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A New Class of Leukotriene Biosynthesis Inhibitors: The Development of ((4- (4 - Chlorophenyl)-1- (4- (2-quinolinylmethoxy)phenyl) butyl)thio)acetic acid, L-674,636

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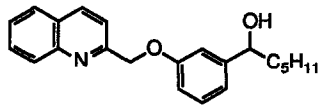
Abstract: A new, potent and orally active leukotriene synthesis inhibitor has been developed.

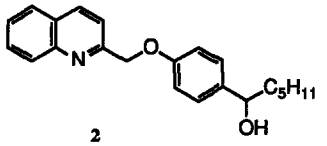
The diverse and potent biological actions of leukotrienes (LT), eicosanoid products of 5-lipoxygenase (5-LO), suggest that these mediators may play important roles in hypersensitivity and inflammatory diseases[1]. It has been shown in human leukocytes that translocation of 5-LO from the cytosol to a membrane site may be a critical early activation step for the enzyme[2]. An indole class of LT synthesis inhibitor, exemplified by MK 886 (**3**), which is active in intact cells but has no effect on purified 5-LO enzyme, inhibits the translocation of 5-LO [3]. The protein target of this class of indirect inhibitor is a novel 18 kDa membrane protein named Five Lipoxygenase Activating Protein (FLAP) which has been purified from rat and human leukocytes using affinity columns based on MK 886[4] and has been shown to be essential for LT biosynthesis[5].

We describe here the development of a second class of a highly potent LT synthesis inhibitor, based on a quinoline structure. These compounds, like MK 886, are inhibitors of cellular LT synthesis and are inactive inhibitors of soluble 5-LO. Such agents also act on the 18 kDa FLAP protein and inhibit 5-LO translocation in a manner analogous to MK 886[6]. A member of this class of compounds, ((4- (4 - Chlorophenyl)-1- (4- (2-quinolinylmethoxy) phenyl)butyl)-thio)acetic acid, L-674,636, showed excellent bioavailability and demonstrated functional and biochemical efficacy in animal models.

Following the discovery that 1- (4- (2-quinolinylmethoxy) phenyl)hexanol, (**2**),[7] was 20 fold more potent as a LT synthesis inhibitor in *vitro* than REV-5901,[8] (human PMN[3] IC_{50} 90nM vs 1800nM respectively) and that, like MK 886, it had no direct effect on 5-LO activity in cell free systems we embarked upon an optimization program. Our goal was to enhance the intrinsic potency and the oral activity and to minimize metabolism at the terminal ω - alkyl site .



REV-5901 (1)



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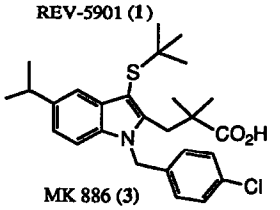
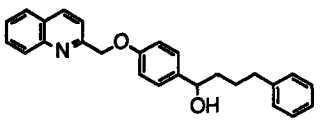


MK 886 (3)

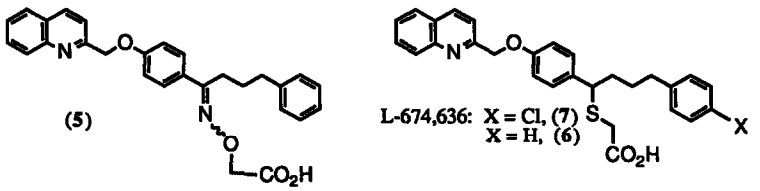


4

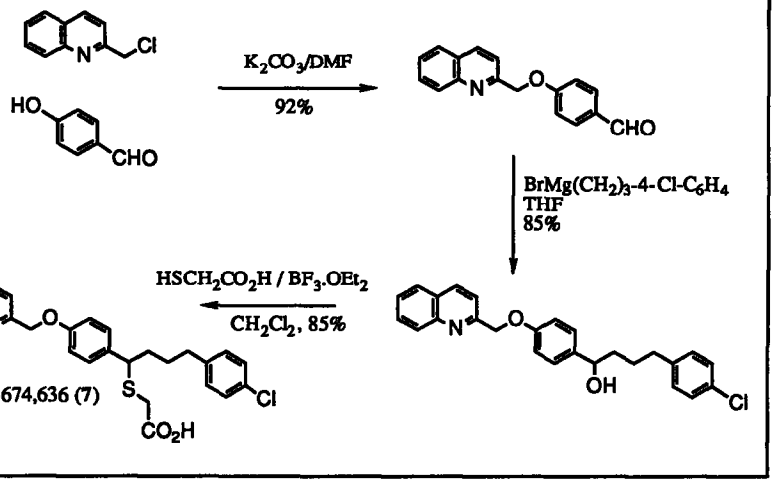
Replacement of the n-pentyl sidechain of **2** with a 3-phenylpropyl sidechain gave the metabolically more stable analog **4**, with a slight enhancement in potency over the initial lead (human PMN IC_{50} 30nM). The 3-phenylpropyl sidechain was found to be superior to both the 2-phenylethyl and the 4-phenylbutyl sidechain. Having secured the optimal chain length, we then turned our attention to other parts of the molecule. It was found that substituents on the quinoline ring usually have detrimental effect on the potency of the compound. The nitrogen atom of the quinoline was essential for the activity since the naphthalene analog was virtually inactive. The methoxy bridge linking the two aromatic units was superior to both methylthio or 1,2-ethyl linkage. The hydroxyl group was not critical for activity since its removal or its replacement with a keto group did not drastically affect the activity.

Since **4** binds to the 18 kDa FLAP protein in the same manner as MK 886[9], and that **4** competes with MK 886 as shown by photoaffinity labelling experiments[9], we postulated that the potency of the quinoline series may be enhanced by the addition of an acid moiety such as is found in MK 886 . This notion was particularly attractive because in addition to potentially picking up an acid binding domain which should not only enhance the intrinsic potency,

the sodium salt of the compound should also be more bioavailable. Towards this end, the carboxylic acid moiety was appended at various sites. After several disappointing attempts in which the activity was completely lost, a successful acid attachment point was identified. This led to **5** (human PMN IC_{50} 80nM), a molecule with comparable potency to the initial lead. Encouraged by this result, the (oximinooxy)acetic acid sidechain was replaced



SCHEME 1. The Synthesis of L-674,636



by 2-thioacetic acid sidechain and we were gratified to find that compound **6** was an extremely potent LT synthesis inhibitor (human PMN IC_{50} 3nM, 10 fold more active than **4**). Like its predecessor, MK 886 and compound **4** , **6** was shown to inhibit by the same mechanism of action[9]. But unlike **4**, the sodium salt of **6** was orally active and was bioavailable in rats and monkeys[10].

Subsequent modifications of compound **6** demonstrated that a variety of acids, both aliphatic and aromatic, are well tolerated. The compound with the best overall profile, in term of biochemical and functional activity and pharmacokinetics was found to be **7**, (L-674,636), the *p*-chloro derivative . This compound has an IC_{50} of 7 nM in the human PMN and an ED_{50} of 1.6 mg/kg in the rat pleuresy assay[3]. In whole animal models, it has an ED_{50} of 35 μg/kg in antigen-induced dyspnea in inbred hyperreactive rats[11] and at a dose of 1mg/kg, it gave an 80% blockade of ascaris-induced bronchoconstriction in conscious squirrel monkey[12]. L-674,636 has good bioavailability in both rats and squirrel monkey (100% and 93% respectively). The synthesis of L-674,636 is outlined in Scheme 1.

In summary, we have developed a new, potent and orally active LT synthesis inhibitor. L-674,636 along with other members of this class of compounds interact specifically with FLAP at the same binding site as MK 886.

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