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A NEW SERIES OF POTENT LTD_4 ANTAGONISTS IN THE STYRYLQUINOLINE CLASS.

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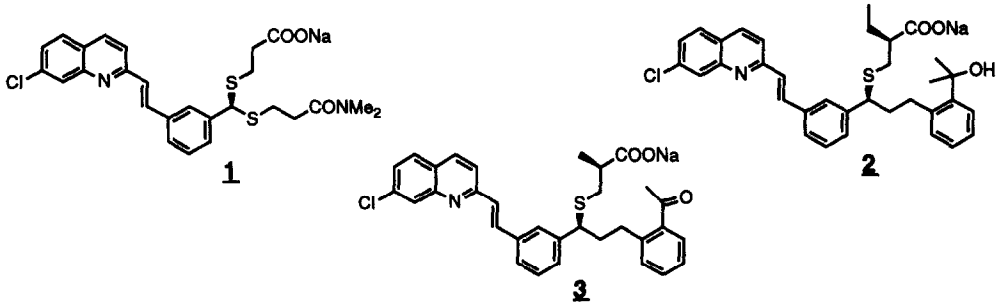
Abstract: A structurally new series of potent leukotriene D_4 antagonists has evolved from modifications of L-695,499.

The peptidoleukotrienes (LTC_4, LTD_4 and LTE_4) are believed to be important biological mediators in several hypersensitivity and allergic diseases, such as asthma[1]. In particular, LTD_4 causes a prolonged constriction of the respiratory smooth muscle[2]. The discovery and development of selective leukotriene antagonists as new therapeutic agents for the treatment of asthma has thus been an intense area of research[3]. Recent reports from these laboratories described Verlukast 1 (MK-0679, (R)-3[[[3-[2-(7-chloroquinolin-2-yl)-(E)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]-thio]methyl]thio]propionic acid) as a potent, orally active LTD_4 antagonist[4]. It has demonstrated efficacy in normal[5] and asthmatic[6] men; it also inhibited both antigen-induced early and late responses in asthmatics[7] accompanied by lung function improvements, reduction in symptom scores and in β-agonist usage[8].

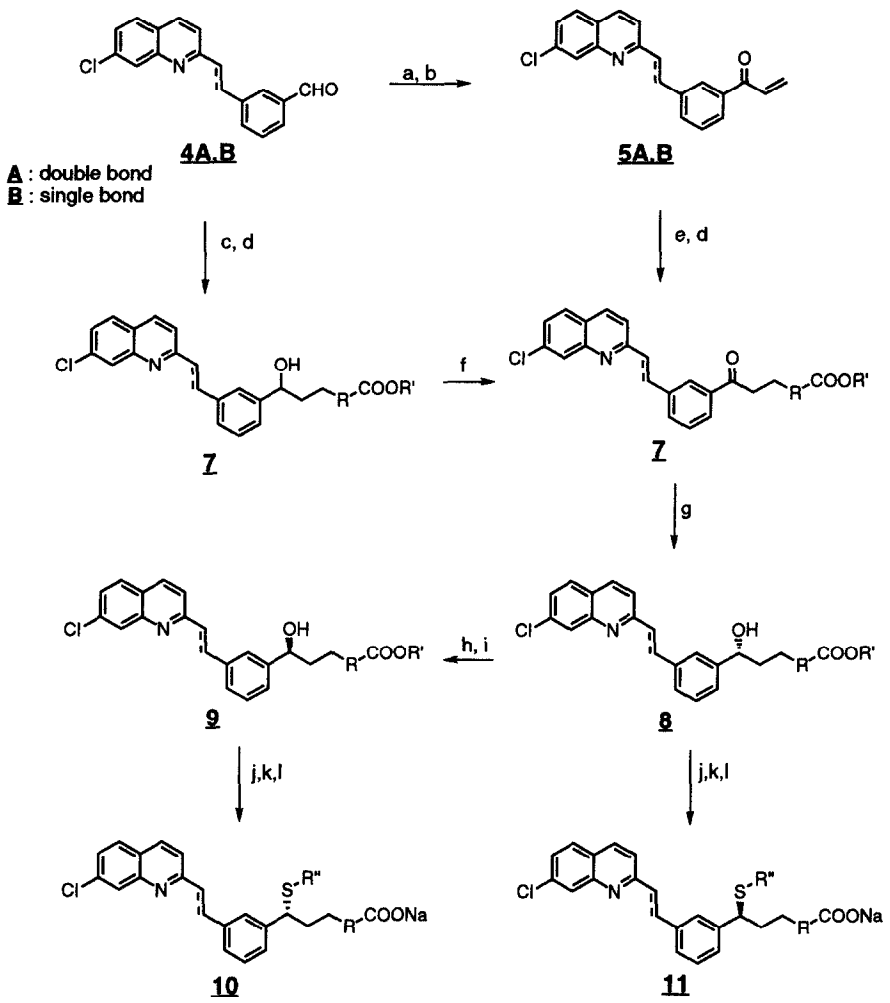
Figure 1 :



As clinical studies with Verlukast 1 were ongoing, we sought to find other potential candidates for clinical development. These compounds would preferably be structurally as different as possible from 1 and be at least equipotent in our *in vitro* and *in vivo* models. As recently

reported, these efforts guided by metabolism and toxicology studies led to the discovery of L-695,499 (**2**)[9] and of L-699,392 (**3**)[10], where the thioacetal in **1** has been replaced by a thioether and where a substituted phenyl ring replaces the dimethylamide group (figure 1). This paper describes other structural modifications which led to another related class of orally active LTD_4 antagonists with potencies similar to **2** and **3**.

Scheme 1

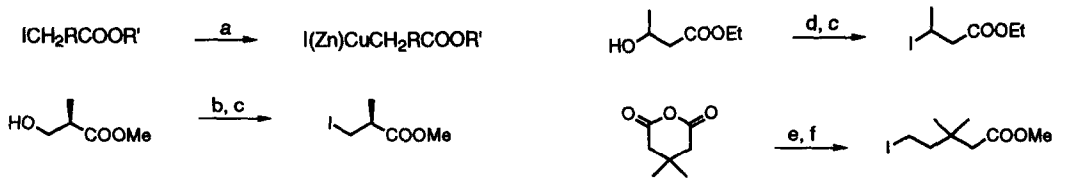


Key : a) $CH_2CHMgBr$, THF b) MnO_2 c) $I(Zn)CuCH_2CH_2RCOOR'$, $BF_3{\cdot}OEt_2$, THF d) HCl aq., R'OH, THF e) $I(Zn)CuRCOOR'$, TMSCl, THF f) TPAP, NMO, CH_2Cl_2, molecular sieves or $(COCl)_2$, DMSO; Et_3N, CH_2Cl_2 g) $BH_3{\cdot}THF$, chiral oxazaborolidine catalyst h) Ph_3P, DEAD, THF, PhCOOH i) MeONa, MeOH j) MsCl, Et_3N k) HSR", Cs_2CO_3, CH_3CN or AcSR", NH_2NH_2, Cs_2CO_3, CH_3CN l) NaOH.

Our approach to modifying **2** was to place the sulfur atom in the other side chain so that the thioether side chain would now hold the hydrogen bond acceptor group. Our working hypothesis was that the absolute stereochemistry of the carbon bearing the sulfur atom relative to the quinoline and to the carboxylic acid residues was a key feature in determining peroxisomal enzyme induction in mice *in vivo*, and we hoped that in contrast to **1** and **2**[11], this structural class would give compounds where the most potent diastereoisomers are not peroxisomal enzyme inducers. Also, based on our own experience[9], we wished to include alkyl substituents α or β to the carboxyl group as this gives a small boost in intrinsic potency but most importantly it reduces metabolism (β-oxidation) therefore improving pharmacokinetics by increasing $t_{1/2}$ of the compounds.

With the readily available[12] aldehydes **4A** and **4B** in hand, we based our strategy for the preparation of these "reversed" thioether compounds on the 1,2- and 1,4-addition of organometallic reagents to aldehydes and enones (scheme 1). Recent reports by Knochel[13] described such reagents in the form of mixed copper-zincate species which can react in a 1,2- or in a 1,4-fashion depending on the reaction conditions. Furthermore, these organometallic reagents are easily prepared from the corresponding iodides which tolerate various functional groups such as esters. However, the compatibility of these mixed copper-zincate reagents with a quinoline or a styrylquinoline as in **4A,B** and **5A,B** was unclear.

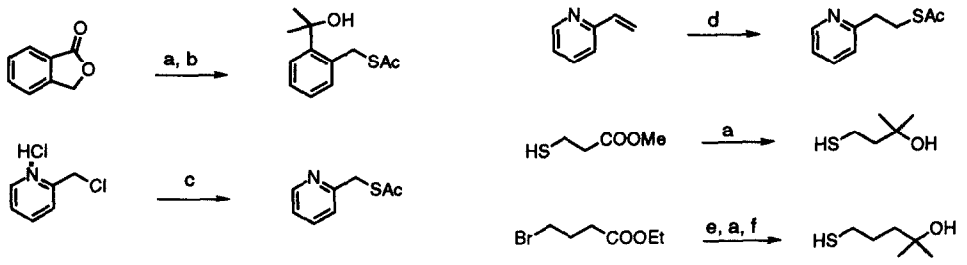
Scheme 2



Key : a) Zn, TMSCl, THF; then CuCN·2LiCl b) CBr_4, DIPHOS, CH_2Cl_2 c) NaI, acetone d) MsCl, Et_3N, CH_2Cl_2 e) $LiAlH_4$, THF f) HI, AcOH

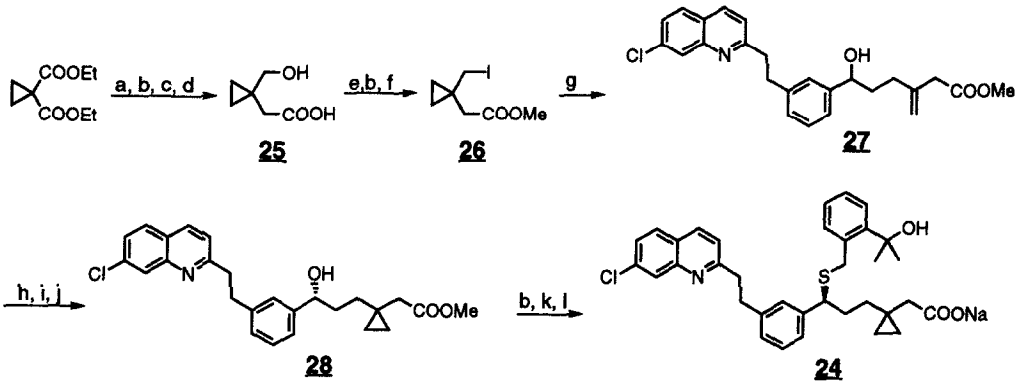
When enones **5** were treated with the mixed copper-zincate reagents derived from the iodides of scheme 2 in the presence of chlorotrimethylsilane[13a], the ketoesters **7** were formed in high yields (≥ 80%). Similarly, addition of these reagents to the aldehydes **4** in the presence of boron trifluoride etherate[13b] gave the hydroxyesters **6** (> 90%) which were oxidized using Ley's[14] or Swern's[15] procedures to give ketoesters **7**. Enantioselective reduction of the latter was accomplished using Corey's oxazaborolidine[16] catalyst with borane affording the chiral hydroxyesters **8**[17] in high yield. The epimeric alcohols **9** could be prepared using the enantiomeric form of the reducing agents or via Mitsunobu[18] inversion of the alcohols **8**. Mesylation followed by S_N2 displacement with the appropriate thiols (prepared as in scheme 3) and hydrolysis gave the desired compounds of general structure **10** and **11**. Finally, introduction of a spirocyclopropane β to the carboxylate group was accomplished as shown in scheme 4.

Scheme 3



Key : a) MeMgBr, toluene b) MsCl, Et_3N, CH_3CN, THF;
then CsSAc c) AcSH, K_2CO_3, CH_3CN d) AcSH e) BnSH, i-Pr_2NEt, THF f) Na, NH_3, THF

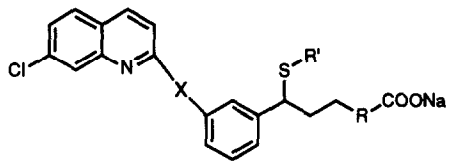
Scheme 4



Key : a) $LiAlH_4$, THF b) PhCOCl, pyr. c)MsCl, Et_3N; NaCN, DMSO d) KOH, EtOH aq. e) CH_2N_2 f) NaI, acetone g) iodide **28** , Zn, TMSCl, THF; then CuCN·LiCl; aldehyde **D**, $BF_3{\cdot}OEt_2$ h) CH_2N_2, $Pd(OAc)_2$, Et_2O i) TPAP, NMO, CH_2Cl_2, molec. sieves j) (+)-Ipc_2BCl, THF k) thioacetate **C**, NH_2NH_2, Cs_2CO_3, CH_3CN l) NaOH.

The intrinsic potency of these compounds (table 1) was measured by their ability to inhibit [^{3}H]-LTD_4 binding to guinea-pig lung membranes. In contrast to compounds in the L-695,499 series where the (R) stereochemistry at the benzylic position results in higher intrinsic potency[9], we could not find any correlation between IC_{50}'s and absolute stereochemistry at the benzylic thioether center. Furthermore, our original hypothesis linking absolute stereochemistry and peroxisomal enzyme induction in mice *in vivo* was refuted and no correlation was found. For example, compounds **18** and **19** showed no statistically significant increase (+39% and +24% respectively) in FACO activity[20] whereas **12**, **15** and **16** turned out to be powerful enzyme inducers with increases of +292%, +610% and +585% respectively. As previously observed in other series[11], although the saturated analogs (**20** - **24**) had sufficient intrinsic potency they suffered from poor pharmacokinetics and higher metabolism.

Table 1: Intrinsic potency and absolute stereochemistry



Compound	X	R	R'	Stereochemistry[a]	IC_{50} (nM)[b]
12	CH=CH	$CH_2CH(Me)$[c]	$CH_2CH_2C(Me)_2OH$	S	2.0 ± 1.0
13	CH=CH	$CH_2CH(Me)$[c]	$CH_2CH_2C(Me)_2OH$	R	0.8 ± 0.2
14	CH=CH	$CH_2CH(Me)$[c]	$CH_2CH_2CONMe_2$	S	2.3 ± 0.3
15	CH=CH	$CH_2CH(Me)$[c]	$CH_2CH_2CONMe_2$	R	0.9 ± 0.1
16	CH=CH	$CH(Me)$[d]CH_2	$CH_2CH_2CH_2C(Me)_2OH$	S	0.5 ± 0.4
17	CH=CH	$C(Me)_2CH_2$	$CH_2CH_2CH_2C(Me)_2OH$	R,S	1.3 ± 0.7
18	CH=CH	$C(Me)_2CH_2$	CH_2(2-)PhC$(Me)_2OH$	S	0.6 ± 0.3
19	CH=CH	$C(Me)_2CH_2$	CH_2(2-)PhC$(Me)_2OH$	R	1.0 ± 0.3
20	CH_2CH_2	$C(Me)_2CH_2$	CH_2(2-)PhC$(Me)_2OH$	S	0.6 ± 0.3
21	CH_2CH_2	$C(Me)_2CH_2$	CH_2(2-)PhC$(Me)_2OH$	R	1.9 ± 0.1
22	CH_2CH_2	$C(Me)_2CH_2$	CH_2(2-)Pyr	S	1.6 ± 0.1
23	CH_2CH_2	$C(Me)_2CH_2$	CH_2CH_2(2-)Pyr	S	2.2 ± 0.3
24	CH_2CH_2	$C(CH_2CH_2)CH_2$	CH_2(2-)PhC$(Me)_2OH$	S	1.4 ± 0

a) Absolute stereochemistry at the sulfur bearing benzylic carbon. b) Inhibition of [^{3}H]LTD_4binding to guinea-pig lung membranes[19]. c) absolute stereochemistry is R. d) R,S mixture.

In summary, modifications of the structure of L-695,499 led to another series of LTD_4 antagonists with comparable potency and very similar profiles. These compounds add to the structural diversity of LTD_4 antagonists and further progress will be reported in due course.

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20. Average (4 males, 4 females)percentage increase over control of fatty acyl Co-A oxidase activity after 4 days of dosing mice at 400 mg/kg.[11] We are grateful to S.J.Grossman from Safety Assessment, Merck and Co., West Point, for performing these experiments.