Leukotriene Receptor Antagonists. 4. Synthesis and Leukotriene D_4/E_4 Receptor Antagonist Activity of 4-(Alkyl)acetophenone Derivatives†

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Analogues of the leukotriene D_4/E_4 receptor antagonist LY171883 (**1a**) were synthesized in which the tetrazole was linked to the hydroxyacetophenone moiety by an all-methylene carbon chain. A key step in the synthesis involved a Wittig olefin-forming reaction between 3-methoxy-2-propylbenzaldehyde and the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide to form the desired carbon chain. A regioselective Fries rearrangement was employed to form the *o*-hydroxyacetophenone. Compounds in which the tetrazole was separated from the acetophenone by four and five methylene groups were compared to the corresponding derivatives in which an oxygen atom linked the tetrazole chain to the aromatic ring for their ability to antagonize LTD_4- or LTE_4-induced contractions of the isolated guinea pig ileum. When compared to **1a**, the "carba" analogue, **7a**, showed nearly identical LTD_4 antagonist activity. The LTE_4 antagonist activity for these two compounds was also identical. In the shorter chain series, the "carba" analogue, **7b**, showed enhanced LTD_4 antagonist activity and approximately 10-fold greater LTE_4 antagonist activity. These results suggest that the oxygen atom para to the acetyl group of **1a** and **1b** is not of major importance for association with the LTD_4 or LTE_4 receptor sites in the guinea pig ileum.

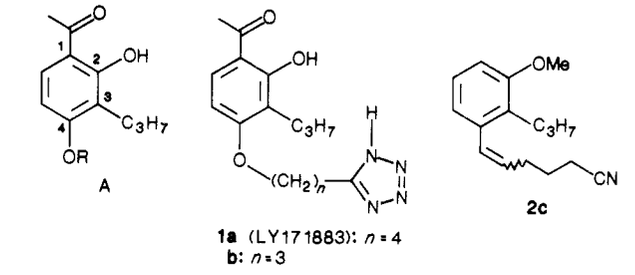
A major goal of our laboratory is the discovery and development of potent and selective antagonists of the leukotrienes. Such agents could potentially provide new therapeutic alternatives for the treatment of allergic asthma,[1] shock,[2] and ischemic heart diseases.[3] One such antagonist, LY171883 (**1a**), is currently in phase II clinical evaluation. The use of this antagonist has led to interesting clinical observations, which further suggest the involvement of leukotrienes in human asthma.[4] Encouraged by these early findings, we have continued to explore the structure–activity relationships of these antagonists.

Structures containing the 3-propyl-4-alkoxy-2-hydroxyacetophenone moiety (Scheme I, A) have affinity for leukotriene LTD_4 and LTE_4 receptors.[5] Compounds containing this group are represented by **1a** and **1b** (Scheme I).[6a,b] In considering the structure–activity relationships for members of this series, we asked what contribution the oxygen atom para to the acetyl group made to the observed antagonist activity. To address this question, we prepared derivatives of **1a** and **1b** in which this oxygen atom was replaced with a methylene group (CH_2).

Substitution of methylene for oxygen in the alkyl tetrazole chains of **1a** and **1b** demanded that an entirely new synthetic strategy be employed. We envisioned construction of the desired methylene chain via a Wittig reaction employing an appropriate Ω-substituted ylide and 3-methoxy-2-propylbenzaldehyde (Scheme II). Reduction of the resultant styrene derivative would produce the desired methylene chain.

3-Methoxy-2-propylbenzaldehyde was prepared by a previously published procedure.[7] When it was reacted with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide in THF, a 2.5:1 mixture of *E* and *Z* styrenes (**2a**) was obtained in 49% yield. The preference for *E* olefin formation is in agreement with results reported by Maryanoff in the reaction of this ylide with benzaldehyde.[8] Likewise, the ylide derived from (3-carboxypropyl)triphenylphosphonium bromide gave the corresponding styrene **2b**, having one less methylene group in the chain, as a 6:1 mixture of olefin isomers. Again, the *E* olefin was the major isomer formed. Double-bond geometry was assigned by the magnitude of the olefinic coupling constants in the NMR spectrum of the product mixture. In both cases, the major isomer gave J = 16–18 Hz, while the minor isomer showed J = 11 Hz. E/Z ratios were determined by integration of the olefin region in the NMR spectrum and were consistent with the ratios de-

Scheme I



Scheme II

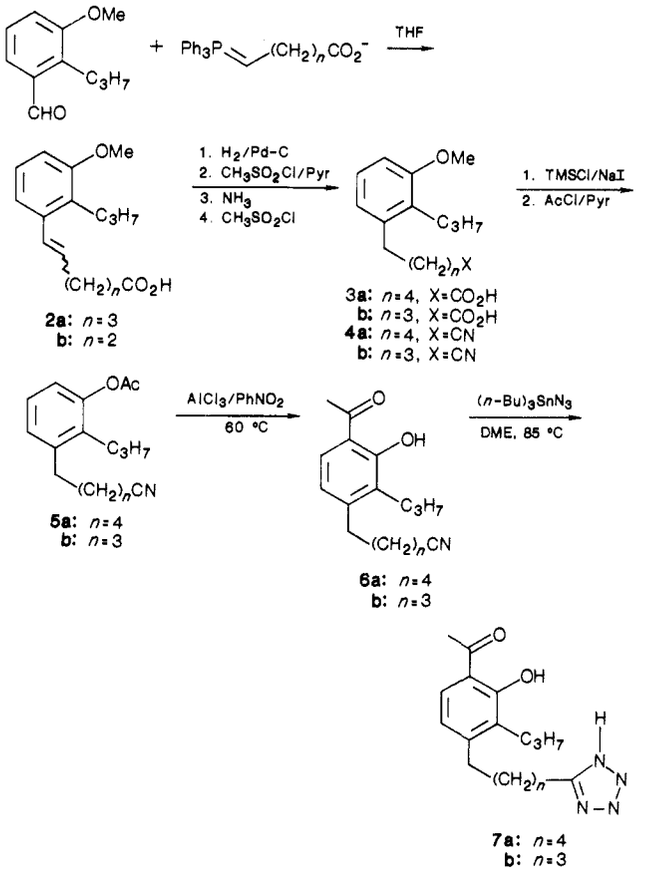


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Table I. Dissociation Constants for Leukotriene Antagonists on LTD_4 Receptors in Guinea Pig Ileum[a]

compd	pK_B	slope of Schild plot
7a (13)[b]	7.08 ± 0.03	0.87 ± 0.08
1a (10)	6.93 ± 0.04	0.84 ± 0.08
7b (13)	6.25 ± 0.04	0.81 ± 0.09
1b (11)	5.47 ± 0.04	0.83 ± 0.11

[a] Values are expressed as means ± standard error of the mean. [b] Number of determinations is in parentheses.

Table II. Dissociation Constants for Leukotriene Antagonists on LTE_4 Receptors in Guinea Pig Ileum[a]

compd	pK_B	slope of Schild plot
7a (11)[b]	7.50 ± 0.04	0.81 ± 0.08
1a (19)	7.21 ± 0.04	0.88 ± 0.06
7b (11)	6.67 ± 0.02	0.91 ± 0.04
1b (11)	5.64 ± 0.04	0.83 ± 0.09

[a] Values are expressed as means ± standard error of the mean. [b] Number of determinations is in parentheses.

termined by GLC integration. A similar reaction was attempted using the ylide derived from (4-cyanobutyl)-triphenylphosphonium bromide. The desired Ω-cyano styrene **2c** was obtained as a 10:1 mixture of olefin isomers in only 27% yield. In this case, the major olefin isomer obtained was the *Z* isomer expected of a nonstabilized ylide. The higher yield and simplified reaction workup made the Ω-carboxy ylide route more appealing.

The mixture of styrene isomers **2a** was catalytically reduced (H_2, 20 psi, Pd/C (5%), ethyl acetate) in 98% yield, giving the saturated acid **3a**. The carboxy group of **3a** was converted into the desired cyano group in 83% yield by the method of Dunn.[9] The methoxy group of **4a** was then demethylated with TMSCl/NaI in acetonitrile,[10] giving the corresponding phenol. Direct Friedel–Crafts acylation of either **4a** or the related phenol with acetyl chloride/$AlCl_3$ in CH_2Cl_2 gave the undesired acetophenone isomer or isomeric mixtures. The desired hydroxyacetophenone could be obtained by a two-step procedure. Thus, after demethylation of **4a**, the resulting phenol was acylated (AcCl/pyridine) and the resulting phenyl acetate subjected to Fries rearrangement. Thus, addition of acetate **5a** to a nitrobenzene solution of $AlCl_3$ (2.5 equiv) at 60 °C gave, after acidic workup, the desired hydroxyacetophenone **6a** in 45% yield. None of the regioisomeric acetophenone could be detected.

The synthesis of **7a** was completed by conversion of nitrile **6a** into the desired tetrazole using tri-*n*-butyltinazide[11] in DME (69%). The identical synthetic sequence was repeated by beginning with carboxylic acid **2b**, giving rise to **7b**, having one less methylene in the chain connecting the tetrazole and the aromatic ring.

Results and Discussion

Compound **1a** and its "carba" analogue, **7a**, showed nearly identical LTD_4 antagonist activity (Table I). The LTE_4 antagonist activity of these two compounds was also very similar, with both showing somewhat better activity as antagonists of LTE_4 than LTD_4 (Table II). Relative to **1b**, the corresponding "carba" analogue, **7b**, showed enhanced LTD_4 antagonist activity. Interestingly, in this case the "carba" derivative, **7b**, showed approximately 10-fold greater LTE_4 antagonist activity when compared to **1b**. Slopes of the Schild plots[14] for all four compounds were close to 1, suggestive of a competitive relationship between agonists and antagonists on ileal leukotriene receptors.

These results suggest that the ether oxygen atom in the tetrazole chain of LTD_4/LTE_4 antagonists such as **1a** is not of major importance for association with either LTD_4 or LTE_4 receptors on the guinea pig ileum. Had this site been critical for receptor binding, antagonists in which the oxygen atom was replaced by a methylene would have been expected to show reduced LTD_4/LTE_4 antagonist activity. However, similar (in the case of **1a**) and even enhanced activity (in the case of **1b**) was found with the "carba" derivatives. It is conceivable that the oxygen atom at this position functions merely as a spacer. Clearly, better leukotriene receptor antagonist activity occurred when the tetrazole and acetophenone groups were separated by five atoms comprising either four carbons and an oxygen or five carbons. Whether other atoms would substitute for carbon or oxygen is unknown at this time. Of interest is the observation that the four compounds tested tended to show greater potency as LTE_4 receptor antagonists than as LTD_4 antagonists although the difference was certainly not significant enough to claim any of them as selective LTE_4 receptor antagonists. Leukotriene receptors are heterogeneous from tissue to tissue;[12] therefore, the above relationships may not hold in all tissue systems.

Experimental Section

Melting points were determined by using a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were obtained by using a GE QE-300 spectrometer. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, br = broad, m = multiplet. All chemical shifts are reported relative to a tetramethylsilane internal standard. IR spectra were determined by using a Nicolet DX10FT-IR spectrometer. Mass spectral data were determined by using a CEC-21-110 electron-impact mass spectrometer. All spectroscopic and analytical data were determined by the Physical Chemistry Department of the Lilly Research Laboratories. Gas–liquid chromatography (GLC) was carried out by using a Hewlett-Packard gas chromatograph equipped with a Hewlett-Packard 3392A integrating recorder and an H/P methyl silicon capillary column. THF that had been stored over 4A molecular sieves was further dried by distillation from sodium/benzophenone ketyl immediately prior to use.

(*E*/*Z*)-6-(3-Methoxy-2-propylphenyl)-5-hexenoic Acid (2a).

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n-BuLi (73 mL, 1.65 M, 118 mmol, Aldrich) was added dropwise to a THF solution (100 mL) of hexamethyldisilazane (25.0 mL, 118 mmol, Aldrich) at 0 °C. The mixture was stirred for 15 min at that temperature. In a three-necked flask fitted with an overhead stirrer and nitrogen inlet, (4-carboxybutyl)triphenylphosphonium bromide (26.0 g, 56 mmol, Aldrich) was suspended in dry THF (250 mL). The THF solution of lithium hexamethyldisilazide was added via cannula to the suspension of the phosphonium salt at 25 °C. When all of the base was added, the solution became homogeneous and deep yellow-orange. The ylide solution was stirred for 30 min at 25 °C. 3-Methoxy-2-propylbenzaldehyde (10.0 g, 56 mmol) was added neat. The color was immediately quenched to a pale yellow. After 30 min at 25 °C, the reaction mixture was poured into an equal volume of ice water. The layers were separated, and the organic layer was extracted with two additional portions of water. The aqueous extracts were acidified to pH 2 with concentrated HCl and extracted thoroughly with ethyl acetate. The combined extracts were dried over $MgSO_4$ and evaporated, leaving a thick yellow oil. The oil was purified by HPLC (Water's Prep LC-500) using a gradient elution system ranging from 15% to 35% ethyl acetate in hexane. Fractions from the major UV-active band were combined to give an *E*/*Z* mixture of the desired styrene derivative, **1a**, as a colorless oil (7.21 g, 49%). Integration of the olefin region of the NMR spectrum revealed a mixture of olefin isomers in a 2.5:1 ratio. The major isomer showed an olefinic coupling constant of 16 Hz and was assigned the *E* geometry. The minor isomer showed an olefinic coupling constant of 11 Hz and was assigned the *Z* olefin geometry. Analysis of the mixture by GLC revealed two components in a ratio of 2.6:1. Major isomer: NMR ($CDCl_3$) δ 7.10 (t, J = 8.0 Hz, 1 H), 7.02 (d, J = 8.0 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.65 (d, J = 16.0 Hz, 1 H), 6.02 (dt, J = 16.0, 7.0 Hz, 1 H), 3.80 (s, 3 H), 2.66 (m, 2 H), 2.42 (t, J = 7.0 Hz, 2 H), 2.30 (m, 2 H), 1.84 (t, J = 7.0 Hz, 2 H), 1.50 (m, 2 H), 0.96 (t, J = 7.0 Hz, 3 H); IR ($CHCl_3$) (cm^{-1}) 2970, 1709, 1575, 1437, 1227, 1053; MS, 262 (M^+, 100). Anal. ($C_{16}H_{22}O_3$) C, H.

(*E*/*Z*)-5-(3-Methoxy-2-propylphenyl)-4-pentenoic acid (2b) was isolated as a pale yellow oil by using a procedure identical with the one above. The product was obtained as a 6:1 *E*/*Z* mixture in a 22% yield. Olefin geometry was assigned as in the previous example. Major isomer: NMR ($CDCl_3$) δ 7.11 (t, J = 7.7 Hz, 1 H), 7.03 (d, J = 7.7 Hz, 1 H), 6.76 (d, J = 7.7 Hz, 1 H), 6.70 (d, J = 17.5 Hz, 1 H), 6.06 (dt, J = 17.5, 6.0 Hz, 1 H), 3.80 (s, 3 H), 2.80–2.50 (m, 6 H), 1.50 (quintet, J = 7.0 Hz, 2 H), 0.96 (t, J = 7.0 Hz, 3 H). Anal. ($C_{15}H_{20}O_3$) C, H.

(*E*/*Z*)-6-(3-Methoxy-2-propylphenyl)-5-hexenenitrile (2c). (4-Cyanobutyl)triphenylphosphonium bromide (3.43 g, 8.1 mmol) was suspended in dry THF (20 mL) in a two-necked flask under nitrogen and cooled to −78 °C. Sodium hexamethyldisilazide (1.48 g, 8.1 mmol, Aldrich) was added in one portion via a Gooch tube. Soon after the addition of base, the yellow ylide color began to appear. The mixture was maintained at −78 °C for 4 h. 3-Methoxy-2-propylbenzaldehyde (1.44 g, 8.1 mmol) was then added via syringe. The yellow color was quenched instantly. The cooling bath was removed and the mixture allowed to come to 25 °C and stirred overnight. The reaction mixture was poured into an equal volume of ice water. The layers were separated, and the water layer was extracted two additional times with ethyl acetate. The combined organic extracts were extracted with brine, dried over $MgSO_4$, and evaporated to dryness. The oily residue was purified by HPLC (Water's Prep LC-500) using a gradient elution system ranging from 5% to 15% ethyl acetate in hexane. Fast-moving fractions gave recovered aldehyde. The major slower moving band contained the desired styrene derivative as a 10:1 mixture of olefin isomers (500 mg, 27%). In the NMR spectrum of the product mixture, the major isomer showed an olefin coupling constant of 10.7 Hz and was assigned the cis olefin geometry. The minor isomer showed an olefin coupling constant of 17 Hz and was assigned the trans olefin geometry. Major isomer: NMR ($CDCl_3$) δ 7.12 (t, J = 8.7 Hz, 1 H), 6.79 (d, J = 8.7 Hz, 1 H), 6.74 (d, J = 8.7 Hz, 1 H), 6.64 (d, J = 10.7 Hz, 1 H), 5.64 (d of t, J = 10.7, 7.7 Hz, 1 H), 3.83 (s, 3 H), 2.60 (t, J = 7.7 Hz, 2 H), 1.50 (quintet, J = 7.0 Hz, 2 H), 0.97 (t, J = 7.0 Hz, 3 H).

3-Methoxy-2-propylbenzenehexanoic Acid (3a). A 2.5:1 mixture of (*E*/*Z*)-6-(3-methoxy-2-propylphenyl)-5-hexenoic acid (7.21 g, 27.5 mmol) was dissolved in ethyl acetate (100 mL) in a fiberglass-coated hydrogenation flask. Palladium on carbon (5%, 50 mg) was added as the catalyst. The mixture was gently shaken under a hydrogen atmosphere (25 psi) at 25 °C, in a Parr hydrogenator. Hydrogen uptake was rapid, with no further uptake occurring after 30 min. The reaction mixture was filtered through a Celite mat and evaporated. The product solidified on standing. The crude acid was recrystallized from ethyl acetate and hexane, giving pure **3a** (7.18 g, 98%): mp 48–49 °C; NMR ($CDCl_3$) δ 7.12 (t, J = 7.7 Hz, 1 H), 6.80 (d, J = 7.7 Hz, 1 H), 6.75 (d, J = 7.87 Hz, 1 H), 3.83 (s, 3 H), 2.62 (m, 4 H), 2.40 (t, J = 7.0 Hz, 2 H), 1.80–1.40 (m, 8 H), 1.02 (t, J = 7.0 Hz, 3 H); IR ($CHCl_3$) (cm^{-1}) 2836, 1709, 1467, 1462, 1206; MS, 264 (M^+), 135 (100). Anal. ($C_{16}H_{24}O_3$) C, H.

3-Methoxy-2-propylbenzenepentanoic acid (3b) was prepared by using the same procedure as described for **3a**: mp 70–71 °C; NMR ($CDCl_3$) δ 7.15 (t, J = 8.0 Hz, 1 H), 6.79 (d, J = 8.0 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H), 3.55 (s, 3 H), 2.74–2.59 (m, 4 H), 2.30 (br t, 2 H), 1.77 (br t, 2 H), 1.52 (m, 2 H), 1.00 (t, J = 7.0 Hz, 3 H); IR ($CHCl_3$) (cm^{-1}) 2960, 1710, 1262, 1206, 1112; MS, 250 (M^+), 161 (100). Anal. ($C_{15}H_{22}O_3$) C, H.

3-Methoxy-2-propylbenzenehexanenitrile (4a). Carboxylic acid **3a** (7.18 g, 27.2 mmol) was dissolved in pyridine (100 mL) and cooled to 0 °C. Methanesulfonyl chloride (2.3 mL, 29.9 mmol) was added dropwise over 5 min. The mixture was stirred for 15 min at 0 °C. Ammonia gas was then bubbled through the reaction mixture for 2 min. The reaction mixture was allowed to warm to 25 °C and stirred for 1 h. Excess ammonia was removed on the rotary evaporator. Additional pyridine was added to restore the volume. The crude amide was converted to the nitrile by cooling to 0 °C and adding methanesulfonyl chloride (18.5 mL, 239 mmol) dropwise over 5 min. The mixture was stirred overnight while slowly warming to 25 °C. The reaction mixture was then poured into 3 volumes of ice water. The aqueous mixture was repeatedly extracted with ethyl acetate. The combined organic extracts were washed with dilute HCl and brine, then dried over $MgSO_4$, and evaporated, yielding a brown oily residue. The crude nitrile was purified by bulb-to-bulb distillation (bp 133–137 °C (0.02 mmHg)), giving the desired product suitable for further transformation (5.50 g, 83%): NMR ($CDCl_3$) δ 7.08 (t, J = 8.7 Hz, 1 H), 6.72 (d, J = 8.7 Hz, 1 H), 6.74 (d, J = 8.7 Hz, 1 H), 3.80 (s, 3 H), 2.60 (m, 4 H), 2.33 (t, J = 8.0 Hz, 2 H), 1.80–1.40 (m, 8 H),0.98 (t, J = 8.0 Hz, 3 H); IR ($CHCl_3$) (cm^{-1}) 2950, 2240, 1582, 1468, 1264, 1114; MS, 245 (M^+), 216 (100). Anal. ($C_{16}H_{23}NO$) C, H, N.

3-Methoxy-2-propylbenzenepentanenitrile (4b) was prepared by the same procedure as described for **4a** (59%): NMR ($CDCl_3$) δ 7.09 (t, J = 7.8 Hz, 1 H), 6.74 (d, J = 7.8 Hz, 1 H), 6.72 (d, J = 7.8 Hz, 1 H), 3.80 (s, 3 H), 2.69–2.55 (m, 4 H), 2.36 (m, 2 H), 1.72 (m, 2 H), 1.50 (quintet, J = 7.5 Hz, 2 H), 0.97 (t, J = 7.5 Hz, 3 H); IR ($CHCl_3$) (cm^{-1}) 2942, 2871, 2250, 1582, 1369, 1260, 1226; MS, 231 (M^+), 202 (100). Anal. ($C_{15}H_{21}NO$) C, H, N.

3-(Acetyloxy)-2-propylbenzenehexanenitrile (5a). The methoxy nitrile **4a** (5.00 g, 20.4 mmol) was dissolved in dry acetonitrile (60 mL). Sodium iodide (6.12 g, 40.6 mmol) was added in one portion. Chlorotrimethylsilane (5.2 mL, 40.6 mmol) was then added dropwise. The reaction mixture immediately became yellow-brown in color, and a precipitate appeared. The reaction mixture was heated to 60 °C and stirred under nitrogen overnight. At this time, an additional equivalent of both the sodium iodide and chlorotrimethylsilane was added. After an additional 6 h of stirring at 60 °C, the reaction mixture was cooled and poured into ice water. The crude product was isolated by extraction with ethyl acetate. The combined organic extracts were washed with a dilute sodium thiosulfate solution and then brine, dried over $MgSO_4$, and evaporated, leaving a pale yellow oil. The crude phenol was not further purified but converted directly to the corresponding acetate. Thus, the phenol was dissolved in ether (60 mL) and cooled to 0 °C. Triethylamine (3.43 mL, 24.6 mmol) was then added, followed by dropwise addition of acetyl chloride (1.74 mL, 24.6 mmol). The reaction mixture was allowed to warm to 25 °C and stirred for 1 h. An equal volume of water was added, and the layers were separated. The organic layer was washed with aqueous 1 N HCl, followed by brine. The crude acetate was isolated as a pale yellow oil after drying ($MgSO_4$) and evaporation of solvent. The acetate was further purified by HPLC (Water's Prep LC-500) using a gradient elution system ranging from 10%

to 25% ethyl acetate in hexane. Appropriate pure fractions were combined to give the desired acetate as a colorless oil (3.21 g, 57%): NMR ($CDCl_3$) δ 7.14 (t, J = 7.2 Hz, 1 H), 7.02 (d, J = 7.2 Hz, 1 H), 6.87 (d, J = 7.2 Hz, 1 H), 2.64 (t, J = 7.0 Hz, 2 H), 2.48 (m, 2 H), 2.35 (t, J = 7.0 Hz, 2 H), 2.32 (s, 3 H), 1.80–1.40 (m, 8 H), 0.99 (t, J = 7.0 Hz, 3 H); IR ($CHCl_3$) (cm^{-1}) 2970, 2250, 1748, 1180; MS, 231 (100), no parent ion. Anal. ($C_{17}H_{23}NO_2$) C, H, N.

3-(Acetyloxy)-2-propylbenzenepentanenitrile (5b) was prepared by the same procedure (73% yield) as used for **5a**: NMR ($CDCl_3$) δ 7.15 (t, J = 8.0 Hz, 1 H), 7.03 (d, J = 8.0 Hz, 1 H), 6.89 (d, J = 8.0 Hz, 1 H), 2.86 (m, 2 H), 2.50 (m, 2 H), 2.38 (br t, J = 7.5 Hz, 2 H), 2.34 (s, 3 H), 1.76 (m, 4 H), 1.52 (m, 2 H), 0.98 (t, J = 7.0 Hz, 3 H); IR ($CHCl_3$) (cm^{-1}) 2970, 2250, 1749, 1181; MS, 217 (100), no parent ion. Anal. ($C_{16}H_{21}NO$) C, H, N.

4-Acetyl-3-hydroxy-2-propylbenzenehexanenitrile (6a). Aluminum chloride (4.04 g, 37.2 mmol) was dissolved in nitrobenzene (40 mL) and the mixture heated to 60 °C. The acetoxy nitrile **5a** (3.21 g, 11.7 mmol) dissolved in nitrobenzene (10 mL) was added dropwise over 1 min. Reaction progress was monitored by TLC. After 3 h all of the starting material had been consumed. The reaction mixture was cooled and poured carefully into a mixture of ice/water/1 N HCl. The mixture was stirred gently until all of the solids had dissolved. Ethyl acetate was added, and the layers were separated. The organic extracts were dried over $MgSO_4$ and evaporated. The residual nitrobenzene was removed by bulb-to-bulb distillation (Aldrich Kugelrohr, 0.5 mmHg, 40 °C). The crude acetophenone was purified by HPLC (Water's Prep LC-500) using a gradient elution system ranging from 10% to 35% ethyl acetate/hexane. The major, highly-UV-active peak yielded the desired acetophenone (**6a**) (1.44 g, 45%) as a pale yellow oil: NMR ($CDCl_3$) δ 12.70 (s, 1 H), 7.51 (d, J = 8.4 Hz, 1 H), 6.68 (d, J = 8.4 Hz, 1 H), 2.62 (m, 4 H), 2.60 (s, 3 H), 2.36 (t, J = 7.2 Hz, 2 H), 1.80–1.50 (m, 8 H), 1.00 (t, J = 7.0 Hz, 3 H); IR ($CHCl_3$) (cm^{-1}) 2962, 2250, 1629, 1408, 1367, 1325; MS, 273 (M^+), 163 (100). Anal. ($C_{17}H_{23}NO_2$) C, H, N.

4-Acetyl-3-hydroxy-2-propylbenzenepentanenitrile (6b) was prepared by using the same procedure as described for **6a** (74% yield): NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.7 Hz, 1 H), 6.71 (d, J = 8.7 Hz, 1 H), 2.69 (m, 4 H), 2.61 (s, 3 H), 2.38 (br t, 3 H), 1.80 (m, 4 H), 1.60 (m, 2 H), 1.03 (t, J = 7 Hz, 3 H).

1-[2-Hydroxy-3-propyl-4-[5-(1*H*-tetrazol-5-yl)pentyl]-phenyl]ethanone (7a). Nitrile **6a** (1.44 g, 5.26 mmol) was dissolved in dry dimethoxyethane (25 mL). Freshly prepared tri-*n*-butyltinazide (5.23 g, 15.8 mmol) was added in one portion. The reaction mixture was then heated to 85 °C and maintained at that temperature for 24 h. The reaction mixture was then cooled to 25 °C. A 10:1 mixture of methanol and 1 N HCl was added (5 mL) and the mixture stirred for 1 h. An equal volume of water was added and the resulting mixture extracted thoroughly with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated, giving a pale yellow oil. The crude tetrazole was purified by HPLC (Water's Prep LC-500) using a gradient elution system ranging from 35% to 75% ethyl acetate in hexane. Each solvent also contained 0.5% acetic acid. The nonpolar tin-containing residues eluted first, followed much later by the highly-UV-active tetrazole. Appropriate pure fractions were combined, yielding the tetrazole as an off-white solid. Recrystallization from ethyl acetate/hexane gave the desired tetrazole in pure form (1.15 g, 69%): mp 116–118 °C; NMR (300 MHz, $CDCl_3$) δ 12.70 (s, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 6.68 (d, J = 8.0 Hz, 1 H), 3.10 (t, J = 7 Hz, 2 H), 2.60 (m, 4 H), 2.59 (s, 3 H), 1.94 (quintet, J = 7 Hz, 2 H), 1.70–1.40 (m, 6 H), 0.96 (t, J = 7.0 Hz, 3 H); IR ($CHCl_3$) (cm^{-1}) 2988, 1629, 1408, 1367, 1325, 1246; MS, 316 (M^+). Anal. ($C_{17}H_{24}N_4O_2$) C, H, N.

1-[2-Hydroxy-3-propyl-4-[4-(1*H*-tetrazol-5-yl)butyl]-phenyl]ethanone (7b) was prepared by using the same procedure as described for **7a** (68% yield): mp 85–87 °C; NMR (300 MHz, $CDCl_3$) δ 12.66 (s, 1 H), 7.48 (d, J = 9.6 Hz, 1 H), 6.66 (d, J = 9.6 Hz, 1 H), 3.14 (t, J = 7 Hz, 2 H), 2.67 (t, J = 7 Hz, 2 H), 2.58 (m, 2 H), 2.59 (s, 3 H), 1.98 (m, 2 H), 1.70 (m, 2 H), 1.48 (m, 2 H), 0.94 (t, J = 7 Hz, 3 H); IR ($CHCl_3$) (cm^{-1}) 3021, 2933, 2873, 1630, 1408, 1367, 1325, 1244; MS, 302 (M^+). Anal. ($C_{16}H_{22}N_4O_2$) C, H, N.

Biological Methods. Male Hartley guinea pigs (Charles River Portage, Portage, MI), weighing 200–400 g, were killed by decapitation. A segment of terminal ileum was removed, the lumen cleaned, and the tissue cut into smaller segments of approximately 2–3 cm. Each segment was tied to the bottom of a tissue holder, leaving the lumen open. The ilea were then transferred to tissue baths and attached to transducers by means of thread. Ilea were equilibrated for approximately 1 h under a maintained resting tension of 0.5 g. Tissues were suspended in 10-mL organ baths containing Krebs' bicarbonate solution of the following composition in millimoles/liter: KCl, 4.6; $CaCl_2 \cdot 2H_2O$, 1.2; KH_2PO_4, 1.2; $MgSO_4 \cdot 7H_2O$, 1.2; NaCl, 118.2; $NaHCO_3$, 24.8; and dextrose, 10.0. Temperature was maintained at 37 °C, and the bathing solutions were aerated with 95% O_2 and 5% CO_2. Isometric measurements were made with a Grass FTO3C force-displacement transducer and recorded on a Grass polygraph as changes in grams of force. Test compounds were assayed for their ability to inhibit contractions induced by synthetic LTD_4 or LTE_4 on guinea pig ileum. Results are expressed as pK_B values, –log of the antagonist concentration that produced a 2-fold rightward shift of the agonist concentration–response curve. This value corresponds to the dissociation constant of the receptor–inhibitor complex.[13] A Schild plot, log (dose ratio – 1) vs –log [antagonist], can be constructed[14] by using these data. Agonist and antagonist are considered to be competitive for the same receptor when the slope of the Schild plot is close to the theoretical value of 1.

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