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A New Class of Leukotriene Biosynthesis Inhibitors: The Discovery of MK0591

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Abstract: The evolution of a quinoline based FLAP inhibitor, L-674,636, into a novel quinoline-indole hybrid compound: MK0591, is described. The new series of compounds are more potent, particularly in binding to FLAP, in inhibiting LTB_4 biosynthesis in stimulated human PMN, and in the human whole blood assay.

Inhibition of leukotriene biosynthesis can be achieved either through the use of direct (or active site directed) 5-lipoxygenase inhibitors or by indirect leukotriene biosynthesis inhibitors, as exemplified by MK-886[1]. The protein target of the indirect inhibitor is a novel 18 kDa membrane protein named Five Lipoxygenase Activating Protein (FLAP) which has been purified and sequenced from rat and human leukocytes[2]. It has been hypothesized that FLAP is essential for the activation of 5-lipoxygenase in cells and that drugs, such as MK-886, block the activation of 5-lipoxygenase enzyme by preventing the translocation of the enzyme from the cytosol to the membrane protein, FLAP[3].

Recently we described a novel series of indirect leukotriene biosynthesis inhibitors from a completely different structural class as exemplified by L-674,636[4]. Like MK-886, this series of compounds act by binding to FLAP[5] and we have been able to combine the salient features of each series into a single, more potent, compound; L-686,708. The evolution of this new hybrid series is described herein.

During work on L-674,636 designed to determine the structural features required for FLAP binding activity, it was of interest to compare the activities of the two enantiomers of L-674,636. The two enantiomers were conveniently prepared by separating the R-(-) - 2,2,2,-trifluoro-1-(9-anthryl) ethyl ester of L-674,636 **1** and subsequent removal of the chiral auxiliary. The (+) - enantiomer **2** has $[\alpha]_D$ = + 160° (*c*1, $CHCl_3$) and the (-) - enantiomer **3** has $[\alpha]_D$ = - 166° (*c*1, $CHCl_3$) respectively. Surprisingly, the leukotriene synthesis inhibition activities of compound **2** and **3** in the HPMN assay[1] were not significantly different, the (-)

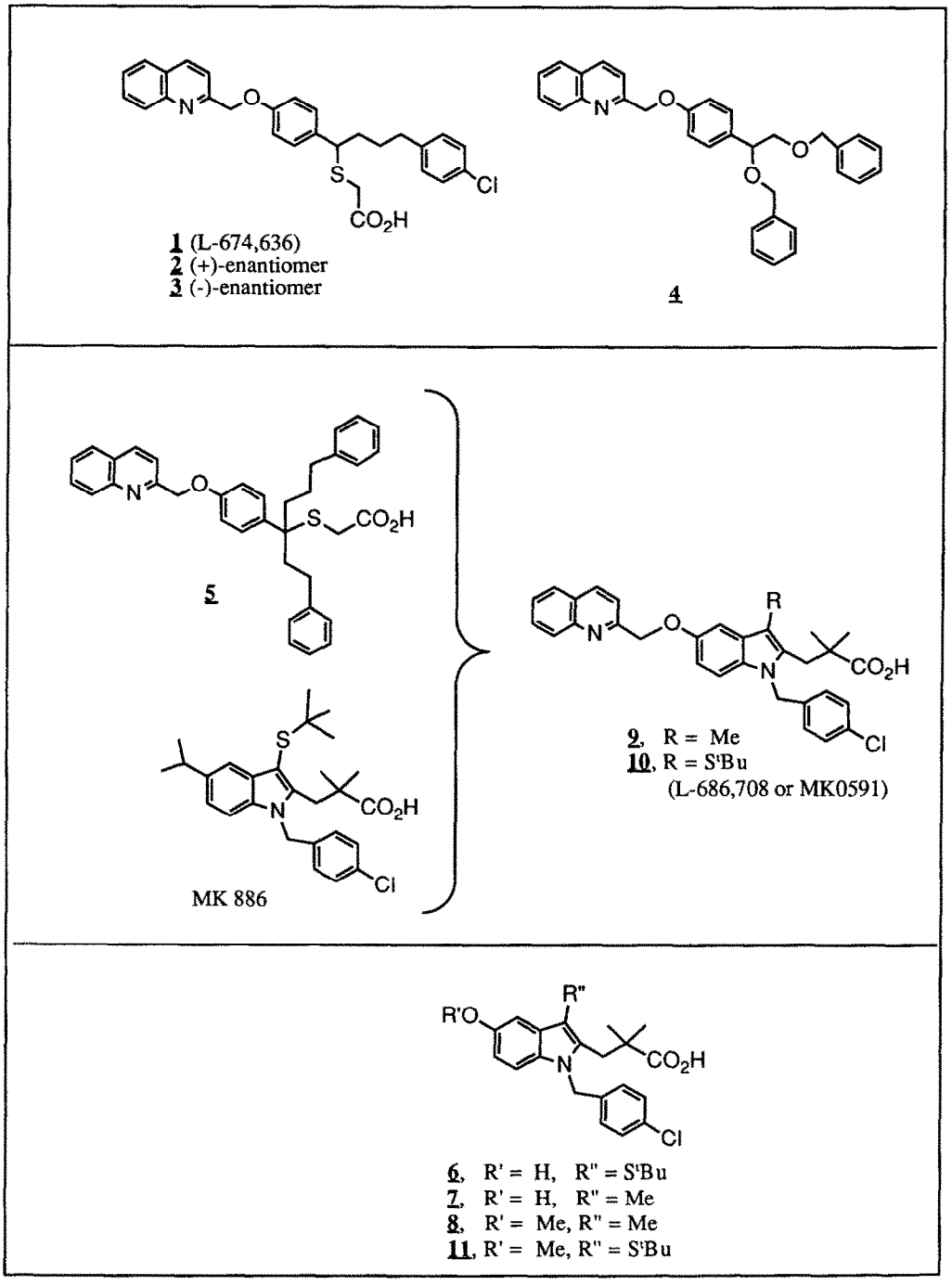
- enantiomer **3** was only two times more potent than the (+) - enantiomer **2** (5 nM vs 10 nM respectively). This result was particularly intriguing since a more dramatic difference was expected as the two sidechains are vastly different.

At the same time we also looked at the effect of the introduction of hetero-atoms on to the lipophilic sidechain to increase the solubility / bioavailability of the series. During this endeavor, it was observed that compound **4** , a synthetic intermediate which contains two lipophilic sidechains but lacking the acidic sidechain, was surprisingly active (HPMN IC_{50} = 30 nM). This led us to the hypothesis that there is an additional lipophilic binding site in the FLAP protein for this class of compounds and hence compound **5** was prepared. Indeed, compound **5** was found to be intrinsically more active than L-674,636 (4 nM Vs 20 nM respectively when the two compounds were tested in parallel leukotriene inhibition assays). Thus, the addition of another binding domain appeared to enhance the potency of the compound. This result may explain why there was not a significant difference in potency between the two enantiomers **2** and **3**. The lipophilic sidechain of **2** may bind with one lipophilic pocket while the sidechain of **3** may bind with the other lipophilic pocket as a consequence of the stereogenic center.

In attempts to rationalize competitive binding of **1** and MK-886 for the site on FLAP, the structural resemblance between compound **5** and the more planar MK-886 can be postulated. Both compounds have an acidic moiety and they both contain two lipophilic sidechains (alkylphenyls for compound **5** and p-chlorobenzyl and t-butylthio groups for MK-886), see Figure. It would appear that the intrinsic potency of MK-886 should be enhanced by the addition of a quinolinylmethoxy moiety at the 5-position of the indole.

The phenol **6**, with the MK-886 sidechains, was not readily available and thus the phenol **7** (derived from the demethylation of the methoxy compound **8**, which was at hand) was coupled with 2 equiv. of 2-chloromethylquinoline in the presence of K_2CO_3 followed by aqueous hydrolysis to afford the hybrid compound **9**. The effect of the quinolinylmethoxy moiety in compound **9** was dramatic as compared to the methoxy compound **8**. For instance, the IC_{50} of **8** in the HPMN assay was 870 nM whereas compound **9** was 3 nM. It, therefore, appeared that the working hypothesis of the overlapping of compound **8** and MK-886 is reasonable. The indole ring of MK-886 is acting as a rigid template orienting the acidic and lipophilic sidechains into the appropriate region.

Stimulated by this observation the corresponding analog of MK-886, compound **10** (L-686,708) was prepared[6]. A brief comparison of its biological activity with that of its progenitors MK-886 and L-674,636 is shown below. The full biological profile has been detailed elsewhere[7] but it is relevant to note the important increase in potency in the human


1 (L-674,636)
2 (+)-enantiomer
3 (-)-enantiomer
4
5
MK 886
9, R = Me
10, R = S'Bu
(L-686,708 or MK0591)
6, R' = H, R" = S'Bu
7, R' = H, R" = Me
8, R' = Me, R" = Me
11, R' = Me, R" = S'Bu

whole blood assay and for the inhibition of binding of [^{125}I] L- 691,831 binding to FLAP[8].

	L-686,708	MK-886	L-674,636
HPMN (IC_{50}, nM)	3	3	20
Human Whole Blood (IC_{50}, nM)	500	2100	>22,000
FLAP Binding (IC_{50}, nM)	2	23	122

The overall profile of **10** (now designated MK0591) has been such to warrant further development and the compound is currently under clinical evaluation. We await the outcome of the these trials to provide some answers on the potential therapeutic role of FLAP inhibitors, and 5-lipoxygenase inhibitors in general, in control of hypersensitivity and inflammatory diseases.

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