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DIARYL ETHER/CARBOXYLIC ACID DERIVATIVES OF LY255283: RECEPTOR ANTAGONISTS OF LEUKOTRIENE B_4

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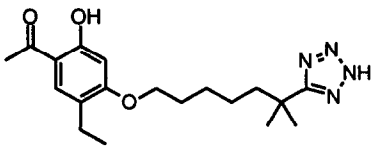
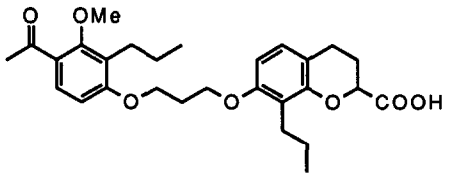
Abstract: The preparation and activity of a series of hydroxyacetophenone/diaryl ether LTB_4 receptor antagonists are described. The key acid-substituted diaryl ether moiety is discussed in relation to the spatial and functional group requirements of the LTB_4 receptor.

There is increasing evidence that the pro-inflammatory lipid LTB_4 may play an important, receptor-mediated, role in disease states ranging from asthma to inflammatory bowel disease (IBD).[1] The development of potent and specific antagonists[2] against LTB_4 is critical to elucidating its function in the initiation of inflammatory pathogenesis. Two recently developed LTB_4 receptor antagonists, LY255283[3] and SC-41930,[4] are hydroxyacetophenone-based



LY255283



SC-41930

structures that evolved from two previous series of LTD_4/LTE_4 antagonists. We became interested in synthesizing new acid components for LY255283 with a goal of improving binding affinity for the LTB_4 receptor. Examination of the acid-bearing scaffolding of SC41930 revealed a constrained structure in which the carboxyl group is directed out-of-plane relative to a chroman aromatic ring containing a secondary lipophilic group.[5] We reasoned that an acid-substituted diaryl ether moiety, similar to the chroman unit of SC-41930, would allow sufficient flexibility to enhance receptor binding. Accordingly, a short series of such diaryl ether units were synthesized and merged into the LY255283 hydroxyacetophenone structure to create a new series of antagonists.

Schemes I-III are representative of the chemistry used to prepare the target compounds. A classical Ullmann procedure[2j] was used to construct the diaryl ethers as shown for phenol **3** (Scheme I) in modest yields.[6] Appendage of an n-propyl side chain was accomplished either through direct alkylation (conversion of **1** to **2**), or Claisen rearrangement and reduction beginning with an allyloxy derivative (conversion of **5** to **7**).[2d] Phenol **8**, the appropriate acid

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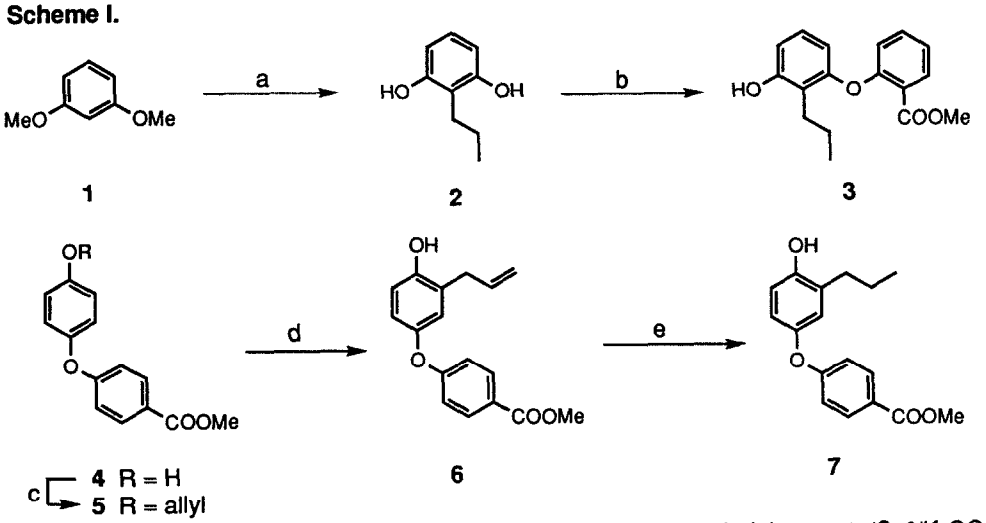
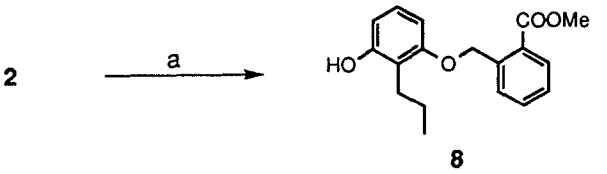
Scheme I.



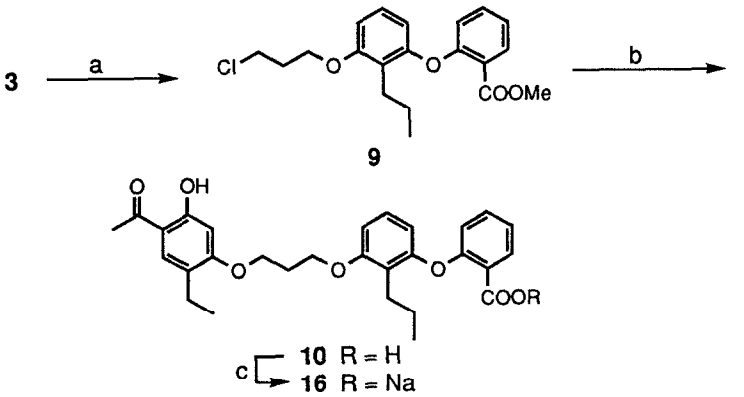
a) (i) n-BuLi/n-PrI/THF (90%), (ii) py-HCl/180 °C (96%); b) methyl 2-iodobenzoate/Cu°/K_2CO_3/py/reflux (36%); c) allyl iodide/K_2CO_3/2-butanone/DMSO (78%); d) neat/225 °C (83%); e) H_2/10% Pd(C)/MeOH (95%).

Scheme II.



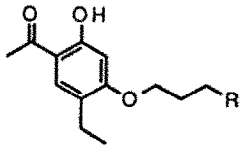
a) (i) NaH/DMF, (ii) methyl 2-(bromomethyl)benzoate (21%).

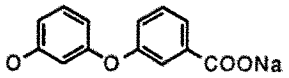
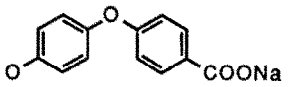
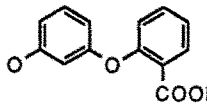
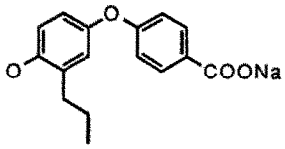
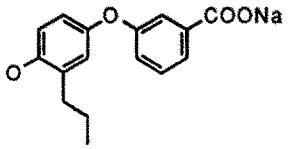
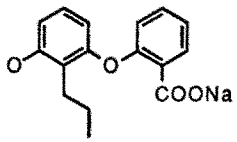
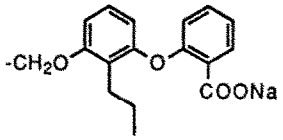
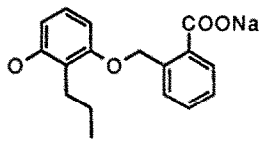
Scheme III.



a) 1-bromo-3-chloropropane/K_2CO_3/DMF (92%); b) 2,4-dihydroxy-5-ethylacetophenone/K_2CO_3/KI/2-butanone/DMSO (54%); c) aq. NaOH/THF/MeOH (70%).

Table I. Inhibition of Specific Binding of ^{3}H-LTB$_4$



Compound	R	Human Neutrophils (IC_{50}, nM)[8]	Guinea-pig Lung Membranes (K_i, nM)[9]
LY255283	--	85 ± 7.9[3]	77 ± 9.4
SC-41930	--	200[4b]	15 ± 3.0
11		460	140 ± 36
12		190	90 ± 20
13		290	130 ± 30
14		330	1200 ± 370
15		160	256 ± 38
16		24	39 ± 11
17		94	59 ± 12
18		130	244 ± 113
LTB_4	--	1.9 ± 0.050[10]	0.12 ± 0.015

function for compound **18**, was synthesized through monoalkylation of 2-propylresorcinol (**2**) as shown in Scheme II. Final coupling of the diaryl ether phenols or phenol **8** to the hydroxyacetophenone moiety is exemplified in Scheme III for the synthesis of compound **16**, and was effected with standard methodology. All compounds were converted to their sodium salts and purified via reversed-phase liquid chromatography.[7]

Initial compounds of the series (**11-13**) proved disappointing in terms of binding affinity for both human neutrophil[8] and guinea-pig lung membrane[9] (Table I). Clearly the presence of a lipophilic group within close proximity to the acid binding function of both LY255283 and SC-41930 is critical for maximum activity, and the gem dimethyl unit of LY255283 could well be playing an analogous role to that of the n-propyl group of SC-41930.[5] While little change was observed in binding affinity with n-propyl-substituted derivatives **14** and **15**, compound **16**, the n-propyl derivative of meta/ortho diaryl ether **13**, resulted in a significant gain in activity. This excercise underscores the sensitive nature of the LTB_4 receptor acid-binding pocket to adjacent lipophilicity and small geometrical permutations in the acid portion of a given series of antagonists. Two attempts were made to refine the binding of **16** through the insertion of a methylene spacer, first in the chain connecting the diaryl ether to the hydroxyacetophenone moiety (compound **17**), and then between the diaryl ether oxygen and the acid-bearing phenyl group (compound **18**). Both modifications resulted in a loss in binding affinity.

Compounds **16**, **17**, and **18** were further evaluated as to their ability to inhibit LTB4-induced chemotaxis of human neutrophils,[11] an important assay when considering the potential antiinflammatory role of LTB4 antagonists. Compound **16** exhibited the greatest activity with an IC_{50} of 0.79 ± 0.13 μM (Figure 1), a value which compares favorably to the inhibitory range reported for SC-41930 (1-5 μM).[4b] As predicted from inspection of neutrophil binding activities, compound **17** was slightly less active than **16**, with an IC_{50} of 3.1 ± 0.70 μM (Figure 2). Surprisingly, compound **18** also fell in the range of SC-41930, with an IC_{50} of 1.2 ± 0.34 μM (Figure 3).

Figure 1. Inhibition of LTB_4-induced Chemotaxis of Human Neutrophils by Compound **16**.

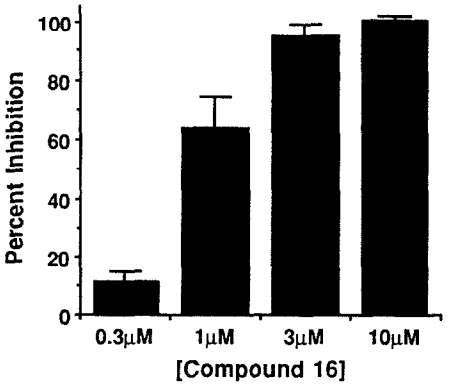


Figure 2. Inhibition of LTB_4-induced Chemotaxis of Human Neutrophils by Compound **17**.

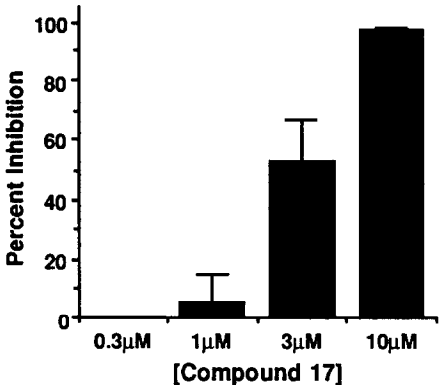
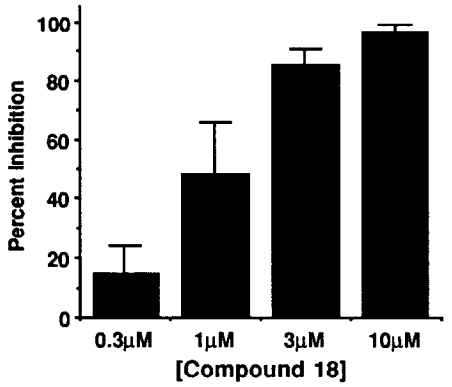


Figure 3. Inhibition of LTB_4-induced Chemotaxis of Human Neutrophils by Compound **18**.



In conclusion, we have developed a short series of hydroxyacetophenone/diaryl ether LTB_4 receptor antagonists. Compound **16** (LY285009)[12] appears to take advantage of some of the major features of LY255283 and SC-41930, including an out-of-plane disposition of an acidic functionality in close proximity to a secondary lipophilic binding group. This new achiral antagonist has a binding affinity for human neutrophils approximately 8-fold higher than the reported value for SC-41930, and is approximately 3-fold more potent than LY255283. We have also demonstrated potent inhibition of LTB4-induced chemotaxis of human neutrophils with **16**. Further exploration of the SAR of this series is in progress.

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(2) For representative examples see: (a) Richards, I. M.; Griffin, R. L.; Oostveen, J. A.; Morris, J.; Wishka, D. G.; Dunn, C. J. *Am. Rev. Respir. Dis.* **1989**, *140*, 1712. (b) Lawson, C. F.; Wishka, D. G.; Morris, J.; Fitzpatrick, F. A. *J. Lipid Mediators* **1989**, *1*, 3. (c) Konno, M.; Sakuyama, S.; Nakae, T.; Hamanake, N.; Miyamoto, T.; Kawasaki, A. *Adv. Prostaglandin Thromboxane Leukotriene Res.* **1992**, *21*, 411. (d) Gapinski, D. M.; Mallett, B. E.; Froelich, L. L.; Jackson, W. T. *J. Med. Chem.* **1990**, *33*, 2798. (e) Gapinski, D. M.; Mallett, B. E.; Froelich, L. L.; Jackson, W. T. *J. Med. Chem.* **1990**, *33*, 2807. (f) Sofia, M. J.; Jackson, W. T.; Saussy, D. L., Jr.; Silbaugh, S. A.; Froelich, L. L.; Cockerham, S. L.; Stengel, P. W. *BioMed. Chem. Lett.* **1992**, *2*, 1669. (g) Sofia, M. J.; Saussy, D. L., Jr.; Jackson, W. T.; Marder, P.; Silbaugh, S. A.; Froelich, L. L.; Cockerham, S. L.; Stengel, P. W. *BioMed. Chem. Lett.* **1992**, *2*, 1675. (h) Huang, F.-C.; Chan, W.-K.; Warus, J. D.; Morrissette, M. M.; Moriarty, K. J.; Chang, M. N.; Travis, J. J.; Mitchell, L. S.; Nuss, G. W.; Sutherland, C. A. *J. Med. Chem.* **1992**, *35*, 4253. (i) Djuric, S. W.; Fretland, D. J.; Penning, T. D. *Drugs Future* **1992**, *17*, 819. (j) Jackson, W. T.; Froelich, L. L.; Gapinski, D. M.; Mallett, B. E.; Sawyer, J. S. *J. Med. Chem.* **1993**, *36*, 1726. (k) Sawyer, J. S.; Baldwin, R. F.; Froelich, L. L.; Saussy, D. L., Jr.; Jackson, W. T., previous paper in this issue.

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(4) (a) Djuric, S. W.; Collins, P. W.; Jones, P. H.; Shone, R. L.; Tsai, B. S.; Fretland, D. J.; Butchko, G. M.; Villani-Price, D.; Keith, R. H.; Zemaitis, J. M.; Metcalf, L.; Bauer, R. F. *J. Med. Chem.* **1989**, *32*, 1147. (b) Tsai, B. S.; Villani-Price, R. H.; Zemaitis, J. M.; Bauer, R. F.; Leonard, R.; Djuric, S. W.; Shone, R. L. *Prostaglandins* **1989**, *38*, 655. (c) Shone, R. L.; Djuric, S. W.; Tsai, B. S.; Fretland, D. J.; Gaginella, T. S.; Cook, C. S. *Drugs Future* **1990**, *15(7)*, 695.

(5) For a discussion of secondary lipophilic group binding in relation to cysteinyl leukotriene antagonists see: Sawyer, J. S.; Baldwin, R. F.; Rinkema, L. E.; Roman, C. R.; Fleisch, J. H. *J. Med. Chem.* **1992**, *35*, 1200.

(6) For an efficient alternative to the Ullmann ether synthesis see: Schmittling, E. A.; Sawyer, J. S. *J. Org. Chem.* **1993**, *58*, 3229.

(7) Satisfactory spectral and analytical data were obtained for all final compounds.

(8) Assay conditions are described in reference 3. For each compound, an inhibition response study was done in triplicate on cells from a single individual. Standard errors for the IC_{50} values of these compounds can be estimated from standard deviations of IC_{50} values for six reference LTB_4 receptor antagonists whose effects were measured on cells from five individuals. The average standard deviation was 15 ± 4% of the mean IC_{50}.

(9) For assay conditions see: Silbaugh, S. A.; Stengel, P. W.; Cockerham, S. L.; Roman, C. R.; Saussy, D. L., Jr.; Spaethe, S. M.; Goodson, T.; Herron, D. K.; Fleisch, J. H. *Eur. J. Pharmacol.* **1992**, *223*, 57.

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(11) For assay conditions see reference 2j.

(12) Characterization of **16**: ^{1}H-NMR (DMSO-d_6) 7.57 (s, 1H), 7.41 (dd, J = 7, 2 Hz, 1H) 7.08 (t, J = 8 Hz, 1H), 6.96 (m, 2H), 6.64 (d, J = 8 Hz, 1H), 6.57 (d, J = 8 Hz, 1H), 6.52 (s, 1H), 6.26 (d, J = 8 Hz, 1H), 4.19 (t, J = 6 Hz, 2H), 4.12 (t, J = 6 Hz, 2H), 2.58 (t, J = 7 Hz, 2H), 2.52 (s, 3H), 2.50 (m, 2H), 2.19 (quintet, J = 6 Hz, 2H), 1.42 (hextet, J = 7 Hz, 2H), 1.07 (t, J = 8 Hz, 3H), 0.79 (t, J = 7 Hz, 3H); MS-FAB (m/e) 538 (p + 2, 28), 537 (p + 1, 82), 545 (100).