Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 1791–1796

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

DEVELOPMENT OF NEW CHROMANOL ANTAGONISTS OF LEUKOTRIENE D_4

R. J. Chambers,* G. W. Antognoli, J. B. Cheng, A. Marfat, J. S. Pillar, J. T. Shirley, and J. W. Watson

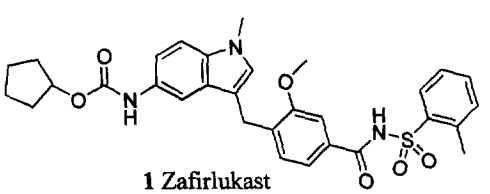
Central Research Division, Pfizer Inc., Groton, CT 06340, U.S.A.

Received 10 March 1998; accepted 4 May 1998

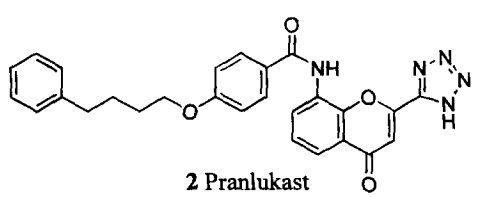
Abstract. By addressing the issues of potency and metabolism in **3**, a new series of LTD_4 antagonists represented by **(+)-26** was developed which is equipotent to clinical LTD_4 antagonists Zafirlukast (**1**) and Pranlukast (**2**).

Leukotriene D_4 (LTD_4) is a product of arachadonic acid metabolism and has been implicated as a key mediator in the progression of asthma.[1] Zafirlukast (**1**) and Pranlukast (**2**) are antagonists of LTD_4 which have shown clinical efficacy in the treatment of asthma thus validating LTD_4 as a therapeutic target (Figure I).[2,3] We have described the discovery of CP-85,958 (**3**), a potent antagonist of LTD_4 whose clinical evaluation was discontinued due to liver toxicity in monkeys.[4] 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**. We hypothesized 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.[5,6] We reasoned that the toxicity in **3** may be avoided by both hindering the formation of lactol **4** with the introduction of a methyl group into the 2-position and by improving potency which would allow for lower efficacious exposure. Synthetically, introduction of a methyl group into the 2-position of **3** would give rise to a third chiral center for which the optimal stereochemical relationship for antagonism of the LTD_4 receptor was unknown. With this in mind we prepared the relative stereoisomers of the 2-methyl analog of **3** (Scheme I).

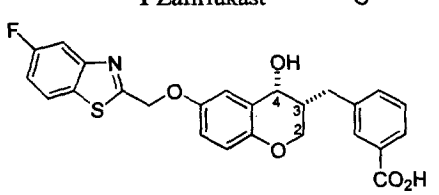
Figure I



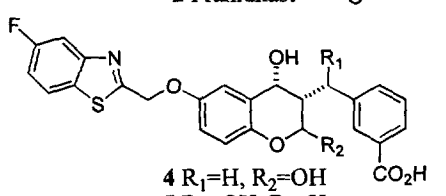
1 Zafirlukast



2 Pranlukast



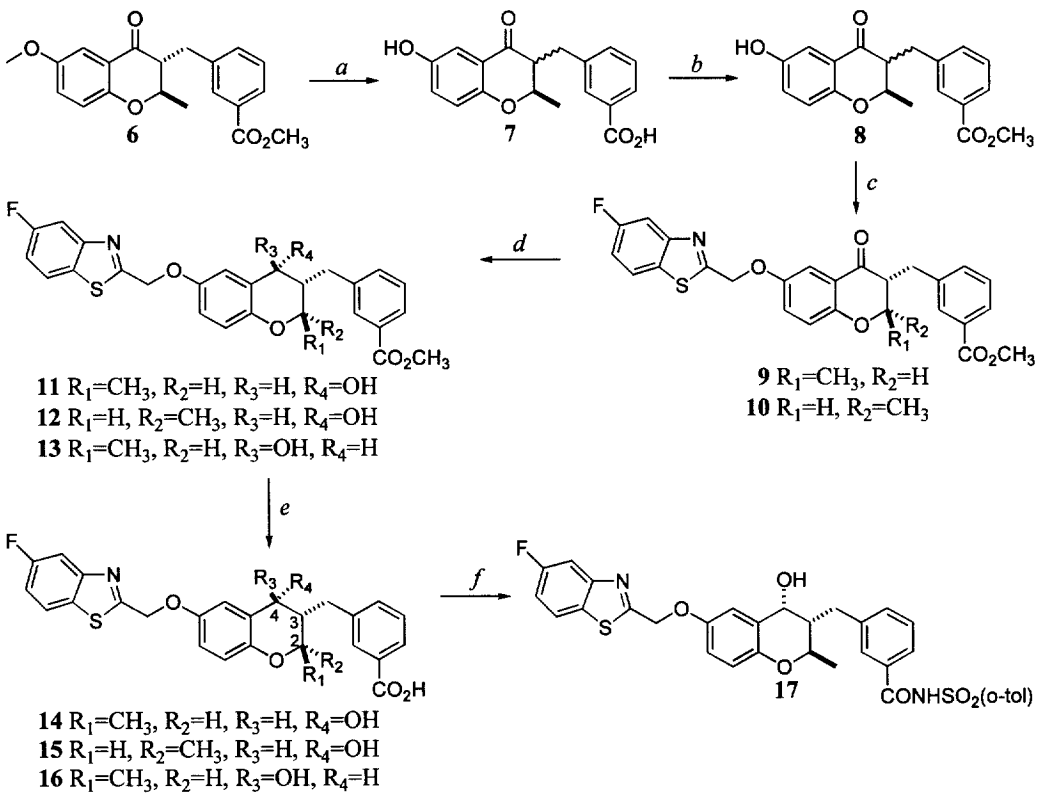
3 CP-85,958



4 R_1=H, R_2=OH
5 R_1=OH, R_2=H

0960-894X/98/$19.00
PII: S0960-894X(98)00273-X

Scheme I



Reagents: *(a) 48% HBr, AcOH, reflux; (b) $(CH_3)_2SO_4$, K_2CO_3, DMF, rt; (c) 2-(chloromethyl)-5-fluorobenzothiazole, K_2CO_3, DMF, rt; (d) $NaBH_4$, $CeCl_3$, MeOH/THF, -50°C; (e) 1 N NaOH, MeOH, reflux; (f) o-toluenesulfonamide, EDAC, DMAP, CH_2Cl_2, rt.*

Demethylation of achiral 2,3-*trans* keto ester **6**[7] with 48% hydrobromic acid occurred with concomitant epimerization and ester hydrolysis to give carboxylic acid **7** (58%) (Scheme I). Esterification of **7** with dimethyl sulfate yielded methyl ester **8** (85%). Alkylation of **8** with 2-(chloromethyl)-5-fluorobenzothiazole[8] afforded a mixture 2,3-*trans* ketone **9** (42%) and 2,3-*cis* ketone **10** (26%) which were separated by chromatography. Reduction of **9** with sodium borohydride in the presence of cerium (III) chloride yielded a mixture of 3,4-*cis* alcohol **11** (45%) and 3,4-*trans* alcohol **13** (29%) which were separated by chromatography. Reduction of **10** with sodium borohydride in the presence of cerium (III) chloride gave exclusively 3,4-*cis* alcohol **12** (82%). Interestingly, the 2β methyl group in **9** induces sufficient steric hindrance to β hydride attack to afford a mixture of alcohols **11** and **13**, whereas the 2α methyl group in **10** offers no steric hindrance to β hydride attack, giving rise to alcohol **12** as the sole stereoisomer. Saponification of alcohols **11**, **12**, and **13** with sodium hydroxide

yielded upon acidification, carboxylic acids **14** (52%), **15** (54%), and **16** (43%), respectively. Coupling of **14** with *o*-toluenesulfonamide gave sulfonamide **17** (53%).

Table I. In vitro LTD_4 receptor antagonism

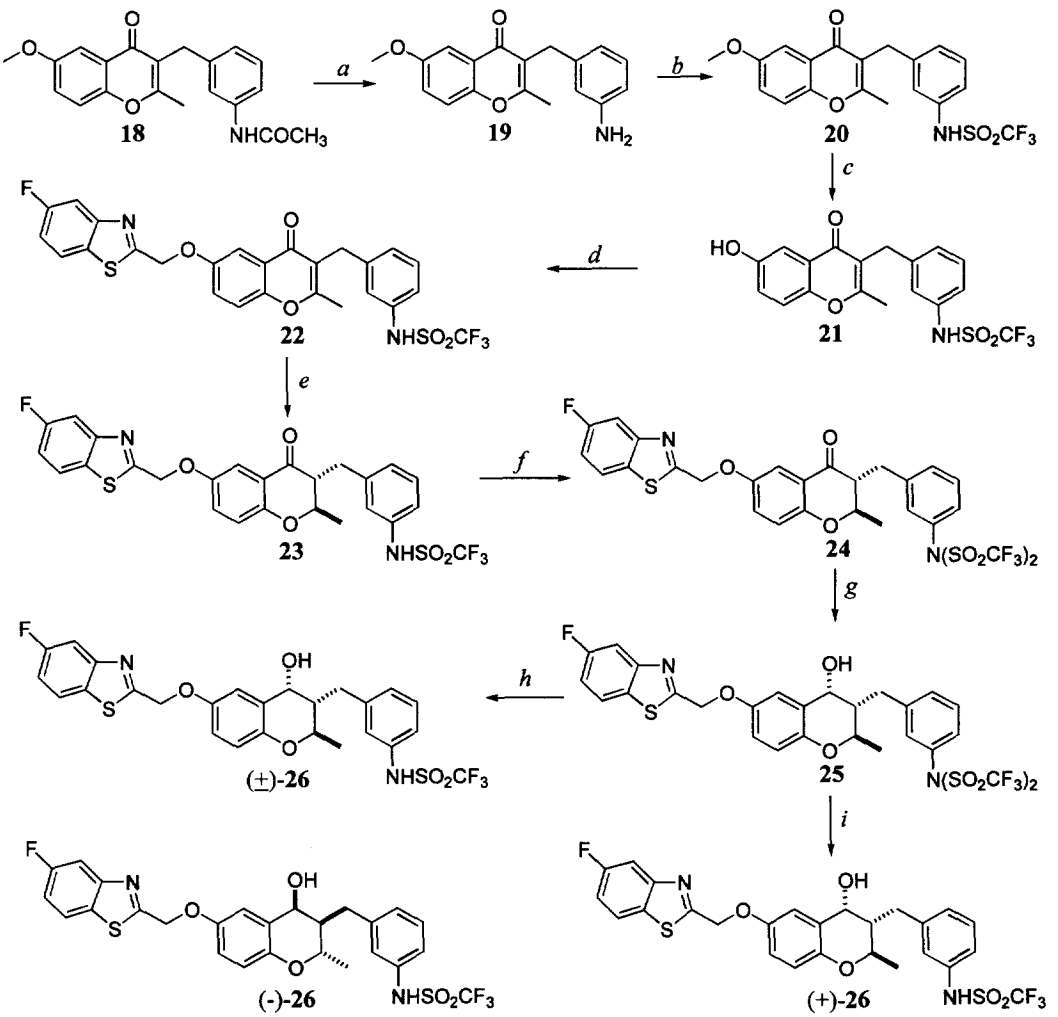
Compound	LTD_4 Binding K_i (μM) ± s.d. (n)	Compound	LTD_4 Binding K_i (μM) ± s.d. (n)
1	0.002 ± 0.0008 (9)	**16**	0.434 (1)
2	0.0008 ± 0.0003 (5)	**17**	0.003 (1)
3	0.014 ± 0.0078 (118)	**26**	0.002 (1)
14	0.027 (1)	(+)-**26**	0.0007 (1)
15	0.092 (1)	(–)-**26**	0.019 (1)

Analogs were evaluated for their ability to antagonize LTD_4 receptors isolated from guinea pig lung membranes since they are readily available and there is a high correlation to LTD_4 receptors isolated from human lung membranes.[9,10] The 2,3-*trans* 3,4-*cis* stereochemistry in **14** proved to be the optimal stereochemistry for LTD_4 receptor antagonism (Table I). Having addressed the issue of metabolism, we next turned our attention towards improving the potency of **14**. In the development of **1** it was found that replacement of a carboxylic acid with an o-tolylsulfonamide lead to a dramatic increase in LTD_4 receptor antagonism.[11] Likewise, replacement of the carboxylic acid in **14** with an *o*-tolylsulfonamide gave **17** which showed an order of magnitude increase in potency. Encouraged by this result, we looked for other replacements for the carboxylic acid in **14** and noted that trifluoromethylsulfonamides have been shown to be a bioisostere for a carboxylic acid.[12] With this in mind, we set out to prepare analogs in which the carboxylic acid in **14** is replaced with a trifluoromethylsulfonamide (Scheme II).

Acidic hydrolysis of achiral amide **18**[7] gave amine **19** (96%) which was treated with triflic anhydride followed by basic hydrolysis to afford sulfonamide **20** (85%). Demethylation of **20** with hydrobromic acid gave phenol **21** (80%) which was alkylated with 2-(chloromethyl)-5-fluorobenzothiazole to yield enone **22** (88%). We have previously shown that conjugate reduction of **18** with L-Selectride® followed by quenching at –78 °C affords exclusively the 2,3-*trans* stereoisomer.[7] Likewise, conjugate reduction of **22** with L-Selectride® gave 2,3-*trans* ketone **23** (48%). Reduction of **23** with sodium borohydride in the presence cerium (III) chloride gave a mixture of the 3,4 *cis* alcohol **26** and the 3,4 *trans* alcohol which could not be purified by column chromatography due to their acidic and polar properties. Alternatively, treatment of **23** with triflic anhydride yielded bis-sulfonamide **24** (44%) which underwent reduction with sodium borohydride in the presence of cerium (III) chloride to afford a mixture of isomeric alcohols from which the desired 3,4-*cis* alcohol **25** was isolated by chromatography (50%). Subsequent basic hydrolysis of **25** yielded sulfonamide (±)-**26** (70%).

Resolution of (±)-**26** was achieved by esterification of **25** with Boc-D-Tryptophan, chromatographic separation of diastereomers and subsequent hydrolysis to afford (+)-**26** (18%) and (–)-**26** (22%). The diastereomeric purity of the intermediate Boc-D-tryptophan esters were determined to be >95% by ^{1}H NMR and the absolute configuration of (+)-**26** was tentatively assigned to be 2*R*,3*S*,4*S* based on an analogous optical rotation to **3**[4].

Scheme II



Reagents: *(a) 6 N HCl, MeOH, reflux; (b) i) Tf_2O, TEA, CH_2Cl_2, 0°C, ii) 2 N NaOH, MeOH, rt; (c) 48% HBr, AcOH, reflux; (d) 2-(chloromethyl)-5-fluorobenzothiazole, K_2CO_3, DMF, rt; (e) L-Selectride®, THF, -78°C; (f) Tf_2O, TEA, CH_2Cl_2, 0°C; (g) $NaBH_4$, $CeCl_3$, MeOH/THF, -50°C; (h) LiOH, THF/H_2O, rt; (i) i) Boc-D-Trp-OH, EDAC, DMAP, CH_2Cl_2, rt, ii) LiOH, THF/H_2O, rt.*

Replacement of the carboxylic acid in **14** with a trifluoromethylsulfonamide gave **26** with an order of magnitude improvement in potency (Table I). Resolution of **26** gave the dextrotatory enantiomer (+)-**26** which was an order of magnitude more potent than the levorotatory enantiomer (–)-**26**. The elevation of cytosolic calcium has been shown to correlate with both LTD_4 biosynthesis and contraction of guinea pig ileum and that antagonists of LTD_4 block these events.[13,14] Analog (+)-**26** blocked the influx of calcium in human U937 cells with similar potency as **1** and **2** and was over three orders of magnitude more potent than **3** (Table II).[15] Both **1** and **2** have been shown to be efficacious in guinea pig models of asthma suggesting that such models may be predictive of clinical efficacy in humans.[16,17] Analog (+)-**26** blocked antigen induced airway obstruction in guinea pigs having the same order of potency as **1** and **2** and was an order of magnitude more potent than **3** (Table II).[18]

Table II. Comparative LTD_4 functional activity of (+)-**26**

	Ca^{+2} mobilization U937 cells	**guinea pig airway obstruction (OA)**
Compound	**IC_{50} μM ± s.d. (n)**	**ED_{50} (mg/kg) ± s.d. @ h po (n)**
1	0.001 ± 0.0004 (55)	0.9 ± 0.42 @ 2.0 h (2)
2	0.001 ± 0.0006 (2)	1.5 @1.0 h (1)
3	0.310 ± 0.0151 (3)	10.2 ± 2.5 @ 2.0 h (3)
(+)-**26**	0.008 (1)	0.5 @ 1.0 h (1)

By addressing issues of metabolism and potency about lead structure CP-85,958 (**3**), we have identified analog (+)-**26** which shows an order of magnitude improvement in potency over **3** and equivalent potency to Zafirlukast (**1**) and Pranlukast (**2**). Analog (+)-**26** (CP-195,494) can be viewed as a template allowing for further optimization of potency and metabolic stability leading to improved antagonists of LTD_4 for the treatment of asthma.

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**, *6*, 177.

3. Grossman, J.; Bronsky, E.; Busse, W.; Montanaro, A.; Southern, L.; Tinkelman, D.; Dubb, J.; Faiferman, I. *J. Allergy Clin. Immunol.* **1995**, *95*, 352.

4. 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.

5. Miki, T.; Hiraga, K.; Masuya, H.; Asako, T.; Fujii, S.; Kawai, K.; Kikuchi, K.; Shintani, S.; Yamazaki, M. *Chem. Pharm. Bull.* **1974**, *22*, 1439.
6. El-Sedawy, A. I.; Hattori, M.; Kobashi, K.; Namba, T. *Chem. Pharm. Bull.* **1989**, *37*, 2435.
7. Chambers, R. J.; Marfat, A. *J. Heterocyclic. Chem.* **1994**, *31*, 1401.
8. Mylari, B. L.; Scott, P. A.; Zembrowski, W. J. *Synth. Commun.* **1989**, *19*, 2921.
9. Cheng, J. B.; Lang, D.; Bewtra, A.; Townley, R. G. *J. Pharm. Exp. Ther.* **1985**, *232*, 80.
10. Frey, E.; Nicholson, D. W.; Metters, K. M. *Eur. J. Pharmacol.* **1993**, *244*, 239.
11. Matassa, V. G.; Maduskiue, T. P.; Shapiro, H. S.; Hesp, B.; Snyder, D. W.; Aharony, D.; Krell, R. D.; Keith, R. A. *J. Med. Chem.* **1990**, *33*, 1781.
12. Duncia, J. V.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Price, W. A.; Wells, G. J.; Wong, P. C.; Calabrese, J. C.; Timmermans, P. M. W. M. *J. Med. Chem.* **1990**, *33*, 1312.
13. Wong, A.; Cook, M. N.; Foley, J. J.; Sarau, H. M.; Marshall, P.; Hwang, S. M. *Biochemistry* **1991**, *30*, 9346.
14. Oliva, D.; Accomazzo, M. R.; Giovanazzi, S.; Nicosia, S. *J. Pharm. Exp. Ther.* **1994**, *268*, 159.
15. Winkler, J. D.; Sarau, H. M.; Foley, J. J.; Crooke, S. T. *J. Pharm. Exp. Ther.* **1988**, *247*, 54.
16. 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.
17. Nakagawa, N.; Obata, T.; Kobayashi, T.; Okada, Y.; Nambu, F.; Terawaki, T.; Aishita, H. *Japan. J. Pharmacol.* **1992**, *60*, 217.
18. Watson, J. W.; Conklyn, M.; Showell, H. J. *Am. Rev. Respir. Dis.* **1990**, *142*, 1093.