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DEVELOPMENT OF 2,2-DIMETHYLCHROMANOL CYSTEINYL LT₁ RECEPTOR ANTAGONISTS

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Abstract. A new series of cysLT₁ receptor antagonists represented by CP-288,886 (7) and CP-265,298 (8) were developed which are equipotent to clinical cysLT₁ receptor antagonists Zafirlukast (1) and Pranlukast (2). © 1998 Elsevier Science Ltd. All rights reserved.

Leukotriene D_4 (cysLT₁) is a product of arachidonic acid metabolism which has been implicated as a key mediator in the progression of asthma.¹ Zafirlukast (1),² Pranlukast (2)³ and Montelukast⁴ are cysLT₁ receptor antagonists which have shown clinical efficacy in the treatment of asthma thus validating intervention at the $cysLT_1$ receptor as a therapeutic target (Figure I). We have described the discovery of CP-85,958 (3), a potent $cysLT_1$ receptor antagonist whose clinical evaluation was discontinued due to unacceptable liver toxicity in monkeys.⁵ Examination of monkey bile after exposure to 3 revealed the formation of a major hydroxylated metabolite whose structure was elucidated as either lactol 4 or alcohol 5. It is possible that the formation of lactol 4 could account for the toxicity observed in 3 since it can undergo ring opening to produce a reactive hydroxy aldehyde intermediate.⁶⁷ Toxicity in **3** may be avoided by both blocking the formation of lactol **4** and improving potency which would allow for lower efficacious exposure. This rationale led to the discovery of CP-195,494 (6), a potent cysLT₁ receptor antagonist in which a methyl group is introduced into the 2-position to prevent ring opening to a reactive hydroxy aldehyde intermediate.⁸ However, 6 can still undergo metabolic hydroxylation in the 2-position⁹ and the long synthetic sequence due to the chiral center in the 2-position, makes the pursuit of analogs of 6 unattractive. In order to address these issues we sought to introduce an additional methyl group into the 2-position of $\mathbf{6}$ which would not only prevent metabolic hydroxylation in the 2-position. but would eliminate an additional chiral center allowing for a more facile synthesis of analogs.

In considering that the major metabolite of **3** in monkey bile may be alcohol **5**, we sought to introduce functional groups into the 4-position of the phenylsulfonamide ring of **6** which would effect metabolic benzylic hydroxylation by either electronic or steric factors. Such substituents could effect the acidity of the trifluoromethylsulfonamide and therefore $cysLT_1$ receptor antagonist activity. We also attempted to further attenuate the electronic character of the 5-fluorobenzothiazole ring in **6** and also potentially block any

metabolism at the 6-position by introducing a 6-fluorine substituent. In addition, we were interested in replacing the 5-fluorobenzothiazole ring in 6 with a 7-chloroquinoline bioisostere¹⁰ and the methylene ether linkage with a *trans* olefin bioisostere.¹¹ In order to explore these issues we designed analogs 7-11 whose synthesis and biological profile we report herein.



We have previously shown in the development of **3** and **6** that the dextrorotatory enantiomer possessing 3S, 4S absolute stereochemistry provides optimal cysLT₁ receptor antagonism.^{5,8} With this structure activity relationship in mind, we developed a general synthesis to analogs **7-10** which is illustrated in the synthesis of **7** (Scheme I). Hydrogenation of **12**¹² afforded phenol **13** (90%) which was alkylated with 2-(chloromethyl)-7-chloroquinoline¹³ to give amine **14** (93%). Treatment of **14** with triflic anhydride followed by basic hydrolysis of the intermediate *bis*-N,N-trifluoromethylsulfonamide yielded the *mono*-N-trifluoromethylsulfonamide **15** (85%). Subsequent reduction of **15** with Super Hydride[®] afforded the *cis* alcohol (±)-**7** (46%). Resolution of (±)-**7** was achieved by esterification with Boc-D-Tryptophan, isolation of the less polar dextrorotatory diastereomer by chromatography

followed by saponifaction to give the dextrorotatory enantiomer (+)-7 (19%). The diastereomeric purity of the intermediate tryptophan ester was judged to be >95% by ¹H-NMR and the absolute configuration of (+)-7 was tentatively assigned as 3S,4S based on an analogous optical rotation to 3 whose absolute stereochemistry was determined by x-ray crystallography.⁵

Scheme I



Scheme I. (a) H_2 , Pd/C, EtOAc/MeOH, 30 psi, rt; (b) i) NaH, DMF, 0°C, ii) 2-(chloromethyl)-7-chloroquinoline; (c) i) Tf_2O , TEA, CH_2Cl_2 , 0°C, ii) 5 N NaOH, MeOH, rt; (d) Super Hydride[®], THF, -78°C; (e) i) Boc-D-Try-OH, EDAC, DMAP, CH_2Cl_2 , rt, ii) 5 N NaOH, MeOH, reflux.

The replacement of the methylene ether linkage in 7 with a *trans* olefin to give 11 was achieved by way of a separate synthetic route (Scheme II). Bromination of 6-methylchromanone 16^{14} with N-bromosuccinimide in the presence of catalytic benzoyl peroxide yielded bromide 17 (58%) which was subjected to oxidation¹⁵ with 4-methylmorpholine-N-oxide to afford aldehyde 18 (53%). Selective acetal formation was achieved by treatment of 18 with one equivalent of ethylene glycol in the presence of *p*-toluenesulfonic acid to yield acetal 19 (77%). Aldol condensation¹² of 19 with 2-methoxy-5-nitro-benzaldehyde¹⁶ gave enone 20 (60%) which was submitted to hydrogenation to afford ketone 21 (91%). Treatment of 21 with two equivalents of triflic anhydride gave the intermediate *bis*-N,N-trifluoromethylsulfonamide which was subjected to basic hydrolysis to yield the *mono*-N-trifluoromethylsulfonamide followed by acidic hydrolysis of the acetal to afford aldehyde 22 in a "one pot" operation (56%). Wittig reaction of 22 with the ylide derived from 23¹⁷ occurred selectively to afford *trans* olefin 24 (92%) and subsequent reduction with Buper Hydride[®] gave 3,4-*cis* alcohol (±)-11 (29%). Resolution of (±)-11 was accomplished by esterification to yield (+)-11 (22%). The diastereomeric purity of the intermediate Boc-D-Tryptophan ester was judged to be > 95% by ¹H-NMR and the absolute stereochemistry of (+)-11 was tentatively assigned as *3S*,4*S* based on an analogous optical rotation to 3.⁵



Scheme II. (a) NBS, $(B_2O)_2O$, CCl_4 , reflux; (b) NMO, 3A sieves, CH_3CN , rt; (c) $HOCH_2CH_2OH$, p-TsOH, PhCH₃, reflux; (d) 2-methoxy-5-nitrobenzaldehyde, $(CH_3O)_4Si$, KF, DMF, 80° C; (e) H_2 , Pd/C, EtOAc, 30 psi, rt; (f) i) Tf_2O , TEA, CH_2Cl_2 , 0° C, ii) 5N NaOH, MeOH, rt; iii) 2N HCl, MeOH, rt; (g) i) 23, n-BuLi, THF, - 50° C to 0° C, ii) 22, THF, - 78° C to rt; (h) Super Hydride[®], THF, - 78° C to 0° C; (i) i) Boc-D-Try-OH, DMAP, EDAC, CH_2Cl_2 , rt, ii) 5N NaOH, MeOH, reflux.

Analogs 7-11 were evaluated for their ability to antagonize $cysLT_1$ receptors isolated from guinea pig lung membranes¹⁸ since they are readily available and there is a high correlation to $cysLT_1$ receptors isolated from human lung membranes (Table I).¹⁹ Modifications about the phenylsulfonamide ring, the methylene linkage or the heterocyclic ring had no significant effect in the antagonism of $cysLT_1$ receptors as analogs 7-11 showed the same order of potency. The elevation of cytosolic calcium has been shown to correlate with both the biosynthesis of leukotrienes²⁰ and the contraction of guinea pig ileum and that $cysLT_1$ receptor antagonists block these events.²¹ The incorporation of a 4-methoxy group as in 7, 8 and 11, led to an marked increase in the inhibition of calcium influx in human U937 cells (Table I).²² Both 1 and 2 have been shown to be efficacious in guinea pig models of asthma^{23,24} suggesting that such models may be predictive of clinical efficacy in humans. Analogs 7-9 and 11 blocked antigen induced airway obstruction in guinea pigs²⁵ with the same order of potency as 1-3 and 6 (Table I).

	cysLT ₁ Binding	Ca ⁺² mobilization U937 cells	guinea pig airway obstruction (OA)
Compound	Ki $(\mu M) \pm s.d.(n)$	$IC_{50} (\mu M) \pm s.d. (n)$	% inh. @ 1 mg/kg \pm s.d. @ hr (n)
1	0.002 ± 0.008 (9)	0.001 ± 0.0004 (55)	51.6 ± 8.0 @ 2hr (13)
2	0.0008 ± 0.0003 (5)	0.001 ± 0.0006 (2)	50.1 ±1.2 @ 1hr (2)
3	0.014 ± 0.0078 (118)	0.310 ± 0.0151 (3)	56.0 ± 8.0 @ 2hr (78)
6	0.0007 (1)	0.008 (1)	66.5 @ 1hr (1)
7	0.004 (1)	0.0005 (1)	57.9 ± 7.6 @ 1hr (2)
8	0.002 (1)	0.0003 (1)	37.8 ± 9.4 @ 2hr (3)
9	0.007 (1)	0.002 (1)	45.8 @ 2hr (1)
10	0.004 (1)	0.017 (1)	not tested
11	0.005 (1)	0.0002 (1)	40.8 @ 2hr (1)

Table I. Comparative in vitro and in vivo profile of analogs 7-11.

Analogs 7 and 8 were shown to have an improved pharmacokinetic profile in rats when compared to 3 (Table II). After intravenous administration, both 7 and 8 showed a moderate rate of hepatic clearance, indicating first pass metabolism. The higher rate of hepatic clearance of 7 and 8 over that of 3 may be attributed to the higher lipophilicity of 7 and 8 and the presence of a metabolically labile 4-methoxy group. However, the higher lipophilicity of 7 and 8 also imparts a higher volume of distribution into the tissues resulting in a longer half life than 3. After oral dosing, analogs 7 and 8 are readily absorbed and show high bioavailibility achieving maximum plasma concentration at 4 hours post dose and sustained plasma concentrations over 8 hours at levels corresponding to those necessary for inhibition of calcium influx in human U937 cells. Interestingly, the predisposition of 7 and 8 to metabolic demethylation of the 4-methoxy group and subsequent glucoronidation and clearance could serve as a facile metabolic pathway thus preventing the buildup of other hydroxylated metabolites which could induce toxicity.

<u></u>	3	7	8
Clp (mL/min/kg)	3.3 ± 0.4	6.7 ± 0.5	16 ± 1
Vdss (L/kg)	0.4 ± 0.1	1.6 ± 0.2	3.8 ± 0.9
t _{1/2} (hr)	1.3	3.6	3.9

Table II. Comparative intravenous rat pharmacokinetics of 3, 7 and 8.

In conclusion, analogs 7 (CP-288,886) and 8 (CP-265,298) were identified as optimized antagonists of the cysLT₁ receptor which have *in vitro* and *in vivo* potency the same order of magnitude as clinical cysLT₁ receptor antagonists Zafirlukast (1), Pranlukast (2) and show improved pharmacokinetics in rats over that of 3.

References and Notes

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Montelukast

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