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THE DISCOVERY OF A NEW STRUCTURAL CLASS OF POTENT ORALLY ACTIVE LEUKOTRIENE D_4 ANTAGONISTS

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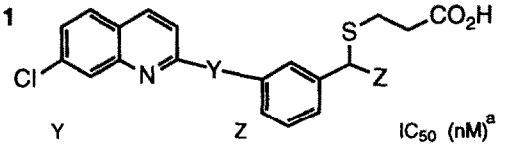
Abstract: A new, potent, orally active leukotriene D_4 receptor antagonist has been discovered. The structure-activity relationship leading to L-695,499 is described.

Verlukast (**MK-0679**, (R)-3[[[3-[2-(7-chloroquinolin-2-yl)-)-(E)-ethenyl]phenyl]]]-3-dimethylamino)-3-oxopropyl]thio]methyl]thio]-propionic acid) **(R)-1** is a LTD_4 antagonist[2,3] characterized by high intrinsic potency, excellent oral bioavailability and *in vivo* activity in a variety of species. More recently, a number of clinical studies have demonstrated that **(R)-1** is an orally active LTD_4-receptor antagonist in normal[4] and asthmatic men[5], that **(R)-1** inhibits both antigen-induced early and late phase reponses in asthmatics[6], that **(R)-1** causes improvements in lung functions, reductions in symptom scores and reduced ß agonist usage during six week studies[7] in asthmatic patients. Effective protection against exercised-induced bronchoconstriction in asthmatics[8] was also demonstrated. When Verlukast entered early clinical studies, it became desirable to find an alternate class of compounds with at least equal potency *in vivo* and *in vitro*, but with maximal structural diversity of functional groups relative to MK-679. Metabolism studies[9] had suggested that the thioacetal group may be a site of oxidation. We had also hoped to remove the olefin link if possible, while maintaining activity. The structural modifications presented in this paper led to the discovery of a new class of LTD_4 antagonists, which was optimized to give **L-695,499**.

Scheme 1



L-number	Y	Z	IC_{50} (nM)[a]
1	(E)-CH=CH	$S(CH_2)_2CONMe_2$	3.0 ± 0.2
2	(E)-CH=CH	$(CH_2)_2CHMeCH_2CONMe_2$	1.3 ± 1.7
3	CH_2O	$(CH_2)_2CHMeCH_2CONMe_2$	8.6 ± 3
4	$(CH_2)_2$	$S(CH_2)_2CONMe_2$	26, 36
5	CH_2S	$S(CH_2)_2CONMe_2$	75
6	CH_2O	$S(CH_2)_2CONMe_2$	14 ± 6

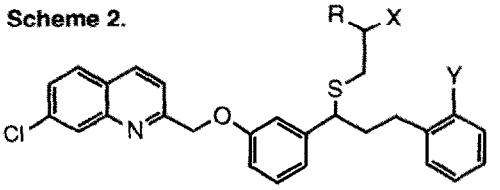
a) Inhibition of [^{3}H]LTD_4 binding to guinea-pig lung membranes[10]. Values are either individual determinations or mean ± S.E.M.

Replacement of the thioacetal by a thioether (**2**, Scheme 1) retained intrinsic potency with an IC_{50} of 1.3 nM for the inhibition of [^{3}H]-LTD_4 binding to guinea-pig lung membranes (gplm)[10]. On the other hand, replacement of the olefin linkage with various 2 atom linkages such as CH_2CH_2 (**4**), CH_2S (**5**) and CH_2O (**6**) led to roughly 10 fold loss in intrinsic potency, as judged by the

IC_{50} values of 31 nM, 75 nM and 14 nM respectively. The combination of the best of those modifications in the ether series (**3**) gave an IC_{50} of 8.6 nM.

In further optimizing the structure of **3**, it was found that addition of an aromatic ring in the amide chain yields up to 5-fold increase in intrinsic potency (**7**; IC_{50} 1.9 nM, Scheme 2). **7** had the level of intrinsic potency of Verlukast, and was further tested *in vivo*. Antigen-induced dyspnea in hyperreactive rats[11] was inhibited by 54% ($p < 0.01$) after dosing with 0.5 mg/kg p.o., 2 hours pretreatment. However, LTD_4-induced bronchoconstriction in conscious squirrel monkeys[12] was significantly inhibited only when the pretreatment time was reduced to 30 minutes instead of 4 h, and at 1 mg/kg p.o. instead of 0.1 mg/kg. This apparent discrepancy between *in vitro* and *in vivo* data in the monkey was rationalized by difference in the plasma levels of **7** and **MK-679** (**(R)-1**), the apparent total plasma clearance[18] of **7** being 12 fold faster than that of **(R)-1** (15 mL/min/kg vs 1.2 mL/min/kg).

Scheme 2.



L-number	X	Y	R	IC_{50} (nM)[a]
7	$CONMe_2$	CO_2H	H	1.9 ± 1.9
8	CO_2H	$CONMe_2$	H	0.95 ± 0.6
9	CO_2H	$CONMe_2$	Me	0.52 ± 0.3
10	CO_2H	$CONMeCH_2OH$	Me	3.6

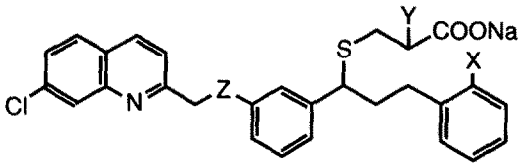
a) Inhibition of [^{3}H]LTD_4 binding to guinea-pig lung membranes[10]. Values are either individual determinations or mean ± S.E.M.

The rapid clearance of **7** in the squirrel monkey was first attributed to the presence of a benzoic acid moiety, which is known to be cleared through conjugation in primates[19]. Interchanging the amide and acid groups gave **8**, which retained high intrinsic potency with an IC_{50} of 0.95 nM, and was active in the squirrel monkey model with up to 1 hour pretreatment at a dose of 1 mg/kg. Introduction of an α-methyl substituent on the acid chain (**9**) gave an increase in duration of action up to 2 hours (1 mg/kg dose). In this case, we could detect a circulating metabolite in the squirrel monkey, which was identified as being the N-hydroxymethyl amide **10**. Metabolism could therefore contribute to the rapid rate of elimination of these compounds, and a surrogate for the dimethyl amide was sought.

Many functional groups were evaluated as replacements for the dimethyl amide. They were prepared according to Scheme 3[13] and are listed in Table 1. A striking feature of these replacements is that the LTD_4 receptor seems rather unselective towards this area of the molecule. Potent compounds were obtained with groups ranging in polarity and size, from H to acyl sulfonamides. It appeared however that compounds bearing hydrogen bond acceptor groups (amides, alcohol, etc.) were more potent antagonists of the LTD_4 receptor than the neutral groups. In contrast to intrinsic potency, the drug disposition appears to be inversely related to the polarity of the group. A good combination of hydrogen bond acceptor and minimal polarity was found in the t-alcohols such as **21**.

Each of the four diastereoisomers of **21** were prepared as shown in Scheme 4 and described in Table 2. As previously observed with **1**, the more potent LTD_4 receptor antagonist isomers unfortunately induced peroxisomal enzymes *in vivo* in the mouse[17]. Neither of the non-inducer ß-isomers was as active as **MK-679 ((R)-1)** *in vivo*.

Table 1. Pharmacodynamics and pharmacokinetics as a function of aromatic substituents.

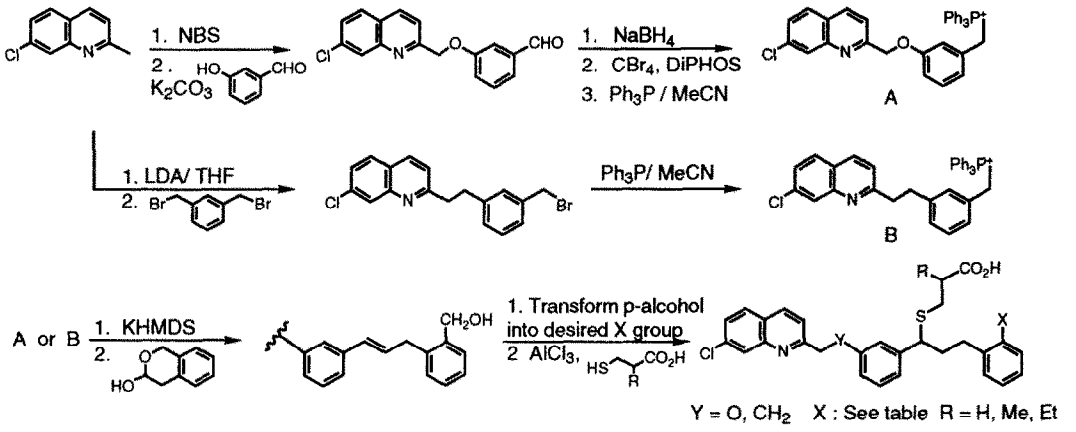


Compound	X	Y	Z	IC_{50} (nM)[a]	Clearance[b]
8	$CONMe_2$	H	O	0.95 ± 0.6	64
11	$CON(CH_2)_5$	H	O	0.6 ± 0.9	55
12	CONHEt	Et	O	0.45 ± 0.3	106
13	$CONH_2$	Et	O	0.47 ± 3.2	58
14	COOH	Et	O	2.0, 1.0	8.8
15	CN	Et	CH_2	1.0	13
16	CN_4H	Et	CH_2	0.8, 0.5	61
17	$CONHSO_2tol$	Et	CH_2	1.4, 6.5	15
18	HNCOOEt	Et	CH_2	0.5, 0.6	8.8
19	CN_4CH_3	Et	CH_2	0.4 ± 0.3	18
20	SO_2CH_3	Et	O	0.6, 1.0	35
21	$C(OH)(CH_3)_2$	Me	O	0.5, 0.85	12
22	H	H	O	6.5 ± 1.8	2.9
23	$CH(CH_3)_2$	Me	O	6.3	2.2
24	NO_2	Me	O	0.4, 0.49	12
25	$HNSO_2CH_3$	H	O	0.56, 0.6	131
26	SO_2NH_2	H	O	0.4, 0.6	106
27	C-Triazolyl	H	O	0.36 ± 0.2	64

a) Inhibition of [^{3}H]LTD_4 binding to guinea-pig lung membranes[10]. Values are either individual determinations or mean ± S.E.M. b) In mL/min Kg. Estimated from the AUC after 5 mg/kg i.v. dosing of rats.

It thus appeared that although the saturated and ether series derived compounds had the desired intrinsic potency, they were associated with poor pharmacokinetics or unacceptable enzyme induction. Based on our experience in these series, we decided to prepare the olefin link equivalents. A close analogue of **28** (Table 2), **L-695,499**, was found to be the most potent compound of this series. A comparative profile of **L-695,499** and **MK-679** is presented in Table 3.

Scheme 3



Scheme 4

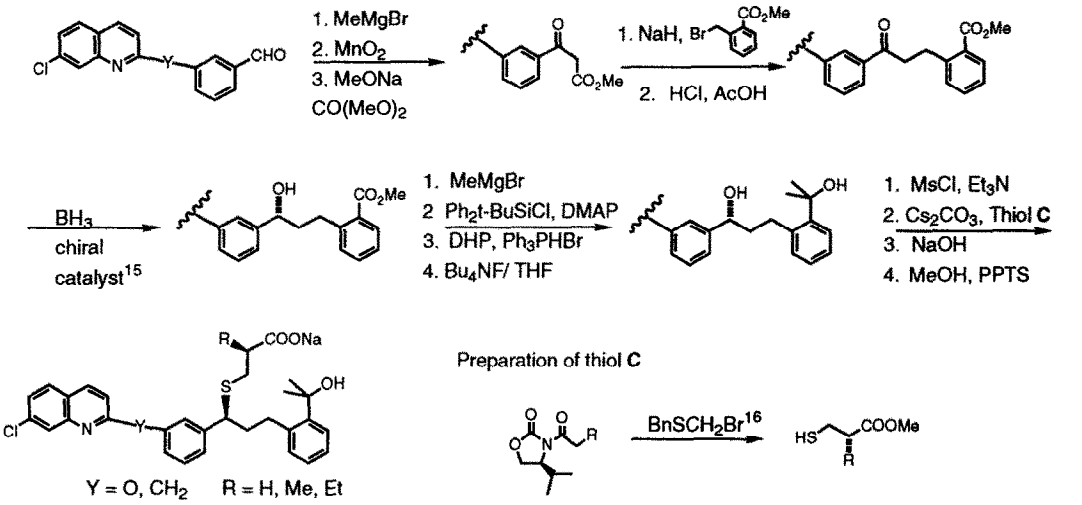
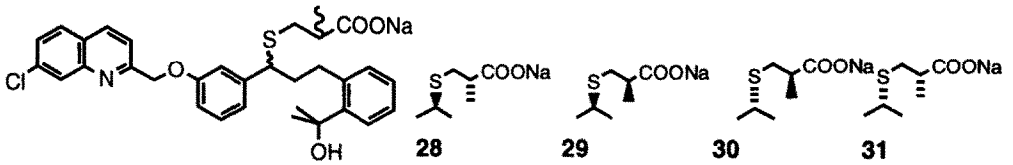


Table 3 shows that **L-695,499** has a similar or improved *in vitro* profile over **MK-679**. This compound is also a very selective LTD_4-receptor antagonist. It showed at least 1000 fold selectivity for inhibition of LTD_4-induced contraction of guinea-pig trachea over that induced by a variety of other mediators such as 5-HT, arachidonic acid and histamine. The *in vivo* profile of **L-695,499** was also improved over that of **MK-679**, with comparable inhibitory activity being observed at an infusion rate of 2.5μg/kg/min instead of the 8μg/kg/min of **MK-679** in the allergic sheep model[14].

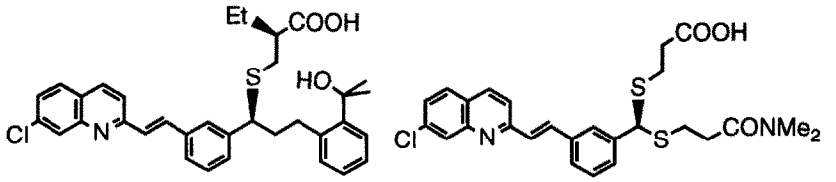
Table 2. Comparison of the isomers of **21**



	28	**29**	**30**	**31**
LTD_4 binding[2] guinea pig (nM)	5,7	17, 20	2, 4	0.2, 0.3
pA_2 guinea pig trachea[2]	8.8 ± 0.16	8.3 ±0.5	9.1 ± 0.5	9.4 ± 0.4
Hyperreactive rat[2] @ 0.5 mg/kg	46%, p<0.1	47%, p<0.02	62%, p<0.01	63%, p<0.01
FACO activity[a]	-7%	+10%	+128[b]	+155%[b]

a) Average (4 males, 4 females) percentage increase of fatty acyl Co-A oxidase activity after 4 days of dosing mice at 400 mg/kg p.o..[17] b) Statistically different from the control group.

Table 3. Comparative profile of **L-695,499** and **MK-679**



L-695,499 **MK-679**

	L-695,499	**MK-679**
LTD_4 binding[2] guinea pig (nM)	0.9 ± 0.6	3.9 ± 1.1
pA_2 guinea pig trachea[2]	8.8 ± 0.3	8.8 ± 0.2
In vivo guinea pig[2] ED_{50} (μg/kg i.v.)	2.0	2.8
Squirrel monkey[a]	72% p<.02	60% p<.02
4h pretreatment @ 0.1 mg/kg p.o.		
FACO activity[b]	+38%	+62%

a) Inhibition of LTD_4-induced bronchoconstriction in squirrel monkey, 4 h pretreatment, 0.1 mg/kg p.o.
b) Average (4 males, 4 females) percentage increase over placebo of fatty acyl Co-A oxidase activity after 4 days of dosing mice at 100 mg/kg p.o. (**L-695,499**) or 400 mg/kg p.o. (**MK-679**).[17]

In summary, the structure of **L-695,499** has been evolved from that of **MK-679**. The thioacetal and the dimethylamide groups were removed and the *in vivo* potency improved significantly. Further data will be reported in another communication.

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