CHAPTER FIFTEEN

Inflammatory Targets for the Treatment of Atherosclerosis

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Contents

1. INTRODUCTION

Atherosclerosis is a complex disease of the arterial wall and is the primary cause of coronary artery disease, peripheral vascular disease, and stroke. The prevalence of these conditions is a leading cause of death worldwide.[1] Atherosclerosis is characterized by the formation of lipid-rich arterial plaques that may eventually rupture causing major adverse cardiovascular events such as myocardial infarct and stroke. Against a backdrop of genetic risk factors,[2] formation of these plaques and the pathogenesis of atherosclerosis derive from unbalanced lipid metabolism and an inappropriate response from the immune system.[3–5] Treatments targeting the modulation of key

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lipids (aimed at increasing or decreasing levels) have been successful at improving outcomes in at risk patients, although significant residual risk remains.[6] For example, treatment aimed at improving the distribution of lipid fractions in patients diagnosed with acute coronary syndrome has had a significant clinical benefit. Yet, the residual risk for major adverse cardiovascular events in this same patient population has been estimated at 70–80%. There is clearly an opportunity for improved treatment paradigms. Recently, an appreciation of the role of inflammation in the pathogenesis of atherosclerosis has led to the identification of various targets suitable for small molecule intervention.[3–5] The development of agents targeted against inflammatory targets in conjunction with lipid modulating therapies should present new treatment modalities for improving outcomes in patients. In this review, clinical and preclinical evidence for anti-inflammatory targets in cardiovascular diseases amenable to small molecule modulation will be presented. Specific examples of compounds either in development or that have helped validate these targets will be discussed. Agents for which the primary mode of action appears to be modulation of lipid metabolism, but which may also impart an anti-inflammatory effect, will not be covered; these agents have been recently reviewed.[5]

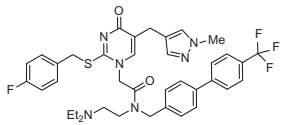
2. PHOSPHOLIPASE A_2

Phospholipase A_2 (PLA_2) is a superfamily of lipolytic enzymes comprised of 15 groups and multiple subgroups.[7,8] There are four main types of PLA_2s: the secreted PLA_2s ($sPLA_2$s), the cytosolic PLA_2s ($cPLA_2$s), the calcium-independent PLA_2s ($iPLA_2$s), and the lipoprotein-associated PLA_2s (Lp-PLA_2s, also known as platelet activating factor acetylhydrolase, PAF-AH). PLA_2s catalyze the hydrolysis of membrane phospholipids at the *sn*-2 position to generate free fatty acids and lysophospholipids that are subsequently converted to prostaglandins and leukotrienes (LTs). All three end products have been recognized for their inflammatory roles; therefore, PLA_2s have been targeted for the treatment of multiple disease indications.[9–12] Among the PLA_2s, $sPLA_2$s and Lp-PLA_2 have been specifically targeted for the treatment of cardiovascular diseases. The most recent advances achieved for the inhibition of $sPLA_2$s and Lp-PLA_2s and the relevance of these two targets to the treatment of cardiovascular diseases are described below.

2.1. Lp-PLA$_2$ inhibitors

Lp-PLA$_2$s are calcium-independent enzymes produced by inflammatory cells (macrophages and monocytes). The role played by Lp-PLA$_2$s in atherosclerosis has been controversial, with initial evidence suggesting an atheroprotective effect due to hydrolysis of the proinflammatory PAF.[13] Subsequent investigations demonstrated that Lp-PLA$_2$s do not play a predominant role in the hydrolysis of PAF. Additionally, it has been demonstrated that Lp-PLA$_2$s accumulate in human atherosclerotic lesions with evidence suggesting a proatherogenic role in the vessel wall.[14] Elevated levels of circulating Lp-PLA$_2$s are associated with plaque vulnerability and endothelial dysfunction, and it has been determined that patients with acute coronary syndromes have higher levels of Lp-PLA$_2$s than normal.[15]

Lp-PLA$_2$s are delivered to lesion-prone segments of the arterial wall by binding to apolipoprotein B (ApoB) on low-density lipoprotein (LDL). Oxidation of LDL leads to the formation of truncated phospholipids in the *sn*-2 position that are subsequently subjected to hydrolysis by Lp-PLA$_2$s. Lysophosphatidylcholine (lysoPC) and oxidized nonesterified fatty acids (oxNEFA) are the products of this hydrolysis and are believed to play a prominent role in the local increase of inflammatory mediators in lesion-prone areas. It has been demonstrated that expression of Lp-PLA$_2$s is highly upregulated in macrophages undergoing apoptosis within the necrotic core and fibrous cap of vulnerable and ruptured plaque.[16] Based on this evidence, Lp-PLA$_2$ inhibitors have been targeted to decrease plaque instability as a treatment for atherosclerosis. Multiple pyrimidone- and pyridinone-based inhibitors (e.g., **1**, **2**, **3**, and **4**) of Lp-PLA$_2$ have been reported.[17–19] SB-568859 (structure not reported) and **3** reached phase I and phase II clinical trials for atherosclerosis, respectively, while **4** is currently under evaluation in a phase III trial.[20] Three ongoing large outcome trials are currently evaluating **4** for primary and secondary prevention.[2,21,22]



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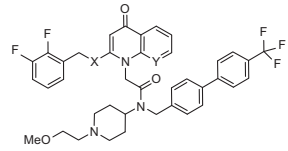
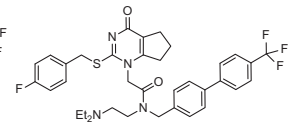


2 X = CH_2, Y = N
3 X = S, Y = CH



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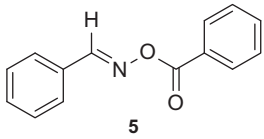
Additional small molecule Lp-PLA$_2$ inhibitors have been reported. Examples include oximes **5**,[23] amides of xanthurenic acid **6**,[24] and tricycle compounds **7**.[25]



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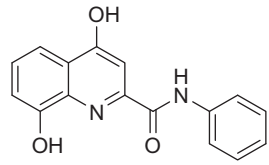

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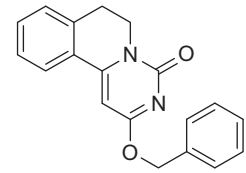

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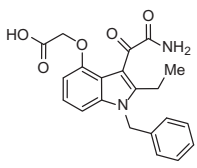
2.2. S-PLA$_2$ inhibitors

S-PLA$_2$s are calcium-dependent enzymes that catalyze the hydrolysis of phospholipids at the *sn*-2 position to release arachidonic acid (AA). Coronary atherosclerotic lesions of patients with acute myocardial infarction contain S-PLA$_2$s which are detected within intimal macrophages, vascular smooth muscle cells, and in extracellular deposits. Levels and activity of S-PLA$_2$s in acute coronary syndrome patients were found to correlate well with disease severity.[26] Multiple sPLA$_2$ inhibitors have been reported and have been reviewed.[11,12] **8** and its methyl ester prodrug, **9**, are sPLA$_2$ inhibitors that have advanced the furthest into development.[27–32] **8** has been evaluated in two phase II clinical trials.[28–30] **9** was studied in phase II[31] and phase III clinical trials for acute chest syndrome.[32] Recent publications have highlighted related analogs including **10**.[33] Additionally, molecular docking studies on 2-oxoamides, **11** and peptide inhibitors have been reported.[34,35]



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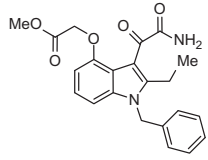

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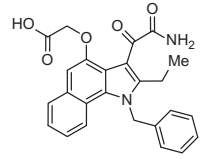

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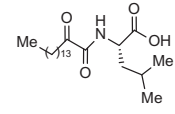

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3. LEUKOTRIENE PATHWAY AND ATHEROSCLEROSIS

The LT pathway constitutes a fundamental series of events underlying the inflammatory component of atherosclerosis.[36–38] The pathway is initiated after release of AA from cell membranes by cPLA$_2$ (Fig. 15.1). Oxidation of AA catalyzed by 5-lipoxygenase (5-LO) generates LTs, lipid mediators that trigger proinflammatory signaling through activation of the

G protein-coupled transmembrane receptors (GPCRs) BLT (for LTB_4) and CysLT (for LTC_4, D_4, and E_4). LT signaling is involved in several processes associated with atherosclerosis, including lipid retention, accumulation of foam cells, and development of intimal plaque. The LT pathway is also believed to contribute to the rupture of plaque, resulting in ischemic injuries, such as myocardial infarct and stroke.

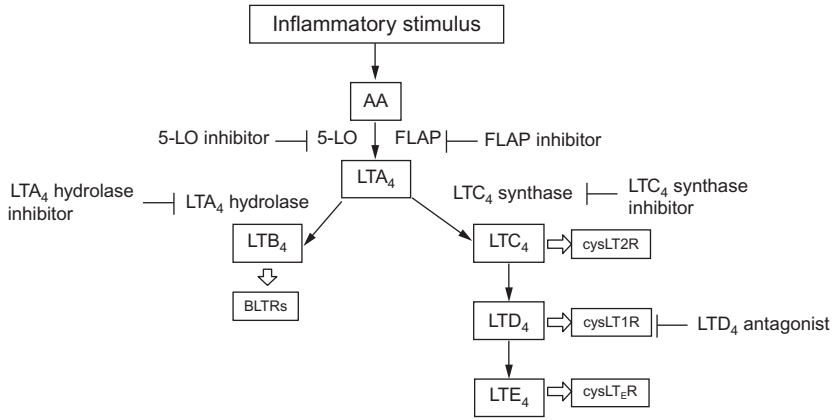
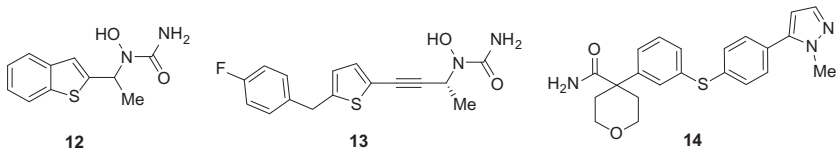


Figure 15.1 Drug targets of the leukotriene (LT) pathway involved in atherogenesis.

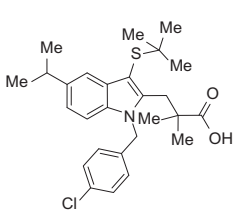
3.1. 5-LO inhibitors

5-LO catalyzes the oxidative metabolism of AA aided by 5-lipoxygenase-activating protein (FLAP) and is a rate-limiting enzyme in LT biosynthesis. Zileuton, **12**, is a marketed 5-LO inhibitor indicated for the treatment of asthma.[39] Although a number of 5-LO inhibitors have been targeted for inflammatory indications such as asthma, allergic rhinitis, rheumatoid arthritis, and inflammatory bowel disease, only atreleuton, **13**, has been developed to treat atherosclerosis.[40] A phase II clinical trial of **13** in patients who had experienced recent acute coronary syndrome has completed, with results showing a reduction in LT production, and imaging data suggestive of a positive effect on atherosclerosis.[41,42] A non-*N*-hydroxyurea containing, selective nonredox 5-LO inhibitor, **14**, showing an IC_{50} of 130 nM in a human whole blood assay has been reported.[43]



3.2. 5-Lipoxygenase-activating protein inhibitors

AA released from phospholipids is transferred to 5-LO via FLAP for oxidative conversion to LTA_4. Four FLAP inhibitors representing three structural classes have advanced into clinical trials: indoles (**15** and **16**), indoloquinolines (**17**), and quinolines (**18**). Phase I and II clinical trials of compounds **15**, **17**, and **18** for the treatment of asthma have completed, with a reduction of urinary LTE_4 excretion being reported for all three compounds.[44–46] Detailed SAR around indoles related to **16** has been reported.[47] **18** advanced to phase III clinical trials for the prevention of myocardial infarction.[48] However, development of this compound has been discontinued due to a problem with its formulation.[49] Patent applications claiming FLAP inhibitors of different scaffold classes, such as benzimidazoles (e.g., **19**) or oxadiazoles (e.g., **20**), have also published.[50–52]



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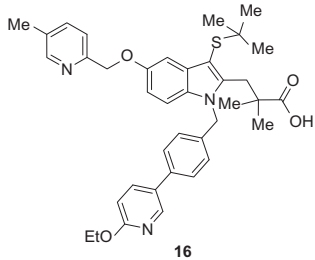

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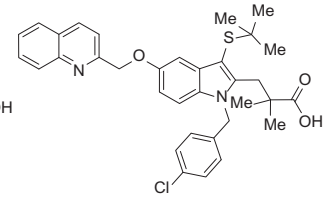

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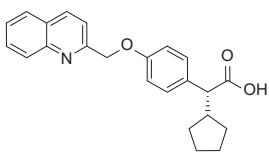

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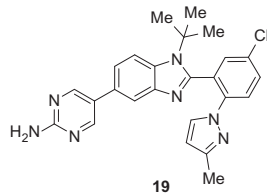

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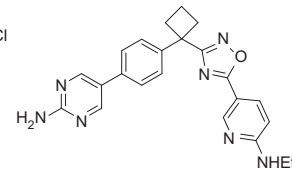

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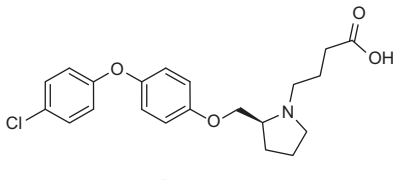
3.3. LTA_4 hydrolase inhibitors and leukotriene C_4 inhibitors

An unstable epoxide, LTA_4, is further transformed to either LTB_4 by LTA_4 hydrolase or leukotriene C_4 (LTC_4) by LTC_4 synthase. Two LTA_4 hydrolase inhibitors, JNJ-40929837 and CTX-4430, have reportedly been in development for the treatment of COPD and/or MS, but structures of these compounds have not been disclosed.[53,54] Only **21** advanced to phase II clinical trials (for treatment of myocardial infarction), but its development has been discontinued.[55] A patent application disclosing benzoic acid-containing potent LTC_4 synthase inhibitors (e.g., **22**, $IC_{50} = 18$ nM) has published.[56]



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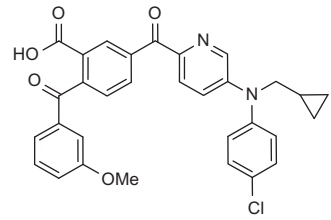

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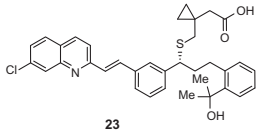
3.4. LTD_4 antagonists

Three cysteinyl leukotriene (CysLT) receptor blockers (montelukast, **23**, zafirlukast, **24**, and pranlukast **25**) have reached market for the treatment of respiratory disorders including allergy, allergic rhinitis, or asthma. Although no CysLT receptor antagonists have been reported to be in development for cardiovascular disease, a retrospective analysis of Swedish asthmatic patients treated with montelukast indicated its potential utility for secondary prevention.[57] These data could support CysLT receptor as a potential target for cardiovascular diseases.



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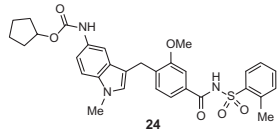

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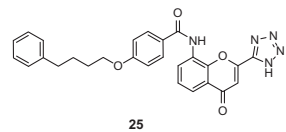

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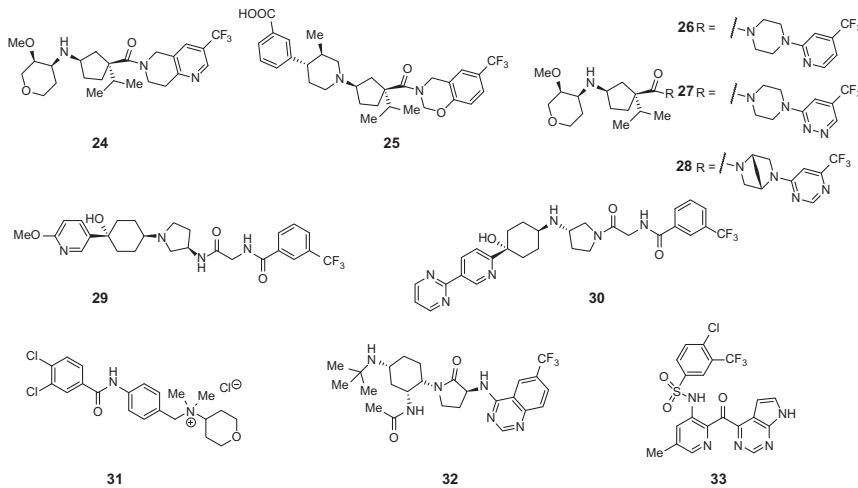
4. CHEMOKINES AND ATHEROSCLEROSIS

The chemokines are secreted proteins that interact with cognate GPCRs to regulate the trafficking and activation of leukocytes. They are named according to the location and number of conserved cysteine residues at the N-terminus (CC, CXC and CX3C). There are more than 60 known chemokines and chemokine receptors (CCRs). Both chemokines and their receptors have been targeted for pharmacologic intervention, Chemokine receptors are more amenable to small molecule intervention than the chemokines themselves and are the focus of this section. Recent studies have shown the role of chemokine signaling in the recruitment of inflammatory cells, including monocytes and T-cells, to developing plaques. CCR2 and CCR5 in particular have been implicated in atherogenesis.[58,59] Antagonists of both receptors are described

below. Chemokine receptor antagonists often contain basic amines which pose challenges to improving oral bioavailability, reducing Pgp-mediated efflux, and achieving selectivity over hERG and other ion channels.

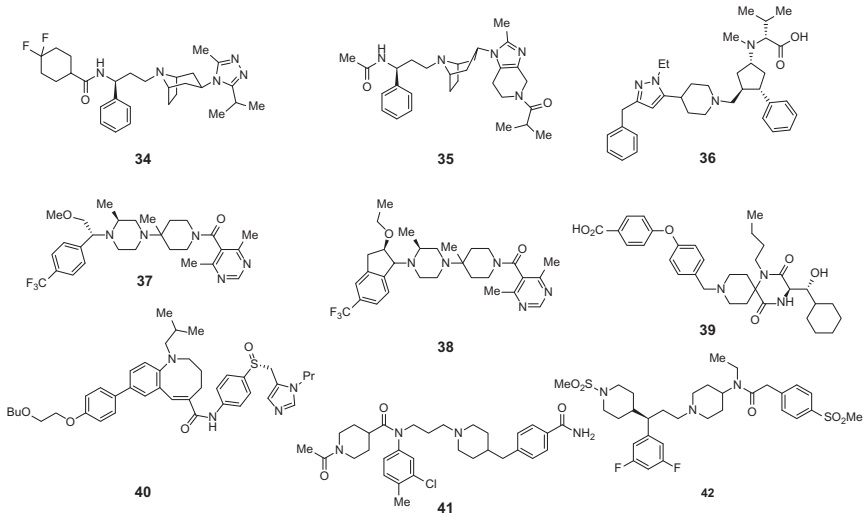
4.1. CCR2 antagonists

There has been significant effort directed toward the optimization of CCR2 antagonists, with several compounds entering clinical trials for indications such as rheumatoid arthritis, multiple sclerosis, neuropathic pain, diabetes mellitus, and allergic rhinitis. The field has recently been reviewed.[60] Several structural classes of CCR2 antagonists have yielded clinical candidates and these are summarized below. The amino cyclopentane carboxamide scaffold has yielded five clinical candidates: **24**, **25**,[61–63] **26**, **27**, and **28**.[64–66] Both **25** and **28** are reported to behave as insurmountable antagonists, displaying long, dissociative half-lives from CCR2.[63,66] A series of cyclohexanols, **29** and **30**, were recently disclosed as clinical candidates.[67,68] The quaternary salt, **31**, administered as a nasal spray, completed a phase II clinical trial.[69,70] BMS-741672 is reported to be in clinical trials.[71] The structure of BMS-741672 has not been disclosed, but may be that of lactam **32**, a compound for which significant characterization was disclosed in a patent application.[72] Clinical development of CCX140 for Type 2 diabetes has been reported.[73] A recent disclosure characterizing the pharmacology of CCX140 and a patent referenced therein suggest the compound is related to sulfonamides such as **33**.[74,75]



4.2. CCR5 antagonists

While emerging evidence points to the role of CCR5 in atherosclerosis,[76] initial interest in the target stemmed from its role as a coreceptor for HIV-1 transmission. Accordingly, there has been significant effort directed toward the optimization of CCR5 antagonists. These efforts have recently been reviewed.[77] Several compounds, which are highlighted below, have entered clinical trials and maraviroc, **34**, has been approved for clinical use. The lead optimization of **34** has been described.[78] A related compound, **35**, has advanced to phase II clinical trials.[79] Amino cyclopentane **36** is under development as a topical agent.[80] A pyrimidinyl amide, vicriviroc, **37**, which has entered late-stage clinical trials, has been described.[81,82] A conformationally restricted analog, **38**, has demonstrated an improved pharmacokinetic profile in phase I.[83] Clinical trials of the spirocyclic carboxylic acid, aplaviroc **39**, were halted due to hepatotoxicity.[84] Biaryl **40** and piperidine **41** have progressed into clinical trials as has the sulfonamide **42**.[85–87]



5. CONCLUSIONS

The key role played by inflammatory mediators in the pathogenesis of atherosclerosis has presented a wealth of targets for small molecule intervention. While lead optimization and clinical programs against inflammatory targets may not have been initially directed toward the potential treatment

of atherosclerosis, the availability of high-quality chemical matter should allow for clinical proof-of-concept studies to be conducted and hypotheses tested.

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