Colitis. The clinical relevance of LTs in a variety of inflammatory and allergic disorders has been explored using **1**. Rectal dialysate samples in ulcerative colitis patients had higher levels of LTB_4 compared to normals, and the severity of the disease correlated with the amounts of LTB_4 present.[62] An initial evaluation of **1**, in 10 ulcerative colitis patients (single 800 mg po), resulted in reduced LTB_4 concentrations (up to 85%) in rectal dialysates with no change in PGE_2 levels.[43] In a placebo-controlled trial in ulcerative colitis, **1** (800 mg bid po for 4 weeks) produced a modest improvement in disease symptoms and histological assessment of the mucosa compared to placebo.[63] During this study a 70% mean inhibition of LTB_4 in rectal dialysate was found. However there was no significant change in sigmoidoscopic score versus placebo indicating no visible improvement in colitis tissue. The results with **1** were comparable to those in patients receiving conventional therapy with sulfasalazine. Combined treatment had no additional benefit.

The potential of a 5-LO inhibitor to induce remission was evaluated with **1** (600 mg qid po for 8 weeks) in 212 patients with active disease.[64] The treatment group receiving **1** showed a 25% remission rate compared to 7% in the placebo group. In a 26 week trial in 308 patients for maintenance of remission, the group treated with **1** was significantly better than placebo in preventing relapse. The group treated with **1** was, however, no more effective than a group treated with 5-aminosalicylic acid.[65] The 5-LO inhibitor **1** demonstrated efficacy in ulcerative colitis but did not define clear therapeutic advantages over the currently prescribed treatments. At the doses of **1** studied, LTB_4 formation was blocked in the range of 70−80% by rectal dialysis measurement. More complete (>90%) inhibition may be required in order to demonstrate improved efficacy for a single-agent therapy in this complicated inflammatory condition.

Second-Generation *N*-Hydroxyurea 5-Lipoxygenase Inhibitors. Potency and Duration Optimization. In humans, the major route of metabolism of **1** is glucuronidation of the *N*-hydroxyurea group and subsequent urinary excretion.[36,66] The estimated oral half-life was thus approximately 3 h. The clinically effective daily dose of 2400 mg (600 mg qid po) provided about 70−80% inhibition of LT formation as measured in urine or *ex vivo* stimulated blood samples. Whether LT inhibition approaching 100% would provide more effective therapeutic benefit remained a fundamental question. Thus, more potent and longer acting *N*-hydroxyurea inhibitors were sought.

To establish the structure−activity relationships (SAR) that would reduce the rate of glucuronidation of the *N*-hydroxyurea group, an *in vitro* assay using microsomal preparations from human or monkey liver was used to evaluate new inhibitors. The predictive capability of this *in vitro* approach was validated by pharmacokinetic evaluation of promising 5-LO inhibitors in cynomolgus monkeys where rapid glucuronidation of **1** ($t_{1/2}$ of 0.3 h) was observed.[67] A key assumption was that the *in vitro* glucuronidation rates and the monkey pharmacokinetic data would be predictive of improved duration in humans. The 1-methylpropynyl link group in combination with a (4-fluorophenoxy)fur-2-yl tem-

Scheme 2. Second-Generation 5-LO Inhibitor Optimization



Scheme 3. Aryl Triether 5-LO Inhibitor Optimization

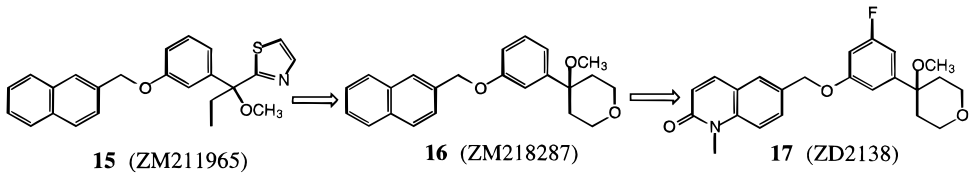


plate as in **11** (Scheme 2) proved to be a more potent 5-LO inhibitor with a reduced *in vitro* glucuronidation rate compared to **1**.[68]

In general, there have not been large differences reported in the inhibitory activity of enantiomers of *N*-hydroxyurea 5-LO inhibitors. The enantiomers of **1** have similar *in vitro* inhibitory activity in both broken cell, intact cell, and whole blood assays. Only minor potency differences were observed for (*R*)-(+)-**12** and (*S*)-(−)-**13** compared to the racemate **11**.[69] Metabolism phenomena were however more sensitive to stereochemistry. A 5-fold difference in glucuronidation rate was observed in monkey microsomes for the racemate **11** with greater resistance toward glucuronidation found for (*R*)-(+)-**12**. These results correlated with the elimination half-lives determined from iv administration to monkeys as follows: 0.4 h for **1**, 4.7 h for racemate **11**, 9.0 h for (*R*)-(+)**12**, and 1.8 h for (*S*)-(−)-**13**. The predictability of these results in humans was validated by a phase I clinical study with racemate **11** where a single 400 mg po dose given to healthly male volunteers exhibited an apparent elimination half-life of about 6.5 h for **12** compared to 2.4 h for **1** leading to the selection of **12** for clinical development.[70,71]

The (*R*)-1-methylpropynyl link group represented a breakthrough for reduced glucuronidation, and alternative templates were examined. The synthetic intermediates for the [(4-fluorophenyl)methyl]-2-thienyl template had improved stability compared to the acid labile furyl intermediates of **12**. The *R* (+) enantiomer **14** (ABT-761) was more resistant to *in vitro* glucuronidation with monkey and human microsomes.[72] In the cynomolgus monkey, an elimination half-life of 16 h was determined. A single 0.5 mg/kg po dose of **14** in monkey resulted in higher plasma levels and greater sustained inhibition of *ex vivo* stimulated LTB_4 formation than **12** at the same dose.

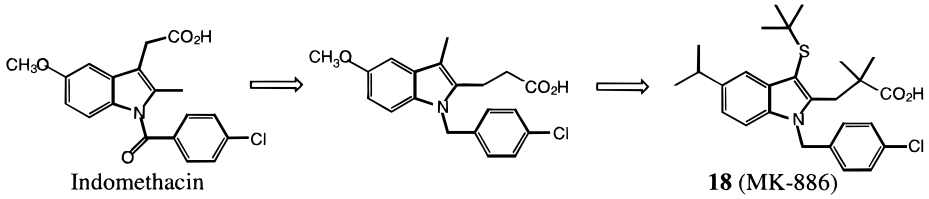
Clinical Studies with 14. Phase I studies of **14** showed excellent oral bioavailability and an extended duration of plasma levels in man (estimated half-life of 15 h at 200 mg qid po and a plasma concentration of >1 μg/mL for up to 24 h postdosing).[72] This single 200 mg dose also provided >95% inhibition of *ex vivo* stimulated LTB_4 formation in blood samples taken at intervals up to 18 h. The clinical investigation of this second-generation 5-LO inhibitor will aid in clarifying outstanding issues regarding the degree of therapeutic benefit that more effective and sustained inhibition of 5-LO could provide. Initial results for a single 200 mg po dose of **14** have shown a significant protective effect against exercise- and adenosine-induced bronchoconstriction in asthmatics.[73,74]

(Heteroarylmethoxy)tetrahydropyran 5-Lipoxygenase Inhibitors. Background. Based on the observed disadvantages of previous redox inhibitors of 5-LO, a strategy to discover active site-targeted 5-LO inhibitors devoid of these properties was developed.[26] The lipophilic (arylmethoxy)thiazole **15** (ZM211965; Scheme 3) had good 5-LO inhibitory activity in whole blood (IC_{50} = 0.4 μM) but limited oral bioavailability.[75] Further structure−activity studies led to the more potent (arylmethoxy)tetrahydropyran 5-LO inhibitor **16** (ZM218287; Scheme 3). Exploring more soluble alternatives to the naphthyl group culminated in the identification of the selective, orally active LT inhibitor **17** (ZD2138; Scheme 3).[76] The discovery of this 5-LO inhibitor without redox or iron ligand-binding functionality was a major achievement in *de novo* inhibitor design.[77]

Clinical Studies with 17. The LT inhibitor **17** (IC_{50} = 24 nM) was approximately 100-fold more potent than **1** in blocking A23187-stimulated LTB_4 formation in human blood.[77] In a 1 month safety study in human volunteers, a single 350 mg po dose of **17** completely inhibited *ex vivo* stimulated LTB_4 formation in blood samples taken over a 24 h period postdosing.[78] The oral half-life in humans (12−16 h) was longer than in rat (1−2 h) or dog (5−6 h). The single 350 mg po dose of **17** provided more effective *ex vivo* inhibition of LT formation in blood than **1** given at 600 mg qid.

Phase II clinical trials with **17** gave mixed results. In an allergen challenge study with asthmatics, **17** (350 mg po) given 4 h prior to antigen challenge had no effect on early and late asthmatic responses.[79] However, measurement of *ex vivo* stimulated LTB_4 in blood samples and urinary LTE_4 excretion indicated significant LT inhibition. In ASA sensitive asthmatics, **17** (350 mg po) given 4 h prior to ASA challenge prevented airway obstruction.[80] In a study of mild to moderate asthmatics challenged with cold air, single 350 and 1000 mg oral doses were effective in attenuating the bronchoconstriction compared to placebo.[81] The development of this compound has been terminated.[82]

Scheme 4. Indole FLAP Inhibitor Optimization



5-Lipoxygenase-Activating Protein (FLAP) Inhibitors

Discovery of FLAP. The discovery of 5-LO-activating protein[83] was made when a series of compounds, represented by **18** (MK-886), that were potent inhibitors of intact cell-stimulated LT biosynthesis were found to be inactive in broken cell 5-LO inhibition assays requiring an explanation for the mechanism of inhibition.[84] Subsequent studies led to the discovery of the FLAP LT inhibition modality.[85]

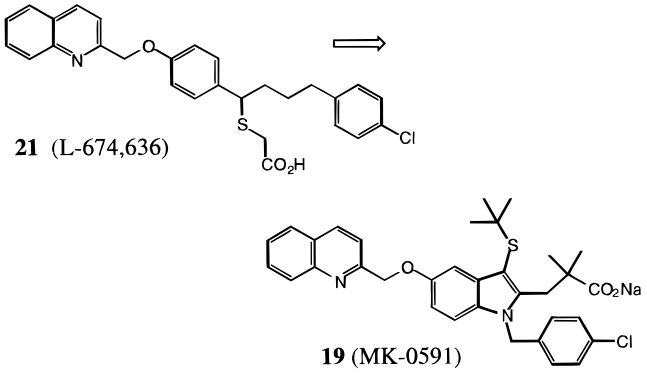
Biochemical studies of A23187 and IgE stimulation of rat and human leukocytes showed that 5-LO could be translocated from the cytosol to a membrane site.[86,87] Additional studies[88] led to the suggestion that inactive 5-LO in the cytoplasm translocates to a membrane site and associates with the unique 18 kDa protein FLAP. In transfected human osteosarcoma cells, both 5-LO and FLAP were required for intact cellular LT biosynthesis.[89]

The mechanism of the cooperativity between these two proteins is not completely understood. Two general proposals have been offered as follows: (i) FLAP is a membrane-docking protein for 5-LO,[88] or (ii) FLAP is an arachidonate-presenting protein.[90] FLAP can enhance the catalytic activity of 5-LO.[91] In human neutrophils the products of cytosolic and membrane-bound 5-LO were compared, and it was noted that the latter was 3−4-fold more efficient in converting 5-HETE into LTA_4.[92] A comparison of cDNAs from six mammalian species to those of human and rat FLAP revealed a high degree of conservation, particularly in two regions of the protein proposed to be important functional sites.[93]

The location for 5-LO activation and catalysis was initially assumed to be the plasma membrane, but two reports[94,95] indicated that FLAP was localized at the inner nuclear membrane and that both 5-LO and the cytosolic PLA_2 that liberates arachidonate translocate to this site, raising the possibility that 5-LO products might be formed in the nucleus and be involved in gene regulation.

Indole Series of FLAP Inhibitors. One approach to generating 5-LO inhibitor leads was to screen libraries of COX inhibitors as 5-LO was considered to be a related oxidative enzyme since it shared the same substrate, arachidonic acid. By screening the extensive indole libraries derived from indomethacin and sulindac COX inhibitor research,[96] several leads were identified that were useful for the design of a new indole-containing LT inhibitor, **18** (MK-866; Scheme 4). Compound **18** is a potent inhibitor of LT biosynthesis (IC_{50} = 3−5 nM in human or rat neutrophils) and has FLAP binding affinity (IC_{50} = 23 nM).[97] It was less potent in a human blood assay (IC_{50} = 2.1 μM), possibly as the result of plasma protein-binding interference. This compound was the first FLAP inhibitor selected for clinical evaluation.

Scheme 5. Second-Generation FLAP Inhibitor **19** (MK-0591)

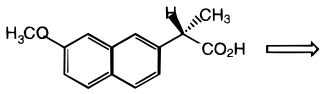


Clinical Studies with 18. Compound **18** was evaluated (500 mg po) in eight atopic asthmatics 1 h before allergen challenge and at 250 mg 2 h afterward. Pulmonary function as compared to the control response was improved by 58% in EAR and 44% in the LAR.[98] This combined 750 mg oral dose of **18** provided approximately 50% inhibition of *ex vivo* A23187-stimulated whole blood LTB_4 biosynthesis and urinary LTE_4 excretion. The degree of LT inhibition measured in stimulated blood and in the urine was disappointing in view of the excellent *in vitro* activity of **18**. Clinical investigation of **18** was subsequently terminated.

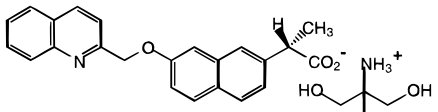
Second-Generation FLAP Inhibitor 19 (MK-0591). Using a FLAP binding assay[99] the (quinolylmethoxy)phenyl compound **20** (Rev-5901)[100] was found to bind to FLAP in a dose-dependent manner. Although **20** was known to be a modest LT inhibitor with weak LTD_4 receptor antagonist activity, the ability to interact with FLAP led to the design of a new structural class of FLAP inhibitors exemplified by **21** (L-674,636; Scheme 5).[101] Compound **21** had FLAP binding activity (IC_{50} = 122 nM) and LT inhibitory activity (IC_{50} = 20 nM) in intact human neutrophils but was inactive below 10 μM in blocking A23187-stimulated LT formation in human blood. The extensive SAR that followed suggested that the quinolylmethoxy substituent at the 5-position of the indole ring in **18** maximized interaction with a proposed lipophilic FLAP binding site.[102] Compound **19** (MK-0591; Scheme 5) proved to have potent FLAP binding activity (IC_{50} = 2 nM) and LT inhibitory activity (IC_{50} = 3 nM) in intact human neutrophils and in stimulated human blood (IC_{50} = 500 nM), leading to its selection for clinical development.[103]

Clinical Studies with 19. In an allergen-induced challenge study in eight atopic asthmatics, **19** (given in three 250 mg po doses at 24, 12, and 1.5 h prior to inhaled allergen) reduced bronchoconstriction in both early phase (79%) and late phase (39%) responses.[104] Allergen-induced airway hyperresponsiveness to histamine was not blocked by **19**. LT biosynthesis measured by *ex vivo* stimulated whole blood was completely

Scheme 6. FLAP Inhibitor **22** (WY 50295 tromethamine)



23 (naproxen)



22 (WY 50295 tromethamine)

inhibited (98%) up to 24 h after allergen challenge, and urinary LT levels were also effectively inhibited (87%) with similar duration.

Compound **19** was also evaluated as adjunctive therapy in moderately severe asthmatics requiring treatment with inhaled corticosteroid.[105] Compound **19** (125 mg bid po for 4 weeks) with combined treatment of inhaled steroids (beclomethasone or budesonide at constant daily dosages of 400−1600 μg) resulted in significant improvements over the placebo group in mean FEV_1 by 6.8%. Both the morning and evening peak expiratory flow improved by 19% and 13%, respectively, and β-agonist usage decreased by 1.1 puffs/day.[105] A larger dose-ranging study of 239 mild to moderate asthmatics involving treatment groups receiving **19** (25 qid or 25, 50, and 125 mg bid) showed that 6 weeks of active therapy resulted in improved pulmonary function tests, but only the 50 mg qid group achieved significance ($p < 0.05$).[106] Rescue β-agonist use decreased for all the bid treatment groups. The high-dose group had consistent improvement in asthma symptoms. Adverse effects were no different than placebo. These studies with **19** demonstrated clinical efficacy for the FLAP approach to LT intervention. However, the degree of improvement observed in the clinical studies was not as good as expected given the excellent biochemical potency.

(Quinolylmethoxy)aryl Series of FLAP Inhibitors. The design and characterization of (quinolylmethoxy)aryl-containing LT inhibitors and LTD_4 antagonists originated from the discovery of **20**.[5] An interesting conceptual approach to designing LT inhibitors was accomplished by attachment of the quinolylmethoxy substituent to clinically useful nonsteroidal anti-inflammatory drugs (NSAIDs) serving as bioavailable aryl templates. By this approach **22** (WY 50295 tromethamine; Scheme 6) was derived from naproxen (**23**).[107] The addition of the 2-quinolylmethoxy substituent in place of the methoxy group of naproxen resulted in an LT inhibitor with moderate activity as a LTD_4 receptor antagonist with dramatic loss of COX inhibitory activity.[108] With the advent of FLAP binding assays,[99] it was found that many quinolylmethoxy analogs had affinity for FLAP, including **22**,[109] explaining why many of these compounds were more potent LT inhibitors in cellular assays when compared to broken cell assays. The tromethamine salt of **22** was evaluated in phase I studies at doses up to 1000 mg. The failure to demonstrate *ex vivo* inhibition of LT formation in blood samples may have been one factor in the decision not to continue the development of this compound.[110]

A new series of chiral cycloalkyl-substituted (quinolylmethoxy)phenylacetic acid FLAP inhibitors was derived from **20** resulting in the identification of **24** (BAY X 1005; Scheme 7).[111−113] Both the *R* and *S* enantiomers of **24** had similar inhibitory activity in rat and mouse neutrophils. However, stereochemical differences in potency were observed against human FLAP. The *R* (−) enantiomer was 6−7-fold more potent in inhibiting A23187-stimulated LT formation in human neutrophils and approximately 30-fold more potent in human whole blood than the *S* (+) enantiomer. The observation of 1 order of magnitude loss of potency against human FLAP versus rat and mouse FLAP indicated species differences in compound interaction with FLAP that could confound the extrapolation of rodent pharmacology to the human situation.

Clinical Studies with 24. Phase I studies of **24** at single doses from 50 to 750 mg showed no clinically significant adverse events.[114] The LT inhibitor **24** was well absorbed achieving maximum plasma levels at about 2−3 h and had an estimated oral half-life ranging from 4 to 8 h in humans. Greater than 50% reduction in urinary LTE_4 was found with a single 500 mg po dose. In allergen-induced challenge studies in asthmatics, **24** (750 mg po) 4 h prior to allergen inhalation attenuated both early and late responses.[115] Similar results were found in a second study with 500 mg bid po for 4 days prior to allergen challenge.[116] In the drug treatment phase, the mean fall in FEV_1 for EAR was attenuated by about 60% and for LAR by 53%. A single dose of **24** (750 mg po) was effective in reducing the bronchoconstriction induced by cold dry air in asthmatics.[117]

In a study of 10 severe, chronic, steroid-dependent asthmatics, **24** (250 mg bid po) in combination with daily steroid treatment (10−30 mg po) in a double-blind placebo-controlled crossover study provided mean FEV_1 improvement of 8.5% over base line for FLAP inhibitor treatment phase compared to 5.7% in the placebo phase.[118] In a multicenter trial of chronic asthmatics receiving inhaled corticosteroids, **24** (250 mg po 4 weeks) produced a 6% improvement in FEV_1 compared to 0.2% for the placebo group.[119] Compound **24** also provided acute bronchodilatory improvement in asthmatics.[120]

A backup candidate, **25**, was 5-fold more potent in blocking LT formation in the human neutrophil (IC_{50} = 42 nM) and about 10-fold more potent in whole blood (IC_{50} = 1.1 μM).[121] Comparable activity to **24** was found for **25** in antigen-induced bronchoconstriction in the guinea pig by both oral and iv routes.

Peptidyl Leukotriene Antagonists That Have Progressed to Clinical Evaluation

Introduction. The report of the first peptidyl LT antagonist, **26** (FPL-55712),[122] predated the elucidation of the structure of the LTs. In the more than 2 decades since this seminal antagonist was identified, many hundreds of cysteinyl LT antagonists have been made.[123−125] The following discussion will focus on LT antagonists that have entered clinical trials (Table 2).

The discovery and development of investigational peptidyl LT antagonists provided clinical tools which helped define LTs as major mediators of asthma. The common first stage in the clinical evaluation of peptidyl LT antagonists was in a bronchoconstriction challenge induced by inhaled LTD_4 in normal volunteers or mild

Table 2. Peptidyl Leukotriene Antagonists for Which Results of Clinical Evaluation Have Been Reported

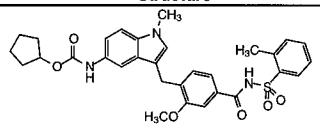
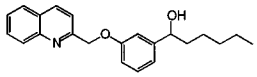
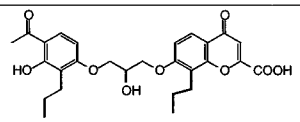
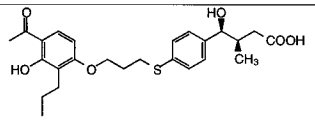
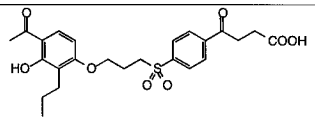
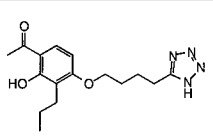
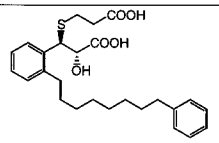
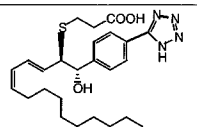
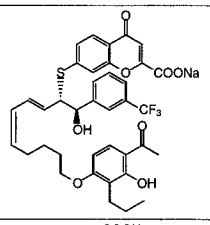
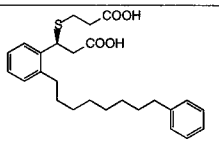
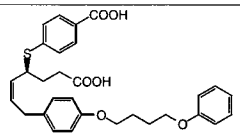
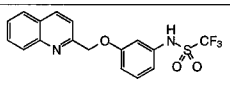
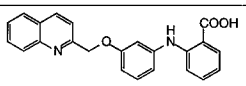
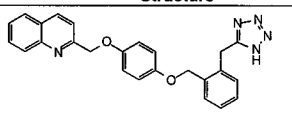
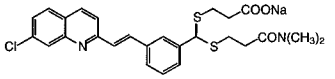
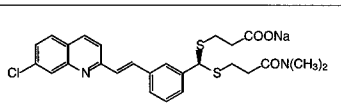
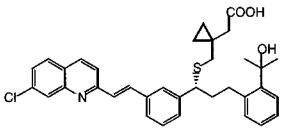
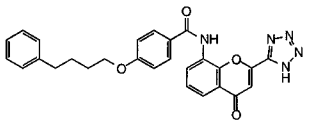
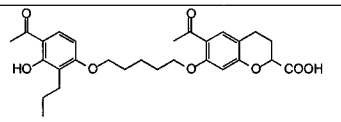
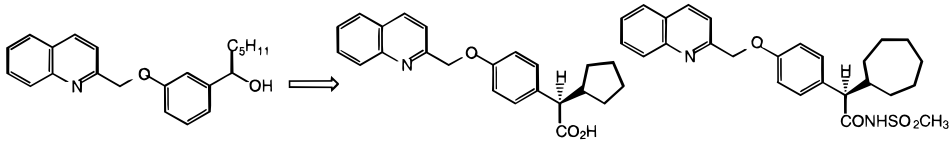
Name	Structure	Developer, Status, Route	LTD_4 Binding	LTD_4 guinea pig trachea contraction	LTD_4 induced bronchoconstriction	Other Clinical Results
ICI-204,219 Accolate™ zafirlukast **2**		Zeneca phase III oral	K_i = 0.3 nM[174]	pA_2 = 9.5[174]	117 fold shift in LTD_4 dose response curve 2 hours after 40 mg oral dose; 5 fold shift persists at 24 hours.[175]	Effective in blocking by allergen following oral[178,252,253] or aeresol[176,177] administration; by exercise following oral[254] or aerosol[255] administration; cold air[256] or by PAF.[257] Provided acute improvement in lung function.[179] Provided improvement in lung function, symptoms after 6[180] or 13[181] weeks in stable asthmatics. Provided symptomatic improvement in allergic rhinitis.[183]
Rev-5901 RG-5901 **20**		Rhone Poulenc Rorer suspended oral	K_i = 700 nM[258]	pK_B = 5.5[258]	No effect on LTD_4 induced broncho-constriction.[259]	
FPL-55712 **26**		Fisons suspended inhalation	IC_{50} = 4000 nM[260]	pA_2 = 6.0[260]	Small inhibition of LTC_4 induced broncho-constriction.[261]	Improved lung function in some asthmatic patients.[262]
L-649923 **27**		Merck suspended oral	K_i = 400 nM[263]	pA_2 = 7.2[263]	3.8 fold shift in LTD_4 dose response curvefollowing 1 g oral dose.[264]	Small effect on the early response but no effect on the late phase following antigen challenge in asthmatics.[127]
L-648051 **28**		Merck suspended inhalation	K_i = 6200 nM[265]	pA_2 = 7.3[266]	Partially blocked LTD_4 induced broncho-constriction following 12 mg aeresol dose.[267]	Small[128,129] or no effect[268] on lung function and bronchial reactiviity after antigen challenge.
LY171883 tomelukast **29**		Lilly suspended oral	K_i = 600 nM[269]	pK_B = 6.9 [270]	4.6–6.1 fold shift in LTD_4 broncho-constriction dose respose curve following a 400 mg oral dose.[271]	Small effect on exercise[130] and cold air induced[131] asthma models Small improvement in early but not late response to inhaled antigen challenge.[132] Six week trial in mild asthmatics yielded an improvement in lung function and some symptoms.[133]
SKF 104353 pobilukast **30**		Smith-Kline Beecham suspended inhalation	K_i = 5 nM[272]	pA_2 = 8.6[272]	10 fold shift in LTD_4 dose response curve 2 h following 100 μg aerosol dose in normal subjects.[273] 2–3 fold shift following 800 μg aeresol dose in mild asthmatics.[153]	Blocks bronchoconstriction by antigen[138] and exercise.[139] Improved lung function in aspirin sensitive asthmatics after challenge. [274]
LY170680 sulukast **31**		Lilly suspended inhalation		pA_2 = 8.3[275]	10 fold shift in LTD_4 dose response curve 1 hour following inhalation of 6 mg in normal volunteers.[276]	No effect on lung function or bronchial reactivity in 8 mild asthmatics following one week treatment with 1 mg, b.i.d.[277]
CGP45715A **32**		Ciba Geigy inhalation	K_i = 26 nM[126]		Evaluated in LTD_4 bronchoconstriction in normal volunteers.	
SKF 106203 **33**		Smith Kline Beecham suspended oral	K_i = 60 nM[137]	pK_B = 7.6[278]	Provided some inhibition of LTD_4 bronchoconstriction following 4 mg/kg oral dose.[279]	
Bay-x7195 **34**		Bayer phase II oral		pK_B = 8.4[140]	8 fold shift in LTD_4 dose response curve 2 hours after 250 mg oral dose.[141]	250 and 500 mg produced a 13.1% and 13.8% increase in FEV1 5 hours after administration to mild to moderate asthmatics.[142]
Wy-48252 ritolukast **35**		American Home Products suspended oral	K_i = 35 nM[280]	pK_B = 7.8[280]		No published clinical data. Development discontinued following observation of toxicity in monkeys[281]
SR-2640 **36**		Leo suspended oral	IC_{50} = 23 nM[282]	pK_B = 8.7[282]	<2 fold shift in LTD_4 dose response curve following 250 mg oral dose [283]	No significant effects in an open-labelled ulcerative collitis trial.[284]

Table 2. (Continued)

Name	Structure	Developer, Status, Route	LTD_4 Binding	LTD_4 guinea pig trachea contraction	LTD_4 induced bronchoconstriction	Other Clinical Results
RG-12525 **37**		Rhone Poulenc Rorer suspended oral	K_i = 3 nM[285]	pA_2 = 8.4[285]	7.5 fold shift in LTD_4 induced broncho-constriction dose respose curve 2 hrs following 800 mg oral dose in mild asthmatics.[286]	Blocked antigen induced broncho-constriction[143] Small but significant improvement in lung function in asthmatic patients after acute[144] or chronic therapy.[145]
MK-571 L-660711 **38**		Merck suspended intravenous, oral	K_i = 0.2 nM[287]	pK_B = 9.3[287]	≥83 fold shift in LTD_4 dose response curve following 280 mg iv dose in asthmatic patients.[147]	Blocks bronchoconstriction induced by exercise[150] and early and late phase responses to antigen.[148,149] Improves baseline lung function in moderate asthmatics. Effect is additive with albuterol.[151] Improved lung function and reduced symptoms in mild to moderate asthmatics.[154]
MK-679 L-668,019 verlukast Venzair™ **39**		Merck suspended aeresol, intravenous, oral	IC_{50} = 3.1 nM[288]	pK_B = 8.8[288]		Blocks bronchoconstriction induced by aspirin[158]. Improves acute baseline lung function in asthmatics by aeresol[157] or intravenous.[156] Improves lung function and upper respiratory symptoms in aspirin sensitive asthmatics.[159] Improves lung function and symptoms in asthmatics after 6 wks of therapy, but liver abnormalities observed in 5% of patients.[160]
MK-476 montelukast Singulair™ **40**		Merck phase III oral	IC_{50} = 0.5 nM[161]	pA_2 = 9.3[161]	>50 fold shift in LTD_4 24 hours following 40 mg oral dose.[162]	100 mg causes prompt bronchodilation in moderate asthmatics which is additive with b-agonists[163] and blocked exercise induced bronchoconstriction 24 hours after dosing.[164] 10 mg once daily for six weeks produced a significant improvement in lung function, quality of life, and β-agonist use.[165]
ONO-1078 pranlukast Onon™ ONO-RS-411 SB205312 **41**		ONO with Smithkline Beecham Launched in Japan Phase III elsewhere oral		pK_B = 7.5[166]	26 fold shift in LTD_4 dose response curve 3.5 hours after 5 days of 450 mg bid; 7 fold shift at 24 hours.[167]	Blocks bronchoconstriction after antigen challenge.[168,289] Small reduction in bronchial hyperresponsiveness, but not baseline lung function in asthmatics.[169] Blocked bronchoconstriction to analgesic challenge in aspirin sensitive asthmatics.[170] Improved lung function, symptoms and reduce β-agonist usage in 4 week chronic study.[171,172]
Ro 23-3544 Ablukast **57**		Roche suspended inhalation	IC_{50} = 4000 nM[260]	pA_2 = 6.6[260]		Induced bronchospasm in mild asthmatics.[290]

Scheme 7. (Quinolylmethoxy)phenyl FLAP Inhibitors



20 (REV 5901) **24** (BAY X 1005) **25** (BAY Y 1015)

to moderate asthmatics. The shift in the LTD_4 dose–response curve with pretreatment by an antagonist provided an assessment of competitive receptor blockade in the airways. Since these initial studies were done with normal volunteers, it as possible to evaluate investigational antagonists by oral or inhaled routes in small clinical trials and acquire efficacy data for preventing provoked airway obstruction by the natural agonist. These results were very relevant to the airway obstruction observed in asthma. Being able to secure this type of relevant airway data from man at a very early clinical stage provided an advantage for the discovery of clinically effective antagonists for the treatment of asthma compared to the limited indirect inhibition data from blood *ex vivo* or whole body urinary LT excretion available from phase I studies with biosynthesis inhibitors. New optimized investigational antagonists shifted to the right (higher concentrations) the LTD_4 inhaled dose–response curve in human subjects.

Hydroxyacetophenone Antagonists. Background. The early peptidyl LT antagonists were structural analogs of **26** (FPL-55712). This series of antagonists contained a common hydroxyacetophenone moiety linked through a flexible spacer to an acidic group. Structure–activity relationship studies on this class of antagonist have led to the conclusion that the hydroxyacetophenone group mimics the lipophilic tail of LTD_4 and the acid moiety is a surrogate for the thioether of the glycinylcysteinyl dipeptide. With receptor binding affinities 3–4 orders of magnitude less than that of LTD_4 itself, these compounds were weak antagonists (K_i = 0.4–6 μM).[126]

This low intrinsic receptor binding affinity translated to unimpressive efficacy in clinical studies. These early compounds provided, at most, a 6-fold shift in the dose–response curve for inhaled LTD_4-induced bronchoconstriction in human volunteers. This proved insufficient to produce unequivocal benefit in clinical models of asthma. For example, high doses of **27** (L-649923)

produced only a small improvement in the EAR resulting from inhaled antigen in asthmatic subjects and had no significant effect on the LAR.[127] No higher dose was evaluated due to side effects of abdominal cramping and diarrhea. Another analog, **28** (L-648051), dosed by inhalation at doses up to 12 mg provided a small effect on EAR without benefit on LAR.[128,129]

Clinical Studies with Tomelukast. Perhaps the best studied of the hydroxyacetophenone class of antagonists is **29** (tomelukast, LY171883). It is also a relatively weak antagonist (K_i = 600 nM) and produced a relatively small shift in the LTD_4-induced bronchoconstriction dose−response curve. Only small effects were observed in acute asthma studies provoked by exercise,[130] inhalation of cold air,[131] or antigen[132] (Table 2). In a placebo-controlled chronic study in mild to moderate asthmatics, **29** (600 mg po for 6 weeks) produced a significant improvement in FEV_1, wheezing, and breathlessness, and a trend for improvement in cough and asthma severity score.[133] There was also a significant reduction in β-agonist usage, particularly among the heaviest users. Interpretation of these results was confounded by the observation that **29** had additional activity as a thromboxane antagonist and phosphodiesterase inhibitor.[134] Tomelukast caused peroxisome proliferation and tumors in rodents, and development was subsequently discontinued.[135,136]

A majority of antagonists described in the early and mid-1980s were members of the hydroxyacetophenone class, and their development has also been discontinued. The clinical experience gained with these first-generation antagonists did not conclusively demonstrate a role for LT antagonists in the management of asthma. However, the results obtained were an impetus for further efforts to discover antagonists with greater potency and selectivity.

Leukotriene D_4 Analogs. Background. Several antagonist analogs of LTD_4 were designed without the benefit of any structural information about the receptor or the bound conformation of the natural agonist (Table 2). Extensive SAR studies guided by *in vitro* receptor binding assays revealed that the tetraene component of LTD_4 could be mimicked by more stable simple phenyl rings, the thiopeptide substituent could be replaced by an alkyl carboxylate, and the C_1 carboxylate was retained.[126] Stereochemistry of functional groups played an important role. The two antagonists **30** (pobilukast, SKB 104353) and **31** (sulukast, LY170680) retained the natural configuration of LTD_4 about the thioether linkage and hydroxyl group. In contrast, **32** (CGP-45715A) has an unnatural configuration at these sites, and its isomer, which corresponds to the natural configuration of LTD_4, was about 20 times less potent. As might be expected of agents structurally related to a natural ligand, some synthetic analogs had agonist properties. As the structures diverged more from that of LTD_4, the agonism was lost such that none of the leading investigational agents display agonist properties.

Many antagonists from this series were plagued with low oral bioavailability and/or short duration of action. For this reason **30**−**32** were limited to aerosol administration for clinical evaluations. Improved oral bioavailability could be achieved if the hydroxyl group of **30** was deleted; however, the resulting compound, **33**, was approximately 10-fold less potent.[137]

Clinical Results with 30. The LTD_4 mimics had intrinsic receptor binding affinity superior to the first-generation hydroxyacetophenone series. In particular, the dose−response curves for LTD_4-induced bronchoconstriction in normal and asthmatic subjects exhibited a greater rightward shift to higher concentrations of LTD_4 required for airway constriction. Consistent with its nanomolar *in vitro* potency, **30** demonstrated several interesting effects in provoked asthma studies. In two separate studies involving mild asthmatic subjects, the compound showed a substantial inhibition of the immediate and delayed bronchoconstrictive response to inhaled allergen.[138] In one trial, 5 of 10 patients failed to experience airway obstruction when challenged with a 10-fold higher dose of antigen than that which elicited a defined drop in lung function in the absence of drug. A small number of patients with a documented LAR to antigen experienced no such response following inhalation of drug. Compound **30** also prevented exercise-induced bronchoconstriction comparable to that achieved with disodium cromoglycate.[139] The results of clinical trials involving **30** in chronic asthma have not yet been reported.

Clinical Results with 34 (Bay-x7195). Compound **34** is an orally active LTD_4 analog with low nanomolar potency (pK_b = 8.4, LTD_4 guinea pig trachea contraction).[140] It produced moderate inhibition of LTD_4-induced bronchoconstriction when administered po in normal volunteers (8-fold shift in LTD_4 dose−response curve 2 h after 250 mg oral dose)[141] and improved base-line lung function after 250 and 500 mg doses.[142]

Quinoline-Containing Antagonists. Background. Compound **20** (Rev-5901) was discovered in the mid-1980s.[100] As previously mentioned, **20** had activity as a FLAP inhibitor and a weak LTD_4 receptor antagonist leading to the synthesis of many other quinoline-containing compounds. These antagonists generally incorporated a 2-substituted quinoline attached through a methyleneoxy or ethenyl bridge to a central aromatic unit that was thought to mimic the tetraene portion of the natural ligand. Often a carboxylate function was included as a proxy for the dipeptide or terminal carboxylate of LTD_4.

Clinical Results. At least seven quinoline-containing antagonists advanced to clinical trials as orally active agents. Early development compounds of this class such as **35** (ritolukast, Wy-48252), **36** (SR-2640), and **37** (RG-12525) displayed potent *in vitro* activity and produced moderate shifts in the LTD_4-induced bronchoconstriction dose−response curve (Table 2). In addition, compound **37** blocked antigen-induced airway obstruction[143] and improved base-line lung function in mild to moderate asthmatics[144] or chronic therapy.[145] The development of these antagonists was not continued.

Quinolyl (Thiolalkyl)carboxylate LTD_4 Antagonists. Background. A major advance in the field occurred with the discovery of **38** (MK-571) which was derived from combining the quinoline template with a thioacetal unit similar to that found in **30**. Compound **38** displayed affinity for the LTD_4 receptor comparable to the natural ligand LTD_4. For analogs of this series, the presence of two acidic side chains was found to be

deleterious to oral activity. By transforming one of the carboxylate functions into an amide, the lipophilicity and polarity of the analogs were readily modified to optimize oral potency.[146]

Clinical Studies with 38. The initial clinical studies with **38** were conducted iv in order to achieve consistent drug plasma concentrations to correlate with clinical parameters. In normal volunteers, LTD_4-induced bronchoconstriction was completely blocked at mean plasma concentrations as low as 0.55 μg/mL. The same plasma concentration in asthmatic patients caused a mean rightward shift in the dose−response curve of at least 44-fold. At mean plasma concentrations of 10 μg/mL (280 mg dose), the shift was at least 83-fold.[147] Although the design of these studies was different from LTD_4 challenge trials described above, the magnitude of the inhibition provided by **38** was clearly greater than that achieved with earlier antagonists.

The excellent potency of **38** facilitated a more definitive understanding of the role of LTD_4 in various clinical models of asthma. An intravenous dose (450 mg) given to asthmatic patients produced in 88% inhibition of the EAR (0−3 h) and 63% inhibition of the LAR (3−8 h) against inhaled antigen.[148] In a second study, **38** (165 mg iv) provided greater than 50% inhibition of both the early and late responses.[149] In a study of exercise-induced airway obstruction in asthmatics, **38** (160 mg iv) produced 70% inhibition of the maximal fall in lung function and also shortened the mean time required for recovery to base-line function after exercise from 33 to 8 min.[150]

Intravenous or oral administration of **38** improved the base-line airway caliber when administered to moderately severe asthmatic subjects but had no effect in normal volunteers.[151,152] Antagonist **38** caused a 20% greater increase in lung function than placebo which began within 20 min after dosing and was maintained throughout the 5 h study. Further improvement in FEV_1 could be achieved by coadminstration of the inhaled β-adrenoreceptor agonist albuterol. The degree of bronchodilation achieved with **38** correlated with the severity of the base-line airway obstruction as patients with more severe disease showed the greatest improvement. The demonstration that **38** provided clinically and statistically significant bronchodilation in moderately severe asthmatic patients was consistent with the previous results of the 5-LO inhibitor **1**.[153] These studies delineated the pathological actions of LTD_4 in contributing to airway obstruction in asthmatics.

Antagonist **38** was evaluated in a 6 week placebo-controlled chronic asthma trial, given 75 mg tid po for 2 weeks followed by 140 mg tid po for 4 weeks.[154] At the end of the trial, FEV_1 was improved 8−14%, morning and evening asthma symptoms were reduced 30%, and β-agonist use was also reduced 30%. These results were comparable to those found for inhibitor **1** and further confirm the therapeutic benefit of LT modulation in patients with chronic asthma. The clinical development of **38** was suspended when it was determined that the compound induced an increase in peroxisomal enzymes in mice, a characteristic that has been linked to the potential occurrence of liver tumors in humans.

Clinical Studies with 39 (Verlukast, MK-679). Further investigation of the enantiomers of racemic **38** revealed that the peroxisome proliferation was completely associated with the *S* enantiomer.[155] The *R*-enantiomer **39** (verlukast, MK-679) which was devoid of peroxisome induction up to 400 mg/kg in mice was selected for further clinical study. Antagonist **39** provided about 13% improvement in lung function following a single intravenous[156] or aerosol[157] dose in moderately severe asthmatics.

As discussed previously, approximately 10% of adult asthmatic subjects displays serious intolerance to aspirin and other NSAIDs. Antagonist **39** (750 mg po) provided a 4.4-fold shift in the bronchoconstriction dose−response curve following inhalation of lysine-ASA when administered to ASA sensitive asthmatics.[158] Three of the eight patients were protected from a 20% loss in lung function at the highest dose of lysine-ASA delivered. In the absence of a challenge, **39** also produced bronchodilation after a single 825 mg po dose in a group of ASA sensitive asthmatic patients.[159] These results were obtained despite the fact that the subjects involved in the trial were concomitantly receiving inhaled corticosteroids. This observation supports the hypothesis that corticosteroids do not block the synthesis of LTs. Furthermore it suggests that LT antagonists may provide added benefit beyond corticosteroids in ASA sensitive asthmatics. These studies with **39** in ASA-induced asthma indicate a prominent pathological role for LTs in aspirin intolerant asthma.

Antagonist **39** was also evaluated in a 6 week chronic asthma trial[160] with similar results as those described previously for the racemate **38**. This antagonist was subsequently withdrawn from clinical development after approximately 5% of the patients developed liver function abnormalities.[160]

Second-Generation Quinoline-Containing Antagonist 40 (Montelukast, MK-476). Continued optimization of early members of the series led to a second-generation quinoline-containing antagonist, **40**. This compound resulted from efforts to identify structurally diverse compounds with even greater potency but, most importantly, that were devoid of effects on peroxisomal enzyme proliferation and other aspects of liver toxicity.[161] Potency was enhanced by replacing one of the thioacetal side chains in **39** with an arylalkyl group. Much of the peroxisomal enzyme induction activity could be removed by incorporation of geminal substituents on the β-carbon of the thiopropionic acid side chain while maintaining receptor binding potency. Final optimization led to **40** which was essentially devoid of liver weight increases or peroxisomal enzyme proliferation even after chronic exposure in rodents at very high doses.

Clinical Studies with 40. The second-generation quinoline compound **40** provided the most potent and longest lasting blockade of LTD_4-induced bronchonconstriction in man reported to date. Twenty-four hours after a 40 mg oral dose, a greater than 50-fold shift in the LTD_4 dose-response curve was still evident.[162] In moderate asthmatics, a single 100 mg dose produced a prompt 10−12% improvement in base-line FEV_1 which persisted throughout the 9 h study.[163] As was observed with **39**, additional bronchodilation was achieved by inhalation of a β-agonist. This dose was also sufficient

Table 3. Leukotriene B_4 Antagonists

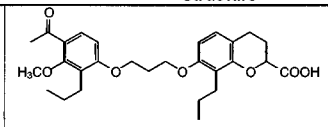
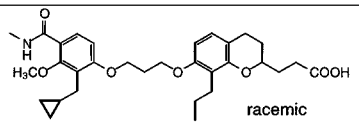
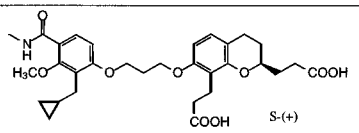
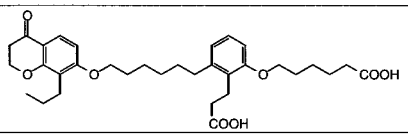
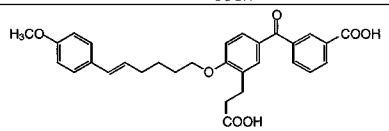
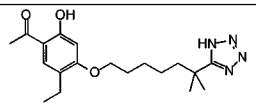
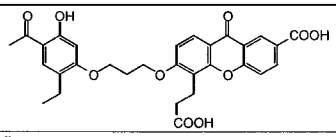
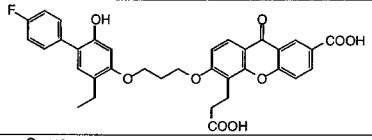
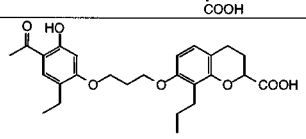
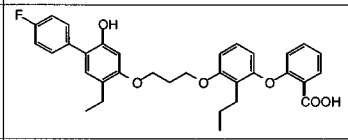
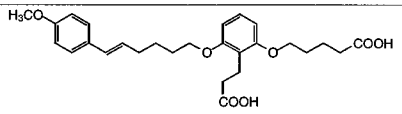
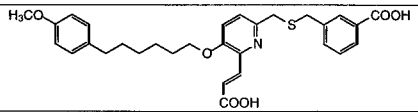
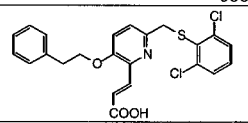
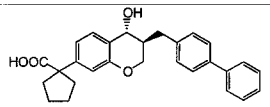
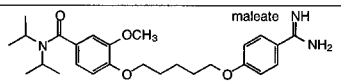
Name	Structure	Developer, Status	LTB_4 binding	Other In Vitro Data	In Vivo Data
SC-41930 **42**		Searle (Monsanto) discontinued	IC_{50} = 20 nM[187]	LTB_4 induced neutrophil degrannulation IC_{50} = 1080 nM; LTB_4 induced chemotaxis IC_{50} = 832 nM[187]	LTB_4 induced neutrophil chemotaxis in guinea pig ED_{50} = 1.7mg/kg, po, duration = 5.5 h[291] PMA induced ear edema ED_{50} = 4.2μmol/ear[292]
SC-51146 **43**		Searle (Monsanto) discontinued	IC_{50} = 1.5 nM[187]	LTB_4 induced chemotaxis: IC_{50} = 38 nM LTB_4 induced neutrophil degrannulation IC_{50} = 29 nM[187]	LTB_4 induced neutrophil chemotaxis in guinea pig ED_{50} = 0.09 mg/kg, po, duration = 21 h[291]
SC-53228 **44**		Searle (Monsanto) active	IC_{50} = 1.3 nM[187]	LTB_4 induced chemotaxis: IC_{50} = 32 nM[187] LTB_4 induced neutrophil degrannulation IC_{50} = 19 nM	LTB_4 induced neutrophil chemotaxis in guinea pig ED_{50} = 0.07 mg/kg, po, duration = 24 h 12*R* HETE induced neutrophil chemotaxis in guinea pigs ED_{50} = 5.8 mg/kg, po PMA induced ear edema ED50 = <2.5 mg/kg, po.[193]
Ro 25-4094 **45**		Roche suspended liver tox	K_i = 1 nM[200]		LTB_4 induced bronchoconstriction guinea pig: ED_{50} < 0.1 mg/kg (2 hr pretreatment); ED_{50} < 1 mg/kg (20 hr pretreatment)[200]
LY223982 **46**		Lilly suspended	IC_{50} = 13 nM[293]	guinea pig and human neutrophil aggregation IC_{50} = 74 nM and 100 nM respectively[294] human neutrophil chemotaxis IC_{50} = 6 μM[294]	LTB_4 induced neutropenia, rabbit ED_{50} = 3 mg/kg, iv Minimal systemic absorption, but no effect in psoriasis scores following 0.5–3% topical application.[206]
LY255283 **47**		Lilly discontinued	IC_{50} = 87 nM[201]	human neutrophil CD11b/CD18 IC_{50} = 2874 nM[210]	LTB_4 induced guinea pig bronchoconstriction: ED_{50} = 2.8 mg/kg iv; 11.0 mg/kg po[205]
LY282210 **48**		Lilly undeveloped	IC_{50} = 4 nM[207]	human neutrophil CD11b/CD18 IC_{50} = 47 nM[208]	
LY292728 **49**		Lilly undeveloped	K_i = 0.47 nM[208]	human neutrophil CD11b/CD18 IC_{50} = 1.2 nM[208]	
LY247826 **50**		Lilly undeveloped	IC_{50} = 39.6 nM[210]	human neutrophil CD11b/CD18 IC_{50} = 1600 nM[210]	LTB_4 induced bronchoconstricition: ED_{50} = 0.23 mg/kg, iv; 0.5 mpk, po.[210]
LY293111 **51**		Lilly phase II asthma	K_i = 25 nM[212,295]	LTB_4 induced Ca mobilization: IC_{50} = 20; human neutrophil CD11b/CD18 IC_{50} = 3.9 nM[213]	LTB_4 induced bronchoconstriction: ED_{50} = 0.04 mpk, iv; 0.4 mpk, po; 60 or 120 mg tid or 200 mg bid inhibited >73% CD11b upregulation at 4 hrs in normal volunteers[295]
ONO-4057 ONO-LB-457 **52**		Ono phase II, psoriasis and IBD	K_i = 3.7 nM[214]	human neutrophil degranulation IC_{50} = 1600 nM[214]	LTB_4 induced neutropenia, guinea pig ED_{50} = 25.6 mg/kg po LTB_4 induced neutrophil influx , guinea pig ED_{50} = 5.3 mg/kg po[214] LTB_4 induced neutrophil Ca mobilization following a 300 mg dose in man[215]
SB-201993 **53**		SmithKline Beecham phase II psoriasis	K_i = 7.1 nM[216]	LTB_4 induced Ca mobilization: IC_{50} = 131 nM; LTB_4 induced neutrophil degrannulation 268 nM[216]	LTB_4 induced mouse peritonnitis ED_{50} = 7.1 mg/kg, po; AA induced ear edema: ED_{50} = 0.58 mg/ear[216]
SB-209247 **54**		SmithKline Beecham phase I eczema	K_i = 0.8 nM[217]	LTB_4 induced Ca mobilization: IC_{50} = 6.6 nM; 12-R-HETE induced Ca mobilization: IC50 = 1.3 nM; LTB_4 induced neutrophil degrannulation IC_{50} =117 nM[217]	AA induced ear edema: ED_{50} =20 μg/ear, topically and 19 mg/kg, po; PMA induced ear edema ED_{50} = 114 μg/ear[217]

Table 3. (Continued)

Name	Structure	Developer, Status	LTB_4 binding	Other In Vitro Data	In Vivo Data
CP 105,696 **55**		Pfizer discontinued	IC_{50} = 8.4 nM[219]	LTB_4 induced chemotaxis of human neutrophil: IC_{50} = 5.0 nM; LTB_4 induced Ca mobilization: IC_{50} = 940 nM human neutrophil CD11b/CD18 upregulation pA_2 = 8.0[219]	LTB_4 induced neutrophil cutaneous influx ED_{50} = 4.2 mg/kg (mouse). 0.3 (guniea pig); Complete inhibition of collagen arthritis at 1 mg/kg[218] Blocks 12(*R*)-HETE skin inflammation (75% at 3 mg/kg, po[220] Causes a 10 fold shift in LTB_4 dose response curve for CD11b upregulation in normal volunteers.[222]
CGS-25019C **56**		Ciba phase II arthritis	IC_{50} = 4 nM[223]	LTB_4 induced Ca mobilization: IC_{50} = 2 nM LTB_4 induced chemotaxis: IC_{50} = 2.4 nM LTB_4 induced CD11b upregulation IC_{50} =0.3nM LTB_4 induced aggregation: IC_{50} = 0.1 nM[225]	rat neutropenia ED_{50} = 4 mg/kg at 4 h, 11 mg/kg at 18 h.[223] AA induced ear edema and MPO release: ED_{50} = 1.4, 1.8 mg/kg po[296] Effective vs collagen arthritis in 1-10 mg/kg range[225] ED_{100} = 300 mg for CD11b upregulation at 4 hrs in normal volunteers[226]

to significantly inhibit exercise-induced bronchoconstriction 24 h after dosing.[164] Evaluation in chronic asthmatics with single daily doses of 10 mg for 6 weeks resulted in a significant improvement in lung function, quality of life, and reduced β-agonist use.[165]

LTD_4 Antagonists of Miscellaneous Structure. Pranlukast (**41**, ONO-1078, SB205312) is the first LTD_4 antagonist to be launched anywhere in the world, having been approved for marketing in Japan in 1995. It has lower intrinsic potency than other antagonists currently in clinical development (pK_B = 7.5, LTD_4-induced guinea pig trachea contraction[166]). Consistent with this modest potency, a 450 mg oral dose administered twice daily for 5 days produced a 26-fold shift in the LTD_4-induced bronchoconstriction dose−response curve[167] with only a 7-fold shift observed at 24 h postdose.

Clinical Studies with 41. Compound **41** (150 mg po for 7 days) produced a 33% decrease in EAR induced by allergen, but an effect on LAR was not reported.[168] A dose of 225 mg bid produced a small but significant reduction in airway hyperreactivity in asthmatic subjects following methacholine challenge.[169] Consistent with the results of LT modulators, **41** significantly inhibited ASA-induced asthma following a single 225 mg dose.[170] The results of chronic asthma studies with **41** in multicenter trials with 4 week treatment at oral doses ranging from 225 to 450 mg bid provided improvement in base-line FEV_1, decreased symptoms, and reduced β-agonist usage.[171,172]

Zafirlukast (**2**, Accolate, ICI-204,219) was identified from an extensive LT research program initiated in the 1980s.[173] This antagonist has structural components resulting from SAR derived from analogs of both FPL-55712 and LTD_4. The [[(cyclopentyloxy)carbonyl]amino]-indole was the replacement for the hydroxyacetophenone portion of FPL-55712, and the *N*-(4-methylbenzoyl)-arylsulfonamide served as the surrogate for the triene system of LTD_4. Antagonist **2** has potent activity *in vitro* (e.g., K_i = 0.3 nM, LTD_4 receptor binding) and *in vivo*.[174]

Clinical Studies with 2. A single 40 mg po dose of **2** given to healthy volunteers produced more than a 100-fold shift in the dose−response curve for LTD_4-induced bronchoconstriction.[175] Significant antagonism was still measurable 24 h following administration of the drug. The antagonist **2** also produced significant inhibition of antigen- and exercise-induced bronchoconstriction following both oral and aerosol administration. A greater shift in the antigen dose−response curve was achieved following a 0.2 mg inhaled dose[176,177] than with a 40 mg po dose.[178] This suggested that a higher local concentration of the drug in the airways may be obtained following inhalation rather than by po delivery. Current LT biosynthesis inhibitors and antagonists are being developed as po formulations because of the superior duration of action, the ability to reproducibly deliver the drug to the lower airways, and the patient preference for a pill rather than an inhaler. However, it remains to be seen whether future LT modulators will be developed for aerosol delivery for alternative potential advantages such as improved onset of action and reduced systemic toxicity or side effects.

Consistent with the results described previously, **2** (po) also provided an acute improvement in lung function in asthmatic subjects.[179] In a 6 week chronic asthma study, **2** (40 mg bid po) also improved lung function (11% increase in FEV_1 versus base line) as well as asthma symptom scores (e.g., 46% reduction in nighttime awakenings) and 30% reduced β-agonist use.[180] Comparable results were observed in a large 13 week phase III trial with 20 mg bid,[181] and as before, **2** provided the greatest benefit in those patients with more severe asthma.[182] These studies clearly indicated the pathological role of LTD_4 on the basal tone of asthmatic airways and that LTD_4 receptor antagonism provided therapeutic benefit in chronic asthma.

Antagonist **2** has also been examined as a therapeutic agent for the management of acute seasonal allergic rhinitis.[183] Significant improvement in nasal congestion, symptoms, sneezing, and rhinorrhea formation was noted following a 20 mg single daily dose in subjects with allergic responses to ragweed. Higher doses (up to 100 mg) did not provide further improvement except in reducing congestion. Effects of the drug were noted within the first 2 h of dosing. Thus, LT modulation may have a beneficial effect in allergic rhinitis. However, additional controlled clinical studies are required to clearly establish the degree of therapeutic benefit provided by LT intervention compared to existing therapy.

Leukotriene B_4 Antagonists That Have Progressed to Clinical Evaluation

The selective intervention of LTB_4-induced pathology has been addressed by antagonists that are selective for the LTB_4 receptor. Unlike cysteinyl LT antagonists for which numerous clinical studies have convincingly established their therapeutic potential, only preliminary reports on the clinical evaluation of LTB_4 antagonists have appeared.[184−186]

LTB_4 Antagonists Related to Hydroxyacetophenone LTD_4 Antagonists. Methylation of the phenolic hydroxyl of close analogs of the LTD_4 antagonist FPL-55712 (**26**) yielded selective LTB_4 antagonists[187] including **42** (SC-41930; Table 3). This compound was a modest antagonist of the LTB_4 receptor (LTB_4-induced neutrophil degranulation IC_{50} = 1080 nM[187]) yet had no affinity for LTD_4 receptor preparations at 10 μM. The compound was found to be effective in several rodent models of colonic inflammation.[188,189] Administration of **42** at 10 mg/kg bid for 56 days in the cotton top tamarin model of spontaneous colitis resulted in lower LTB_4 levels in rectal dialysates, improved quality of life parameters, and decreased histology scores.[190] It was also found to inhibit the production of LTB_4 in cultured rectal mucosal biopsies obtained from ulcerative colitis patients.[191] Antagonist **42** was subsequently found to possess other pharmacological modes of action[192] including inhibition of fMLP-induced superoxide release and 5-LO. In view of these other activities, it was not clear whether the LTB_4 antagonism of **42** was the primary factor responsible for the anti-inflammatory activities observed *in vivo*.

Further structure−activity analysis led to the discovery of the antagonist **43**. In this compound the acetyl group of **42** was replaced with a methylacetamide, a propyl group was replaced with a cyclopropylmethyl group, and the carboxylic acid was extended two carbons from the chromane nucleus.[193] These changes substantially improved the LTB_4 receptor binding potency (IC_{50} = 1.5 nM[187]) and also enhanced the selectivity of action.

Compound **43** was resolved, and both enantiomers were found to be potent LTB_4 receptor antagonists. The *S* enantiomer **44** (SC-53228) was slightly more active (IC_{50} = 1.3 nM) and was chosen for further evaluation.[193] It exhibited nearly 100% bioavailability in the guinea pig, had a half-life of 9 h, and blocked LTB_4-induced neutrophil chemotaxis into guinea pig skin with an ED_{50} of 70 μg/kg, and a 3 mg/kg oral dose produced significant inhibition for more than 20 h.[194] The half-life of **44** was surprisingly short in the rat (0.5 h[195]), yet it was highly bioavailable and effective in acute colonic inflammation.[196]

One rationale proposed for the investigation of LTB_4 antagonists was that they might block the agonist action of 12-R-HETE at the LTB_4 receptor or they might cross-react with a putative 12-R-HETE receptor.[197,198] This may be of particular significance in the treatment of psoriasis where elevated levels of 12-R-HETE were detected in lesions.[199] In addition to blocking LTB_4 effects, **44** inhibits 12-R-HETE-induced neutrophil chemotaxis in guinea pig skin (ED_{50} of 5.8 mg/kg).[194] This ED_{50} value is nearly 100-fold weaker than that reported for LTB_4-induced chemotaxis. It is unclear whether this discrepancy relates to differences in the potency relative to the two agonists or to differences in the conditions of the assay. Antagonist **44** showed very little potential to induce peroxisomal proliferation in rodents.[193] It was selected for clinical evaluation,[194] but no results have yet appeared.

Modifications of LTD_4 antagonists and subsequent optimization resulted in the discovery of **45** (Ro 25-4094) where the acetophenone moiety was cyclized with the phenol to yield a chromanone group.[184] Consistent with previous observations, the conversion of the phenol to an ether group enhanced selectivity for the LTB_4 versus LTD_4 receptor. Further potency enhancement was achieved by replacing the chromane acid by a diacid-substituted phenyl moiety. Antagonist **45** was a potent and long-lived inhibitor of LTB_4-induced bronchoconstriction in guinea pigs.[200] The compound displayed an ED_{50} of less than 1 mg/kg even when administered orally 20 h prior to challenge. Development of **45** was discontinued due to animal liver toxicity.[200]

LTB_4 Antagonists Related to the Structure of LTB_4. Compounds **46** (LY223982) and **47** (LY255283) have structural elements resembling those of LTB_4.[201] The acidic tetrazole and the phenolic hydroxyl of **47** were suggested to mimic the carboxylic acid and 12-hydroxy of LTB_4, while the planar acetophenone was hypothesized to be a surrogate for the extended diene moiety of the natural ligand. This type of analysis led to even more refined structures.[202] Compound **47** was extensively evaluated in a variety of *in vitro* assays and animal models and found to have moderate potency.[203−205] No clinical studies were reported. However, the more potent antagonist **46**, when applied topically to patients with psoriasis (0.5−3.0% formulations), was well tolerated and resulted in little systemic exposure.[206] However, no significant improvement in the clinical parameters of psoriasis was observed.

Fusing the hydroxyacetophenone moiety of **47** with the benzophenone unit of **46** resulted in a more potent hybrid.[207] Further, cyclizing the benzophenone into a xanthone ring system provided **48** (LY282210) which was 16-fold more potent at inhibiting LTB_4-induced aggregation than the corresponding fMLP-induced response. This was in contrast to only a 2-fold selectivity observed for **46**. Replacement of the acetyl unit of the acetophenone group with phenyl resulted in a substantial increase in potency. The resulting antagonist **49** (LY292728) exhibited receptor binding affinity in the subnanomolar range.[208]

LTB_4 Antagonists with Structural Features Combined from Other Series. The *gem*-dimethyl tetrazole moiety of **47** was replaced by the chromane acid from **43** to yield **50** (LY247826) which displayed affinities comparable to its predecessors against human receptors.[209,210] However, a significant enhancement in potency versus guinea pig lung membrane preparations was observed.[209] The potency found for human versus guinea pig receptor affinities supported a premise for significant LTB_4 receptor species differences. These potential receptor species differences complicate the interpretion and relevance of the results from animal models.

Further optimization of **50** included incorporation of the fluorophenyl ring and replacement of the chromane acid with a diphenyl ether carboxylic acid,[211] resulting in **51** (LY293111).[212] Compound **51** blocked LTB_4-induced activation of neutrophils in whole blood as

assessed by the upregulation of the expression of the cell surface adhesion molecule CD11b/CD18 (IC_{50} = 3.9 nM).[213] It had improved selectivity, being about 10 000-fold more potent in inhibiting LTB_4-induced CD11b upregulation relative to the corresponding fMLP-mediated response in human neutrophils. It was also highly effective in LTB_4-induced acute airway obstruction in guinea pigs when administered orally or intravenously with ED_{50} values of 0.4 and 0.04 mg/kg, respectively. It blocked LTB_4-induced pulmonary granulocyte infiltration at doses as low as 0.3 mg/kg and calcium ionophore-induced lung inflammation in guinea pigs for 1 h after dosing, albeit not at longer time intervals.

The ability of LTB_4 to upregulate the expression of CD11b/CD18 has been used to assess the activity of **51** in clinical trials. When blood from volunteers receiving 200 mg bid of **51** was challenged with LTB_4, CD11b/CD18 expression was inhibited by greater than 73% at 4 h.

The LTB_4 antagonist **52** (ONO-4057) is structurally related to **46**.[214] It was a modestly potent antagonist of LTB_4-induced responses in human neutrophils *in vitro* (IC_{50} = 1600 nM, human neutrophil degranulation) and in guinea pigs following po administration (ED_{50} = 5.3 mg/kg, LTB_4-induced neutrophil influx). Following administration of 300 mg to human volunteers, ONO-4057 inhibited LTB_4-induced calcium mobilization *ex vivo* in blood.[215]

A series of antagonists represented by **53** (SB-201993) and **54** (SB-209247) were reported with structural features also in common with **46** and **52**.[216,217] As was observed with related compounds, the presence and spatial relationship of the carboxylate groups were crucial for potent LTB_4 binding. Compound **54** displayed high affinity for the human neutrophil LTB_4 receptor (K_i = 0.8 nM) and blocked LTB_4 and 12-R-HETE-induced calcium mobilization with similar potency (6.6 and 1.3 nM, respectively[217]). As discussed previously, the ability of LTB_4 antagonists to modulate the effects of 12-R-HETE may be an important advantage over LT biosynthesis inhibitors particularly in the treatment of psoriasis.

LTB_4 Antagonists with Miscellaneous Structures. The LTB_4 antagonist **55** (CP 105,696) was designed using LTB_4 as a template and optimized by analogy with other known G-protein-coupled receptors and their antagonists (including NK-1 and CP-96345).[218,219] It displays high affinity for the LTB_4 receptor (IC_{50} = 8.4 nM) and for the LTB_4-induced cellular responses (see Table 3). Following oral administration, the compound blocked LTB_4-induced intradermal neutrophil accumulation in mice and guinea pigs (ED_{50} values of 4.2 and 0.26 mg/kg, respectively). A 3 mg/kg oral dose in guinea pigs blocked 75% of the neutrophil response induced by 12-R-HETE.[220]

One of the more interesting activities of **55** was its ability to limit the incidence and severity of the lesions in a collagen-induced mouse arthritis model. At oral doses of 10 mg/kg and higher, **55** prevented the histological damage associated with leukocyte influx and the body weight loss associated with this model.[218]

Phase I studies for **55** used the *ex vivo* inhibition of LTB_4-induced CD11b upregulation to measure the efficacy in healthy volunteers in a rising single-dose safety study.[221] The compound produced a 10-fold shift in the dose−response curve[222] and was well tolerated at doses of 40−640 mg but suspended from clinical development because of its exceptionally long half-life in man ($t_{1/2}$ = 420 h).

The LTB_4 receptor antagonist **56** (CGS-25019C) has a basic amidine functionality in place of the more commonly applied carboxylate group.[223] The role of this basic group in the LTB_4 receptor interaction is unknown. Compound **56** was active at <10 nM in several *in vitro* assays and also highly effective in inhibiting LTB_4-induced neutropenia in the rat (ED_{50} = 4 mg/kg) when administered po 4 h following challenge. An ED_{50} value of 11 mg/kg was observed at 18 h in this assay, demonstrating a long duration of action in the rat. Compound **56** also blocked edema formation and neutrophil influx following AA application to the mouse ear with ED_{50} values of 1.4 and 1.8 mg/kg po.[224] In comparison, **50** (3 mg/kg po) inhibited edema and neutrophil influx by 30% and 40%, respectively. Compound **56** also blocked collagen-induced arthritis in the rat in a dose-dependent manner when administered orally at doses of 1, 3, and 10 mg/kg.[225] Differences in the experimental protocol make it difficult to compare the activity observed here with that described previously for **55**.

In phase I clinical trials, **56** provided maximal inhibition of *ex vivo* LTB_4-induced CD11b upregulation 3−4 h after oral dosing in healthy volunteers, and 100% inhibition was observed at doses of 300 mg and above.[226] Gastrointestinal side effects were observed at doses above 500 mg. In a 7 day multiple-dose study, once a day dosing was judged to be as effective as twice daily dosing with this *ex vivo* assay.[227] Further clinical studies are required to correlate this *ex vivo* readout to significant efficacy in treatment parameters.

Future Directions

Several approaches have been used in the discovery of LT modulators. These have resulted in several new classes of compounds: (i) inhibitors of 5-LO, (ii) inhibitors of FLAP, (iii) peptidyl LT (LTD_4) receptor antagonists, and (iv) LTB_4 receptor antagonists. The biosynthesis inhibitors have the potential to offer a broader therapeutic benefit in LT-mediated pathology since they ameliorate the diverse activities of all members of the LT pathway (Figure 1). However it should be emphasized that there are many 5-LO-derived metabolites whose biological role and relevance to disease processes have yet to be elucidated, for example, the lipoxins.[228,229] Initially the biosynthesis inhibitor approach appeared very attractive, but in practice it was plagued by significant barriers to the identification of orally bioavailable and safe clinical investigational agents. This was likely a result of the initial ease in discovering inhibitors of 5-LO particularly with nonspecific antioxidant compounds. The enthusiasm for quick success was short-lived as further evaluation of the early inhibitors revealed problems with oral bioavailability, inhibitor specificity, and safety which precluded clinical development. Disappointments in the LT inhibitor approach directed some efforts to the design of receptor antagonists.

In humans, distinct types of receptor-mediated pathophysiology were observed for the LTD_4 receptor and the LTB_4 receptor, respectively. In general, the antagonist

activities could be classified as (i) modulating airway obstruction phenomena for LTD_4 antagonists and (ii) modulating inflammation amplification phenomena for LTB_4 antagonists.

Dose-dependent efficacy has been observed in asthma for orally administered 5-LO inhibitors, FLAP inhibitors, and LTD_4 antagonists. LT modulators provided improvements in airway obstruction comparable in magnitude to current asthma treatment regimens. The therapeutic outcome was uniquely related to LT modulation and did not directly duplicate the modalities of current treatments such as β-agonists or corticosteroids. In fact, the LT modulators were effective as add-on therapy in reducing the use of β-agonists or corticosteroids. LT intervention provided an acute improvement in airway obstruction within the first hour of dose. LT blockade returned airway tone to a less hyperreactive state. LT-mediated effects are clearly evident in aspirin intolerant asthmatics, a subgroup that dramatically respond to anti-LT therapy. The plausible rationale for efficacy was that continuous LT biosynthesis occurs as an outcome of the pathological basis of disease found in those asthmatics responding to LT modulation therapy.

The advancement in clinical trials of several classes of compounds with different mechanisms that modulate LT production and/or the effects of LT metabolites on tissue function provides an important opportunity to assess which mechanistic approach is appropriate in achieving therapeutic benefit in a specific disorder. For LT inhibitors, therapeutic benefit has been frequently correlated with *ex vivo* LT inhibition or the amount of excreted LTE_4. For LTD_4 antagonists, their ability to shift the dose−response curve to the right for inhaled LTD_4 can be correlated with the degree of therapeutic benefit in asthmatics. Given the nanomolar potency of the LTs, it would seem reasonable that very small amounts would have the potential to trigger substantial biological effects. However, it still remains to be established whether complete (>99%) inhibition of LT production and/or activity at the disease target is required for the optimal clinical response. Whether complete and prolonged inhibition would reveal side effects associated with any beneficial physiological actions of the LTs also remains to be determined.

Compounds like **14**, which is a potent and long-acting 5-LO inhibitor, offer the potential to exceed the dose providing 100% inhibition of *ex vivo* stimulated LTB_4 in blood or urinary LTE_4. This would establish whether further improvement in clinical outcomes is achievable with prolonged, complete LT inhibition.

With receptor antagonist therapy, the possibility that there may be heterogeneity for LT receptors[230] and their respective signaling pathways in different pathophysiological conditions may result in variable responses in the general patient population. The problem is compounded further if the purported receptor subtypes are differentially induced in a given inflammatory or allergic condition.

If a more selective LT intervention than 5-LO inhibition appears warranted in the future, there are several potential downstream targets. Inhibition of the enzyme LTA_4 hydrolase[231] blocks the formation of LTB_4. Several inhibitors have been reported, but none have yet progressed to clinical evaluation.[232,233] Significant research has been advanced in characterizing, cloning, and expressing LTC_4 synthase, an enzyme unlike other glutathione transferases.[234−236] Inhibition of LTC_4 synthase provides a selective blockade of the complete cascade of peptidyl LT metabolites derived from LTA_4.[237] The reported structural homology of LTC_4 synthase to FLAP and the reported inhibition of LTC_4 synthase by the FLAP inhibitor **18** suggest a starting point for the design of more potent inhibitors.[235,238] Analogs of **18** have been evaluated, and several weak ($IC_{50} \approx 10\ \mu M$) LTC_4 synthase inhibitors were indentified.[239] This approach eliminates all the unknown pitfalls of putative peptidyl LT receptor heterogeneity. Since the enzyme LTC_4 synthase is derived from a unique gene family, it would seem plausible that potent selective inhibitors could be identified.

Future research in the area of LT modulation requires due consideration of the use of presently available compounds in chronic therapy and the necessity for a good safety index, especially in non-life-threatening disease states. Evidence to date indicates that LT modulation can provide symptomatic relief of inflammatory conditions rather than disease process attenuation or reversal. In addition, clinical trials for the leading agents have only been concluded for asthma, while there is intriguing data from the evaluation of 5-LO inhibitors and LT receptor antagonists in other inflammatory disease targets. With an ongoing trend toward an increased incidence of inflammatory disease, especially associated with the aging process, it may be anticipated that the currently available agents are but the first generation of a series of chemical entities that modulate LT function.

Biographies

Clint D. W. Brooks (also known as Dee W. Brooks) received his B.S. degree in chemistry from the University of Lethbridge and Ph.D. degree in organic chemistry from the University of Alberta with Professor Satoru Masamune. After a 1 year postdoctoral position at Massachusetts Institute of Technology, he joined the faculty of the Chemistry Department, Purdue University, in 1979. He moved to Abbott Laboratories in 1984 as Chemistry Group Leader and from 1987 to 1995 was the Project Leader of the Leukotriene Biosynthesis Regulators Project. In 1996, he became Director of Chemical Sciences.

James B. Summers received his B.S. degree in chemistry from Denison University and his Ph.D. degree in organic chemistry from Harvard University with Richard W. Johnson. He joined Abbott Laboratories in 1983, where he is currently Director of Inflammation Research.

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