Development of a Series of Phenyltetrazole Leukotriene D_4 (LTD_4) Receptor Antagonists

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A hypothetical model for receptor binding of leukotriene D_4 (LTD_4) was deduced from conformational analysis of LTD_4 and from the structure-activity relationships (SAR) of known LTD_4 receptor antagonists. A new structural series of LTD_4 receptor antagonists exemplified by 5-[4-(4-phenylbutoxy)phenyl]-2-[4-(tetrazol-5-yl)butyl]-2*H*-tetrazole was designed in which a phenyltetrazole moiety was incorporated as a receptor binding equivalent of the triene unit of LTD_4. A number of these phenyltetrazoles were prepared and found to possess LTD_4 receptor antagonist activity. The structure-activity relationship (SAR) of this series is described.

The cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4) together comprise the slow-reacting substance of anaphylaxis (SRS-A).[1] These mediators have been shown to be potent bronchoconstrictors and to increase vascular permeability. They are thought to play a role in a variety of disease states including asthma. Since the discovery of these substances and elucidation of their structures, efforts have been underway to discover antagonists of their receptor binding, and inhibitors of their biosynthesis and release.

At the time we initiated this work two major chemical approaches to the development of receptor antagonists had been pursued. The first involved structural modification of the LTD_4 receptor antagonist FPL-55712 (Figure 1).[2] Most of these compounds (exemplified by LY171883)[3] contained the hydroxyacetophenone moiety. The second approach centered upon structures related to the agonist itself, as exemplified by SKF-104,353.[4] Subsequent to the initiation of this work, reports of "third-generation" receptor antagonists of novel structure such as ICI-198,615[5] appeared in the literature.

The goal of this work was to design potent novel leukotriene receptor antagonists having simple, easily synthesized structures. It was hoped that these compounds would be useful both as research tools to elucidate the role of leukotrienes in human pathology and as potential therapeutic agents.

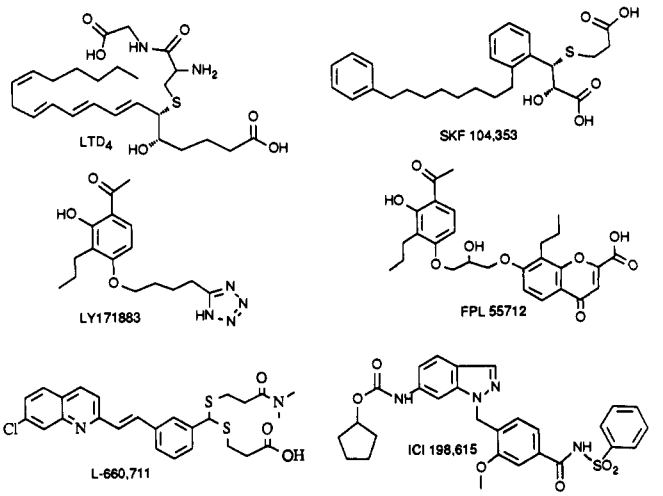


Figure 1. Structures of LTD_4 and representative antagonists.

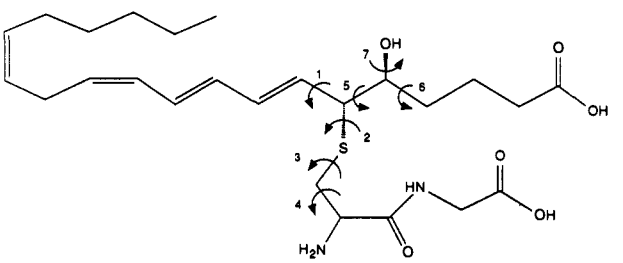


Figure 2. Rotatable bonds for SYBYL search of LTD_4.

Since the structure of the LTD_4 receptor has not been determined, our design of binding antagonists of this receptor was based on molecular modeling of the natural agonist and potential receptor antagonists, and on the structure-activity relationships (SAR) of LTD_4 and of known receptor antagonists. The conformational space of LTD_4 was explored using the SYBYL[6] search facility as described in the Experimental Section. Seven bonds considered most critical to the conformation of the molecule were allowed to rotate (Figure 2). Five structures (conformations 61, 63, 67, 69, and 70) were discovered within 0.5 kcal/mol of the lowest energy achieved in this experiment. Three of these structures (conformations 61, 67, and 70) are shown in Figure 3. Two pairs of conformations (63 and 67, and 69 and 70) differ from each other only in rotation about the hydroxyl O-H bond (rotation about rotatable bond 7 in Figure 2) and only one member of each pair is shown. Since these conformations are all relatively similar, conformation number 67 was arbitrarily

(1) Lewis, R. A.; Austen, K. F.; Soberman, R. J. Leukotrienes and other products of the 5-lipoxygenase pathway. Biochemistry and relation to pathobiology in human diseases. *N. Engl. J. Med.* **1990**, *323*, 645-655.
(2) Chand, N. FPL 55712—An Antagonist of Slow Reacting Substance of Anaphylaxix (SRS-A): A Review. *Agents Actions* **1979**, *9*, 133-140.
(3) Fleisch, J. H.; Rinkema, L. E.; Haisch, K. D.; Swanson-Bean, D.; Goodson, T.; Ho, P. P. K.; Marshall, W. S. LY171883, 1-(2-hydroxy-3-propyl-4-(4-(1H-tetrazole-5-yl)butoxy)-phenyl)ethanone, an orally active leukotriene D_4 antagonist. *J. Pharmacol. Exp. Ther.* **1985**, *233*, 148-157. Marshall, W. S.; Goodson, T.; Cullinan, G. J.; Swanson-Bean, D.; Haisch, K. D.; Rinkema, L. E.; Fleisch, J. H. Leukotriene Receptor Antagonists. 1. Synthesis and Structure-Activity Relationships of Alkoxyacetophenone Derivatives. *J. Med. Chem.* **1987**, *30*, 682-689.
(4) Gleason, J. G.; Hall, R. F.; Perchonock, K. F.; Erhard, K. F.; Frazee, J. S.; Ku, T. W.; Kondrad, K.; McCarthy, M. E.; Mong, S.; Crooke, S. T.; Chi-Rosso, G.; Wasserman, M. A.; Torphy, T. J.; Muccitelli, R. M.; Hay, D. W.; Tuchker, S. S.; Vickery-Clark, L. High-Affinity Leukotriene Receptor Antagonists. Synthesis and Pharmacological Characterization of 2-Hydroxy-3-[(2-carboxyethyl)thio]-3-[2-(8-phenyloctyl)-phenyl]propanoic Acid. *J. Med. Chem.* **1987**, *30*, 959-961.
(5) Aharony, D.; Falcone, R. C.; Krell, R. D. Inhibition of ^{3}H-Leukotriene (LT) D_4 Binding to Guinea-Pig Lung Membrane Receptors by the Novel Leukotriene Antagonist ICI 198,615. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1987**, *46*, 691.

(6) Commercial software from Tripos Associates of St. Louis.

0022-2623/92/1835-1191$03.00/0

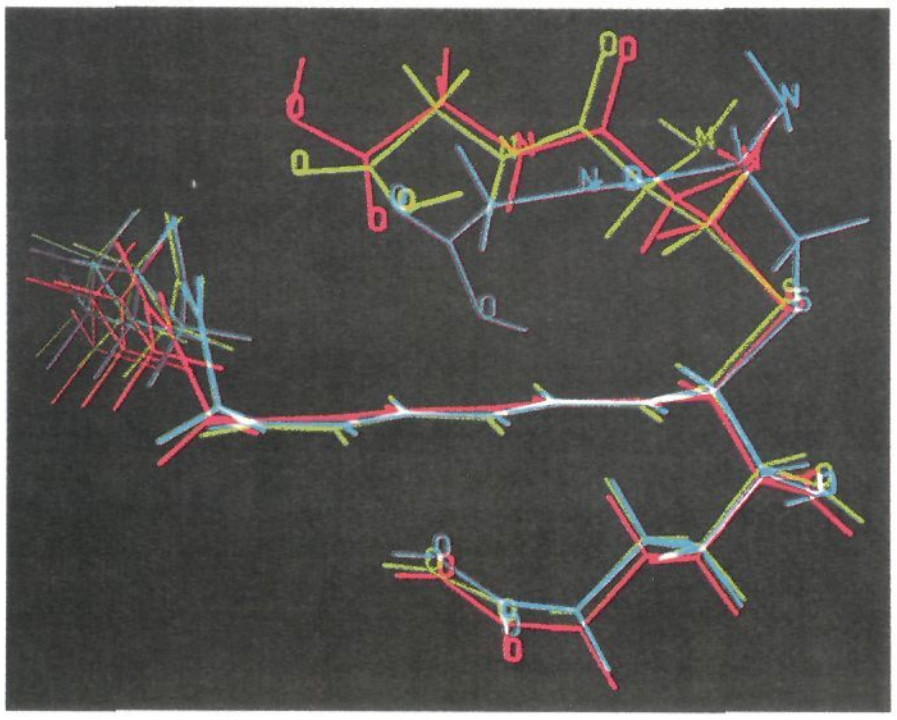


Figure 3. Low-energy conformations from SYBYL search. (Con61, green; Con67, red; Con70, blue).

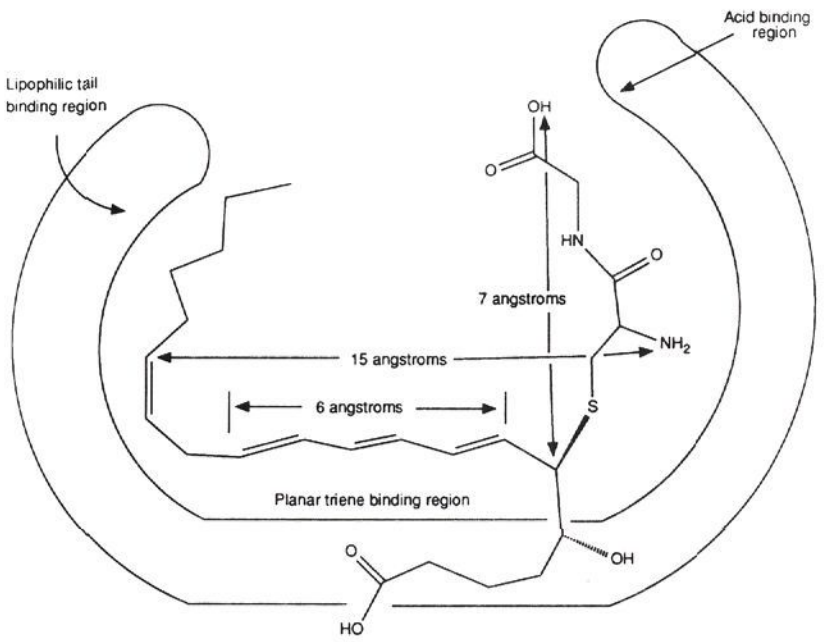


Figure 4. LTD_4 receptor model showing dimensions of the ligand.

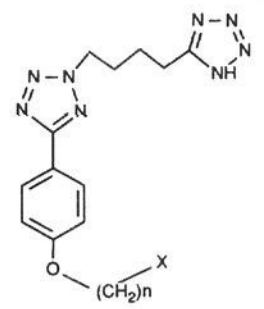
chosen as representative for purposes of this study. The C1-acid chain and the acid end of the peptide side chain in each case curl back upon the central triene portion of the molecule. The lipophilic tail also curls back towards the triene due to a sharp bend at the methylene between the two cis double bonds. The important features of this agonist are an acidic group at one end, a lipophilic region at the other end, and a central triene region.[7] Based on these features, a hypothetical receptor binding model was developed (Figure 4).

The structures of potential receptor antagonists were similarly derived. The shape of the acidic head portion and the lipophilic tail were assumed to be relatively independent of one another. They were treated separately in two conformational searches. The low-energy structures were examined for similarity of size and shape with the LTD_4 structure.

Modeling of a number of possible groups that might fill the triene portion of the receptor led to selection of the phenyltetrazole group. The triene of LTD_4 and the phenyltetrazole are each approximately 6 Å in length; each is similarly unsaturated and flat. The phenyltetrazole also

(7) Ku, T. W.; McCarthy, M. E.; Weichman, B. M.; Gleason, J. G. Synthesis and LTD_4 Antagonist Activity of 2-Norleukotriene Analogues. *J. Med. Chem.* **1985**, *28*, 1847–1853.

Table I. Effect of Lipid Tail Portion Length on Activity



compd no.	X	*n*	pK_B[a]
3	Ph	2	6.51 ± 0.09
4	Ph	3	6.79 ± 0.35
5	Ph	4	6.91 ± 0.23
6	CF_3	4	5.92 ± 0.16
7	Ph	5	5.90 ± 0.05
8	CF_3	5	5.82 ± 0.07
9	Ph	6	5.83 ± 0.21
10	CF_3	7	5.43 ± 0.12

[a] pK_B = –log of that concentration of antagonist that produces a 2-fold rightward shift of the LTD_4 concentration–response curve.

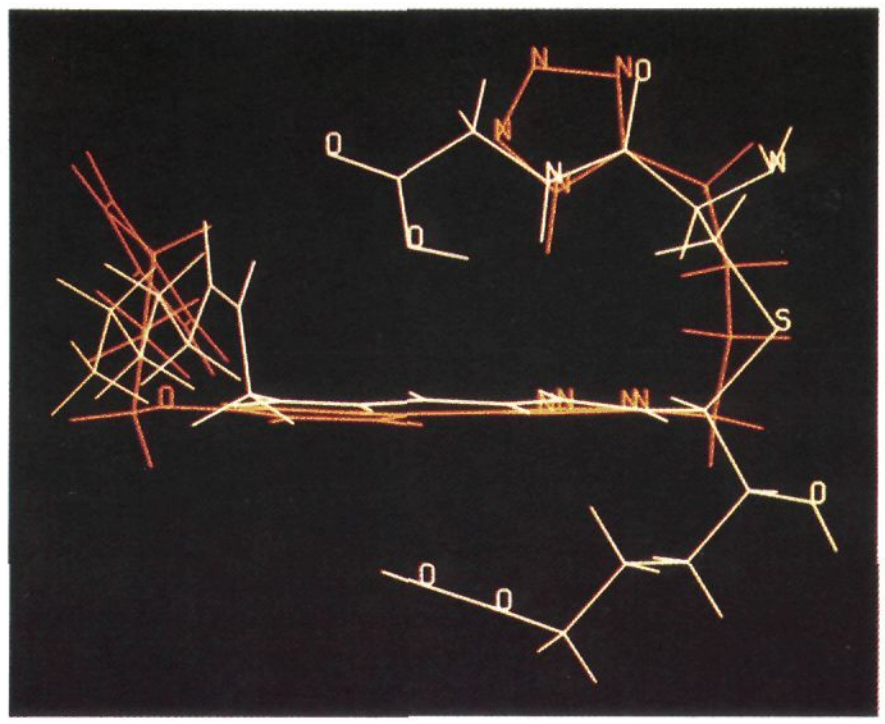
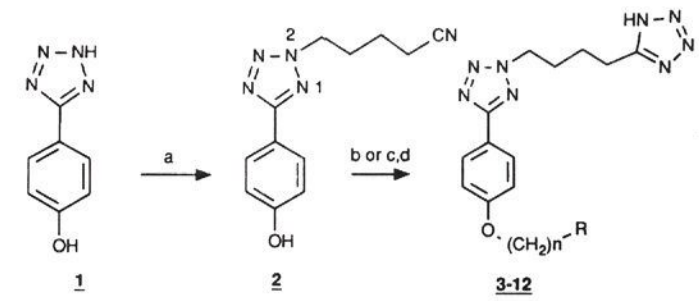


Figure 5. Comparison of LTB_4 (Con67, yellow) with **5** (red).

Scheme I[a]



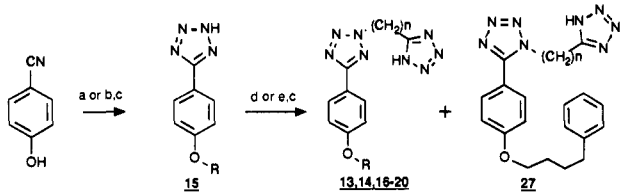
[a] (a) MEK, KI, $NaHCO_3$, $Br(CH_2)_4CN$; (b) (1) NaH, DMF (N_2), (2) $MsO(CH_2)_nR$; (c) MEK, KI, K_2CO_3, $Br(CH_2)_nR$; (d) $(n\text{-}Bu)_3SnN_3$, DEE, reflux.

appeared to provide appropriate geometry for the acid and lipophilic groups. A polymethylenephenyl moiety was added at one end to fill the lipophilic region, and a polymethylenetetrazole at the other end as a mimic of an acid group of the peptide side chain. A number of different chain lengths were examined. Compound **5** (Table I) compared with LTD_4 in Figure 5 appeared to be a good fit to our hypothetical model.

Chemistry

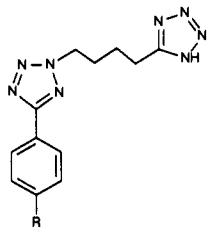
The compounds of this study were prepared as shown in Schemes I–VII. The tetrazole-containing derivatives

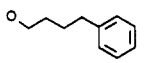
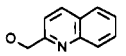
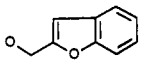
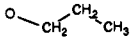
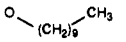
Scheme II[a]



[a] (a) (1) NaH/DMF, (2) $MsO(CH_2)_4Ph$; (b) MEK, K_2CO_3, RI, reflux; (c) $(n\text{-}Bu)_3SnN_3$, DEE, reflux; (d) MEK, KI, K_2CO_3, $Br(CH_2)_nCN$; (e) (1) NaH/DMF; (2) $Br(CH_2)_4CN$/KI.

Table II. Effect of the Nature of the Lipid Tail on Activity



compd no.	R	pK_B[a]
5		6.91 ± 0.23
11		6.68 ± 0.12
12		6.36 ± 0.29
13		5.52 ± 0.10
14		5.09 ± 0.07

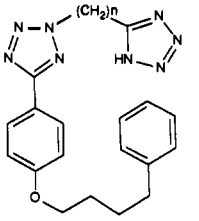
[a] See Table I.

were prepared by reaction of the corresponding nitrile with tri-*n*-butyltin azide[8] in 1,2-diethoxyethane (DEE). Alkylation of the phenol was readily accomplished utilizing the appropriate alkyl halide with potassium carbonate in 2-butanone (methyl ethyl ketone, MEK), and a catalytic amount of potassium iodide. Alternatively, alkylation can be effected utilizing sodium hydride in DMF and the corresponding mesylate. While the tetrazole can be alkylated under the same conditions, it is significantly more acidic than the phenol and can be alkylated selectively in the presence of an unprotected phenol using potassium bicarbonate as the base. Alkylation of the tetrazole generally leads to a mixture of the 1- and 2-isomers which are readily separable by chromatography. The 2-isomer predominates greatly in all cases. The trifluoroalkyl bromides used in preparation of compounds **6**, **8**, and **10** were made by treatment of the corresponding carboxylic acids with sulfur tetrafluoride in a pressure vessel.[9]

Results

Exploration of the SAR of the lipophilic side chain (Table I) showed propylphenyl (**4**) and butylphenyl (**5**) to be about equally potent, with activity declining for longer connecting chains. While ethylphenyl compound **3** is not statistically different from **4**, it is less active than **5**, showing a trend toward diminished activity for shorter chain lengths. ω-(Trifluoromethyl)alkyl derivatives were also tried as lipophilic groups. These showed a trend to lower activity for chains longer than five carbon atoms, and

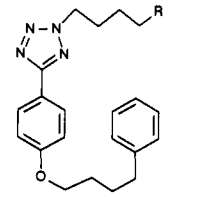
Table III. Effect of Chain Length of the Acid Group on Activity

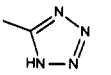
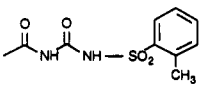
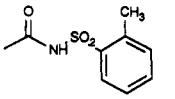
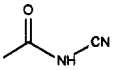


compd no.	n	pK_B[a]	compd no.	n	pK_B[a]
5	4	6.91 ± 0.23	18	6	6.24 ± 0.10
16	3	6.86 ± 0.13	19	7	5.96 ± 0.21
17	5	6.54 ± 0.23	20	8	5.70 ± 0.17

[a] See Table I.

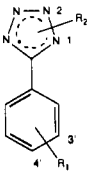
Table IV. Effect of the Nature of the Acidic Group on Activity



compd no.	R	pK_B[a]
5		6.91 ± 0.23
21	-COOH	5.97 ± 0.12
22	$-CONH_2$	5.41 ± 0.05
23		5.86 ± 0.08
24		5.92 ± 0.05
25		6.10 ± 0.15

[a] See Table I.

Table V. Effect of Substitution about the Phenyltetrazole Moiety on Activity



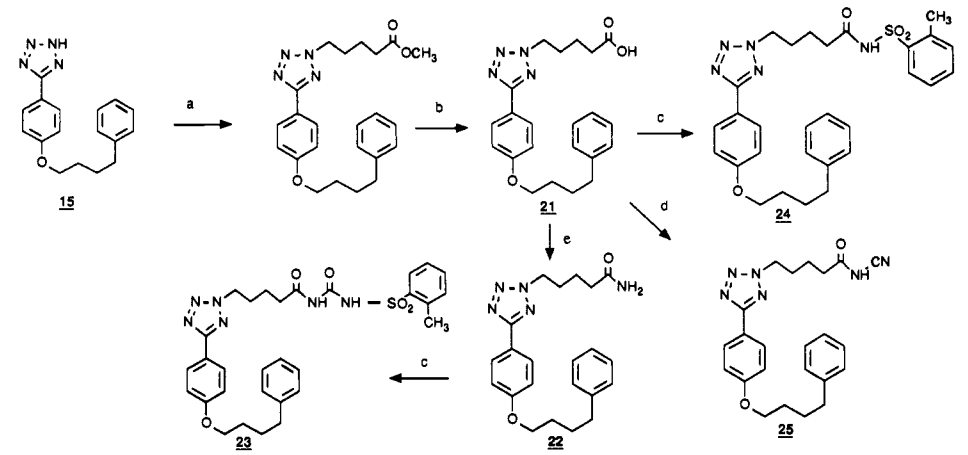
compd no.	R_1	R_2	pK_B[a]
5	4'-$O(CH_2)_4Ph$[b]	2-$(CH_2)_4Tet$[c]	6.91 ± 0.23
15	4'-$O(CH_2)_4Ph$	H	5.92 ± 0.14
26	3'-$O(CH_2)_4Ph$	2-$(CH_2)_4Tet$	5.38 ± 0.27
27	4'-$O(CH_2)_4Ph$	1-$(CH_2)_4Tet$	6.31 ± 0.07
28	4'-$O(CH_2)_4Tet$	2-$(CH_2)_4Ph$	5.80 ± 0.11
29	4'-$O(CH_2)_4Tet$	2-$(CH_2)_4Tet$	inactive
30	4'-$O(CH_2)_4Tet$	1-$(CH_2)_4Tet$	inactive
31	3'-CH_2S-(2-quinolyl)	2-$(CH_2)_4Tet$	6.57 ± 0.56

[a] See Table I. [b] Ph = phenyl. [c] Tet = 5-tetrazole.

(8) Sisido, K.; Nabika, K.; Isida, T.; Kozima, S. Formation of Organotin–Nitrogen Bonds III. *N*-Trialkyltin-5-Substituted Tetrazoles *J. Organomet. Chem.* 1971, *33*, 337–346.

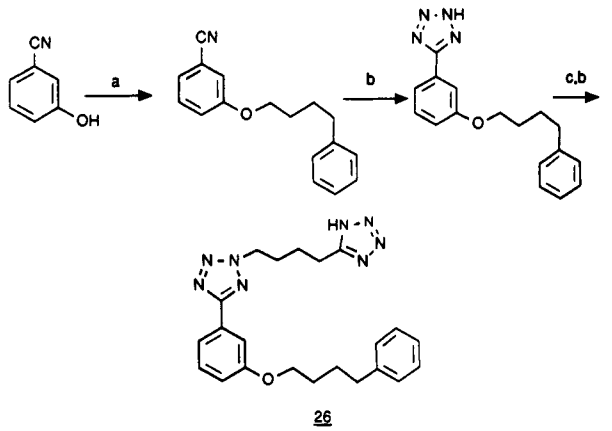
(9) Hasek, W. R. 1,1,1-Trifluoroheptane. *Organic Synthesis*, Wiley: New York, 1973; Collect. Vol. V, pp 1082–1084.

Scheme III[a]



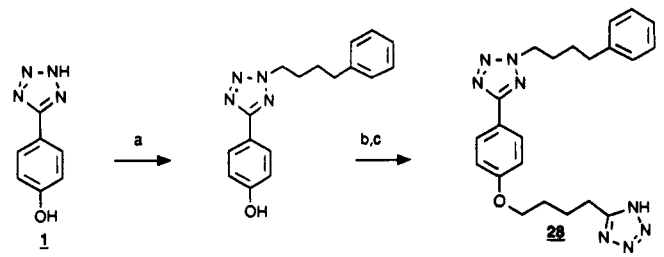
[a] (a) $Br(CH_2)_4CO_2CH_3$, KI, K_2CO_3, MEK, reflux; (b) NaOH, H_2O; (c) 2-tolylsulfonyl isocyanate; (d) (1) $(COCl)_2$, (2) NH_2CN, NaOH, H_2O; (e) (1) $(COCl)_2$, (2) NH_4OH, H_2O.

Scheme IV[a]



[a] (a) (1) NaH, DMF; (2) $MsO(CH_2)_4Ph$; (b) $(n\text{-}Bu)_3SnN_3$, DEE, reflux; (c) MEK, KI, K_2CO_3, $Br(CH_2)_4CN$, reflux.

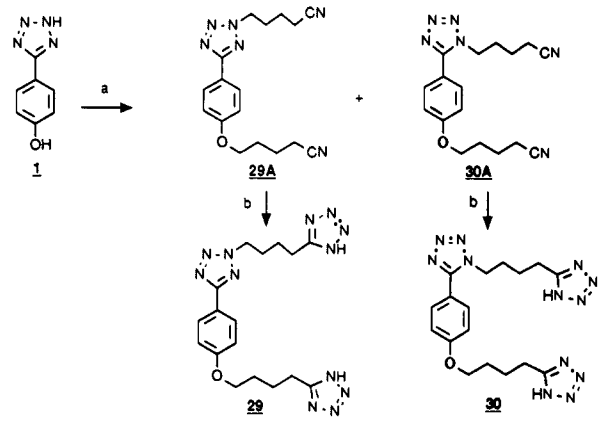
Scheme V[a]



[a] (a) MEK, KI, K_2CO_3, $Cl(CH_2)_4Ph$; (b) MEK, KI, K_2CO_3, $Cl(CH_2)_4CN$; (c) $(n\text{-}Bu)_3SnN_3$, DEE, reflux.

are somewhat less active than the aromatic derivatives. Considerable structural diversity is possible in the aromatic portion of the lipophilic groups. Quinoline, which is also part of the lipophilic region of other receptor antagonists, such as L-660,711[10] (Figure 1), was examined in this series.

Scheme VI[a]



[a] (a) MEK, KI, K_2CO_3, $Br(CH_2)_4CN$; (b) $(n\text{-}Bu)_3SnN_3$, DEE, reflux.

Quinoline 11 (Table II) is about as active as **5** while benzofuran **12**, which has a distinctly different geometry, is less active than **5**. Compounds with aliphatic lipophilic substituents (**13**, **14**) are essentially inactive.

The importance of the acidic group can be appreciated by comparing compounds **5** and **15** in Table V. Significant activity is lost if the acidic group is removed. A number of acidic functional groups were explored, including the phenyl sulfonamide moiety found also in ICI-198,615 (Figure 1). Tetrazole is the most active of the acid groups evaluated (Table IV). Activity declines when the polymethylenetetrazole acidic chain contains more than five carbon atoms (Table III); the derivatives with three to five carbon atoms are about equipotent (**5**, **16**, **17**). Compound **28**, with the lipid tail and the acid head portions of the molecule interchanged, is much less active, and the compounds with acidic groups at both ends (**29** and **30** of Table V) are inactive. Thus, it can be seen that the SAR of both the acidic and lipophilic groups are essentially in accord with our receptor binding model.

The importance of the overall shape of the molecule is also seen in the effect of substitution about the phenyltetrazole (Table V). The 1-substituted phenyltetrazole **27** is less active than its 2-substituted isomer **5**. Modeling of the 1- and 2-substituted derivatives showed them to have very different shapes, the phenyltetrazole of the 2-isomer having an essentially planar phenyltetrazole unit, while the 1-isomer has about a 39° dihedral angle between the tetrazole and the phenyl group. The *m*-butylphenyl deriva-

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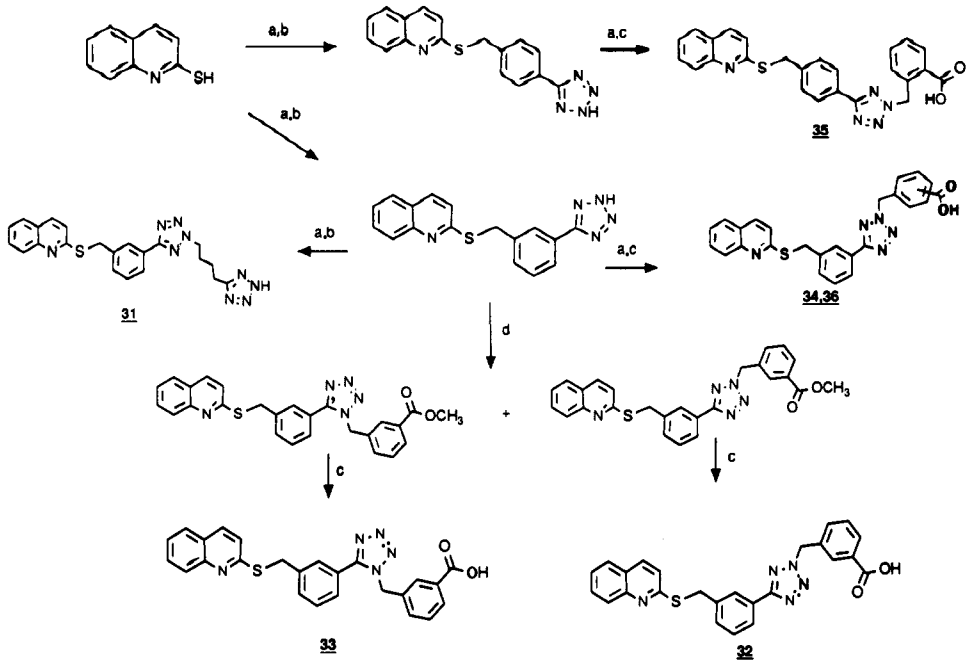
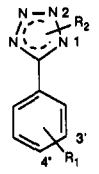
Scheme VII[a]



[a] (a) BrR, K_2CO_3, KI, MEK, reflux; (b) NaN_3, triethylammonium bromide, 1-methylpyrrolidone, 130 °C; (c) NaOH, methanol, water; (d) $Br(CH_2)C_6H_4(3\text{-}CO_2H)$, K_2CO_3, KI, Cs_2CO_3, reflux.

Table VI. Structure–Activity Relationship of Quinoline Derivatives



compd no.	R_1	R_2	pK_B[a]
26	3′-$O(CH_2)_4Ph$[b]	2′-$(CH_2)_4$Tet[c]	5.38 ± 0.27
31	3′-CH_2S-(2-quinolyl)	2′-$(CH_2)_4$Tet	6.57 ± 0.56
32	3′-CH_2S-(2-quinolyl)	2-$CH_2C_6H_4$-3-CO_2H	5.62 ± 0.12
33	3′-CH_2S-(2-quinolyl)	1-$CH_2C_6H_4$-3-CO_2H	6.20 ± 0.49
34	3′-CH_2S-(2-quinolyl)	2-$CH_2C_6H_4$-4-CO_2H	5.88 ± 0.11
35	4′-CH_2S-(2-quinolyl)	2-$CH_2C_6H_4$-2-CO_2H	5.87 ± 0.24
36	3′-CH_2S-(2-quinolyl)	2-$CH_2C_6H_4$-2-CO_2H	7.02 ± 0.19

[a] See Table I. [b] Ph = phenyl. [c] Tet = 5-tetrazole.

tive **26** is inactive, while the para isomer **5** is the most active member of this series. However, substituting the *m*-[2-(methylthio)quinolinyl] substituent (**31**) for the *m*-butoxyphenyl restores activity to the same level observed for compound **5**. The geometries of the lipophilic tails of **5** and **31** must be quite different. The alkoxybenzene would be predicted to be planar based on computer modeling and previous ^1H NMR studies,[11] while the alkylbenzene should be out of plane.

Methylene benzoic acids were examined as acid chains (Table VI). Again, 1-substituted tetrazole **32** is more active than the 2-substituted derivative **33**, in the *m*-benzoic acid series. The meta- and para-substituted benzoic acids are equally active, while the ortho isomer is significantly more active (**32**, **34**, **36**). Unlike the compounds with phenylbutyl lipophilic chains, in the methylene benzoic acid series meta substitution about the phenyltetrazole results in better activity than para substitution (**5**, **26** and **35**, **36**).

In summary, we calculated the energetically favorable conformations of LTD_4, constructed a hypothetical model of its receptor binding, and used this model to design a novel series of compounds (exemplified by **5**) with LTD_4 receptor antagonist activity. The structure–activity relationship of this series is found to be consistent with our model. The acidic head portion of the molecule was essential for activity. A lipophilic tail group was also necessary. Pharmacologic activity was lost when the planarity of the phenyltetrazole was disrupted.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectra were determined with a CEC-21-110 electron-impact mass spectrometer or a MAT-731 spectrometer using field desorption (FD) conditions. Nuclear magnetic resonance (^1H NMR) spectra were determined on a GE QE300 spectrometer. Chemical shift values are reported in parts per million (δ) relative to tetramethylsilane. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. With the exception of NMR spectra, all spectroscopic and analytical data were determined by the Physical Chemistry Department (MC525) of the Lilly Research Laboratories. All analytical data are within ±0.4% unless otherwise indicated. HPLC was carried out on a Waters Prep 500 using Waters PrepPAK 500 silica gel cartridges. Medium-pressure chromatography was carried out using an FMC pump with Altec columns packed with silica gel (EM Science silica gel 60, 230–400 mesh ASTM) at a maximum pressure of 50 psi.

Unless otherwise noted all organic extracts were washed with saturated aqueous sodium chloride and dried over $MgSO_4$, and the solvent was removed under reduced pressure using a rotary evaporator. Unless otherwise noted all tributyltin azide reactions were worked up as follows: a mixture was prepared by addition of 25 mL of concentrated hydrochloric acid to ice, followed by addition of water to make 100 mL of solution, to which was added 100 mL of hexane. The reaction mixture was then poured in, and the reaction vessel rinsed with ethyl acetate, which was also poured into the aqueous mixture. The mixture was allowed to stir for about 2 h while being warmed to room temperature. Sodium hydride was used as a 60% slurry in mineral oil.

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Biology Protocol. Terminal ilea were removed from male Hartley guinea pigs, the lumens cleaned, and the tissue cut into 2–3-cm segments. The bottom of each segment was tied to a tissue holder leaving the lumen open and the top was attached to a force-displacement transducer. Ilea were suspended in 10-mL tissue baths containing Krebs' bicarbonate buffer of the following composition in millimoles/liter: KCl, 4.6; KH_2PO_4, 1.2; $MgSO_4 \cdot 7H_2O$, 1.2; NaCl, 118.2; $NaHCO_3$, 24.8; dextrose, 10.0; and $Ca^{2+}(CaCl_2 \cdot H_2O)$, 1.2. The temperature was maintained at 37 °C, and baths were aerated with 95% O_2 and 5% CO_2. Resting tension was maintained at 0.5 g. Concentration–response curves (CRC) to LTD_4 were obtained using the cumulative concentration technique of Van Rossum.[12] Antagonists were kept in contact with the tissues for 30 min prior to obtaining the final LTD_4 CRC. Results were expressed as pK_B values (±SEM), -log of that antagonist concentration producing a 2-fold rightward shift of the LTD_4 CRC. Calculations were performed by the method of Furchgott.[13]

Molecular Modeling. As part of previous studies from this laboratory,[14] a model of LTD_4 had been constructed using structural information from the work of Sugiura[15] based on ^1H NMR spectroscopy in aqueous solution. The initial working model was constructed using SYBYL,[6] and was minimized by MM2.1[16] to provide a reasonable standard geometry.

The SYBYL SEARCH facility was used to scan the conformational space of these molecules. SEARCH rotates up to 10 bonds by a specified increment. At each point it checks for van der Waals contacts. If two atoms are within a van der Waals radius of one another, the conformation is discarded. If not, a single-point energy calculation is performed using the SYBYL MAXIMIN force field. If the energy is less than a selectable amount above the current global minimum, the conformation is saved for later examination.

Seven bonds in LTD_4 were initially chosen for rotation. These were the bonds we considered most critical in determination of the overall shape of the molecule. They were each rotated through a complete 360° revolution by 15° increments. The increments were calculated relative to the starting conformation. All conformers within 0.5 kcal/mol of the current global minimum were saved. This resulted in a total of 70 structures. Five of the 70 structures were within 0.5 kcal/mol of the final global minimum.

Similar methodology was applied to generate representative conformations of the proposed receptor antagonists. The flexible head and tail portions of these molecules were assumed to be conformationally independent, and were modeled separately.

4-[2-(4-Cyanobutyl)-2*H*-tetrazol-5-yl]phenyl (2). A mixture of 1[17] (1.0 g, 6.2 mmol), $NaHCO_3$ (0.52 g, 6.2 mmol), and 0.2 g of potassium iodide (catalytic) in 30 mL of MEK was heated for 1 h. 5-Bromopentanonitrile (1.0 g, 6.2 mmol) was added in one lot, and the resultant mixture heated under reflux overnight. The mixture was cooled, water was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate. The residue was subjected to medium-pressure chromatography, eluting with ethyl acetate/hexane (3:2). Compound **2** was obtained as a white crystalline solid (125 mg, 8% yield): mp 121–123 °C; ^1H NMR (DMSO-d_6) δ 1.61 (m, 2 H), 2.04 (m, 2 H), 2.55 (t, J = 7.1 Hz, 2 H), 4.72 (t, J = 6.9, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 7.85 (d, J = 8.7, Hz, 2 H), 9.97 (s, 1 H). Anal. ($C_{12}H_{13}N_5O$) C, H, N.

2-[4-(1*H*-Tetrazol-5-yl)butyl]-5-[4-(2-phenylethoxy)phenyl]-2*H*-tetrazole (3). A mixture of **2** (2.2 g, 9 mmol), (2-bromoethyl)benzene (1.85 g, 10 mmol), potassium carbonate (1.4 g, 10 mmol), and potassium iodide (0.2 g, catalytic) in 100 mL of MEK was heated under reflux overnight. After cooling, water was added, and the aqueous layer was extracted with ethyl acetate. The product was isolated by HPLC, eluting with ethyl acetate/hexane (35:65).

The nitrile was combined with 3.0 g (9 mmol) of tributyltin azide in 20 mL of DEE and heated under reflux for 3 days. Following the standard workup, **3** was air-dried and recrystallized from ethyl acetate/hexane (0.7 g, 20% yield based on phenol **2**): mp 110–111 °C; ^1H NMR (DMSO-d_6) δ 1.72 (m, 2 H), 2.01 (m, 2 H), 2.94 (t, J = 7.5 Hz, 2 H), 3.06 (t, J = 6.8 Hz, 2 H), 4.26 (t, J = 6.8 Hz, 2 H), 4.74 (t, J = 6.9 Hz, 2 H), 7.08 (d, J = 8.7 Hz, 2 H), 7.2–7.40 (m, 5 H), 7.94 (d, J = 8.7 Hz, 2 H). Anal. ($C_{20}H_{22}N_8O$) C, H, N.

Compounds **6**, **8**, **10**, and **12** were prepared by the methodology described for compound **3**.

2-[4-(1*H*-Tetrazol-5-yl)butyl]-5-[4-[(5,5,5-trifluoropentyl)oxy]phenyl]-2*H*-tetrazole (6). Compound **6** was obtained in 56% yield by recrystallization from ethyl acetate/hexane: mp 116–119 °C; ^1H NMR (DMSO-d_6) δ 1.60–1.89 (m, 6 H), 2.02 (m, 2 H), 2.24–2.42 (m, 2 H), 2.94 (t, J = 7.6 Hz, 2 H), 4.08 (t, J = 6.2 Hz, 2 H), 4.74 (t, J = 6.8 Hz, 2 H), 7.08 (d, J = 8.6 Hz, 2 H), 7.96 (d, J = 8.6 Hz, 2 H). Anal. ($C_{17}H_{21}F_3N_8O$) C, H, N.

2-[4-(1*H*-Tetrazol-5-yl)butyl]-5-[4-[(6,6,6-trifluorohexyl)oxy]phenyl]-2*H*-tetrazole (8). Recrystallization from ethyl acetate/hexane gave **8** as a white crystalline solid in 34% yield: mp 97–99 °C; ^1H NMR (DMSO-d_6) δ 1.53 (m, 4 H), 1.76 (m, 4 H), 2.01 (m, 2 H), 2.27 (m, 2 H), 2.94 (t, J = 7.5 Hz, 2 H), 4.04 (t, J = 6.4 Hz, 2 H), 4.74 (t, J = 6.8 Hz, 2 H), 7.07 (d, J = 8.8 Hz, 2 H), 7.94 (d, J = 8.6 Hz, 2 H); MS-FD m/z 425 (M+). Anal. ($C_{18}H_{23}F_3N_8O$) C, H, N.

2-[4-(1*H*-Tetrazol-5-yl)butyl]-5-[4-[(8,8,8-trifluorooctyl)oxy]phenyl]-2*H*-tetrazole (10). Compound **10** was obtained in 66% yield: mp 96–99 °C; ^1H NMR (DMSO-d_6) δ 1.30–1.56 (m, 6 H), 1.74 (m, 4 H), 2.02 (m, 2 H), 2.14–2.34 (m, 2 H), 2.95 (t, J = 7.5 Hz, 2 H), 4.04 (t, J = 6.5 Hz, 2 H), 4.75 (t, J = 6.9 Hz, 2 H), 7.07 (d, J = 8.7 Hz, 2 H), 7.94 (d, J = 8.7 Hz, 2 H). Anal. ($C_{20}H_{27}F_3N_8O$) C, H, N.

2-[[4-[2-[4-(1*H*-Tetrazol-5-yl)butyl]-2*H*-tetrazol-5-yl]-phenoxy]methyl]benzofuran (12). Recrystallization from ethyl acetate/hexane gave **12** in 27% yield: mp 160–163 °C; ^1H NMR (DMSO-d_6) δ 1.71 (m, 2 H), 2.00 (m, 2 H), 2.92 (t, J = 7.5 Hz, 2 H), 4.74 (t, J = 6.9 Hz, 2 H), 5.34 (s, 2 H), 7.08 (s, 1 H), 7.21–7.34 (m, 4 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 7.7 Hz, 1 H), 7.98 (d, J = 8.7 Hz, 2 H); MS-FD m/z 417 (M+). Anal. ($C_{21}H_{20}N_9O_2$) C, H, N.

2-[4-(1*H*-Tetrazol-5-yl)butyl]-5-[4-[(3-phenylpropyl)oxy]phenyl]-2*H*-tetrazole (4). Sodium hydride (0.66 g of 60% NaH in mineral oil, 17 mmol of NaH) was suspended in 35 mL of DMF under nitrogen atmosphere. Phenol **2** (2.0 g, 8.2 mmol) was added in 10 mL of DMF. The mixture was allowed to stir at room temperature for about 45 min (gas evolution had ceased). 3-Phenylpropyl methanesulfonate (1.8 g, 8.4 mmol) was added rapidly. After stirring overnight at room temperature, the reaction mixture was poured into water and allowed to stir for about 1 h. The solid was collected, washed with fresh water, and air-dried. The product (2.37 g, 80% yield) was converted to the tetrazole without further purification.

The nitrile was combined with 5.0 g (15 mmol) of tributyltin azide in 20 mL of DEE and heated under reflux for 3 days. Following the standard workup the aqueous mixture was allowed to stir for about 2 h. The product was isolated by filtration, washed with fresh hexane, and recrystallized from ethyl acetate/hexane. Compound **4** was obtained as a pale yellow crys-

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talline solid in 47% yield (based on 2): mp 129–131 °C; ^{1}H NMR (DMSO-d_6) δ 1.75 (m, 2 H), 2.04 (m, 4 H), 2.76 (t, J = 7.3 Hz, 2 H), 2.94 (t, J = 7.5 Hz, 2 H), 4.04 (t, J = 6.4, 2 H), 4.04 (t, J = 6.8, 2 H), 7.08 (d, J = 8.7 Hz, 2 H), 7.14–7.32 (m, 5 H), 7.96 (d, J = 8.7 Hz, 2 H). Anal. ($C_{21}H_{24}N_8O$) C, H, N.

Compounds **7** and **9** were prepared by the methodology described for **4**.

2-[4-(1*H*-Tetrazol-5-yl)butyl]-5-[4-(5-phenylpentoxy)phenyl]-2*H*-tetrazole (7). Recrystallization from ethyl acetate/hexane gave **7** as a white crystalline solid in 29% yield: mp 118–120 °C; ^{1}H NMR (DMSO-d_6) δ 1.44 (m, 2 H), 1.58–1.84 (m, 6 H), 2.02 (m, 2 H), 2.60 (t, J = 7.7 Hz, 2 H), 4.02 (t, J = 7.5 Hz, 2 H), 4.74 (t, J = 6.9 Hz, H), 7.06 (d, J = 8.8 Hz, 2 H), 7.10–7.30 (m, 5 H), 7.94 (d, J = 8.7 Hz, 2 H). Anal. ($C_{23}H_{28}N_8O$) C, H, N.

2-[4-(1*H*-Tetrazol-5-yl)butyl]-5-[4-[(6-phenylhexyl)oxy]phenyl]-2*H*-tetrazole (9). Compound **9** was obtained by recrystallization from ethyl acetate/hexane in 26% yield: mp 88–89 °C; ^{1}H NMR (DMSO-d_6) δ 1.28–1.52 (m, 4 H), 1.60 (m, 2 H), 1.72 (m, 4 H), 2.01 (m, 2 H), 2.57 (t, J = 7.6 Hz, 2 H), 2.94 (t, J = 7.6 Hz, 2 H), 4.02 (t, J = 6.4 Hz, 2 H), 4.74 (t, J = 6.8 Hz, 2 H), 7.06 (d, J = 8.8 Hz, 2 H), 7.09–7.27 (m, 5 H), 7.94 (d, J = 8.7 Hz, 2 H). Anal. ($C_{24}H_{30}N_8O$) C, H, N.

5-[4-(4-Phenylbutoxy)phenyl]-2-[4-(1*H*-tetrazol-5-yl)butyl]-2*H*-tetrazole (5). A mixture of **15** (27.5 g, 0.93 mol), 5-bromopentanenitrile (13.0 mL, 0.111 mol), and potassium carbonate (28.0 g, 0.206 mol) in 200 mL of MEK was heated under reflux overnight. After cooling, water was added and extraction was carried out with ethyl acetate. The nitrile was used without further purification.

The nitrile (9.7 g, 26 mmol) was combined with 18.0 g (52 mmol) of tributyltin azide in 25 mL of DEE and heated under reflux for 3 days. Following the standard workup the aqueous mixture was allowed to stir for about 2 h. The product was isolated by filtration and washing with fresh hexane and recrystallization from methanol/ethyl acetate. The product (5.49 g, 50% yield) was obtained as a crystalline solid: mp 85–88 °C; ^{1}H NMR (DMSO-d_6) δ 1.74 (br, 6 H), 2.02 (m, 2 H), 2.65 (br, 2 H), 2.95 (t, J = 7 Hz, 2 H), 4.05 (br, 2 H), 4.74 (t, J = 7 Hz, 2 H), 7.06 (d, J = 9 Hz, 2 H), 7.10–7.32 (m, 5 H), 7.94 (d, J = 9 Hz, 2 H). Anal. ($C_{22}H_{26}N_8O$) C, H, N.

Compounds **16–20** were prepared by the method of compound **5**.

5-[4-(4-Phenylbutoxy)phenyl]-2-[3-(1*H*-tetrazol-5-yl)propyl]-2*H*-tetrazole (16). Recrystallization from ethyl acetate/hexane gave **16** as a white crystalline solid in 25% yield: mp 104–105 °C; ^{1}H NMR (DMSO-d_6) δ 1.72 (m, 4 H), 2.40 (t, J = 7.4 Hz, 2 H), 2.63 (br, 2 H), 2.97 (t, J = 7.6 Hz, 2 H), 4.04 (br, 2 H), 4.781 (t, J = 6.8 Hz, 2 H), 7.07 (d, J = 8.9 Hz, 2 H), 7.1–7.3 (m, 5 H), 7.94 (d, J = 8.8 Hz, 2 H); MF-FD m/z 405 (M+). Anal. ($C_{21}H_{24}N_8O$) C, H, N.

5-[4-(4-Phenylbutoxy)phenyl]-2-[5-(1*H*-tetrazol-5-yl)pentyl]-2*H*-tetrazole (17). Product **17** was isolated as a white crystalline solid by recrystallization from ethyl acetate/hexane in 27% yield: mp 95–97 °C; ^{1}H NMR (DMSO-d_6) δ 1.30 (m, 2 H), 1.72 (m, 6 H), 1.96 (m, 2 H), 2.63 (br, 2 H), 2.85 (t, J = 7.5 Hz, 2 H), 4.03 (br, 2 H), 4.67 (t, J = 6.9 Hz, 2 H), 7.06 (d, J = 8.7 Hz, 2 H), 7.1–7.3 (m, 5 H), 7.94 (d, J = 8.7 Hz, 2 H); MS-FD m/z 433 (M+). Anal. ($C_{23}H_{28}N_8O$) C, H, N.

5-[4-(4-Phenylbutoxy)phenyl]-2-[5-(1*H*-tetrazol-5-yl)hexyl]-2*H*-tetrazole (18). Compound **18** was obtained as a white crystalline solid following recrystallization from ethyl acetate/hexane in 32% yield: mp 82–84 °C; ^{1}H NMR (DMSO-d_6) δ 1.31 (m, 4 H), 1.6–1.8 (m, 6 H), 1.92 (m, 2 H), 2.63 (br, 2 H), 2.83 (t, J = 7.6 Hz, 2 H), 4.04 (br, 2 H), 4.67 (t, J = 6.9 Hz, 2 H), 7.06 (d, J = 8.8 Hz, 2 H), 7.1–7.3 (m, 5 H), 7.94 (d, J = 8.7 Hz, 2 H); MS-FD m/z 447 (M+). Anal. ($C_{24}H_{30}N_8O$) C, H, N.

5-[4-(4-Phenylbutoxy)phenyl]-2-[5-(1*H*-tetrazol-5-yl)heptyl]-2*H*-tetrazole (19). Recrystallization of the crude solid from ethyl acetate/hexane gave **19** as a white crystalline solid in 50% yield: mp 85–87 °C; ^{1}H NMR (DMSO-d_6) δ 1.29 (br, 6 H), 1.6–1.8 (m, 6 H), 1.92 (m, 2 H), 2.63 (br, 2 H), 2.83 (t, J = 7.5 Hz, 2 H), 4.04 (br, 2 H), 4.67 (t, J = 6.9 Hz, 2 H), 7.06 (d, J = 8.7 Hz, 2 H), 7.1–7.3 (m, 5 H), 7.91 (d, J = 8.7 Hz, 2 H); MS-FD m/z 447 (M+). Anal. ($C_{25}H_{32}N_8O$) C, H, N.

5-[4-(4-Phenylbutoxy)phenyl]-2-[5-(1*H*-tetrazol-5-yl)octyl]-2*H*-tetrazole (20). Compound **20** was obtained in 39% yield by recrystallization from ethyl acetate/hexane: mp 85–87 °C; ^{1}H NMR (DMSO-d_6) δ 1.26 (br, 8 H), 1.6–1.8 (m, 6 H), 1.91 (m, 2 H), 2.63 (br, 2 H), 2.82 (t, J = 7.6 Hz, 2 H), 4.03 (br, 2 H), 4.66 (t, J = 6.9 Hz, 2 H), 7.06 (d, J = 8.8 Hz, 2 H), 7.1–7.3 (m, 5 H), 7.93 (d, J = 8.7 Hz, 2 H); MS-FD m/z 475 (M+). Anal. ($C_{26}H_{34}N_8O$) C, H, N.

2-[[4-[2-[4-(1*H*-Tetrazol-5-yl)butyl]-2*H*-tetrazol-5-yl]phenyl]methyl]quinoline (11). A mixture of **2** (1.0 g, 4.1 mmol), 2-(chloromethyl)quinoline hydrochloride (0.87 g, 4.1 mmol), potassium carbonate (1.31 g, 8.2 mmol), and potassium iodide (0.68 g, 4.1 mmol) in 50 mL of MEK was heated under reflux for 24 h. An additional equivalent each of 2-(chloromethyl)quinoline hydrochloride, potassium carbonate, and potassium iodide was added, and heating was continued overnight. Another equivalent of each of the three reagents was added, and heating continued overnight again. The mixture was cooled, water was added, and extraction was carried out with ethyl acetate. The solid residue was slurried in methylene chloride/hexane, filtered, and washed with ethyl acetate.

The nitrile (0.3 g, 0.78 mmol) was combined with 0.8 g (2.4 mmol) of tributyltin azide in 5 mL of DEE and heated under reflux for 3 days. Following the standard workup the aqueous mixture was allowed to stir for about 2 h. The product was isolated by filtration, washed with fresh hexane, and recrystallized from methanol/ethyl acetate/hexane. Compound **11** (0.11 g, 8% yield) was obtained as a crystalline solid: ^{1}H NMR (DMSO-d_6) δ 1.66 (m, 2 H), 2.00 (m, 2 H), 2.95 (t, J = 7.5 Hz, 2 H), 4.74 (t, J = 6.8 Hz, 2 H), 5.56 (s, 2 H), 7.25 (d, J = 8.8 Hz, 2 H), 7.72 (t, J = 7.5 Hz, 1 H), 7.83 (d, J = 8.6 Hz, 1 H), 7.90 (t, J = 7.8 Hz, 1 H), 7.99 (d, J = 8.7 Hz, 2 H), 8.10 (d, J = 8.1 Hz, 1 H), 8.17 (d, J = 8.5 Hz, 1 H), 8.66 (d, J = 8.5 Hz, 1 H); MS-FD m/z 429 (M+). Anal. ($C_{22}H_{21}N_9O$) C, H, N; C: calcd, 61.81; found, 61.00. N: calcd, 29.49; found, 28.50.

5-(4-Propoxyphenyl)-2-[4-(1*H*-tetrazol-5-yl)butyl]-2*H*-tetrazole (13). 4-Cyanophenol (25.0 g, 0.21 mol) was combined with 3-iodopropane (22.0 mL, 0.23 mol) and 30.0 g (0.22 mol) of potassium carbonate in 100 mL of MEK and heated under reflux overnight. The mixture was cooled and water was added. The solution was extracted with ethyl acetate. The combined organics were concentrated under reduced pressure to a colorless oil, which subsequently crystallized and was used without further purification.

The nitrile (32.5 g, 0.20 mol) was combined with 83.5 g (0.25 mol) of tri-*n*-butyltin azide in 200 mL of DEE and heated under reflux overnight. The reaction mixture was cooled and poured into a mixture of cold water and hexane, containing 35 mL of concentrated hydrochloric acid and a small amount of acetone. After stirring for about 2 h the solid was isolated by filtration and recrystallized from ethyl acetate/methanol. The tetrazole was used without further characterization.

The tetrazole (14.5 g, 71 mmol) was combined with 10.0 mL (85 mmol) of 5-bromopentanenitrile, 12.0 g (87 mmol) of potassium carbonate, and 3.0 g (catalytic) of potassium iodide in 200 mL of MEK. The mixture was heated under reflux for about 5 h and then allowed to stir at room temperature overnight. Water was added and the solution was extracted with ethyl acetate. The intermediate nitrile as recrystallized from ethyl acetate/hexane as a white crystalline solid.

The nitrile (11.3 g, 42 mmol) was combined with tri-*n*-butyltin azide (30.0 g, 90 mmol) in 50 mL of DEE, and heated under reflux overnight. The mixture was cooled and poured into water/hexane containing about 30 mL of concentrated hydrochloric acid and a small amount of ethyl acetate. The product **13** crystallized on stirring and was recrystallized from ethyl acetate/hexane (24% yield): mp 113–115 °C; ^{1}H NMR (DMSO-d_6) δ 0.95 (t, J = 7.4 Hz, 2 H), 1.71 (m, 4 H), 2.00 (m, 2 H), 2.92 (t, J = 7.5 Hz, 2 H), 3.94 (d, J = 6.5 Hz, 2 H). 4.73 (t, J = 6.9 Hz, 2 H), 7.06 (d, J = 8.7 Hz, 2 H), 7.94 (d, J = 8.7 Hz, 2 H). Anal. ($C_{15}H_{20}N_8O$) C, H, N.

5-[4-(Decyloxy)phenyl]-2-[4-(1*H*-tetrazol-5-yl)butyl]-2*H*-tetrazole (14). Recrystallization from methanol/ethyl acetate afforded **14** in 40% yield: mp 115–117 °C; ^{1}H NMR (DMSO-d_6) δ 0.83 (t, J = 6.5, 3 H), 1.2–1.5 (m, 14 H), 1.6–1.8 (m, 4 H), 2.00 (m, 2 H), 2.90 (t, J = 7.5 Hz, 2 H), 4.00 (t, J = 6.5 Hz, 2 H). 4.73 (t, J = 6.9 Hz, 2 H), 7.06 (d, J = 8.8 Hz, 2 H), 7.94 (d, J = 8.7 Hz, 2 H); MS-FD m/z 427 (M+). Anal. ($C_{22}H_{34}N_8O$) C, H, N.

5-[4-(4-Phenylbutoxy)phenyl]-2*H*-tetrazole (15). Sodium hydride (5.2 g, 0.13 mol) was suspended in 50 mL of DMF under a nitrogen atmosphere and cooled in an ice/water bath. 4-Cyanophenol (15.7 g, 0.13 mol) was added in about 15 mL of DMF (the cold bath was removed when the mixture became viscous), and the mixture allowed to stir for about 1 h. The cold bath was replaced and 4-phenylbutyl methanesulfonate (30.0 g, 0.13 mmol) was added dropwise in 15 mL of DMF (the bath removed when the mixture began to thicken), and the mixture allowed to stir overnight at room temperature. The mixture was poured into ice/water and extracted with ethyl acetate. The nitrile was isolated by medium-pressure chromatography, eluting with ethyl acetate/hexane (1:9).

The intermediate nitrile (3.13 g, 12.5 mmol) was combined with tri-*n*-butyltin azide (12.5 g, 37.5 mmol), and 15 mL of DEE and heated under reflux for 3 days. Following the standard workup, **15** (3.61 g; 50% yield) was isolated by filtration, washed with fresh ethyl acetate and hexane, and then air-dried: mp 165–167 °C; ^{1}H NMR (DMSO-d_6) δ 1.72 (br, 4 H), 2.63 (br, 2 H), 4.06 (br, 2 H), 7.05–7.35 (m, 7 H), 7.93 (d, J = 8.8 Hz, 2 H). Anal. ($C_{17}H_{18}N_4O$) C, H, N.

5-[4-(4-Phenylbutoxy)phenyl]-2*H*-tetrazole-2-pentanoic Acid Methyl Ester. Compound **16** (11.0 g, 37.4 mmol) was combined with 5-bromopentanoic acid methyl ester (7.3 g, 37.4 mmol), potassium carbonate (5.16 g, 37.3 mmol), and 2.0 g of potassium iodide (catalytic) in 50 mL of MEK. The resultant mixture was heated under reflux for 20 h then cooled, and water was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The residue was subjected to HPLC, eluting with ethyl acetate/hexane (1:9). 5-[4-(4-Phenylbutoxy)phenyl]-2*H*-tetrazole-2-pentanoic acid methyl ester was obtained as a white crystalline solid (10.7 g, 70% yield): mp 121–123 °C; ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 2 H), 1.87 (br, 4 H), 2.12 (m, 2 H), 2.40 (t, J = 7.3 Hz, 2 H), 2.72 (br, 2 H), 3.68 (s, 3 H), 4.12 (br, 2 H), 4.66 (t, J = 7.0 Hz, 2 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.2–7.4 (m, 5 H), 8.06 (d, J = 8.8 Hz, 2 H). Anal. ($C_{23}H_{28}N_4O_3$) C, H, N.

5-[4-(4-Phenylbutoxy)phenyl]-2*H*-tetrazole-2-pentanoic Acid (21). 5-[4-(4-Phenylbutoxy)phenyl]-2*H*-tetrazole-2-pentanoic acid methyl ester (8.5 g, 21 mmol) was combined with 5 mL of 5 N sodium hydroxide, 20 mL of water, and 150 mL of methanol and heated under reflux for 3 h. Following acidification to pH 6 with concentrated hydrochloric acid, inorganic salts were removed by filtration. The product was obtained as a white crystalline solid following vacuum filtration and air-drying (3.27 g; 40% yield): mp 89–91 °C; ^{1}H NMR (DMSO-d_6) δ 1.45 (m, 2 H), 1.71 (br, 4 H), 1.91 (m, 2 H), 2.08 (t, J = 7.3 Hz, 2 H), 2.62 (br, 2 H), 4.02 (br, 2 H), 4.65 (t, J = 7.1 Hz, 2 H), 7.05 (d, J = 8.8 Hz, 2 H), 7.1–7.3 (m, 5 H), 7.94 (d, J = 8.7 Hz, 2 H). Anal. ($C_{22}H_{26}N_4O_3$) C, H, N.

5-[4-(4-Phenylbutoxy)phenyl]-2*H*-tetrazole-2-pentanamide (22). A mixture of **21** (4.37 g, 11.1 mmol) and excess thionyl chloride (about 30 mL) was allowed to stir at room temperature overnight. Excess thionyl chloride was removed under reduced pressure to give the acid chloride as a yellow oil. Excess ammonium hydroxide (about 30 mL) was added to the acid chloride in a separatory funnel and the mixture was agitated vigorously. Product **22** was collected by vacuum filtration and recrystallized from ethyl acetate as a white crystalline solid (2.5 g, 51% yield): mp 112–113 °C; ^{1}H NMR (DMSO-d_6) δ 1.48 (m, 2 H), 1.72 (br, 4 H), 1.92 (m, 2 H), 2.08 (t, J = 7.3 Hz, 2 H), 2.63 (br, 2 H), 4.04 (br, 2 H), 4.66 (t, J = 7.0 Hz, 2 H), 7.07 (d, J = 8.8 Hz, 2 H), 7.1–7.3 (m, 5 H), 7.94 (d, J = 8.8 Hz, 2 H). Anal. ($C_{22}H_{27}N_5O_2$) C, H, N.

N-[[[(2-Methylphenyl)sulfonyl]amino]carbonyl]-5-[4-(4-phenylbutoxy)phenyl]-2*H*-tetrazole-2-pentanamide (23). A mixture of **22** (0.5 g, 1.3 mmol) and (2-methylphenyl)sulfonyl isocyanate (250 mg, 1.3 mmol) in 30 mL of toluene was heated under reflux for 5 h. An additional 200 mg (1 mmol) of sulfonyl isocyanate was added. The mixture was heated under reflux overnight, cooled, and concentrated under reduced pressure. Compound **23** was obtained as a white crystalline solid by recrystallization from ethyl acetate/hexane (0.55 g, 79% yield): mp 131–133 °C; ^{1}H NMR (DMSO-d_6) δ 1.52 (m, 2 H), 1.72 (br, 4 H), 1.92 (m, 2 H), 2.43 (t, J = 7.4 Hz, 2 H), 2.53 (s, 3 H), 2.63 (br, 2 H), 4.04 (br, 2 H), 4.68 (t, J = 6.9 Hz, 2 H), 7.07 (d, J = 9.0 Hz, 2 H), 7.1–7.3 (m, 5 H), 7.43 (t, J = 7.4 Hz, 2 H), 7.60 (t, J = 6.9 Hz, 2 H), 7.95 (t, J = 8.8 Hz, 2 H), 10.88 (s, 1 H); MS-FD m/z 590 (M+). Anal. ($C_{30}H_{34}N_6O_5S$) C, H, N.

***N*-[(2-Methylphenyl)sulfonyl]-5-[4-(4-phenylbutoxy)-phenyl]-2*H*-tetrazole-2-pentanamide (24).** Compound **21** (1.0 g, 2.5 mmol) was dissolved in 5 mL of toluene under a nitrogen atmosphere, and three drops of triethylamine were added followed by (2-methylphenyl)sulfonyl isocyanate (1.0 g, 5.1 mmol). The mixture was placed in an oil bath maintained at 60 °C, with magnetic stirring. Vigorous gas evolution commenced immediately. Heating was continued for about 4 h. The mixture was cooled and concentrated under reduced pressure. **24** (0.35 g, 25% yield) was isolated as fine white needles by medium-pressure chromatography, eluting with ethyl acetate/hexane (1:1): mp 117–119 °C; ^{1}H NMR (DMSO-d_6) δ 1.41 (m, 2 H), 1.7–1.9 (m, 6 H), 2.27 (t, J = 7.3 Hz, 2 H), 2.52 (s, 3 H), 2.63 (br, 2 H), 4.04 (br, 2 H), 4.62 (t, J = 7.0 Hz, 2 H), 7.06 (d, J = 8.7 Hz, 2 H), 7.1–7.4 (m, 7 H), 7.52 (t, J = 7.4 Hz, 1 H), 7.60 (t, J = 6.9 Hz, 2 H), 7.92 (m, 3 H), 12.16 (br, 1 H); MS-FD m/z 547 (M+). Anal. ($C_{29}H_{33}N_5O_4S$) C, H, N.

***N*-Cyano-5-[4-(4-phenylbutoxy)phenyl]-2*H*-tetrazole-2-pentanamide (25).** Conversion of **21** to the corresponding acid chloride was effected by treatment with excess oxalyl chloride at room temperature. After gas evolution had ceased, stirring was continued for about 1 h, and then excess reagent was removed under reduced pressure. The residue was dissolved in about 20 mL of acetone and added to a mixture of cyanamide (0.5 g, 1.2 mmol), 15 mL of 1N sodium hydroxide (2.5 equiv), and 40 mL of water, at ice/water bath temperature. The cold bath was removed, and the resultant mixture was allowed to stir for about 45 min while being warmed to room temperature. The solution was acidified to pH 2 with concentrated hydrochloric acid, and the resultant precipitate collected by suction filtration. After washing with fresh water and air-drying, **25** was recrystallized from ethyl acetate/hexane (1.68 g, 68% yield): decomposed on melting (indefinite mp); ^{1}H NMR (DMSO-d_6) δ 1.51 (m, 2 H), 1.72 (br, 4 H), 1.96 (m, 2 H), 2.20–2.45 (m, 2 H), 2.63 (br, 2 H), 4.04 (br, 2 H), 4.69 (t, J = 7.0 Hz, 2 H), 7.06 (d, J = 8.8 Hz, 2 H), 7.1–7.3 (m, 5 H), 7.94 (d, J = 8.8 Hz, 2 H); MS-FD m/z 418 (M+). Anal. ($C_{23}H_{26}N_6O_2$) C, H, N; N: calcd, 20.08; found, 16.50.

5-[3-(4-Phenylbutoxy)phenyl]-2-[4-(1*H*-tetrazol-5-yl)butyl]-2*H*-tetrazole (26). Sodium hydride (1.85 g, 46 mmol) was suspended in 30 mL of DMF under a nitrogen atmosphere. 3-Cyanophenol (5.0 g, 42 mmol) dissolved in 10 mL of DMF was added dropwise. The reaction mixture was allowed to stir at room temperature for about 1 h (gas evolution had ceased). Phenylbutanol methylsulfonate (11.5 g, 50 mmol) was added in one lot. After stirring at room temperature for 3 days the mixture was poured into water and extracted with ethyl acetate. The benzonitrile was isolated as a colorless oil by HPLC eluting with ethyl acetate/hexane (1:99) in 55% yield, and used without further characterization.

The benzonitrile (5.79 g, 23 mmol) was combined with tri-*n*-butyltin azide (15.4 g, 46 mmol) and 35 mL of DEE and heated under reflux for 40 h. Following standard workup, the aqueous mixture was allowed to stir for about 1 h. The tetrazole was isolated in 66% yield by filtration and washed thoroughly with fresh hexane.

The tetrazole (4.28 g, 14.5 mmol) was combined with 5-bromopentanenitrile (2.36 g, 14.5 mmol), potassium carbonate (2.0 g, 14.5 mmol), and potassium iodide (300 mg, catalytic) in about 100 mL of MEK and heated under reflux for 4 h. After stirring at room temperature over 2 days, water was added, and extraction with ethyl acetate was carried out. The nitrile was isolated in 76% yield as a colorless oil by HPLC eluting with ethyl acetate/hexane (25:75). Recrystallization was effected from ethyl acetate/hexane to give **26** (2.76 g, 60% yield): mp 102–104 °C; ^{1}H NMR (DMSO-d_6) δ 1.73 (br, 6 H), 2.01 (m, 2 H), 2.64 (br, 2 H), 2.93 (t, J = 7.5 Hz, 2 H), 4.05 (br, 2 H), 4.76 (t, J = 6.9 Hz, 2 H), 7.0–7.3 (m, 6 H), 7.43 (t, J = 7.9 Hz, 1 H), 7.51 (s, 1 H), 7.60 (d, J = 7.5 Hz, 1 H); MS-FD m/z 419 (M+). Anal. ($C_{22}H_{26}N_8O$) C, H, N.

5-[4-(4-Phenylbutoxy)phenyl]-1-[4-(1*H*-tetrazol-5-yl)butyl]-1*H*-tetrazole (27). Sodium hydride (0.4 g, 10 mmol) was suspended in 30 mL of DMF under a nitrogen atmosphere. Compound **17** (3.0 g, 10 mmol) was added in a small amount of DMF and the mixture allowed to stir for 1 h (gas evolution had

ceased). 5-Bromopentanenitrile (1.5 g, 10 mmol) was combined with potassium iodide (1.66 g, 10 mmol) in DMF and allowed to stand for about 15 min with occasional agitation, then added to the sodium hydride suspension. After stirring at room temperature overnight the reaction mixture was poured into water, allowed to stir for 1 h, and then extracted with ethyl acetate. After trituration with hexane, the crude, gummy solid product was purified by medium-pressure chromatography, eluting with ethyl acetate/hexane (4:6). 5-[4-(4-Phenylbutoxy)phenyl]-1*H*-tetrazole-1-pentanenitrile (0.22 g, 6% yield) was obtained as a crystalline solid: ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 2 H), 1.89 (br, 4 H), 2.14 (br, 2 H), 2.41 (t, J = 7.0 Hz, 2 H), 2.73 (br, 2 H), 4.07 (br, 2 H), 4.49 (t, J = 6.9 Hz, 2 H), 7.07 (d, J = 8.7 Hz, 1 H), 7.2–7.4 (m, 5 H), 7.61 (d, J = 8.7 Hz, 1 H).

The isomeric product 5-[4-(4-phenylbutoxy)phenyl]-2*H*-tetrazole-2-pentanenitrile (2.35 g, 62% yield) was also obtained as a yellow oil.

5-[4-(Phenylbutoxy)phenyl]-1*H*-tetrazole-1-pentanenitrile (0.2 g, 0.5 mmol) was combined with 0.5 g (1.5 mmol) of tributyltin azide in 5 mL of DEE and heated under reflux for 2 days. Compound **27** was isolated by filtration and washed thoroughly with fresh hexane (180 mg, 81% yield): ^{1}H NMR (DMSO-d_6) δ 1.61–1.93 (m, 8 H), 2.64 (br, 2 H), 2.84 (t, J = 7.4 Hz, 2 H), 4.07 (br, 2 H), 4.48 (t, J = 7 Hz, 2 H), 7.05–7.30 (m, 7 H), 7.68 (d, J = 8.7 Hz, 1 H); MS-FD m/z 419 (M+). Anal. ($C_{22}H_{26}N_8O$) C, H, N; C: calcd, 63.14; found, 62.02. N: calcd, 26.78; found, 24.86.

2-(4-Phenylbutyl)-5-[4-[4-(1*H*-tetrazol-5-yl)butoxy]phenyl]-2*H*-tetrazole (28). A mixture of 1 (1.62 g, 10 mmol), chloro-4-phenylbutane (1.69 g, 10 mmol), potassium bicarbonate (2.0 g, 20 mmol), and potassium iodide (1.7 g, 10 mmol) in 50 mL of MEK was heated under reflux for 48 h, cooled, and water was added. 2-(4-Phenylbutyl)-5-(4-hydroxyphenyl)-2*H*-tetrazole (0.7 g, 24% yield) was isolated by extraction with ethyl acetate followed by medium-pressure chromatography, eluting with ethyl acetate/hexane (25:75): ^{1}H NMR (DMSO-d_6) δ 1.56 (m, 2 H), 1.93 (m, 2 H), 2.60 (t, J = 7.6 Hz, 2 H), 4.69 (t, J = 6.9 Hz, 2 H), 6.89 (d, J = 8.7 Hz, 2 H), 7.1–7.3 (m, 5 H), 7.84 (d, J = 8.7 Hz, 2 H), 9.97 (s, 1 H).

The phenol (0.7 g, 2.4 mmol) was combined with 5-bromopentanenitrile (0.4 g, 2.4 mmol), potassium carbonate (0.35 g, 2.5 mmol), and potassium iodide (0.3 g, 1.8 mmol) in 30 mL of MEK heated under reflux for 72 h. After cooling, water was added and extraction was carried out with ethyl acetate. The viscous oil obtained subsequently crystallized. The product was utilized without further purification.

The nitrile obtained above (0.56 g, 1.5 mmol) was combined with 1.0 g (3 mmol) of tributyltin azide in 5 mL of DEE and heated under reflux for 3 days. Compound **28** (0.2 g, 32% yield) was isolated by filtration, washed with fresh hexane, and recrystallized from ethyl acetate/hexane: mp 91–93 °C; ^{1}H NMR (DMSO-d_6) δ 1.58 (m, 2 H), 1.72–2.02 (m, 6 H), 2.62 (t, J = 8 Hz, 2 H), 2.96 (t, J = 8 Hz, 2 H), 4.06 (t, J = 7 Hz, 2 H), 4.71 (t, J = 7 Hz, 2 H), 7.06 (d, J = 9 Hz, 2 H), 7.14 (d, J = 7 Hz, 2 H), 7.22 (t, J = 7 Hz, 2 H), 7.93 (d, J = 9 Hz, 2 H), MS-FD m/z 419 (M+). Anal. ($C_{22}H_{26}N_8O$) C, H, N.

5-[4-[4-(1*H*-Tetrazol-5-yl)butoxy]phenyl]-2-[4-(1*H*-tetrazol-5-yl)butyl]-2*H*-tetrazole (29) and 5-[4-[4-(1*H*-Tetrazol-5-yl)butoxy]phenyl]-2-[4-(1*H*-tetrazol-5-yl)butyl]-2*H*-tetrazole (30). A mixture of 1 (3.15 g, 20 mmol), 5-bromopentanenitrile (6.0 g, 41 mmol), potassium carbonate (5.4 g, 39 mmol), and potassium iodide (2.0 g, 12 mmol), in 50 mL of MEK, was heated under reflux for 3 days. After cooling, water was added, and extraction was effected with ethyl acetate. The intermediate nitriles **29A** and **30A** were isolated by medium-pressure chromatography, eluting with ethyl acetate/hexane (1:1).

Nitrile **29A** (3.9 g, 12 mmol) and tributyltin azide (20.0 g, 60 mmol) were combined in 35 mL of DEE and heated under reflux for 4 days. Following workup in the standard way, **29** was recrystallized from methanol/ethyl acetate (3.58 g, 73% yield): mp 138–144 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.66–1.94 (m, 8 H), 2.95 (m, 4 H), 4.06 (t, J = 6.0 Hz, 2 H), 4.73 (t, J = 6.8 Hz, 2 H), 7.08 (d, J = 8.7 Hz, 2 H), 7.94 (d, J = 8.7 Hz, 2 H); MS-FD m/z 411 (M+). Anal. ($C_{17}H_{22}N_{12}O$) C, H, N.

Compound **30A** (0.6 g, 1.9 mmol) was combined with 3.8 g (11.4 mmol) of tributyltin azide in 10 mL of DEE and heated under reflux for 4 days. Following the usual workup, the product was extracted with ethyl acetate. The oily residue was triturated with hexane and crystallized from ethyl acetate/hexane to give **30** (112 mg, 15% yield) as a white crystalline solid: mp 151–153 °C; ^{1}H NMR (DMSO-d_6) δ 1.64 (m, 2 H), 1.74–1.95 (m, 6 H), 2.84 (t, J = 7.4 Hz, 2 H), 2.96 (t, J = 7.2 Hz, 2 H), 4.09 (t, J = 5.9 Hz, 2 H), 4.48 (t, J = 7.0 Hz, 2 H), 7.12 (d, J = 8.7 Hz, 2 H), 7.69 (d, J = 8.7 Hz, 2 H); MS-FD m/z 411 (M+). Anal. ($C_{17}H_{22}N_{12}O$) C, H, N.

2-[[[3-[2-[4-(2*H*-Tetrazol-5-yl)butyl]-2*H*-tetrazol-5-yl]phenyl]methyl]thio]quinoline (31). 2-Quinolinethiol (5.0 g, 31.0 mmol), 3-(bromomethyl)benzonitrile (6.08 g, 31.0 mmol), potassium carbonate (10.7 g, 77.5 mmol), and potassium iodide (5.15 g, 31.0 mmol) were combined in MEK (100 mL) and heated under reflux for 6 h. The mixture was cooled, diluted with ether, washed with water, and dried over sodium sulfate. Following filtration and concentration under reduced pressure the crude product was isolated as yellow crystals. Recrystallization from ethyl acetate/hexane provided 7.02 g (82%) of intermediate nitrile as clear yellow plates.

The nitrile prepared above (6.40 g, 23.2 mmol), sodium azide (4.52 g, 69.6 mmol), and triethylammonium bromide (6.33 g, 34.8 mmol) were combined in 1-methyl-2-pyrrolidinone (80 mL) and heated at 130 °C for 6 h, then at 120 °C overnight. The mixture was cooled and diluted with 1 N hydrochloric acid solution until a precipitate formed. The crude product was collected via vacuum filtration and recrystallized from methanol to provide the tetrazole (6.25 g, 72% yield) as a brown crystalline material.

A mixture of the tetrazole (8.0 g, 25.1 mmol), 5-bromovaleronitrile (4.06 g, 25.1 mmol), potassium carbonate (10.35 g, 75.0 mmol), and potassium iodide (4.15 g, 25.0 mmol) in 200 mL of MEK was heated under reflux for 6 h. The mixture was cooled, diluted with ether, washed with water, dried over sodium sulfate, filtered, and concentrated at reduced pressure to provide a tan solid. The product was converted to the tetrazole, without purification.

The intermediate tetrazole was combined with sodium azide (4.90 g, 75.4 mmol), and triethylammonium bromide (6.80 g, 37.4 mmol) in 1-methyl-1-pyrrolidone (100 mL), and heated at 150 °C for 16 h. The mixture was cooled, diluted with 1 N hydrochloric acid, and extracted with dichloromethane. The combined organics were concentrated at reduced pressure, and the residue was dissolved in 1 N sodium hydroxide and washed with ether. The aqueous layer was acidified with 5 N hydrochloric acid and the resulting precipitate collected by vacuum filtration. Compound **31** was recrystallized from methanol/ethyl acetate as a fibrous solid (4.10 g, 37% yield): mp 95–100 °C; ^{1}H NMR (DMSO-d_6) δ 1.70 (m, 2 H), 1.97 (m, 2 H), 2.92 (t, J = 7.5 Hz, 2 H), 4.69 (s, 2 H), 4.74 (t, J = 6.9 Hz, 2 H), 7.48 (m, 3 H), 7.65 (d, J = 7.8 Hz, 1 H), 7.72 (t, J = 6.9 Hz, 1 H), 7.88 (m, 2 H), 7.98 (d, J = 8.3 Hz, 1 H), 8.21 (d, J = 8.7 Hz, 1 H), 8.26 (s, 1 H), 10.25 (br s, 1 H); MS-FD m/z 444 (M+). Anal. ($C_{22}H_{21}N_9S\cdot 2.4H_2O$) C, H, N.

3-[[5-[3-[(2-Quinolinylthio)methyl]phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid (32) and 3-[[5-[3-[(2-Quinolinylthio)methyl]phenyl]-1*H*-tetrazol-1-yl]methyl]benzoic Acid (33). 2-Quinolinethiol (5.0 g, 31.0 mmol), 3-(bromomethyl)-benzonitrile (6.08 g, 31.0 mmol), potassium carbonate (10.7 g, 77.5 mmol), and potassium iodide (5.15 g, 31.0 mmol) were combined in MEK (100 mL) and heated under reflux for 6 h. The mixture was cooled, diluted with ether, washed with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide yellow crystals. Recrystallization from ethyl acetate/hexane provided 7.02 g (82%) of intermediate nitrile as clear yellow plates.

The nitrile prepared above (6.40 g, 23.2 mmol), sodium azide (4.52 g, 69.6 mmol), and triethylammonium bromide (6.33 g, 34.8 mmol) were combined in 1-methyl-2-pyrrolidinone (80 mL) and heated at 130 °C for 6 h, then at 120 °C overnight. The mixture was cooled and diluted with 1 N hydrochloric acid solution until a precipitate formed. The crude product was collected via vacuum filtration and recrystallized from methanol to provide the tetrazole (5.12 g, 69% yield) as a brown crystalline material.

The tetrazole (2.00 g, 6.27 mmol), methyl 3-(bromomethyl)-benzoate (1.44 g, 6.27 mmol), potassium carbonate (2.17 g, 15.7 mmol), potassium iodide (1.04 g, 6.27 mmol), and cesium carbonate (210 mg, 0.630 mmol) were combined in MEK (25 mL) and heated

under reflux for 18 h. The mixture was cooled, diluted with ether, washed with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide an orange oil. The products of alkylation of the tetrazole on the 1- and on the 2-position were separated by HPLC. The methyl ester of **32** was obtained as a yellow oil (2.44 g, 83% yield). The methyl ester of **33** was also obtained as a yellow oil (0.42 g, 14% yield).

The methyl ester of **32** (2.44 g, 5.22 mmol) and 5 N sodium hydroxide (2 mL, 10 mmol of sodium hydroxide) were combined in 30 mL of 2:1 methanol/THF and allowed to stir at room temperature for 6 h. The reaction mixture was washed with ether, and the pH was adjusted to 6 with 1 N hydrochloric acid. The resultant precipitate was collected by vacuum filtration. Compound **32** was obtained as a white microcrystalline material (2.10 g, 89% yield) by recrystallization from ethyl acetate/hexane: mp 155 °C; ^{1}H NMR (DMSO-d_6) δ 4.64 (s, 2 H), 6.07 (s, 2 H), 7.36 (d, J = 8.7 Hz, 1 H), 7.40–7.58 (m, 3 H), 7.64 (m, 3 H), 7.90 (m, 4 H), 7.98 (s, 1 H), 8.12 (d, J = 8.7 Hz, 1 H), 8.25 (s, 1 H), 13.12 (s, 1 H). Anal. ($C_{25}H_{19}N_5O_2S$) C, H, N, S.

Compound **33** was similarly prepared by hydrolysis of the other ester in 35% yield: mp 96 °C; ^{1}H NMR (DMSO-d_6) δ 4.63 (s, 2 H), 5.81 (s, 2 H), 7.25 (d, J = 7.9 Hz, 1 H), 7.34 (m, 2 H), 7.49 (m, 2 H), 7.55 (d, J = 7.8 Hz, 1 H), 7.67 (m, 2 H), 7.74 (d, J = 7.6 Hz, 1 H), 7.76–8.95 (m, 4 H), 8.13 (d, J = 8.7 Hz, 1 H), 13.09 (s, 1 H). Anal. ($C_{25}H_{19}N_5O_2S$) C, H, N, S.

Prepared by the same method were compounds **34–36**.

4-[[5-[3-[(2-Quinolinylthio)methyl]phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid (34). Compound **34** was obtained as a white crystalline solid in 65% yield: mp 184 °C; ^{1}H NMR (DMSO-d_6) δ 4.64 (s, 2 H), 6.08 (s, 2 H), 7.37 (d, J = 8.7 Hz, 1 H), 7.44 (m, 4 H), 7.65 (m, 2 H), 7.88 (m, 3 H), 7.93 (d, J = 8.1 Hz, 2 H), 8.14 (d, J = 8.7 Hz, 1 H), 8.26 (s, 1 H); MS-FD m/z 454 (M+). Anal. ($C_{25}H_{19}N_5O_2S$) C, H, N, S.

2-[[5-[4-[(2-Quinolinylthio)methyl]phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid (35). Compound **35** was obtained as a white crystalline solid in 17% yield: mp 203–204 °C; ^{1}H NMR (DMSO-d_6) δ 4.62 (s, 2 H), 6.29 (s, 2 H), 7.18 (d, J = 7.5 Hz, 1 H), 7.37 (d, J = 8.7 Hz, 1 H), 7.49 (m, 2 H), 7.57 (t, J = 7.4 Hz, 1 H), 7.66 (d, J = 8.2 Hz, 2H), 7.71 (t, J = 7.2 Hz, 1 H), 7.87 (d, J = 7.9 Hz, 1 H), 7.94 (m, 4 H), 8.14 (d, J = 8.7 Hz, 1 H); MS-FD m/z 454 (M+). Anal. ($C_{25}H_{19}N_5O_2S$) C, H, N, S.

2-[[5-[3-[(2-Quinolinylthio)methyl]phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid (36). Compound **36** was obtained as a white crystalline solid in 13% yield: mp 201–206 °C; ^{1}H NMR (DMSO-d_6) δ 4.64 (s, 2 H), 6.30 (s, 2 H), 7.18 (d, J = 7.4 Hz, 1 H), 7.38 (d, J = 8.7 Hz, 1 H), 7.42–7.54 (m, 3 H), 7.57 (t, J = 7.4 Hz, 1 H), 7.66 (m, 2 H), 7.87 (m, 3 H), 7.96 (t, J = 7.4 Hz, 1 H), 8.15 (d, J = 8.6 Hz, 1 H), 8.23 (s, 1 H); MS-FD m/z 454 (M+). Anal. ($C_{25}H_{19}N_5O_2S$) C, H, N.

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Registry No. **1**, 51517-88-5; **2**, 138630-92-9; **3**, 138630-93-0; **4**, 138630-94-1; **5**, 138630-95-2; **6**, 138630-96-3; **7**, 138630-97-4; **8**, 138630-98-5; **9**, 138630-99-6; **10**, 138631-00-2; **11**, 138631-01-3; **11** nitrile, 138631-02-4; **12**, 138631-03-5; **13**, 138631-04-6; **13** tetrazole, 138631-05-7; **13** nitrile, 138631-06-8; **14**, 138631-07-9; **15**, 138631-08-0; **15** nitrile, 138631-09-1; **16**, 138631-10-4; **17**, 138631-11-5; **18**, 138631-12-6; **19**, 138631-13-7; **20**, 138631-14-8; **21**, 138631-15-9; **22**, 138631-16-0; **23**, 138631-17-1; **24**, 138631-18-2; **25**, 138631-19-3; **26**, 138631-20-6; **27**, 138631-21-7; **28**, 138631-23-9; **28** alcohol, 138631-24-0; **28** nitrile, 138631-25-1; **29**, 138631-26-2; **29A**, 138631-27-3; **30**, 138631-28-4; **30A**, 138631-29-5; **31**, 138631-30-8; **31** intermediate nitrile, 138631-31-9; **31** tetrazole, 138631-32-0; **31** nitrile, 138631-33-1; **32**, 138631-34-2; **32** methyl ester, 138631-35-3; **33**, 138631-36-4; **33** methyl ester, 138631-37-5; **34**, 138631-38-6; **35**, 138631-39-7; **36**, 138631-40-0; Ph-$(CH_2)_3OSO_2Me$, 69804-99-5; $Ph(CH_2)_5OSO_2Me$, 75803-20-2; Ph-$(CH_2)_4OSO_2Me$, 65512-08-5; $Ph(CH_2)_4O$-p-C_6H_4-CN, 138631-41-1; p-$PrOC_6H_4CN$, 60758-84-1; $CF_3(CH_2)_5Br$, 111670-37-2; Ph-$(CH_2)_6OSO_2Me$, 61440-48-0; $CF_3(CH_2)_7Br$, 407-67-0; $CN(CH_2)_6Br$, 20965-27-9; $CN(CH_2)_3Br$, 5332-06-9; o-$MeC_6H_4SO_2N{=}C{=}O$, 32324-19-9; m-$CNC_6H_4O(CH_2)_4Ph$, 138631-42-2; 5-[4-(4-phenylbutoxy)phenyl]-2*H*-tetrazole-2-pentanoic acid methyl ester, 138631-43-3; 5-bromopentanonitrile, 5414-21-1; (2-bromoethyl)benzene, 103-63-9; tributyltin azide, 17846-68-3; 2-(chloromethyl)quinoline hydrochloride, 3747-74-8; 3-iodopropane, 107-08-4; 4-cyanophenol, 767-00-0; 2-(bromomethyl)benzofuran, 41014-27-1; 1,1,1-trifluoro-5-bromopentane, 54932-74-0; 8-bromooctanenitrile, 54863-44-4; 6-bromohexanenitrile, 6621-59-6; 9-bromononanenitrile, 54863-45-5; 1-iododecane, 2050-77-3; 5-bromopentanoic acid methyl ester, 5454-83-1; 3-cyanophenol, 873-62-1; chloro-4-phenylbutane, 4830-93-7; 2-quinolinethiol, 2637-37-8; 3-(bromomethyl)benzonitrile, 28188-41-2; methyl 3-(bromomethyl)benzoate, 1129-28-8; methyl 2-(bromomethyl)benzoate, 2417-73-4; methyl 4-(bromomethyl)benzoate, 2417-72-3; leukotriene D_4, 73836-78-9.

Optimization of the Quinoline and Substituted Benzyl Moieties of a Series of Phenyltetrazole Leukotriene D_4 Receptor Antagonists[1]

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This report describes the development of a series of highly potent quinoline-based leukotriene D_4 (LTD_4) receptor antagonists containing an *N*-benzyl-substituted phenyltetrazole moiety. They were designed to provide both the correct positioning of the acidic function and secondary lipophilic domain required for strong receptor binding. Members of this series possess high activity in blocking LTD_4-induced contractions of isolated guinea pig ileum. Compound **32**, LY287192 (2-[[5-[3-[2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-2*H*-tetrazol-2-yl]methyl]-5-fluorobenzoic acid sodium salt), blocked contraction with a pK_B value of 9.1 ± 0.3. Qualitative structure–activity studies have demonstrated specific requirements for the best activity. In particular, ortho substitution of the benzyl group with an acidic function was crucial for maximum potency. In cases similar to **32**, where the benzyl group possesses an ortho carboxylate, the N-2-substituted tetrazole isomer showed 100-fold greater activity relative to the corresponding N-1 isomer. This pattern was reversed when the acid was substituted at the para position. The quinoline unit may be replaced by other nitrogen-containing heterocycles.

Products of the arachidonic acid cascade, including the leukotrienes, have been implicated in several inflammatory disease states.[2] Interest in the cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) continues to be strong as evidenced by numerous reports of structurally distinct leukotriene antagonists.[3,4] Several leukotriene D_4 (LTD_4) receptor antagonists have undergone clinical evaluation, and three recent reports suggest that these agents may prove efficacious in the treatment of asthma.[5] The initial publi-

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