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DISCOVERY OF CP-199,330 AND CP-199,331: TWO POTENT AND ORALLY EFFICACIOUS CYSTEINYL LT_1 RECEPTOR ANTAGONISTS DEVOID OF LIVER TOXICITY

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Abstract: CP-199,330 (**3**) and CP-199,331 (**4**) are $cysLT_1$ receptor antagonists that are equipotent to marketed $cysLT_1$ receptor antagonists zafirlukast and pranlukast, show good pharmacokinetics in rats and monkeys, and are devoid of liver toxicity in monkeys as seen in CP-85,958 (**1**).

The cysteinyl leukotrienes (cysLT) are products of arachidonic acid metabolism that have been implicated as key mediators in the progression of asthma.[1] Zafirlukast, pranlukast, and montelukast are antagonists of the $cysLT_1$ receptor that have shown clinical efficacy in the treatment of asthma, thus validating intervention at the $cysLT_1$ receptor as a therapeutic target.[2] We have described the discovery of CP-85,958 (**1**), a potent antagonist of the $cysLT_1$ receptor whose clinical evaluation was discontinued due to unacceptable liver toxicity in monkeys (Figure I).[3] Analysis of monkey bile after dosing with **1** showed the presence of a major hydroxylated metabolite thought to be lactol (**2**). It is possible that lactol (**2**) could induce toxicity since it can undergo ring opening to produce a reactive hydroxy aldehyde intermediate. To circumvent the toxicity in CP-85,958 (**1**), we recently described an approach in which we were able to block the formation of lactol (**2**) and increase potency, which allowed for lower efficacious exposure.[4,5] Alternatively, we also incorporated groups that both increased potency and were metabolically labile allowing for an alternative metabolic route.[6] This effort lead to the identification of **3** and **4** as optimized antagonists of the $cysLT_1$ receptor in this series.

The synthesis of **3** and **4** proceeds via a eleven step route utilizing amine **15** as a common intermediate as illustrated in the synthesis of **3** (Scheme 1). Demethylation of **5**[7] followed by alkylation of phenol **6** with benzyl bromide gave benzyl ether **7** (Scheme 1). Aldol condensation of **7** with aldehyde **8**[8] and subsequent hydrogenation of enone **9** yielded ketone **10**. Reduction of **10** with sodium borohydride in the presence of cerium (III) chloride afforded *cis*-alcohol **11** as a racemic mixture. Resolution was achieved by esterification of **11** with Boc-D-Tryptophan, chromatograhic isolation of the dextrorotatory diastereomer **12**, followed by

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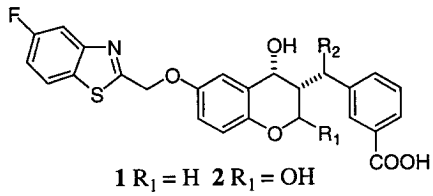
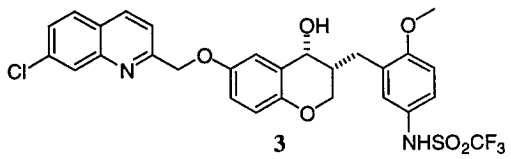
saponification to give the dextrorotatory alcohol **13** as a single enantiomer. Curtius rearrangement of **13** and subsequent hydrogenation of carbamate **14** yielded amine **15**. Alkylation of **15** with chloride **16**[9] gave amine **17**. Treatment of **17** with triflic anhydride followed by saponification of the intermediate *bis-N,N*-trifluoromethylsulfonamide yielded **3** in a 5% yield overall. The diastereomeric purity of **12** was judged to be >95% by ^{1}HNMR and the absolute configuration of **3** was tentatively assigned as *3S,4S* based on an analogous optical rotation to **1** whose absolute stereochemistry was determined by X-ray crystallography.[3]

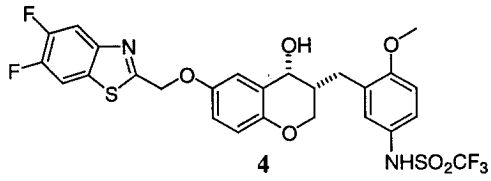
Figure 1



1 R_1 = H **2** R_1 = OH



3

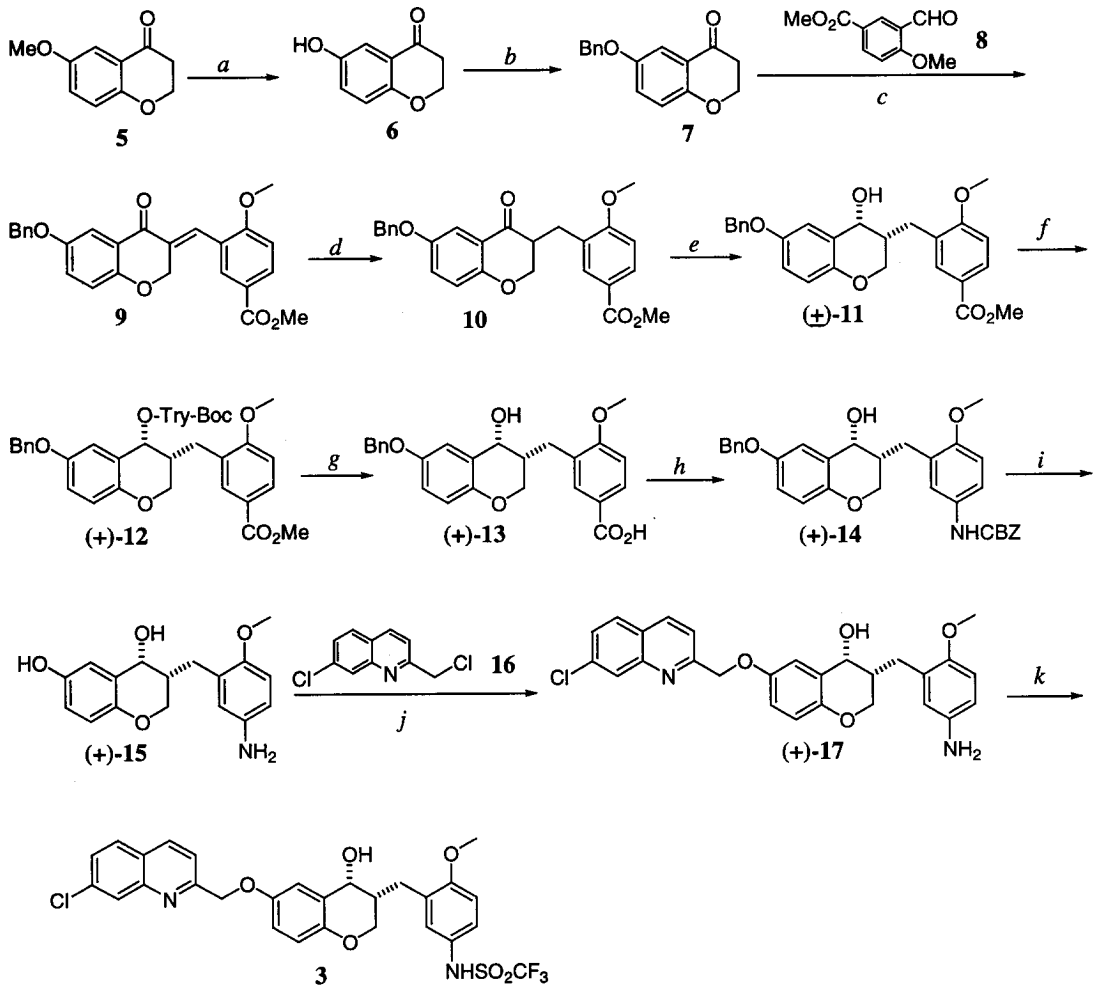


4

A high correlation has been demonstrated between cysLT$_1$ receptors isolated from human lung membranes and those isolated from readily available guinea pig lung membranes.[10,11] Analogs **3** and **4** proved to be equipotent to both zafirlukast and pranlukast in binding to cysLT$_1$ receptors derived from guinea pig lung (Table 1). The elevation of cytosolic calcium has been shown to correlate with both cysteinyl leukotriene biosynthesis and contraction of guinea pig ileum, events which cysLT$_1$ receptor antagonists block.[12,13] Analogs **3** and **4** showed comparable potency to that of zafirlukast and pranlukast in blocking extracellular calcium influx in human U937 cells (Table I).[14] Zafirlukast and pranlukast have been shown to be efficacious in guinea pig models of asthma suggesting that such models may be predictive of clinical efficacy in humans.[15,16] Analogs **3** and **4** blocked both antigen and cysLT$_1$ receptor induced airway obstruction in guinea pigs being equipotent to zafirlukast and pranlukast (Table 2).[17]

The pharmacokinetic profile of **3** and **4** in rats and monkeys shows low hepatic clearance, moderate terminal half-life and high oral bioavailability (Table 3). Analysis of rat and monkey plasma reveals that **3** and **4** undergo O-demethylation of the methoxy group to give the corresponding phenols as the major metabolite. In both cases, no lactol formation was detected.

Scheme 1



Scheme 1. (a) 48% HBr, HOAc, reflux, 93%; (b) BnBr, K_2CO_3, acetone, 88%; (c) **8**, pyrollidine, MeOH, 80% (d) H_2, Pd/C, EtOAc, 10 psi, 57% (e) $NaBH_4$, $CeCl_3$, MeOH/THF, 80%; (f) *t*-Boc-D-Try-OH, DEC, DMAP, CH_2Cl_2, 46%; (g) 1 N NaOH, MeOH, reflux, 91%; (h) DPPA, BnOH, TEA, dioxane, 63%; (i) H_2, $Pd(OH)_2$, 93%; (j) **16**, NaH, DMF, 81%; (k) i. Tf_2O, TEA, CH_2Cl_2, ii. 1 N NaOH, MeOH, 82%.

Since **3** and **4** do not undergo metabolic lactol formation it is possible that the liver toxicity associated with **1** in monkeys might be avoided. When dosed in monkeys over five days, **3** and **4** showed no liver toxicity at plasma concentrations in excess of an order of magnitude higher than those predicted for clinical efficacy. It has been reported that several clinical $cysLT_1$ receptor antagonists induce hepatic peroxisome proliferation and although humans appear to be refractory, this activity has been associated with liver tumor formation in

rodents.[18 - 25] When dosed in rats over fourteen days, **3** and **4** showed no hepatic peroxisomal proliferation at plasma concentrations in excess of an order of magnitude higher than those predicted for clinical efficacy.

Table 1. Comparative in vitro profile of **3** and **4**.

Compound	$cysLT_1$ Receptor Binding K_i (nM) ± s.d. (n)	Ca^{+2} mobilization U937 cells IC_{50} (nM) ± s.d. (n)
zafirlukast	2.0 ± 0.8 (9)	1.0 ± 0.4 (55)
pranlukast	0.8 ± 0.3 (5)	1.0 ± 0.6 (2)
3	0.6 ± 0.15 (3)	0.7 ± 0.06 (3)
4	0.4 ± 0.05 (4)	0.3 ±0.06 (3)

Table 2. Comparative in vivo profile of **3** and **4**.

Compound	guinea pig airway obstruction (OA) ED_{50} (mg/kg) ± s.d. @ h po (n)	guinea pig airway obstruction ($cysLT_1$) ED_{50} (mg/kg) @ h po (n)
zafirlukast	0.9 ± 0.42 @ 2.0 hr (2)	0.52 @ 2.0 hr (1)
pranlukast	1.5 @ 1.0 hr (1)	not tested
3	0.46 ± 0.08 @ 1.0 hr (3)	0.12 @ 1.0 hr (1)
4	0.52 ± 0.19 @ 1.0 hr (3)	0.08 @ 1.0 hr (1)

Table 3. Comparative pharmacokinetics of **3** and **4**.

	3		**4**	
	rat	**monkey**	**rat**	**monkey**
Clp (mL/min/kg)	8.9	6.5	8.3	4.2
$t_{1/2}$ (hr)	0.8	2.1	8.8	9.4
% F	53	100	46	72

In conclusion, by designing compounds with increased intrinsic potency and preferential metabolism we were able to identify **3** (CP-199,330) and **4** (CP-199,331) which are equipotent to marketed $cysLT_1$ antagonists zafirlukast and pranlukast, show good pharmacokinetics in rats and monkeys and are devoid of liver toxicity as seen in CP-85,958 (**1**).

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