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EVOLUTION OF A SERIES OF NON-QUINOLINE LEUKOTRIENE D_4 RECEPTOR ANTAGONIST; SYNTHESIS AND SAR OF BENZOTHIAZOLES AND THIAZOLES SUBSTITUTED BENZYL ALCOHOLS AS POTENT LTD_4 ANTAGONISTS

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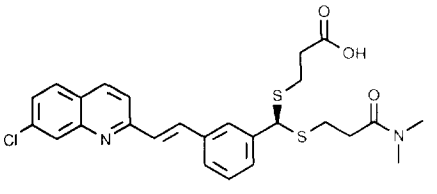
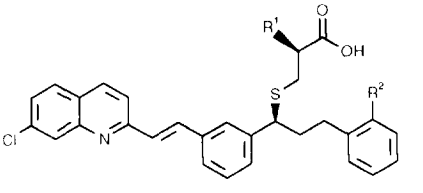
Abstract: Replacement of the quinoline pharmacophore of verlukast by alkylthiazoles and benzothiazoles has lead to the discovery of a new series of potent and orally active LTD_4 receptor antagonists. The synthesis and structure activity relationships of this series of compounds are described.

Peptidoleukotrienes (LTC_4, LTD_4, LTE_4) have been implicated in the pathology of bronchial asthma. However, the precise role of leukotrienes became well defined only with the availability of a number of potent and orally active leukotriene D_4 receptor antagonists for clinical evaluation. Clinical studies with verlukast (**1**) (MK-0679)[1] as well as other potent LTD_4 antagonists such as ICI-204,219,[2] SK&F-104,353,[3] ONO-1078,[4] and R-12525[5] have shown that LTD_4 receptor antagonists can inhibit antigen- and exercise-induced bronchoconstriction in asthmatics, block airway obstruction induced by aspirin in aspirin-intolerant asthmatics; induce bronchodilatation, improve FEV_1 and symptom scores, and reduce β-agonist usage in patients with moderate, stable asthma.[1-4] Selective and potent antagonists of the peptidoleukotrienes thus appear to represent an effective new class of therapeutic agents for the treatment of asthma.

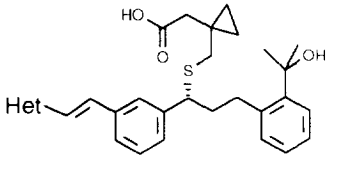


1 (verlukast)

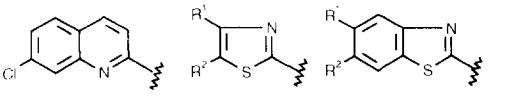


2 (L-695,392) R^1 = Me, R^2 = $C(O)CH_3$

3 (L-695,499) R^1 = Et, R^2 = $C(CH_3)_2OH$



Het =



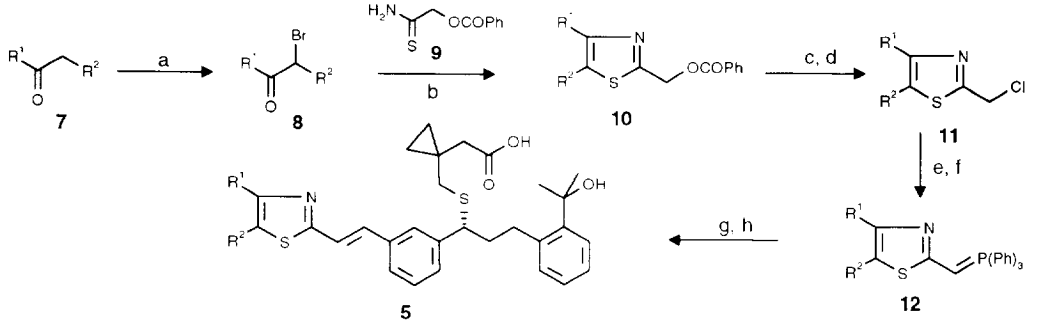
4 (montelukast) **5** **6**

The demonstration of effectiveness of verlukast in the treatment of asthmatic patents has prompted us to look for more potent and structurally different analogs. Further elaboration of the verlukast structure has lead to the identification of L-699,392 (**2**),[6] L-695,499 (**3**)[7] and montelukast (**4**) (MK-0476).[8] In montelukast, several potential sites of metabolism of verlukast have been replaced. For example, the thiopropionic acid was replaced by the thiomethylcyclopropaneacetic acid and the amide by a tertiary benzyl alcohol. These modifications conferred both greater metabolic stability and higher intrinsic potency. The styryl double bond, which was considered to be a potential liability due to the extended chromophore, had also been studied extensively. However, none of the alternatives investigated was found to be superior.[7] Attempts to replace the quinoline moiety of verlukast with other heterocycles have met with little success in the past. However, with the recent optimization of the two polar chains as exemplified by montelukast, it was found possible to replace the quinoline with other nitrogen containing heterocycles without loss of activity. Herein, we report the development of two series of thiazole and benzothiazole analogs (**5** and **6**) of montelukast which lead to the identification of L-708,734 (**6c**) as an optimally potent and orally active leukotriene D_4 receptor antagonist.

Chemistry: The general syntheses of both the thiazole and benzothiazole benzylalcohols **5** and **6** are outlined in Schemes 1 and 2. Both involve, as the key step, the coupling of the corresponding 2-thiazolo- or 2-benzothiazolomethylene triphenylphosphoranes **12** and **14** with the aldehyde **26**. Various substituted 2-thiazolomethylene triphenylphosphorane were prepared from ethanone **7** (Scheme 1). Bromination of **7** with either bromine in methanol (for aliphatic ketones) or pyridinium bromide perbromide in acetic acid (for aryl ketones) gave the α-bromoketone **8**. Reaction of bromoketone **8** with 2-benzoyloxythioacetamide **9** in pyridine[9] gave thiazole **10**. Hydrolysis of the benzoate **10** followed by treatment of the resulting alcohol with thionyl chloride resulted in chloride **11**. Treatment of chloride **11** with triphenylphosphine in acetonitrile gave the corresponding phosphonium salt which when treated with *n*-butyllithium afforded the phosphorane **12**. Condensation of **12** with **26**, followed by saponification yielded compound **5**. Similarly, various substituted 2-methylbenzothiazoles were brominated with N-bromosuccinimide in CCl_4 in the presence of two 500 W flood lamps. The resulting bromide was converted to the phosphorane **14** which was then condensed with **26** to give, after saponification, compound **6** (Scheme 2).

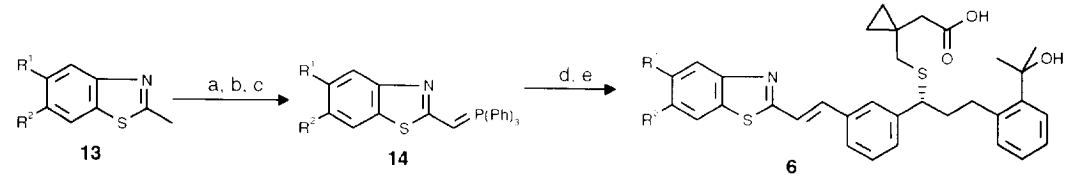
The aldehyde **26** was prepared from diethyl 1,1-cyclopropane dicarboxylate **15** and isophthaldehyde **20** (Scheme 3). Reduction of the diester **15** with diborane in THF followed by treatment of the resulting alcohol with thionyl chloride gave the cyclic sulfite **16**. Sodium cyanide opening of the cyclic sulfite gave the cyano alcohol **17**. The alcohol was converted to the corresponding mesylate which was then displaced by potassium thioacetate to give the nitrile thioacetate **18**. Acid hydrolysis of both the nitrile and the thioacetate in methanol gave the thiol-ester **19**. Isophthaldehyde **20** was selectively reduced to the monoalcohol with sodium borohydride which was then protected as a tetrahydropyranyl ether **21**. Vinyl Grignard addition to aldehyde **21** gave the allylic alcohol **22**

Scheme 1



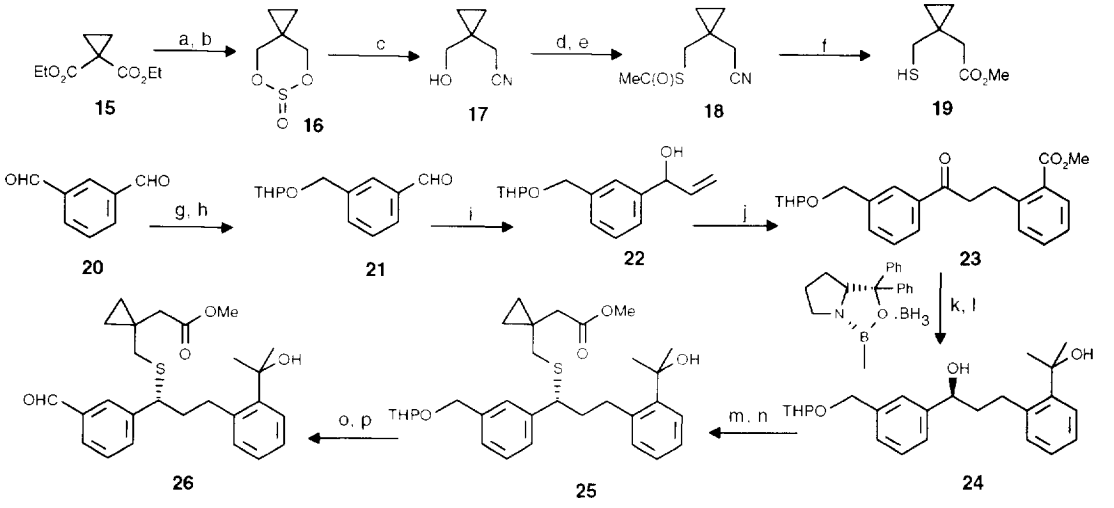
(a) Br_2, NaOH or pyridine•HBr_3, HOAc; (b) EtOH, Δ; (c) NaOH, EtOH; (d) $SOCl_2$, Δ; (e) Ph_3P, CH_3CN, Δ; (f) n-BuLi, THF, -78°C; (g) **26**; (h) NaOH, EtOH

Scheme 2



(a) NBS, AIBN, hv; (b) Ph_3P, CH_3CN, Δ; (c) n-BuLi, THF, -78 °C; (d) **26**; (e) NaOH, EtOH

Scheme 3



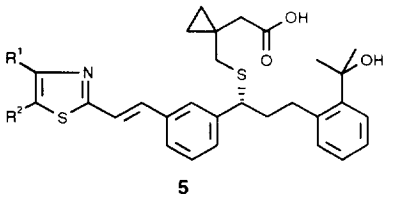
(a) BH_3•THF, THF, Δ, 6 h; (b) $SOCl_2$, CH_2Cl_2; (c) NaCN, DMF, 90 °C, 3h; (d) MsCl, Et_3N; (e) $KSCOCH_3$; (f) H_2SO_4, MeOH, Δ, 20 h; (g) $NaBH_4$, EtOH, 0 °C; (h) DHP, CH_2Cl_2; (i) CH_2=$CHMgBr$, $PhCH_3$, 0 °C; (j) 2-BrPhCO_2Me, $Pd(OAc)_2$, LiCl, LiOAc•$2H_2O$, n-$Bu_4N^+Cl^-$, DMF, 100 °C; (k) THF, -45 °C; (l) MeMgCl, $CeCl_3$, THF, -5 °C; (m) MsCl, (i-pr)$_2$EtN, CH_3CN-DMF, -42 °C; (n) KO(t-Bu), **19**; (o) PPTS, MeOH, 55 °C, 3 h; (p) MnO_2, EtOAc, 50 °C

which was then coupled to methyl 2-bromobenzoate in the presence of $Pd(OAc)_2$ to afford ketoester **23**. The ketone moiety of compound **23** was enantioselectively reduced with tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrolo[1,2-c][1,3,2]oxazoborole-borane adduct [10] to the corresponding (S)-hydroxybenzoate which was then treated with excess methyl Grignard to give the diol **24**. The secondary alcohol was selectively mesylated and reacted with the potassium salt of the thioester **19** giving the thioether **25** with the (R) configuration. Treatment of **25** with pyridinium *p*-toluenesulfonate (PPTS) in methanol followed by oxidation of the resulting alcohol with manganese dioxide gave the key intermediate aldehyde **26**.[11]

Results and discussions: The *in vitro* LTD_4 binding affinities for compounds **5** and **6** were determined using guinea-pig lung membrane[12] and the results are summarized in Tables 1 and 2 respectively. The unsubstituted thiazole (**5a**) is much less potent (IC_{50} = 381 nM) than verlukast (IC_{50} = 3.9 nM), the standard for our comparison (Table 1). In general, thiazoles substituted with a small alkyl or cycloalkyl group at the 4 position of the thiazole ring (**5b**-**5i**) are more potent than the corresponding 4-aryl substituted analogs. Among the aliphatic alkyl substituents, the ω-trifluoroisobutyl derivative (**5c**) is the most potent, whereas the larger phenylthiomethyl substituted compound (**5d**) suffers significant loss of potency. The 4-cyclobutyl substituted analog (**5g**) is optimal among the cycloalkyl substituents, and **5c** and **5g** are more potent than verlukast *in vitro*. Disubstituted thiazoles like **5j** and **5k** are less potent than the corresponding monosubstituted analog (**5b**). Replacing the Cl of **5j** by CH_3 (**5k**) lead to a surprising increase of 15-fold in potency. However, the cyclohexylthiazole (**5l**) and cyclopentylthiazole (**5m**) are as potent as verlukast. The 4-(4-fluorophenyl)thiazole (**5q**) is the most potent analog among the 4-aryl substituted thiazoles. However, there seems to be no correlation of activity with electronic effect of various substituents on the aryl ring. In contrast, the electronic effect of substituents on the fused benzene ring seems to play a significant role in the binding affinity of the benzothiazole series. The most electron deficient 5,6-difluorobenzothiazole (**6d**) is the most potent compound *in vitro* in this series with an IC_{50} = 0.8 nM *vs* 3.9 nM for verlukast.

Even though both the thiazole series and the benzothiazole series have compounds that are more potent than verlukast with IC_{50} < 1 nM *in vitro*, compounds in the benzothiazole series are generally superior *in vivo*. As a class, they have better bioavailability and pharmacokinetics, with slower clearance in general . The 5-fluoro-benzothiazole (**6c**) represents the compound with the best overall profile among the two series. Table 3 shows that compound **6c** (L-708,734) has an *in vitro* and *in vivo* profile similar to or better than verlukast and superior to **5b**, a representative compound of the thiazole series. At 0.03 mg/kg p.o. (4 h pretreatment), compound **6c** inhibits 73 % of the changes in airway resistance (R_L) and 100% of the reduction in dynamic compliance (C_{dyn}) induced by inhalation of LTD_4 in the concious squirrel monkey.[13] In conclusion, we have demonstrated that alkylthiazoles and benzothiazoles are effective heterocycle replacements for the quinoline function in LTD_4 antagonists such as montelukast. L-708,734 (**6c**), in particular is potent and orally effective in blocking LTD_4-induced bronchoconstriction in the squirrel monkey.

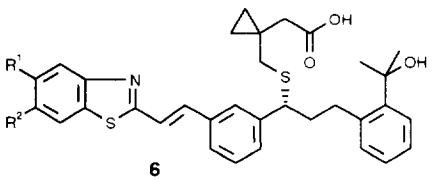
Table 1.



5

compd. #	R^1	R^2	IC_{50} (nM)[a]
5a	H	H	381
5b	$CH(CH_3)_2$	H	1.9 ± 1.4
5c	$CH(CH_3)(CH_2CF_3)$	H	0.7, 1.0
5d	$CH_2SC_6H_5$	H	42.2
5e	$C(CH_3)_3$	H	2.0, 3.3
5f	c-propyl	H	1.7, 3.3
5g	c-butyl	H	0.6, 0.5
5h	c-pentyl	H	1.4, 0.8
5i	c-hexyl	H	2.1 ± 1.0
5j	$CH(CH_3)_2$	Cl	170, 197
5k	$CH(CH_3)_2$	CH_3	12.8, 5.2
5l	$-(CH_2)_4-$		1.5 ± 0.4
5m	$-(CH_2)_3-$		3.0, 4.6
5o	C_6H_5	H	11.0, 6.7
5p	4-Cl-(C_6H_5)	H	79.3, 99.7
5q	4-F-(C_6H_5)	H	6.7, 15.4
5r	4-OCH_3-(C_6H_5)	H	98.7, 138
verlukast			3.9 ± 1.1

Table 2.



6

compd. #	R^1	R^2	IC_{50} (nM)[a]
6a	H	H	16.8 ± 14.3
6b	Cl	H	7.7, 6.0
6c	F	H	3.3 ± 3.7
6d	F	F	0.8 ± 0.3
6e	CF_3	H	7.5, 11.6
6f	H	OCH_3	47.6

Table 3

Compound	IC_{50} (nM)	pK_b[b]	Squirrel Monkey[c]			Liver wt.[d]	PEI[d]
5b	1.9 ± 1.4	9.1 ± 0.1	R_L = 40%	C_{dyn} = -8%	@ 0.03 mg/kg[e]	+ 9%	+ 62
6c (L-708,734)	3.3 ± 3.7	8.8 ± 0.2	R_L = 73%	C_{dyn} = 100%	@ 0.03 mg/kg[e]	+ 12%	+ 120
verlukast	3.9 ± 1.1	8.9	R_L = 59%	C_{dyn} = 56%	@ 0.1 mg/kg	0%	+ 65

a. Inhibition of [H^3]-LTD_4 binding on guinea-pig lung membranes. Values are either individual determinations or mean ± S.E.M.; b. Inhibition of LTD4-induced contraction of guinea-pig tracheal chains expressed as pK_b values; c. Inhibition of LTD_4-induced broncoconstriction in conscious squirrel monkey; d. Average of 4 male and 4 female mice percentage liver weight increase and peroxisomal enzyme induction (PEI) over control animals, after 4 days dosing at 400 mg/kg p.o. The fatty acyl Co-A oxidase activity increase is used as a measure of the PEI; e. Average of 2 monkeys.

References and notes:

1. a) Hendeles, L.; Davidson, D.; Blake, K.; Harman, E.; Cooper, R.; Margolskee, D. *J. Allergy Clin. Immunol.* **1990**, *85*, 197; b) Manning, P. J.; Watson, R. M.; Margolskee, D. J.; Williams, V. C.; Schwartz, J. I.; O'Byrne, P. M. *N. Engl. J Med.* **1990**, *323*, 1736; c) Margolskee, D.; Bodman, S.; Dockhorn, R.; Israel, E.; Kemp, J.; Mansmann, H.; Minotti, D. A.; Spector, S.; Stricker, W.; Tinkelman, D.; Townley, R.; Winder, J.; Williams, V. C. *J. Allergy Clin. Immunol.* **1991**, *87*, 309; d) Impens, N.; Reiss, T. F.; Teahan, J. A.; Desmet, M.; Rossing, T. H.; Shingo, S.; Ji, Z.; Schandevyl, W.; Verbesselt, R.; Dupont, A. G. *Am. Rev. Respir. Dis.* **1993**, *147*, 1442; e) Dahlén, B.; Kumlin, M.; Margolskee, D. J.; Larsson, C.; Blomqvist, H.; Williams, V. C.; Zetterstrom, O.; Dahlén, S.-E. *Eur. Respir. J.* **1993**, *6*, 1018; f) Dahlen, B.; Margolskee, D. J.; Zetterström, O; Dahlén, S.-E. *Thorax* **1993**, *48*, 1205; g) Lammers, J.-W.; Van Daele, P.; Van den Elshout, F. M.; Decramer, M.; Buntinx, A.; De Lepeleire, I.; Friedman, B. *Pulmonary Pharmacol.* **1992**, *5*, 121.

2. a) Findlay, S. R.; Easley, C. B.; Glass, M. P.; Barden, J. M. *J. Allergy Clin. Immunol.* **1990**, *85, (1), Supplement, 197, Abstract 215*; b) Taylor, I. K.; O'Shaughnessy, K. M.; Fuller, R. W.; Dollery, C. T. *Lancet* **1991**, *337*, 690; c) Hui, K. P.; Barnes, N. C. *Lancet* **1991**, *337*, 1062.

3. a) Smith, C.; Christie, P. E.; Lee, T. H. *J. Allergy Clin. Immunol.* **1991**, *87*, 139; b) Robuschi, M.; Fuccella, L. M.; Riva, E.; Vida, E.; Barnabe, R.; Rossi, M.; Gambaro, G.; Spagnotto, S.; Bianco, S. *Am. Rev. Respir. Dis.* **1991**, *143*, A642.

4. Nakagawa, T.; Mizushima, Y.; Ishii, A.; Nambu, F.; Motoishi, M.; Yui, Y.; Shida, T.; Miyamoto, T. *Adv. Prostaglandin Thromboxane Leukot. Res.* **1991**, *21a*, 465.

5. Wahedna, I.; Wisniewski, A. F.; Britton, J. R.; Tattersfield, A. E. *Am. Rev. Respir. Dis.* **1991**, *143*, A642.

6. Labelle, M.; Belley, M.; Champion, E.; Gordon, K.; Hoogsteen, K.; Jones, T. R.; Leblanc, Y.; Lord, A.; McAuliff, M.; McFarlane, C.; Masson, P.; Metters, K. M.; Nicoll-Griffith, D.; Ouimet, N.; Piechuta, H.; Rochette, C.; Sawyer, N.; Xiang, Y. B.; Yergey, J.; Ford-Hutchinson, A. W.; Pickett, C. B.; Zamboni, R. J.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1994**, 4, 463.

7. 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.; Lau, C. K.; Leblanc. Y.; Léger, 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.

8. Labelle, M.; Belley, M.; Gareau, Y.; Gauthier, J. Y.; Guay, D.; Gordon, R.; Grossman, S. G.; Jones, T. R.; Leblanc,Y.; McAuliffe, M.; McFarlane, C.; Masson, P.; Metters, K. M.; Ouimet, N.; Patrick, D. H.; Piechuta, H.; Rochette, C.; Sawyer, N.; Xiang, Y. B.; Pickett, C. B.; Ford-Hutchinson, A. W.; Zamboni, R. J.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1995**, 5, 283.

9. Brown, D. J.; Cook, A. H.; Heilbron, I. *J. C. S.* **1949**, *Part I-III*, S106.

10. a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925; c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861.

11. For full experimental details, see: Zamboni, R.; Lau, C. K.; Dufresne, C. World Patent applications 93/21168 and 93/21169, Oct. 28, 1993.

12. Pong, S. S.; DeHaven, R. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 7415.

13. McFarlane, C. S.; Hamel, R.; Ford-Hutchinson, A. W. *Agents Actions* **1987**, *22*, 63.

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