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THE DISCOVERY OF L-699,392, A NOVEL POTENT AND ORALLY ACTIVE LEUKOTRIENE D_4 RECEPTOR ANTAGONIST

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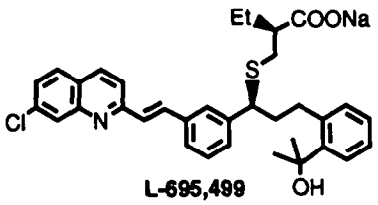
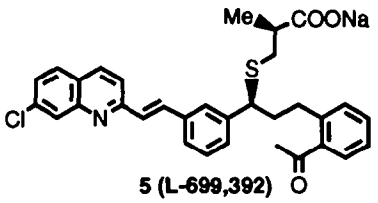
Abstract: The styryl quinoline thioether **5** (**L-699,392**) is a potent and orally active leukotriene D_4 antagonist. The structure-activity studies leading to its discovery are described.

Recent clinical studies with specific antagonists of the LTD_4 receptor such as **MK-571**, **MK-679**[1-6] and **ICI-204219**[7] have demonstrated that blockade of this part of the leukotriene pathway can provide beneficial effects in human bronchial asthma. We have recently described[8] a new series of styryl quinoline thioethers exemplified by **L-695,499**, which are potent and orally active LTD_4 antagonists. Unfortunately, further studies revealed that **L-695,499** exhibited acute toxicity at high doses in mice. We have therefore continued structure-activity relationship studies in this series, with particular emphasis on modifications of the thioether side chain and the aryl substituent group, which have both previously been found to impart potent activity in this series. The evolution of these studies and the discovery of **L-699,392** are described below.



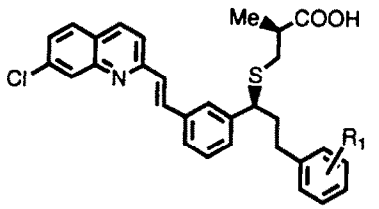
L-695,499



5 (L-699,392)

Initial studies undertaken to determine the effects of alkyl substitution in the thioalkanoic side chain indicated that methyl or ethyl substitution α to the acid group led to little consistent change either in intrinsic potency or pharmacokinetics. It was noted, however, that there was a clear trend towards reduced acute toxicity in mice for the methyl-substituted analogs (data not shown). The more readily available methyl analogs were therefore investigated further and the structure-activity relationship studies were continued with replacements for the tertiary alcohol group of **L-695,499**.

Table 1. Effect of R_1 on Intrinsic Potency and Pharmacokinetics



COMPOUND	R_1	IC_{50}[a] (nM)	RAT PLASMA CLEARANCE[b] (mL/min•Kg)
1	o-$C(CH_3)_2OH$	2.7 ± 0.5	14
2	o-CH_2OH	3.1 ± 0.7	5
3	o-$CH_2C(CH_3)_2OH$	1.0 ± 0.7	33
4	m-CH_2OH	2.1 ± 1.5	2.5
5	o-$COCH_3$	3.0 ± 0.7	11
6	m-$COCH_3$	5.9 ± 1.5	2.0
7	o-$COCH_2CH_3$	3.7 ± 1.7	13
8	o-COPh	4.3 ± 0.9	18
9	o-CHO	2.0 ± 0.1	6
10	o-$CO_2CH_2CH_3$	3.7 ± 0.5	4.8
11	m-CO_2CH_3	7 ± 4	6

a) Inhibition of binding of [^{3}H]LTD_4 to guinea pig lung membrane[16]. Values are mean ± S.E.M. (n=3)

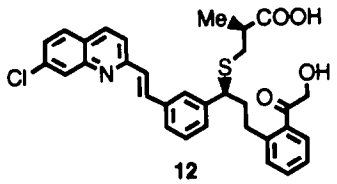
b) Estimated from the area under the curve of the drug concentration vs time, after 5 mg/kg i.v. dosing of rats.

Table 1 shows a series of substitutions for the tertiary alcohol of **1**. As we have found before[8], the tolerance of the receptor for the group R_1 is surprisingly large. Alcohols, ketones, esters and aldehydes are roughly equivalent as determined by the IC_{50} values for inhibition of [^{3}H]LTD_4 specific binding to guinea-pig lung membranes. The pharmacokinetic profile in the rat was more variable however, with initial clearance rates ranging from 2.5 to 33 mL/min as

determined by blood level analysis after i.v. dosing.

The analysis of plasma levels in the rat of compounds **2**, **4** and **9** by HPLC revealed the presence of significant circulating metabolites. In comparison, the ketones **5**, **7** and **8**, exhibited high plasma levels of the parent drug and relatively low levels (<5%) of circulating metabolites in the rat. On the basis of these results and of superior *in vivo* activity in monkey[9] and rat[10] models, the methyl ketone analog **5** was determined to have the best overall biological profile.

The plasma level graphs of **5** in squirrel monkey is shown in Graph 1. The compound is well absorbed with an apparent bioavailability of 52%. A circulating metabolite was observed, slightly more mobile than the parent on RP-HPLC. This peak was identified by HPLC-MS (75% MeOH, 25% 0.1M NH_4OAc on a Nova-Pak C18 column, thermospray MS: MH^+ 560) and by comparison with synthetic material as being the α-hydroxyketone **12**. Two other minor peaks (<5%) were observed as circulating metabolites in squirrel monkey plasma. They were identified as the diastereomeric sulfoxides of **5** by RP-HPLC comparison with synthetic material.



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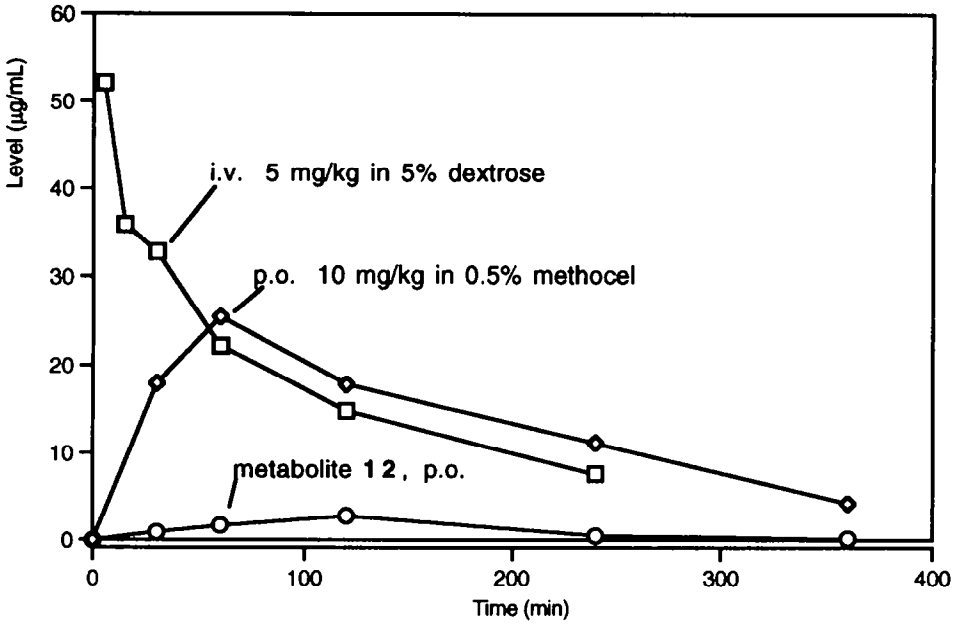
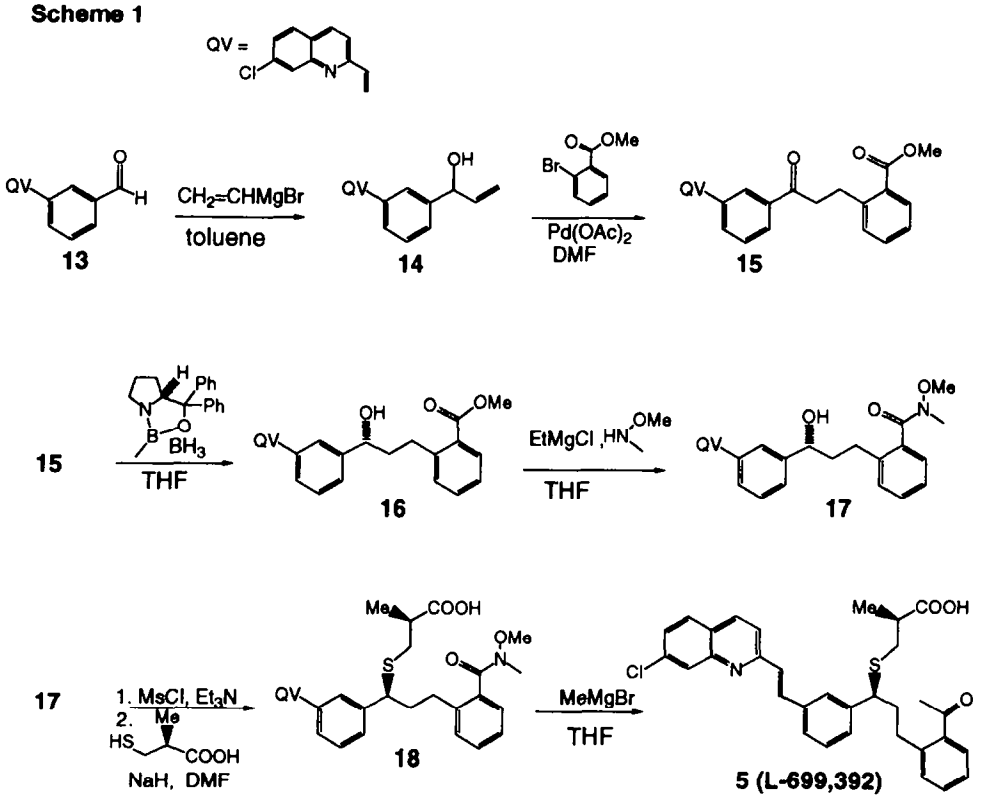
Graph 1. Plasma levels of **5** (L-699,392) in squirrel monkey



The stereospecific synthesis of **5** is shown in Scheme 1[11]. The aldehyde[12] **13** was treated with vinylmagnesium bromide to give the allylic alcohol **14**, which was treated with methyl 2-bromobenzoate in the presence of palladium acetate[13] to give the keto-ester **15**. Using the chiral oxazaborolidine-borane method[14], the ketone was reduced to the (R)-alcohol **16** with 90% to 95% ee. The ester was transformed into the activated amide **17** using the magnesium salt of N,O-dimethylhydroxylamine. The thiol chain was introduced by first activating the alcohol as the mesylate, followed by displacement with the thiolate[15] to give **18**. The synthesis of **L-699,392** was completed by reacting **18** with methylmagnesium bromide to form the methyl ketone.

Scheme 1



In summary, **L-695,499** has been evolved to identify the superior analog **5** (**L-699,392**). Many groups can replace the t-alcohol group of **L-695,499** without loss in intrinsic potency. The methyl ketone **L-699,392** is the compound with the best overall biological profile.

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