Bioorganic & Medicinal Chemistry Letters 27 (2017) 4770–4776

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Structure-activity relationship study of β-oxidation resistant indole-based 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE) receptor antagonists

Qiuji Ye [a], Shishir Chourey [a], Rui Wang [a], Nagendra Reddy Chintam [a], Sylvie Gravel [b], William S. Powell [b], Joshua Rokach [a,*]

[a] Claude Pepper Institute and Department of Chemistry, Florida Institute of Technology, 150 West University Boulevard, Melbourne, FL 32901, USA
[b] Meakins-Christie Laboratories, Centre for Translational Biology, McGill University Hospital Centre Research Institute, 1001 Decarie Blvd, Montreal, QC H4A 3J1, Canada

ARTICLE INFO

Article history:
Received 19 July 2017
Revised 15 August 2017
Accepted 16 August 2017
Available online 19 August 2017

Keywords:
5-Oxo-ETE
Eosinophil
Structure-activity relationship
Antagonist
Asthma

ABSTRACT

5-Oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE) is formed from 5*S*-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE) by the 5-lipoxygenase (5-LO) pathway under conditions associated with oxidative stress. 5-Oxo-ETE is an important pro-inflammatory mediator, which stimulates the migration of eosinophils via a selective G-protein coupled receptor, known as the OXE receptor (OXE-R). Previously, we designed and synthesized structural mimics of 5-oxo-ETE such as **1** using an indole scaffold. In the present work, we added various substituents at C-3 of this moiety to block potential β-oxidation of the 5-oxo-valerate side chain, and investigated the structure-activity relationships of the resulting novel β-oxidation-resistant antagonists. Cyclopropyl and cyclobutyl substituents were well tolerated in this position, but were less potent as the highly active 3*S*-methyl compound. It seems likely that 3-alkyl substituents can affect the conformation of the 5-oxovalerate side chain containing the critical keto and carboxyl groups, thereby affecting interaction with the OXE-receptor.

Arachidonic acid (AA, **2**) is an ω-6 polyunsaturated fatty acid that is a key precursor of a large number of biologically active metabolites formed by different oxygenation pathways, one of the most important of which is the 5-lipoxygenase (5-LO) pathway.[1,2] 5-LO converts AA (**2**) in the presence of 5-LO activating protein (FLAP) to 5*S*-hydroperoxy6,8,11,14-eicosatetranoic acid (5*S*-HpETE, **3**) that is further metabolized to 5*S*-hydroxy-6,8,11,14-eicosatetraenoic acid (5*S*-HETE, **4**) and leukotrienes (LTs), Fig. 1. In the presence of nicotinamide adenine dinucleotide phosphate ($NADP^+$), 5-HETE (**4**) is oxidized by the enzyme 5-hydroxyeicosanoid dehydrogenase (5-HEDH) to 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE, **5**), which stimulates a variety of responses in human eosinophils and neutrophils.[2] Notably, 5-oxo-ETE (**5**) is the most potent chemoattractant for human eosinophils among lipid mediators.[3] The actions of 5-oxo-ETE are regulated by a selective Gi protein-coupled receptor known as the OXE receptor (OXE-R), which is most highly expressed in eosinophils compared to other cell types. Because of these effects, activation of the OXE-R by 5-oxo-ETE could be a key event in the progression of eosinophilic diseases such as asthma.[2,3] Unlike cysteinyl leukotriene receptor ($CysLT_1$) antagonists, such as Singulair (**6**, Fig. 1), at present there is no drug targeting the OXE receptor. For this reason, we embarked on a search for selective OXE-R antagonists that could block the potent proinflammatory effects of 5-oxo-ETE and thereby be useful therapeutic agents in eosinophilic diseases such as asthma. To this end, we designed 5-oxo-ETE receptor antagonists based on the structural mimics of 5-oxo-ETE (Fig. 2).[5,6]

To design OXE receptor antagonists, we first identified the essential structural elements of 5-oxo-ETE (**5**) required for the activation of the OXE-R. Structure-activity relationship (SAR) studies revealed that the C1-carboxyl group, the 5-keto group coupled to an adjacent conjugated system, and the hydrophobic region at the ω-end of the molecule were all required for biological activity (**5**, Fig. 2).[4] Based on these results, we replaced the tetraene conjugated system of 5-oxo-ETE with an aromatic system such as

Abbreviations: AA, arachidonic acid; 5-HETE, 5-hydroxy-6*E*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid; 5-oxo-ETE, 5-oxo-6*E*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid; 5-HEDH, 5-hydroxyeicosanoid dehydrogenase; 5-HpETE, 5-hydroperoxyeicosatetraenoic acid; LT, leukotriene; $NADP^+$, nicotinamide adenine dinucleotide phosphate; HPLC, high-performance liquid chromatography; TLC, thin layer chromatography; Hex, hexane; EtOAc, ethyl acetate; Rt, room temperature.

* Corresponding author.
E-mail address: jrokach@fit.edu (J. Rokach).

http://dx.doi.org/10.1016/j.bmcl.2017.08.034
0960-894X/

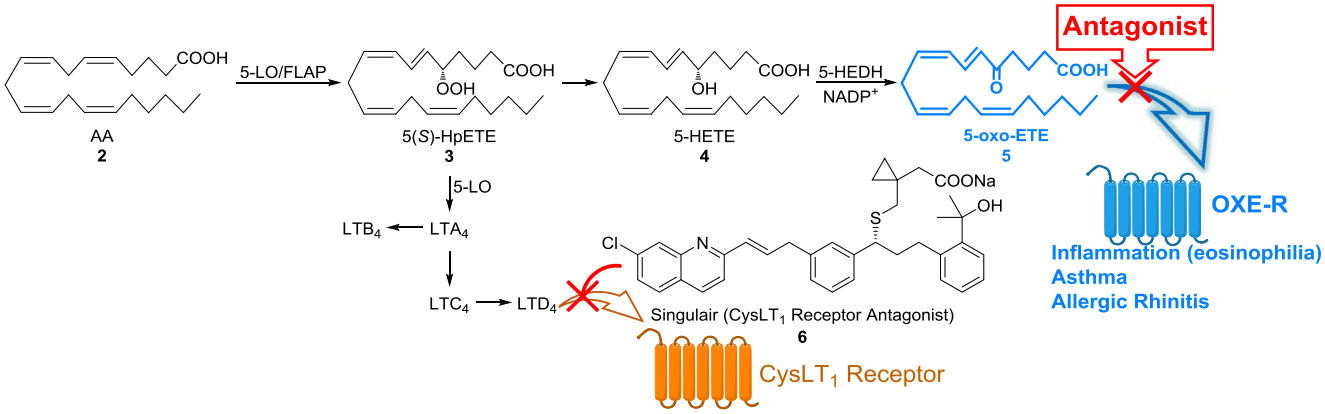

Fig. 1. Biochemical formation of eicosanoids by the 5-lipoxygenase (5-LO) pathway. The development of OXE receptor antagonist can stop eosinophil-induced inflammation.

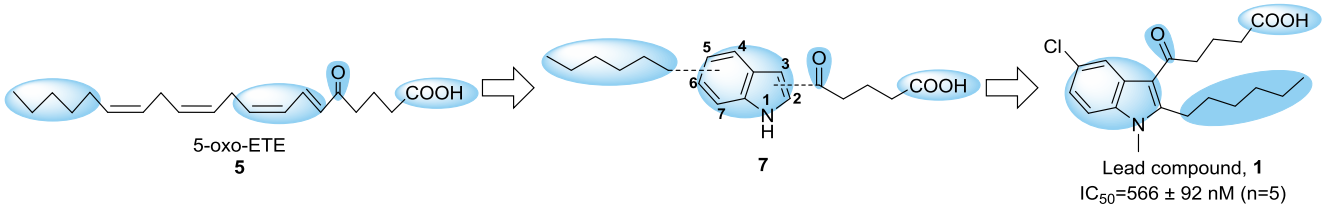

Fig. 2. The design of indole-based 5-oxo-ETE receptor antagonists as structural mimics of 5-oxo-ETE. Regions required for activation of the OXE-R are highlighted in blue.

naphthalene, benzofuran, and indole, to which we attached the carboxyl end and the alkyl (ω) end of 5-oxo-ETE as two separate groups. Among these aromatic scaffolds, indole (**7**, Fig. 2) gave the most promising results.[5] Using our Ca^{++} mobilization assay we screened a series of indoles containing 5-oxovalerate and hexyl groups in different positions and found that an indole containing a hexyl group in the 2-position and a 5-oxovalerate group in the 3-position was the most potent. Further modification of this compound by the addition of a chloro group in the 5-position resulted in a 4-fold increase in antagonist potency and led to the lead compound **1**, which has an IC_{50} of 566 nM in inhibiting 5-oxo-ETE-induced Ca^{++} mobilization in neutrophils.[6]

Because the 5-oxovalery side chain of the lead compound **1** can potentially undergo β-oxidation,[7,8] we decided to modify the carboxyl side chain of **1**, to block this metabolism. To accomplish this, we introduced various substituents at the C-2 and C-3 positions of **1** (such as **9**, and **11** respectively, Fig. 3). In this paper, the syntheses and systematic SAR of these novel indole derivatives as OXE receptor antagonists are reported.

*Introduction of a dimethyl group at different positions of the lead compound (**1**).* In the development of a potent and specific leukotriene biosynthesis inhibitor, MK-886 (**8**, Fig. 3A), a dimethyl group was incorporated in an attempt to prevent β-oxidation of the propionic acid side chain (Fig. 3A).[9] We first substituted a dimethyl group at C-2 position of the lead compound **1** and prepared **9** (Fig. 3B). In the preparation of **9**, a small amount of the 4,4-dimethyl substituted compound **10** was generated as a side product (Scheme 2). We separated the two isomers by column chromatography and measured their antagonist activities. Both **9** and **10** showed substantial decreases in potency of seven and

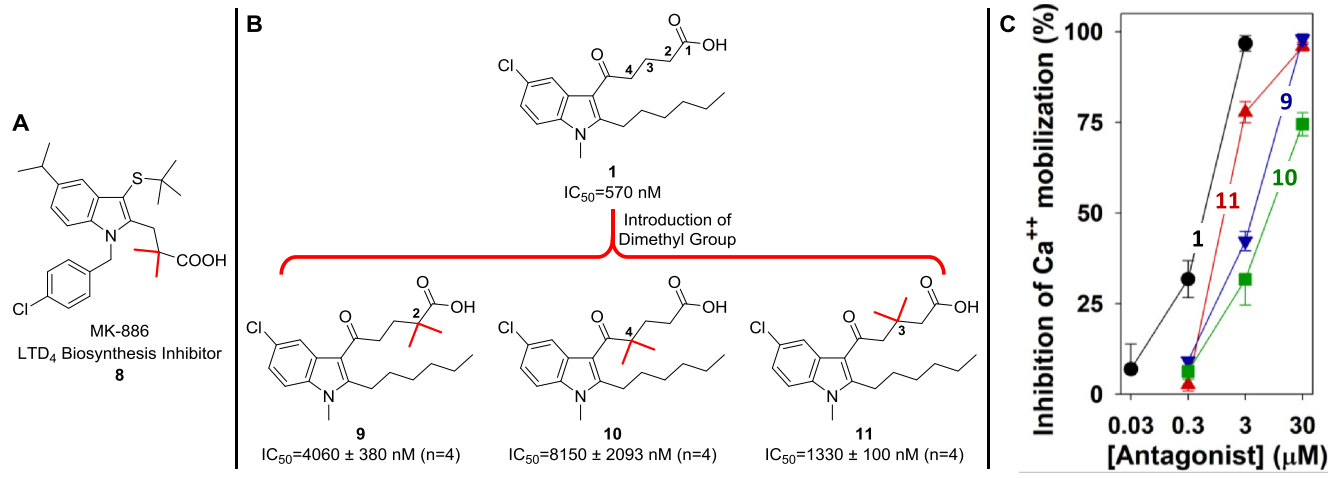

Fig. 3. Panel A shows the structure of MK-886 (**8**), a potent leukotriene biosynthesis inhibitor. Panel B shows the structures of the dimethylated compounds (**9**–**11**). Panel C shows the concentration-response curves for the indole compounds (**1** and **9**–**11**).