Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 3577–3582

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

# DEVELOPMENT OF 2,2-DIMETHYLCHROMANOL CYSTEINYL $LT_1$ RECEPTOR ANTAGONISTS

R. J. Chambers*, G. W. Antognoli, J. B. Cheng, A. V. Kuperman, T. C. Liston, A. Marfat, B. S. Owens, J. S. Pillar, J. T. Shirley, J. W. Watson.

*Central Research Division, Pfizer Inc., Groton, CT 06340, USA*

Received 14 August 1998; accepted 27 October 1998

**Abstract.** A new series of $cysLT_1$ receptor antagonists represented by CP-288,886 (**7**) and CP-265,298 (**8**) were developed which are equipotent to clinical $cysLT_1$ receptor antagonists Zafirlukast (**1**) and Pranlukast (**2**).

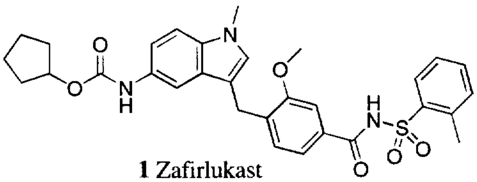

Leukotriene $D_4$ ($cysLT_1$) is a product of arachidonic acid metabolism which has been implicated as a key mediator in the progression of asthma.[1] Zafirlukast (**1**),[2] Pranlukast (**2**)[3] and Montelukast[4] are $cysLT_1$ receptor antagonists which have shown clinical efficacy in the treatment 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.[6,7] 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 $cysLT_1$ 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-position[9] 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 **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

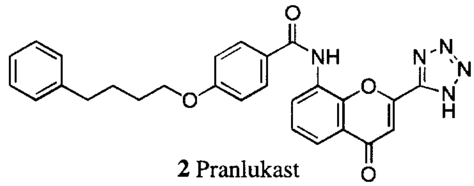
0960-894X/98/$ - see front matter 
*PII:* S0960-894X(98)00654-4

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 bioisostere[10] 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.

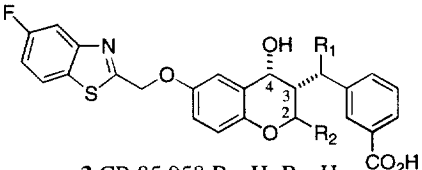
**Figure I**



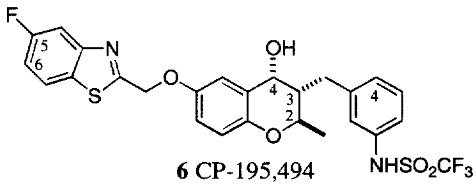

**1** Zafirlukast



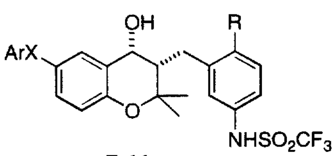

**2** Pranlukast



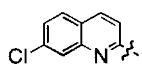
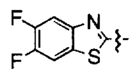
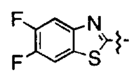
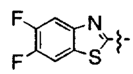
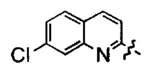

**3** CP-85,958 $R_1$=H, $R_2$=H
**4** $R_1$=H, $R_2$=OH
**5** $R_1$=OH, $R_2$=H




**6** CP-195,494

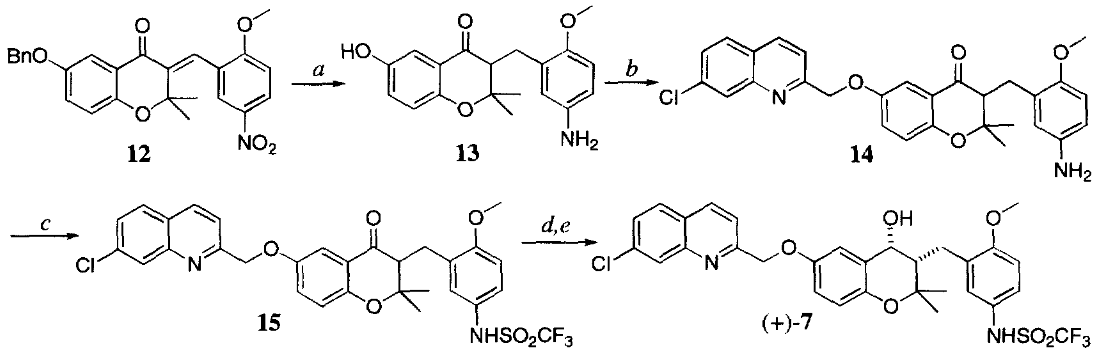



**7-11**

| Compound | Ar | R | X |
|---|---|---|---|
| **7** |  | $OCH_3$ | $CH_2O$ |
| **8** |  | $OCH_3$ | $CH_2O$ |
| **9** |  | H | $CH_2O$ |
| **10** |  | Cl | $CH_2O$ |
| **11** |  | $OCH_3$ | (E)-CH=CH |

We have previously shown in the development of **3** and **6** that the dextrorotatory enantiomer possessing *3S,4S* absolute stereochemistry provides optimal cys$LT_1$ 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-chloroquinoline[13] 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 $^{1}$H-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]

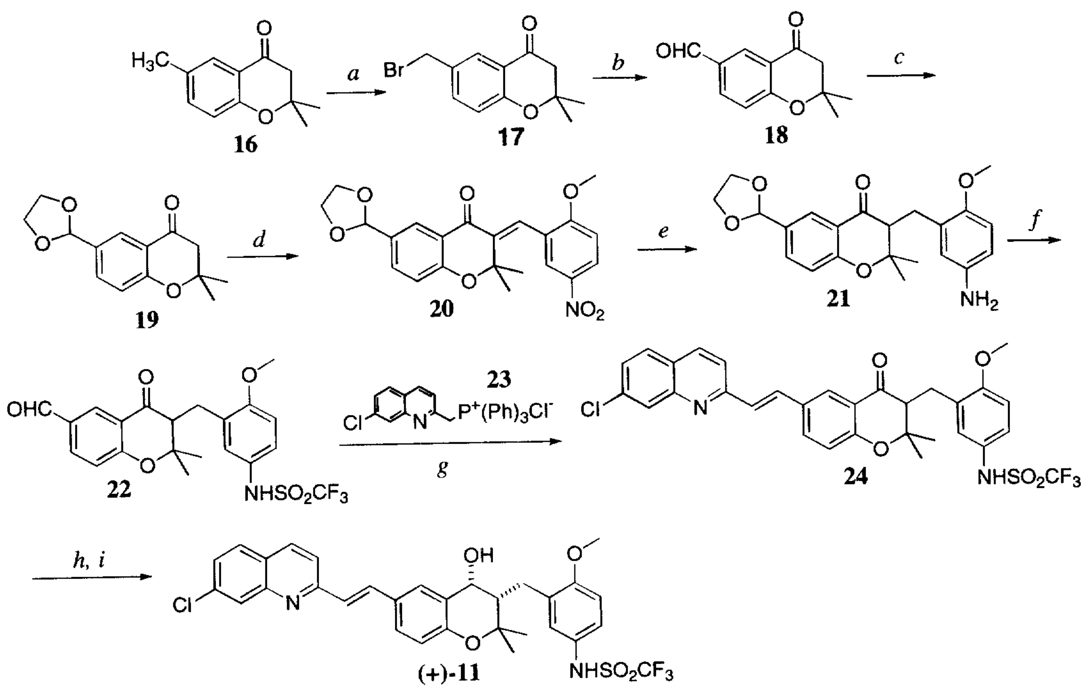
**Scheme I**




**Scheme I.** *(a) $H_2$, Pd/C, EtOAc/MeOH, 30 psi, rt; (b) i) NaH, DMF, 0°C, ii) 2-(chloromethyl)-7-chloro-quinoline; (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 oxidation[15] 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 condensation[12] of **19** with 2-methoxy-5-nitro-benzaldehyde[16] 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 **23**[17] occurred selectively to afford *trans* olefin **24** (92%) and subsequent reduction with Super Hydride® gave 3,4-*cis* alcohol (±)-**11** (29%). Resolution of (±)-**11** was accomplished by esterification with Boc-D-Tryptophan, isolation of the less polar diastereomer by chromatography and saponification to yield (+)-**11** (22%). The diastereomeric purity of the intermediate Boc-D-Tryptophan ester was judged to be > 95% by $^{1}$H-NMR and the absolute stereochemistry of (+)-**11** was tentatively assigned as *3S,4S* based on an analogous optical rotation to **3**.[5]

**Scheme II**




**Scheme II.** *(a) NBS, $(BzO)_2O$, $CCl_4$, reflux; (b) NMO, 3A sieves, $CH_3CN$, rt; (c) $HOCH_2CH_2OH$, p-TsOH, $PhCH_3$, 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 membranes[18] 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 leukotrienes[20] 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 pigs[25] with the same order of potency as **1-3** and **6** (Table I).

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

| Compound | $cysLT_1$ Binding Ki (μM) ± s.d. (n) | $Ca^{+2}$ mobilization U937 cells $IC_{50}$ (μM) ± s.d. (n) | guinea pig airway obstruction (OA) % inh. @ 1 mg/kg ± 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) |

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.

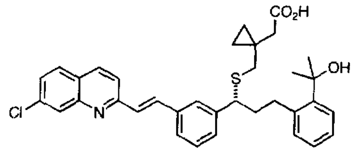
**Table II.** Comparative intravenous rat pharmacokinetics of **3**, **7** and **8**.

| | **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 |

In conclusion, analogs **7** (CP-288,886) and **8** (CP-265,298) were identified as optimized antagonists of the $cysLT_1$ receptor which have *in vitro* and *in vivo* potency the same order of magnitude as clinical $cysLT_1$ receptor antagonists Zafirlukast (**1**), Pranlukast (**2**) and show improved pharmacokinetics in rats over that of **3**.

## References and Notes


1. O'Byrne, P. M.; *Ann. N. Y. Acad. Sci.* **1994**, *744*, 251.
2. Suissa, S.; Dennis, R.; Ernst, P.; Sheehy, O.; Wood-Dauphinee, S. *Ann. Inter. Med.* **1997**, *126*, 177.
3. Hamilton, A.; Faiferman, I.; Stober, P.; Watson, R. M.; O'Byrne, P. M. *J. Allergy Clin. Immunol.* **1998**; *102*, 177.
4. Montelukast is the third cysLT$_1$ receptor antagonist which has recently shown clinical efficacy in the treatment of asthma; Markham, A.; Faulds, D. *Drugs* **1998**; *56*, 251.



Montelukast

5. Andrews, E. G.; Antognoli, G. W.; Breslow, R.; Carta, M. P.; Carty, T. J.; Chambers, R. J.; Cheng, J. B.; Cohan, V. L.; Collins, J. L.; Damon, D. B.; Delehunt, J.; Eggler, J. F.; Eskra, J. D.; Freiert, K. W.; Hada, W. A. Marfat, A.; Masamune, H.; Melvin, L. S.; Mularski, C. J.; Naclerio, B.A.; Pazoles, C. J.; Pillar, J. S.; Rappach, L. A.; Reiche, P.; Rusek, F. W.; Sherman, H.; Shirley, J. T.; Sweeney, F. J.; Tickner, J. T.; Watson, J. W.; Wright, C. F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1365.
6. Miki, T.; Hiraga, K.; Masuya, H.; Asako, T.; Fujii, S.; Kawai, K.; Kikuchi, K.; Shintani, S.; Yamazaki, M. *Chem. Pharm. Bull.* **1974**, *22*,1439.
7. El-Sedawy, A. I.; Hattori, M.; Kobashi, K.; Namba, T. *Chem. Pharm. Bull.* **1989**, *37*, 2435.
8. Chambers, R. J.; Antognoli, G. W.; Cheng, J. B.; Marfat, A.; Pillar, J. S.; Shirley, J. T.; Watson, J. W. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1791.
9. Fouda, H. G.; Lukaszewicz, J.; Clark, D. A.; Hulin, B. *Xenobiotica* **1991**; 21, 925.
10. Marfat, A.; Chambers, R.; Cheng, J.; Cooper, K.; Damon, D.; Delehunt, J.; Eggler, J.; Masamune, H.; Melvin, L.; Watson, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1377.
11. Labelle, M.; Prasit, P.; Belley, M.; Blouin, M.; Champion, E.; Charette, L.; DeLuca, J. G.; Dufresne, C.; Frenette, R.; Gauthier, J. Y.; Grimm, E.; Grossman, S. J.; Guay, D.; Herold, E. G.; Jones, T. R.; Lau, C. K.; Leblanc, Y.; Leger, S.; Lord, A.; McAuliffe, M.; McFarlane, C.; Masson, P.; Metters, K. M.; Ouimet, N.; Patrick, D. H.; Perrier, H.; Pickett, C. B.; Piechuta, H.; Roy, P.; Williams, H.; Wang, Z.; Xiang, Y. B.; Zamboni, R. J.; Ford-Hutchinson, A. W.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1141.
12. Chambers, R. J.; Marfat, A. *J. Heterocyclic Chem.* **1995**, *32*, 1401.
13. Larsen, R. D.; Corley, E. G.; King, A. O.; Carroll, J. D.; Davis, P.; Vehoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y. *J. Org. Chem.* **1996**, *61*, 3398.
14. Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846.
15. Griffith, W. P.; Jolliffe, J. M.; Ley, S. V.; Springhorn, K. F.; Tiffin, P. D. *Syn. Comm.* **1992**, *22*, 1967.
16. Rydon, H. N.; Siddappa, S. *J. Chem. Soc.* **1951**, 2462.
17. Young, R. N.; Gauthier, J. Y.; Therien, M.; Zamboni, R. *Heterocycles* **1989**, *28*, 967.
18. Cheng, J. B.; Lang, D.; Bewtra, A.; Townley, R. G. *J. Pharm. Exp. Ther.* **1985**, *232*, 80.
19. Frey, E.; Nicholson, D. W.; Metters, K. M. *Eur. J. Pharmacol.* **1993**, *244*, 239.
20. Wong, A.; Cook, M. N.; Foley, J. J.; Sarau, H. M.; Marshall, P.; Hwang, S. M. *Biochemistry* **1991**, *30*, 9346.
21. Oliva, D.; Accomazzo, M. R.; Giovanazzi, S.; Nicosia, S. *J. Pharm. Exp. Ther.* **1994**, *268*, 159.
22. Winkler, J. D.; Sarau, H. M.; Foley, J. J.; Crooke, S. T. *J. Pharm. Exp. Ther.* **1988**, *247*, 54.
23. Krell, R. D.; Aharony, D.; Buckner, C. K.; Keith, R. A.; Kusner, E. J.; Snyder, D. W.; Bernstein, P. R.; Matassa, V. G.; Yee, Y. K.; Brown, F. J. *Am. Rev. Respir. Dis.* **1990**, *411*, 978.
24. Nakagawa, N.; Obata, T.; Kobayashi, T.; Okada, Y.; Nambu, F.; Terawaki, T.; Aishita, H. *Japan. J. Pharmacol.* **1992**, *60*, 217.
25. Watson, J.W.; Conklyn, M.; Showell, H. J. *Am. Rev. Respir. Dis.* **1990**, *142*, 1093.