Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 13, pp. 1365-1370, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00225-1

SYNTHESIS AND PHARMACOLOGICAL PROFILE OF TWO NOVEL HETEROCYCLIC CHROMANOLS, CP-80,798 AND CP-85,958, AS POTENT LTD4 RECEPTOR ANTAGONISTS.

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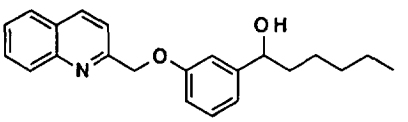
Abstract: The development of two novel LTD_4 receptor antagonists as clinical candidates for the treatment of asthma is described. The first generation compound, CP-80,798, was found to be a balanced 5-lipoxygenase inhibitor (5-LOI)/LTD_4 antagonist (LTD_4-A), while the second generation compound, CP-85,958, is a selective LTD_4 antagonist.

The peptidoleukotrienes are thought to be important mediators in the pathophysiology of inflammatory diseases such as asthma, and thus, there has been an intensive search over the last decade for potent leukotriene modulators.[1] One class of such compounds is the quinoline class of leukotriene antagonists, as pioneered by compounds like REV-5901, **1**, a combined 5-lipoxygenase inhibitor (5-LOI)[2] and leukotriene D_4 antagonist (LTD_4-A).[3]

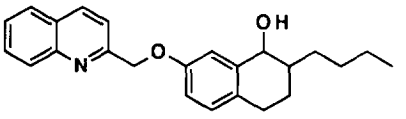


1

The early reports of REV-5901[4] sparked our interest and research was initiated at Pfizer into the design and synthesis of such agents. Our initial objective was to develop a more balanced 5-LOI/LTD_4-A so that both activities would be expressed at the same drug levels; while a second objective was to obtain an intrinsically more potent LTD_4-A. As a reference point, REV-5901 has an K_i of 8.0 ± 2.4 μM (n = 4) for the inhibition of [^{3}H]-LTD_4 binding in guinea pig lung membranes and an IC_{50} of 0.15 ± 0.033 μM (n = 4) for the inhibition of 5-lipoxygenase (5-LO) activity in rat basophilic leukemic cells.[5]

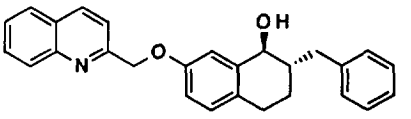
Our initial structural analysis of how to improve on the potency of **1** focussed on reducing its conformational mobility, with the objective of fixing the molecule in a bioactive conformer. As a first step we fixed the position of the hydroxyalkyl side chain of **1** by tying it into a fused six membered

carbocycle. A slight potentiation of the LTD_4-A activity was seen with this first example **2**,[6] indicating that conformational restriction might be a fruitful approach. We then applied two SAR observation from the literature. Firstly, it had been suggested[7] that compounds such as **1** are good mimics of the leukotriene structure, particularly with respect to the leukotriene C-15 to C-20 sidechain overlaying the pentyl side chain of **1**. Secondly, it had been observed in the prostaglandin antagonist literature that an alkyl phenyl group was found to be an effective bioisostere of the C6 ω chain of the prostaglandin template[8]. Combining these observations suggested the replacement of the butyl substituent of **2** with a benzyl group and led to compound **3** which was indeed more potent.



2

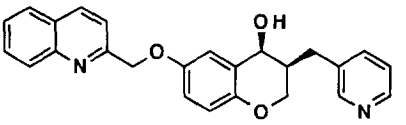
LTD_4 K_i = 6.8 μM



3

LTD_4 K_i = 1.5 μM

When this compound was tested further however, it was found to be devoid of any *in vivo* activity. This was attributed to the high lipophilicity of **3**, resulting in high metabolic clearance and therefore poor bioavailability. With this in mind, further structural modifications were made with the goal of increasing the bioavailability of this series, through the replacement of selected carbons by heteroatoms to reduce the overall lipophilicity. This ultimately led to the synthesis of CP-80,798 **4**, a balanced 5-LOI/LTD_4-A (Table I).



4

(-)-CP-80,798

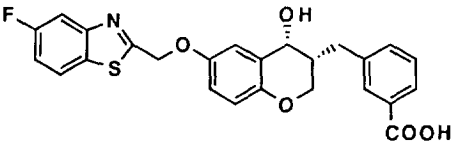
Table I. In Vitro and In Vivo Pharmacology of CP-80,798

5-LO Inh.[9] IC_{50} (μM)[a]	LTD_4 Binding[10] K_i (μM)[a]	Pulm. Func. (LTD_4)[11] ED_{50} (mg/kg, p.o.)[b]	Pulm. Func. (OA)[11] ED_{50} (mg/kg, p.o.)[b]	Airway Obstr. (OA)[12] ED_{50} (mg/kg, p.o.)[c]
1.9 ± 0.1	0.65 ± 0.04	3.0	20	16.0 ± 9.6

[a]Values are the mean ± SD of 4 or more assays. [b]Values determined from a single dose response curve. [c]Value is the mean ± SD of 3 dose response curves.

The in vitro profile illustrates that we had achieved our desired goal of an increase in LTD_4 receptor antagonist potency over REV-5901, as well as generating a more balanced agent. Furthermore, upon oral administration ~ 2 h pre-antigen (OA) or LTD_4 challenge to guinea pigs, CP-80,798 significantly suppressed the increase seen in lung resistance. The difference in the ED_{50}'s between the LTD_4 and ovalbumin challenges in the pulmonary function models is consistent with what has been observed with other LTD_4 antagonists.[13] CP-80,798 also blocked the airway obstruction induced by aerosolized antigen with an ED_{50} of 16.0 mg/kg.[12] Based on this pharmacological data, CP-80,798 was advanced into pre-clinical development, but it was subsequently dropped due to acute toxicity in rats.[14]

At the same time as CP-80,798 was being evaluated pre-clinically, thought was given to the pharmacological profile of a back-up and the decision was made to pursue a more selective and potent LTD4-A. With this in mind, two major structural modifications were made to CP-80,798. The first was to replace the quinoline functionality. One of the more successful replacements was the benzothiazole group which was predicated on SAR developed in the aldose reductase inhibitor project, wherein the benzothiazole was found to be a good bioisostere for the quinoline sidechain.[15] The second major modification was to modify the pyridine sidechain with the goal of introducing structural diversity and the potential for a change in tissue distribution. A range of substituents were introduced but the most interesting modification was the benzoic acid functionality which when combined with the quinolone replacements led to the synthesis of CP-85,958 **5**, a potent, selective LTD_4-A.



5

(+)-CP-85,958

Table II. In Vitro and In Vivo Pharmacology of CP-85,958

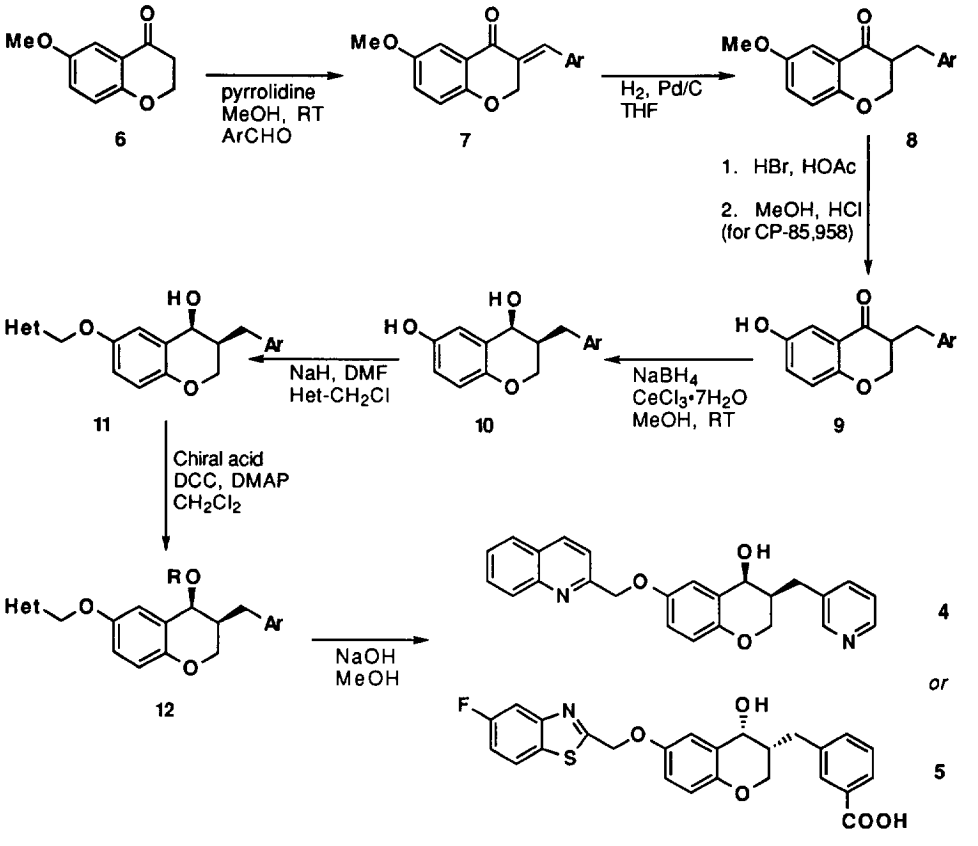
5-LO Inh.[9] IC_{50} (μM)[a]	LTD_4 Binding[10] K_i (nM)[a]	Pulm. Func. (LTD_4)[11] ED_{50} (mg/kg, p.o.)[b]	Airway Obstr. (LTD_4) ED_{50} (mg/kg, p.o.)[b]	Airway Obstr. (OA)[12] ED_{50} (mg/kg, p.o.)
8.1 ± 4	24 ± 3	0.49	0.43	10.8 ± 2.1[c]
ICI-204,219	2.3 ± 0.3		0.52	3.5[b]

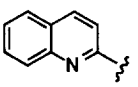
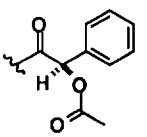
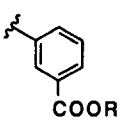
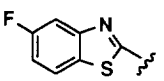
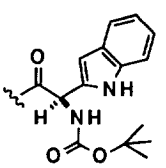
[a]Values are the mean ± SD of 4 or more assays. [b]Values determined from a single dose response curve. [c]Value is the mean ± SD of 2 dose response curves.

This second generation compound, CP-85,958 met our candidate criteria, with a 50 fold increase in potency over CP-80,798 in LTD_4 antagonism and a 500 fold selectivity for LTD_4 antagonism over 5-LO enzyme inhibition. This increase in potency was also reflected in vivo, although not to the same extent, wherein CP-85,958 was 6 fold more active in the pulmonary function test and 1.5 fold more potent in the aerosolized antigen induced airway obstruction model. It was also comparable in the airway obstruction model to ICI-204,219, using an LTD_4 challenge, but was 3 fold less potent using an ovalbumin challenge. With this pharmacological profile, a significant improvement over CP-80,798 was expected and CP-85,958 was advanced into clinical development. Unfortunately, it was subsequently withdrawn due to the discovery of unexpected acute toxicity in monkeys.[16]

Both CP-80,798 and CP-85,958 were synthesized in a straightforward manner as illustrated in Scheme I. The aldol reaction of the commercially available chromanone **6**[17] with either nicotinaldehyde (for **4**) or 3-carbomethoxybenzaldehyde (for **5**) yielded compounds **7**, which after hydrogenation provided compound **8**. The methyl protecting group was cleanly removed by treatment with HBr in acetic acid and the ketone then reduced with sodium borohydride. In our SAR, we had determined that the *cis* stereochemistry was more desirable and that the inclusion of cerium chloride in the $NaBH_4$ reduction gave the best *cis:trans* ratio (97:3). The diol **10** was then coupled to either 2-chloromethylquinoline (for **4**) or 5-fluoro-2-chloromethylbenzothiazole[15] (for **5**) to yield the racemate **11** (the minor and undesirable *trans* isomer was removed by chromatography). Compound **11** was then resolved by ester coupling with R-(-)-O-acetyl mandelic acid (for **4**) or t-BOC-D-tryptophan (for **5**). After column chromatography to separate diastereomers **12**, hydrolysis of the chiral ester yielded the desired products **4** or **5**. CP-80,798 **4** and CP-85,958 **5** have the absolute configurations indicated, as well as opposite rotations as determined from x-ray crystal structures of both compounds (CP-80,798 is the (-) enantiomer and CP-85,958 is the (+) enantiomer).

Scheme I



	Ar =	Het =	R =
CP-80,798			
CP-85,958			

R = Me (H for the last step)

In summary, the discovery of two clinical candidates for the treatment of asthma has been briefly described, starting from REV-5901. The first of these candidates is a quinoline chromanol with a balanced 5-LOI/LTD_4-A profile, while the second is a benzothiazole chromanol with potent LTD_4 antagonist activity. Although neither of these candidates is currently under development, we are continuing our efforts to develop efficacious agents for the treatment of asthma. Full pharmacology papers on CP-80,798 and CP-85,958 will be reported shortly.

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(*Received in USA* 23 *March* 1995; *accepted* 23 *May* 1995)