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.

Acknowledgment. We thank the Lilly Research Laboratories Physical Chemistry Department for collection of physical data on these compounds and Jack Cambell for the high pressure fluorination reactions.

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]-2H-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]-2H-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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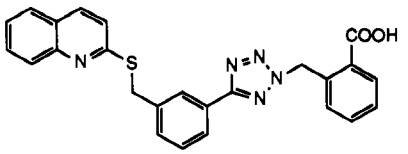
0022-2623/92/1835-1200$03.00/0

cation in this series reported on the design and synthesis of a novel series of phenyltetrazole-containing LTD_4 receptor antagonists.[1a] The initial structure–activity exploration of this series led to the 2-thio-substituted quinoline compound LY231898. We now describe further



LY231898

optimization of this series with particular emphasis on the nature of the substituted benzyl moiety.

Many of the potent LTD_4 antagonists described in recent years have been of the "dual-chain" variety, for example MK-571[6] and LY170680[7] (Chart I). Each contains a primary acid binding group (presumably equivalent to one of the carboxylic acid groups of LTD_4) and a secondary group that may be either acidic or polar in nature. Other notable antagonists such as ICI-204219[8] and MCI-826[9] achieve excellent potency through utilization of a single-

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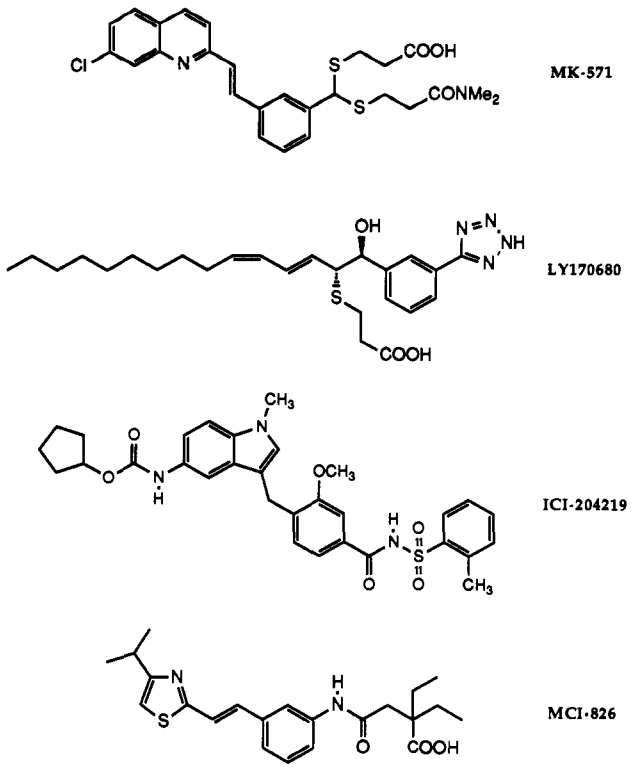
Chart I

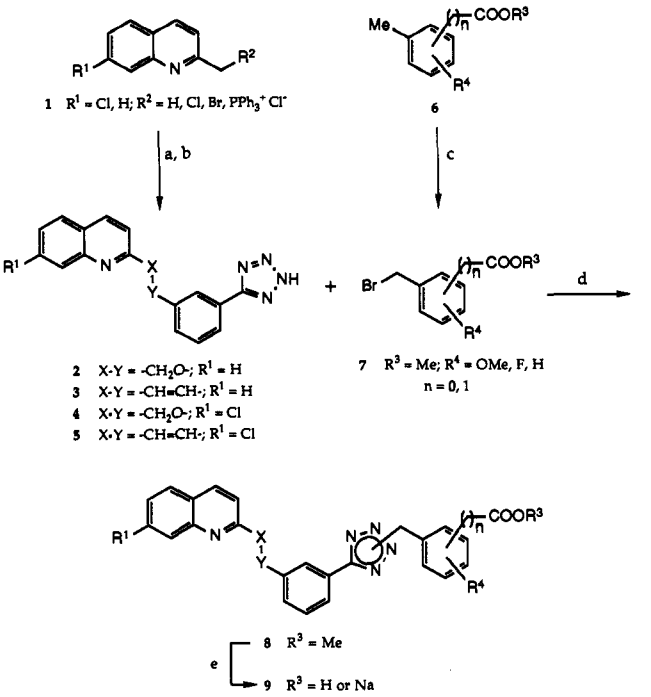


chain strategy. Extensive molecular modeling[1a,10] suggests that, in low energy conformations of LTD_4, the two polar arms lie in a plane situated approximately 90° to a second plane containing the triene/lipophilic tail. One common feature of the structures depicted in Chart I is the use of a specific grouping of atoms, for example the benzyl linkage in ICI-204219, designed to twist one or two binding chains out-of-plane relative to a triene/lipophilic tail mimic. In addition, ICI-204219 and MCI-826 also feature a secondary lipophilic binding domain represented by, respectively, an ortho-substituted methylphenyl group and a *gem*-diethyl group. In each case this domain lies close to, and even beyond, the acid binding group relative to the triene equivalent. We reasoned that the benzyl-substituted phenyltetrazole manifold of LY231898 is most likely playing an equivalent role.[1a]

Chemistry

The general synthetic pathway for the preparation of compounds in Table I is illustrated in Scheme I. Formation of the methyleneoxy-linked quinoline phenyltetrazole intermediates proceeded via the sodium hydride mediated alkylation of 3-cyanophenol with either 2-(chloromethyl)quinoline or 7-chloro-2-(bromomethyl)-quinoline[11] to provide the corresponding nitriles; these were then converted to tetrazoles **2**[4j,12] and **4** with lithium azide and triethylammonium bromide in either 2-methoxyethanol (method 1) or dimethylformamide (method 2). We found with our series that the use of lithium azide gave consistently higher and more reproducible yields than other tetrazole formation methods.[4j,13] Styryl quinoline intermediate **3** was prepared via the Wittig coupling of the corresponding phosphorous ylide (generated from *n*-butyllithium and 2-[(triphenylphosphonium)methyl]-quinoline chloride) with 3-cyanobenzaldehyde. Intermediate **5** was prepared by the acetic anhydride mediated condensation of 3-cyanobenzaldehyde with 7-chloroquinaldine.[14] The trans olefins predominated in both cases (>95:5 *E*/*Z*). Bromination of the tolyl derivatives **6** with *N*-bromosuccinimide provided benzyl bromides **7**.

Scheme I[a]



[a] (a) R^2 = H: 3-cyanobenzaldehyde, Ac_2O, xylenes, reflux. R^2 = Cl or Br: NaH, DMF, then 3-cyanophenol. $R^2 = PPh_3^+Cl^-$: *n*-BuLi,THF, then 3-cyanobenzaldehyde. (b) LiN_3, triethylammonium bromide, either 2-methoxyethanol (method 1) or DMF (method 2), 120 °C. (c) NBS, benzoyl peroxide, CCl_4, *hν*. (d) K_2CO_3, KI, 2-butanone, reflux. (e) Aqueous NaOH, MeOH/THF.

Alkylation of tetrazoles **2–5** with benzyl bromides **7** proceeded uneventfully under standard conditions. All alkylation reactions studied favored the less sterically crowded N-2-substituted tetrazoles. The ratio of N-2 to N-1 isomers in most examples was 4:1. In a few cases, as with the more sterically demanding benzyl bromides, only formation of the N-2 isomer was detected. The resulting generic esters **8** were hydrolyzed with aqueous sodium hydroxide to obtain the corresponding carboxylic acids or carboxylate salts **9**. Compounds **15–18**, **21–28**, and **32** were prepared via the methods outlined above. Compound **19** was obtained by alkylation of **2** with benzyl bromide **10** (Scheme II) followed by acid hydrolysis, sodium salt formation, and reverse-phase chromatography. Compounds **29–31** were prepared in an analogous manner from quin-

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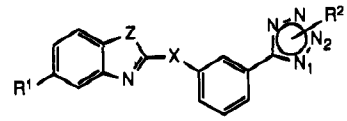
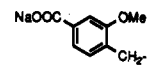
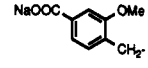
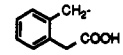
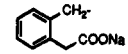
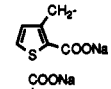
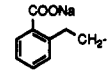
Table I. In Vitro Antagonism of LTD_4-Induced Guinea Pig Ileum Contraction



compd	R^1	Z	X	substitution at tetrazole nitrogen[a]	R^2	pK_B[b]
15	H	—CH=CH—	—CH_2O—	N-2		8.3 ± 0.1
16	H	—CH=CH—	—CH_2O—	N-2		8.4 ± 0.1
17	H	—CH=CH—	—CH_2O—	N-1		6.5 ± 0.1
18	H	—CH=CH—	—CH=CH—	N-2		8.5 ± 0.1
19	H	—CH=CH—	—CH_2O—	N-2		8.4 ± 0.1
20	H	—CH=CH—	—CH_2O—	N-2		9.1 ± 0.3
21	H	—CH=CH—	—CH=CH—	N-2		7.1 ± 0.1
22	H	—CH=CH—	—CH=CH—	N-2		7.4 ± 0.2
23	H	—CH=CH—	—CH=CH—	N-1		8.2 ± 0.1
24	H	—CH=CH—	—CH_2O—	N-2		7.6 ± 0.05
25	H	—CH=CH—	—CH=CH—	N-2		7.7 ± 0.1
26	H	—S—	—CH_2O—	N-2		8.3 ± 0.03
27	Cl	—CH=CH—	—CH_2O—	N-2		8.7 ± 0.1
28	Cl	—CH=CH—	—CH=CH—	N-2		8.8 ± 0.1
29	H	—CH=CH—	—CH=CH—	N-2		7.9 ± 0.1
30	Cl	—CH=CH—	—CH=CH—	N-2		7.8 ± 0.1
31	Cl	—CH=CH—	—CH=CH—	N-2		7.9 ± 0.1
32 (LY287192)	Cl	—CH=CH—	—CH=CH—	N-2		9.1 ± 0.3

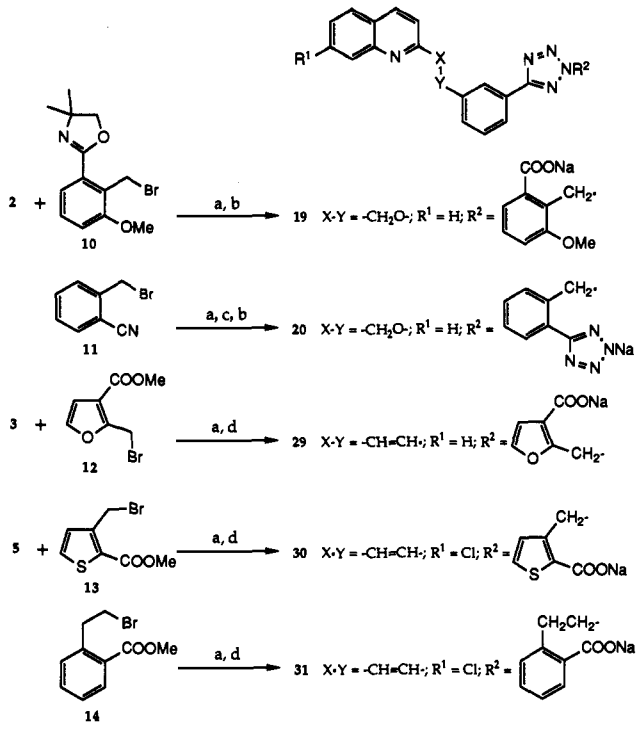
[a] Substitution pattern for the N-2 isomers is as depicted for LY231898. [b] Mean values ±SEM of a minimum of four tissue determinations. [c] Tet = 2*H*-tetrazol-5-yl.

oline phenyltetrazole **3** (or **5**) via bromides **12**–**14**. Alkylation of **2** with 2-(bromomethyl)benzonitrile (**11**) and subsequent tetrazole formation (method 1), followed by conversion to the sodium salt, provided compound **20**.

Results and Discussion

Our initial studies showed that LY231898 inhibits the LTD_4-induced contraction of isolated guinea pig ileum with a pK_B value of 7.0.[1a] Substitution of the thiomethyl group with a methyleneoxy group gave a large increase in potency (compound **15**, Table I), possibly due in part to the shorter bond lengths associated with the methyleneoxy linkage. No difference was observed between the activities of the methyleneoxy-linked compounds and those linked by a trans olefin (compare **16** with **18**), a phenomenon found in other quinoline-based series.[41] In general, only the so-

Scheme II[a]



[a] (a) K_2CO_3, KI, 2-butanone, reflux. (b) Aqueous HCl, then aqueous NaOH, HP-20 chromatography. (c) LiN_3, triethylammonium bromide, 2-methoxyethanol, 120 °C (method 1). (d) Aqueous NaOH, MeOH/THF, HP-20 chromatography.

dium salts were evaluated. These proved easier to purify and exhibited consistently better aqueous solubility than the free acids. Tetrazole analogue **20** exhibited somewhat better activity than the corresponding carboxylic acid derivative **16**, a trend also observed in other series.[4c]

Substitution of the carboxylic acid in the ortho position proved superior to the meta (compare **18** and **21**) or para (compare **19** and **22**) analogues in the N-2-substituted series. In compound **16**, containing an ortho carboxylate benzyl group, the major N-2-substituted isomer showed 100-fold greater activity on guinea pig ileum (compare **16** with **17**). In the case of isomers **22** and **23**, however, the pattern was reversed, although not to the same degree. This observation underscores the sensitive nature of the primary acid binding domain of the receptor. N-1-Substituted tetrazole **23** takes advantage of the para disposition of the carboxylic acid to inhibit LTD_4-induced contractions with equal effectiveness relative to ortho-substituted N-2 isomer **18** or **19**. Compound **23** manages this despite the crowded nature characteristic of the N-1-substituted tetrazoles, an environment known to force the tetrazole ring out-of-plane relative to the phenyl group.[1a] The methoxy group in **22/23** was originally incorporated in an attempt to further crowd the area around the benzyl linkage and thus vary the position of the acidic group, a strategy used successfully in antagonists such as ICI-204219[15] (see Chart I). No change in activity was observed when a methoxy was placed ortho to the benzyl methylene group in the ortho acid series (compound **19**). Any advantage gained by introduction of a methoxy, as in **19**, might possibly be countered by the decreased acidity resulting from the presence of an electron-donating group.

Methylene spacers were inserted at two key points to further adjust the position of the benzyl carboxyl group. Spacing the acid directly off the ortho position by one carbon led to a pronounced decrease in activity (compare **16/18** with **24/25**). Placing one carbon between the benzyl methylene and the tetrazole nitrogen, as in compound **31**, likewise led to reduced activity.

Chlorine substitution of the quinoline group at the 7-position has been shown to increase intrinsic potency of the quinoline-based antagonists.[6b] As predicted, increased activity was observed when we incorporated a 7-chloroquinoline into our series (compare **16/18** with **27/28**), although the gain was marginal at best. There is possibly a lipophilic binding pocket at the receptor that accommodates this chlorine atom. Alternatively, an electronic effect of the chlorine may significantly perturb the electron density of the quinoline nitrogen. This nitrogen is critical in the quinoline-based antagonists and may be a metal chelating atom.[6b,16] Another nitrogen-containing heterocycle may be substituted for quinoline without loss of activity (compare **16** with benzothiazole **26**); this also has been observed previously in other series.[4j] The addition of a highly electron-withdrawing halogen to the benzyl group, as in compound **32** (LY287192), appears to slightly enhance activity, perhaps as a result of the increased acidity of the carboxyl group.

We attempted to incorporate methyl-substituted heterocyclic systems as a replacement for the benzyl group. Substitution with a 5-membered ring would be expected to slightly perturb the geometry of the associated carboxyl group. This might have a significant effect on potency provided that the electronic nature of the heterocycle did not further compromise the system. Alternatively, a heterocycle may be unable to fulfill the role of a secondary lipophilic binding group to the same degree as phenyl. In the event, the two examples prepared resulted in a decrease in activity (compare compounds **18** and **29**, and compounds **28** and **30**). The ortho-substituted benzyl group appears to be optimal in our quinoline phenyltetrazole series.

In summary, the SAR of a series of highly potent quinoline-based phenyltetrazole[17] LTD_4 receptor antagonists was optimized and resulted in a 100-fold increase in activity over our original quinoline lead LY231898. The incorporation of a benzyl group with an ortho-substituted acid moiety was found to be optimal for the best activity. The *N*-benzyl methylene linkage provides the necessary out-of-plane twist characteristic of the more potent LTD_4 receptor antagonists. The bulk of the benzyl group may also fill a secondary lipophilic binding domain as described above. In addition, preliminary results indicate that members of this series possess in vivo activity via both the iv and oral routes.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were determined on a GE QE-300 spectrometer. All chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. Chemical shifts of aromatic protons of quinoline species in DMSO-d_6 are concen-

(15) Brown, F. J.; Yee, Y. K.; Cronk, L. A.; Hebbel, K. C.; Krell, R. D.; Snyder, D. W. Evolution of a Series of Peptidoleukotriene Antagonists: Synthesis and Structure-Activity Relationships of 1,6-Disubstituted Indoles and Indazoles. *J. Med. Chem.* **1990**, *33*, 1771–1781.

(16) Musser, J. H.; Kreft, A. F.; Chang, J.; Lewis, A. J. Synthesis of [[(Naphthaleneylmethoxy)- and [[(Quinolinylmethoxy)-phenyl]amino]oxoalkanoic Acid Esters. A Novel Series of Leukotriene D_4 Antagonists and 5-Lipoxygenase Inhibitors. *J. Med. Chem.* **1986**, *29*, 1429–1435.

(17) For other examples of leukotriene antagonists incorporating a phenyltetrazole scaffold, see ref 4j, 4o, and 12. See also: Brown, F. J.; Bernstein, P. R.; Yee, Y. K. European Patent 179619, 1986.

tration dependent. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, b = broad, m = multiplet. Infrared spectra were determined on a Nicolet DX10 FT-IR spectrophotometer. Mass spectral data were determined on a CEC-21-110 spectrometer using electron impact (EI) conditions, a MAT-731 spectrometer using free desorption (FD) conditions, or a VG ZAB-3F spectrometer using fast atom bombardment (FAB) conditions. With the exception of NMR spectra, all spectroscopic and analytical data were determined by the Physical Chemistry Department (MC525) of the Lilly Research Laboratories. Reported analytical data are within ±0.4% of the theoretical values unless otherwise indicated. High-pressure liquid chromatography (HPLC) purification was performed on a Waters Prep LC-500 using ethyl acetate/hexane gradients. Reverse-phase chromatography was performed on MCI CHP20P gel using an acetonitrile/water gradient. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. All reactions were conducted under argon atmosphere with stirring unless otherwise noted; yields were not optimized. All styryl quinoline compounds are light sensitive and should be stored in total darkness.

2-[2-[3-(2*H*-Tetrazol-5-yl)phenyl]ethenyl]quinoline (3). (a) 2-[2-(3-Cyanophenyl)ethenyl]quinoline (3a). To a solution of 2-[(triphenylphosphonium)methyl]quinoline chloride (41.4 g, 94.1 mmol, prepared in the usual manner from 2-(chloromethyl)quinoline and triphenylphosphine)[11] in THF (500 mL) was added 1.6 M *n*-BuLi in hexane (64.4 mL, 103 mmol) dropwise at room temperature. After the mixture stirred for 0.5 h a solution of 3-cyanobenzaldehyde (12.3 g, 94.1 mmol) dissolved in a minimum of THF was added dropwise, and the resulting mixture stirred at room temperature for 5 h. The mixture was diluted with ethyl acetate and washed with water (1×), dried (sodium sulfate), filtered, and concentrated in vacuo. The resulting material was chromatographed (LC-500) to provide 17.1 g (71%) product: ^{1}H NMR (DMSO-d_6) 8.35 (d, J = 9 Hz, 1 H), 8.21 (s, 1 H), 8.06 (d, J = 9 Hz, 1 H), 7.52–8.02 (m, 9 H); MS-FD m/e 256 (p); IR (KBr, cm^{-1}) 3400 (b), 2230, 1597, 1504, 976, 824. Anal. ($C_{18}H_{12}N_2$) C, H, N.

(b) General Procedure for Tetrazole Formation Method 1. Compound 3. A mixture of **3a** (17.2 g, 67.3 mmol), lithium azide (8.20 g, 167 mmol), and triethylammonium bromide (11.0 g, 60.4 mmol) in 2-methoxyethanol (250 mL) was heated at 120 °C for 3 h. A further portion of lithium azide (1.60 g, 32.7 mmol) was added and the resulting mixture heated for an additional 0.5 h. The reaction mixture was cooled to room temperature and diluted with 1 N HCl solution. The resulting precipitate was collected via vacuum filtration. Recrystallization from methanol provided 16.5 g (82%) product: mp 239 °C; ^{1}H NMR (DMSO-d_6) 8.43 (s, 1 H), 8.37 (d, J = 10.5 Hz, 1 H), 7.86–8.04 (m, 6 H), 7.73 (t, J = 9 Hz, 1 H), 7.62–7.69 (m, 2 H), 7.56 (t, J = 9 Hz, 1 H); MS-FD m/e 299 (p); IR (CHCl$_3$, cm^{-1}) 3400 (b), 1634, 1614, 1425, 1150, 961, 816. Anal. ($C_{18}H_{13}N_5 \cdot 0.5H_2O$) C, H, N.

7-Chloro-2-[[3-(2*H*-tetrazol-5-yl)phenoxy]methyl]quinoline (4). (a) General Procedure for Phenol Alkylations. 7-Chloro-2-[(3-cyanophenoxy)methyl]quinoline (4a). To a solution of 3-cyanophenol (1.19 g, 10.0 mmol) in dry dimethylformamide (25 mL) was carefully added 95% sodium hydride (278 mg, 11.0 mmol) in small portions at room temperature. After stirring for 0.5 h, 2-(bromomethyl)-7-chloroquinoline[11] (2.58 g, 10.0 mmol) was added in one portion and the resulting mixture allowed to stir for 3 h. The mixture was diluted with ethyl acetate and washed with water (2×), dried (sodium sulfate), filtered, and concentrated in vacuo. The resulting material was chromatographed (LC-500) to provide 2.00 g (68%) product: ^{1}H NMR (DMSO-d_6) 8.48 (d, J = 9 Hz, 1 H), 8.06 (m, 2 H), 7.72 (d, J = 10 Hz, 1 H), 7.65 (dd, J = 10, 2 Hz, 1 H), 7.57 (d, J = 2 Hz, 1 H), 7.50 (t, J = 9 Hz, 1 H), 7.41 (m, 2 H), 5.42 (s, 2 H).

(b) Compound 4. Compound **4a** (2.00 g, 6.80 mmol) was subjected to tetrazole formation method 1 described above for the preparation of compound **3**. This protocol provided 2.29 g (100%) product: mp > 220 °C dec, ^{1}H NMR (DMSO-d_6) 8.48 (d, J = 8.6 Hz, 1 H), 8.07 (s, 1 H), 8.05 (d, J = 8.9 Hz, 1 H), 7.73 (d, J = 8.5 Hz, 1 H), 7.72 (s, 1 H), 7.65 (m, 2 H), 7.52 (t, J = 8.1 Hz, 1 H), 7.28 (dd, J = 8.2, 2.4 Hz, 1 H), 5.46 (s, 2 H).

7-Chloro-2-[2-[3-(2*H*-tetrazol-5-yl)phenyl]ethenyl]quinoline Hydrochloride (5). (a) 7-Chloro-2-[2-(3-cyanophenyl)ethenyl]quinoline (5a). A solution of 7-chloroquinaldine (8.90 g, 50.1 mmol), 3-cyanobenzaldehyde (6.60 g, 150 mmol), and acetic anhydride (15.3 g, 150 mmol) in xylenes (100 mL) was refluxed for 7 h.[14] The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with water (1×), dried (sodium sulfate), filtered, and concentrated in vacuo to reveal an off-white solid. Recrystallization from ethyl acetate/hexane provided 8.90 g (61%) product: mp 137–139 °C dec; ^{1}H NMR (DMSO-d_6) 8.39 (d, J = 9 Hz, 1 H), 8.19 (s, 1 H), 8.02 (d, J = 8 Hz, 1 H), 7.97 (s, 1 H), 7.95 (d, J = 8 Hz, 1 H), 7.82 (m, 3 H), 7.60 (m, 3 H); MS-FD m/s 292 (p + 1, 36), 291 (p, 25), 290 (p - 1, 100); IR (CHCl$_3$, cm^{-1}) 2976, 2235, 1611, 1597, 1499, 1072. Anal. ($C_{18}H_{11}N_2Cl$) C, H, N.

(b) General Procedure for Tetrazole Formation Method 2. Compound 5. A mixture of **5a** (8.90 g, 30.7 mmol), lithium azide (4.60 g, 93.9 mmol), and triethylammonium bromide (8.50 g, 46.7 mmol) in dimethylformamide (100 mL) was heated at 120 °C for 18 h. The reaction mixture was cooled in an ice bath and 5 N HCl solution was added until precipitate formation ceased. The crude product was collected via vacuum filtration and recrystallized from methanol/ethyl acetate to provide 10.0 g (98%) product as yellow crystals: mp 195 °C dec; ^{1}H NMR (DMSO-d_6) 10.45 (bs, 1 H), 8.52 (s, 1 H), 8.46 (d, J = 8.7 Hz, 1 H), 8.09 (d, J = 7.8 Hz, 1 H), 8.05 (d, J = 1.7 Hz, 1 H), 7.92–8.01 (m, 3 H), 7.87 (d, J = 7.8 Hz, 1 H), 7.65 (d, J = 5.5 Hz, 1 H), 7.55–7.62 (m, 2 H); MS-FD m/e 335 (p + 1, 43), 334 (p, 51), 333 (p - 1, 100); IR (KBr, cm^{-1}) 3494 (b), 2597 (b), 1594, 1496, 1019, 968, 831. Anal. ($C_{18}H_{12}N_5Cl \cdot HCl$) C, H, N.

2-[[5-[3-(Quinolin-2-ylmethoxy)phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid (15). (a) General Procedure for Tetrazole Alkylations. 2-[[5-[3-(Quinolin-2-ylmethoxy)phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid Methyl Ester (15a) and 2-[[5-[3-(Quinolin-2-ylmethoxy)phenyl]-1*H*-tetrazol-1-yl]methyl]benzoic Acid Methyl Ester (17a). A mixture of **2**[4j] (10.0 g, 33.2 mmol), methyl 2-(bromomethyl)benzoate (7.60 g, 33.2 mmol, prepared by the bromination of methyl *o*-toluate using the procedure described below for the preparation of compound **10**), potassium carbonate (22.8 g, 165 mmol), and potassium iodide (5.50 g, 33.1 mmol) in 2-butanone (500 mL) was refluxed for 8 h. The mixture was cooled to room temperature, diluted with ethyl acetate, washed with water (1×), dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (LC-500) provided products **15a** (9.01 g, 60%) and **17a** (1.10 g, 7%).

15a: mp 126–128 °C; ^{1}H NMR (DMSO-d_6) 8.38 (d, J = 8.6 Hz, 1 H), 8.00 (d, J = 8.4 Hz, 1 H), 7.95 (m, 2 H), 7.75 (t, J = 8.4 Hz, 1 H), 7.58–7.70 (m, 5 H), 7.51 (t, J = 7.5 Hz, 1 H), 7.45 (t, J = 7.9 Hz, 1 H), 7.29 (d, J = 7.2 Hz, 1 H), 7.21 (dd, J = 7.9, 2.0 Hz, 1 H), 6.27 (s, 2 H), 5.45 (s, 2 H), 3.78 (s, 3 H); MS-FD m/e 451 (p); IR (CHCl$_3$, cm^{-1}) 3020, 2950, 1719, 1267, 1284. Anal. ($C_{26}H_{21}N_5O_3$) C, H, N.

17a: ^{1}H NMR (DMSO-d_6) 8.39 (d, J = 8 Hz, 1 H), 7.96 (m, 2 H), 7.90 (d, J = 8 Hz, 1 H), 7.74 (t, J = 7 Hz, 1 H), 7.66 (d, J = 9 Hz, 1 H), 7.57 (m, 3 H), 7.48 (d, J = 8 Hz, 1 H), 7.44 (s, 1 H), 7.31 (m, 2 H), 7.06 (d, J = 8 Hz, 1 H), 5.98 (s, 2 H), 5.42 (s, 2 H), 3.63 (s, 3 H).

General Procedure for Ester Hydrolysis. Compound 15. A solution of **15a** (3.00 g, 6.65 mmol) in methanol (20 mL)/THF (15 mL) was treated at room temperature with 5 N NaOH solution (2.0 mL). When the reaction was judged complete via TLC, the mixture was diluted with water and washed with ether (1×). The aqueous layer was adjusted to pH 6 with 5 N HCl solution and the resulting precipitate collected via vacuum filtration (in cases where the product was an oil methylene chloride was used as the extracting solvent). Recrystallization from ethyl acetate/methanol provided 2.81 g product (97%) as a white crystalline material: mp 233–236 °C; ^{1}H NMR (DMSO-d_6) 8.65 (d, J = 8.6 Hz, 1 H), 8.16 (d, J = 8.5 Hz, 1 H), 8.10 (d, J = 8.1 Hz, 1 H), 7.99 (d, J = 1 Hz, 1 H), 7.89 (t, J = 6.9 Hz, 1 H), 7.86 (d, J = 8.4 Hz, 1 H), 7.71 (t, J = 7.5 Hz, 1 H), 7.71 (s, 1 H), 7.46–7.66 (m, 4 H), 7.23 (m, 2 H), 6.31 (s, 2 H), 5.57 (s, 2 H); MS-EI m/e 437 (p, 2), 142 (100), 105 (75); IR (KBr, cm^{-1}) 3450 (b), 2800 (b), 1714, 1241, 1222. Anal. ($C_{25}H_{19}N_5O_3$) C, H, N.

General Procedure for Sodium Salt Formation and Purification. 2-[[5-[3-(Quinolin-2-ylmethoxy)phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid Sodium Salt (16). Compound **15** (2.81 g, 6.43 mmol) was dissolved in ~0.5 N NaOH solution and chromatographed on HP-20 resin. Pure deionized water was

initially passed down the column after sample loading until the eluent reached approximately pH 8. The combined fractions were freeze-dried to provide 1.75 g (61%) product: ^{1}H NMR (DMSO-d_6) 8.40 (d, J = 8.5 Hz, 1 H), 8.00 (d, J = 8.9 Hz, 1 H), 7.97 (d, J = 9.0 Hz, 1 H), 7.84 (dd, J = 7.3, 1.6 Hz, 1 H), 7.76 (t, J = 6.9 Hz, 1 H), 7.71 (s, 1 H), 7.69 (d, J = 8.6 Hz, 1 H), 7.62 (t, J = 8.1 Hz, 1 H), 7.59 (t, J = 7.0 Hz, 1 H), 7.45 (t, J = 7.9 Hz, 1 H), 7.22 (m, 3 H), 6.74 (d, J = 7.2 Hz, 1 H), 6.48 (s, 2 H), 5.44 (s, 2 H); MS-FAB m/e 460 (p + 1, 32), 438 (20); IR ($CHCl_3$, cm^{-1}) 3450 (b), 3018, 1610, 1594, 1569, 1391, 1213. Anal. ($C_{25}H_{18}N_5O_3Na\cdot H_2O$) C, H, N.

2-[[5-[3-(Quinolin-2-ylmethoxy)phenyl]-1*H*-tetrazol-1-yl]methyl]benzoic Acid Sodium Salt (17). Compound **17a** (500 mg, 1.11 mmol) was hydrolyzed by the general procedure described above for the preparation of compound **15**. The crude acid was converted to the sodium salt and purified as described above for the preparation of compound **16** to provide 382 mg (75%) product: ^{1}H NMR (DMSO-d_6) 8.39 (d, J = 8.4 Hz, 1 H), 8.00 (d, J = 7.6 Hz, 1 H), 7.97 (d, J = 7.5 Hz, 1 H), 7.78 (dt, J = 7.1, 1.3 Hz, 1 H), 7.76 (dt, J = 7.0, 1.4 Hz, 1 H), 7.65 (d, J = 8.5 Hz, 1 H), 7.60 (t, J = 7.1 Hz, 1 H), 7.44 (s, 1 H), 7.43 (t, J = 8.1 Hz, 1 H), 7.12–7.30 (m, 4 H), 6.42 (d, J = 7.4 Hz, 1 H), 6.19 (s, 2 H), 5.34 (s, 2 H); MS-FAB m/e 460 (p + 1, 25); IR ($CHCl_3$, cm^{-1}) 3450 (b), 3019, 1610, 1594, 1568, 1391, 1213. Anal. ($C_{25}H_{18}N_5O_3Na\cdot 1.5H_2O$) C, H, N.

2-[[5-[3-(2-Quinolin-2-ylethenyl)phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid Sodium Salt (18). **(a) 2-[[5-[3-(2-Quinolin-2-ylethenyl)phenyl]-2*H*-tetrazol-2-yl]methyl]-benzoic Acid Methyl Ester (18a).** Compound **3** (4.00 g, 13.4 mmol) was alkylated with methyl 2-(bromomethyl)benzoate according to the general tetrazole alkylation procedure described above for the preparation of compound **15a**. Chromatography (LC-500) and subsequent recrystallization from ethyl acetate/hexane provided 3.75 g (65%) product: mp 132–134 °C; ^{1}H NMR (DMSO-d_6) 8.35 (d, J = 9 Hz, 1 H), 8.32 (s, 1 H), 7.89–8.02 (m, 7 H), 7.74 (t, J = 8 Hz, 1 H), 7.65 (t, J = 9 Hz, 1 H), 7.50–7.61 (m, 4 H), 7.33 (d, J = 8 Hz, 1 H), 6.33 (s, 2 H), 4.82 (s, 3 H); MS-FD m/e 447 (p); IR ($CHCl_3$, cm^{-1}) 3011, 1718, 1597, 1267, 1142. Anal. ($C_{27}H_{21}N_5O_2$) C, H, N.

(b) Compound 18. Compound **18a** (2.00 g, 4.39 mmol) was hydrolyzed by the general procedure described above for the preparation of compound **15**. The crude acid was converted to the sodium salt and purified as described above for the preparation of compound **16** to provide 1.23 g (60%) product as a fluffy white solid: ^{1}H NMR (DMSO-d_6) 8.36 (d, J = 4.2 Hz, 1 H), 8.34 (d, J = 4.4 Hz, 1 H), 7.90–8.05 (m, 6 H), 7.81 (dd, J = 7.2, 2.0 Hz, 1 H), 7.74, (t, J = 8.3 Hz, 1 H), 7.50–7.64 (m, 3 H), 7.24 (t, J = 5.3 Hz, 1 H), 7.20 (t, J = 7.2 Hz, 1 H), 6.76 (d, J = 8.6 Hz, 1 H), 6.50 (s, 2 H); MS-FAB m/e 457 (p + 1, 14), 331 (17), 329 (22), 257 (17); IR ($CHCl_3$, cm^{-1}) 3400 (b), 1634, 1612, 1595, 1432. Anal. ($C_{26}H_{18}N_5O_2Na\cdot 1.5H_2O$) C, H, N.

3-Methoxy-2-[[5-[3-(quinolin-2-ylmethoxy)phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid Sodium Salt (19). **(a) 2-[2-(Bromomethyl)-3-methoxyphenyl]-4,4-dimethyl-2-oxazoline (10).** A mixture of 2-(3-methoxy-2-methylphenyl)-4,4-dimethyl-2-oxazoline[18] (3.50 g, 16.0 mmol), *N*-bromosuccinimide (2.85 g, 16.0 mmol), and benzoyl peroxide (10 mg) in carbon tetrachloride (50 mL) was gently refluxed with a heat lamp for 3 h. The mixture was cooled, diluted with methylene chloride, washed with water (1×), dried (sodium sulfate), filtered, and concentrated in vacuo to provide 4.54 g (95%) product that was used directly without further purification: ^{1}H NMR (DMSO-d_6) 7.39 (t, J = 8 Hz, 1 H), 7.32 (d, J = 8 Hz, 1 H), 7.20 (d, J = 1 Hz, 1 H), 5.21 (s, 2 H), 4.08 (s, 2 H), 3.89 (s, 3 H), 1.30 (s, 6 H).

(b) 2-[3-Methoxy-2-[[5-[3-(quinolin-2-ylmethoxy)-phenyl]-2*H*-tetrazol-2-yl]methyl]phenyl]-4,4-dimethyl-2-oxazoline (19a). Compound **2**[4j] (3.00 g, 9.90 mmol) was alkylated with compound **10** according to the general tetrazole alkylation procedure described above for the preparation of compound **15a**. Chromatography (LC-500) provided 3.02 g (59%) product as a colorless oil: ^{1}H NMR (DMSO-d_6) 8.38 (d, J = 9 Hz, 1 H), 8.01 (d, J = 9 Hz, 1 H), 7.96 (d, J = 9 Hz, 1 H), 7.76 (t, J = 8 Hz, 1 H), 7.67 (d, J = 9 Hz, 1 H), 7.37–7.63 (m, 6 H), 7.27 (d, J = 9 Hz, 1 H), 7.20 (dd, J = 8, 1 Hz, 1 H), 6.35 (s, 2 H), 5.43 (s, 2 H), 3.95 (s, 2 H), 3.77 (s, 3 H), 1.10 (s, 6 H).

(c) Compound 19. Compound **19a** (3.00 g, 5.77 mmol) was dissolved in 5 N HCl solution (150 mL) and refluxed for 24 h. After cooling to room temperature the resulting precipitate was collected via vacuum filtration. The crude acid was converted to the sodium salt and purified as described above for the preparation of compound **16** to provide 1.95 g (73%) product as a fluffy white solid: ^{1}H NMR (DMSO-d_6) 8.39 (d, J = 8.5 Hz, 1 H), 8.01 (d, J = 8.6 Hz, 1 H), 7.98 (d, J = 9.5 Hz, 1 H), 7.77 (t, J = 8 Hz, 1 H), 7.68 (d, J = 8.5 Hz, 1 H), 7.62 (s, 1 H), 7.54 (m, 2 H), 7.40 (m, 2 H), 7.28 (t, J = 8.0 Hz, 1 H), 7.18 (dd, J = 8, 1 Hz, 1 H), 6.93 (d, J = 8.1 Hz, 1 H), 6.43 (s, 2 H), 5.43 (s, 2 H), 3.63 (s, 3 H); MS-FAB m/e 490 (p + 1, 35), 468 (35), 152 (50); IR ($CHCl_3$, cm^{-1}) 3400 (b), 1600, 1579, 1466, 1395, 1263. Anal. ($C_{28}H_{20}N_5O_4Na\cdot H_2O$) C, H, N.

2-[[3-[2-[[2-(2*H*-Tetrazol-5-yl)phenyl]methyl]-2*H*-tetrazol-5-yl]phenoxy]methyl]quinoline Sodium Salt (20). **(a) 2-[[5-[3-(Quinolin-2-ylmethoxy)phenyl]-2*H*-tetrazol-2-yl]-methyl]benzonitrile (20a).** Compound **2**[4j] (4.00 g, 13.2 mmol) was alkylated with 2-(bromomethyl)benzonitrile (11) according to the general tetrazole alkylation procedure described above for the preparation of compound **15a**. Chromatography (LC-500) provided 4.11 g (74%) product: ^{1}H NMR (DMSO-d_6) 8.39 (d, J = 9 Hz, 1 H), 8.00 (d, J = 9 Hz, 1 H), 7.95 (d, J = 8 Hz, 1 H), 7.92 (d, J = 8 Hz, 1 H), 7.65–7.80 (m, 5 H), 7.61 (m, 3 H), 7.45 (t, J = 8 Hz, 1 H), 7.24 (dd, J = 9, 1 Hz, 1 H), 6.15 (s, 2 H), 5.43 (s, 2 H); MS-FD m/e 418 (p). IR (KBr, cm^{-1}) 2238, 1619, 1489, 1424, 1186, 1090, 901, 837. Anal. ($C_{25}H_{18}N_6O$) C, H, N.

(b) Compound 20. Compound **20a** (4.00 g, 9.57 mmol) was submitted to the general tetrazole formation method 1 described above for the preparation of compound **3**. The crude tetrazole was converted to the sodium salt and purified as described above for the preparation of compound **16** to provide 1.85 g (40%) product as a fluffy white solid: ^{1}H NMR (DMSO-d_6) 8.39 (d, J = 8.5 Hz, 1 H), 8.09 (d, J = 6.7 Hz, 1 H), 8.00 (d, J = 8.6 Hz, 1 H), 7.97 (d, J = 7.8 Hz, 1 H), 7.76 (t, J = 6.9 Hz, 1 H), 7.67 (m, 2 H), 7.59 (m, 2 H), 7.44 (t, J = 8.1 Hz, 1 H), 7.38 (t, J = 7.2 Hz, 1 H), 7.24 (m, 2 H), 7.00 (d, J = 7.5 Hz, 1 H), 6.58 (s, 2 H), 5.44 (s, 2 H); MS-FAB m/e 484 (p + 1, 17), 462 (29), 143 (37); IR (KBr, cm^{-1}) 3400 (b), 1621, 1607, 1350, 1243. Anal. ($C_{25}H_{18}N_9ONa\cdot 2H_2O$) C, H; N: calcd, 24.27; found, 22.96.

3-[[5-[3-(2-Quinolin-2-ylethenyl)phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid Sodium Salt (21). **(a) 3-[[5-[3-(2-Quinolin-2-ylethenyl)phenyl]-2*H*-tetrazol-2-yl]methyl]-benzoic Acid Methyl Ester (21a).** Compound **3** (1.49 g, 5.00 mmol) was alkylated with methyl 3-(bromomethyl)benzoate according to the general tetrazole alkylation procedure described above for the preparation of compound **15a**. Chromatography (LC-500) provided 1.53 g (69%) product: ^{1}H NMR (DMSO-d_6) 8.36 (d, J = 8 Hz, 1 H), 8.33 (s, 1 H), 7.90–8.08 (m, 8 H), 7.72 (m, 2 H), 7.50–7.65 (m, 4 H), 6.13 (s, 2 H), 3.83 (s, 3 H).

(b) Compound 21. Compound **21a** (1.50 g, 3.36 mmol) was hydrolyzed by the general procedure described above for the preparation of compound **15**. The crude acid was converted to the sodium salt and purified as described above for the preparation of compound **16** to provide 709 mg (46%) product as a fluffy yellow solid: ^{1}H NMR (DMSO-d_6) 8.35 (d, J = 8.3 Hz, 1 H), 8.34 (s, 1 H), 7.87–8.06 (m, 7 H), 7.83 (d, J = 7.3 Hz, 1 H), 7.74 (t, J = 8.4 Hz, 1 H), 7.60 (s, 1 H), 7.52–7.64 (m, 2 H), 7.32 (m, 2 H), 6.01 (s, 2 H); MS-FAB m/e (no parent ion); IR ($CHCl_3$, cm^{-1}) 1616, 1599, 1406. Anal. ($C_{26}H_{18}N_5O_2Na$) C, H, N.

3-Methoxy-4-[[5-[3-(2-quinolin-2-ylethenyl)phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid Sodium Salt (22). **(a) 3-Methoxy-4-[[5-[3-(2-quinolin-2-ylethenyl)phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid Methyl Ester (22a) and 3-Methoxy-4-[[5-[3-(2-quinolin-2-ylethenyl)phenyl]-1*H*-tetrazol-1-yl]methyl]benzoic Acid Methyl Ester (23a).** Compound **3** (1.79 g, 6.01 mmol) was alkylated with methyl 4-(bromomethyl)-3-methoxybenzoate[15] according to the general tetrazole alkylation procedure described above for the preparation of compound **15a**. Chromatography (LC-500) provided products **22a** (1.52 g, 54%) and **23a** (0.45 g, 16%).

22a: ^{1}H NMR ($CDCl_3$) 8.47 (s, 1 H), 8.15 (d, J = 9 Hz, 1 H), 8.13 (t, J = 7 Hz, 1 H), 7.82 (d, J = 9 Hz, 1 H), 7.65–7.78 (m, 6

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H), 7.63 (s, 1 H), 7.54 (m, 3 H), 7.24 (d, J = 9 Hz, 1 H), 5.94 (s, 2 H), 3.95 (s, 3 H), 3.92 (s, 3 H).

23a: ^{1}H NMR ($CDCl_3$) 8.18 (d, J = 9 Hz, 1 H), 8.12 (d, J = 9 Hz, 1 H), 8.83 (m, 2 H), 7.74 (t, J = 7 Hz, 1 H), 7.71 (d, J = 18 Hz, 1 H), 7.50–7.66 (m, 7 H), 7.32 (d, J = 18 Hz, 1 H), 7.08 (d, J = 8 Hz, 1 H), 5.74 (s, 2 H), 3.93 (s, 3 H), 3.82 (s, 3 H).

(b) Compound 22. Compound **22a** (1.50 g, 3.14 mmol) was hydrolyzed by the general procedure described above for the preparation of compound **15**. The crude acid was converted to the sodium salt as described above for the preparation of compound **16** to provide 619 mg (41%) product as a tan solid: ^{1}H NMR (DMSO-d_6) 8.35 (d, J = 9 Hz, 1 H), 8.30 (s, 1 H), 7.95 (m, 6 H), 7.75 (t, J = 8 Hz, 1 H), 7.55 (m, 4 H), 7.47 (d, J = 9 Hz, 1 H), 7.18 (d, J = 8 Hz, 1 H), 5.90 (s, 2 H), 3.78 (s, 3 H); MS-FAB m/e 487 (p + 1, 2); IR (KBr, cm^{-1}) 1610, 1597, 1558, 1409, 1392, 1247. Anal. ($C_{27}H_{20}N_5O_3Na\cdot2.5H_2O$) C, H, N.

3-Methoxy-4-[[5-[3-(2-quinolin-2-ylethenyl)phenyl]-1*H*-tetrazol-1-yl]methyl]benzoic Acid Sodium Salt (23). Compound **23a** (450 mg, 0.943 mmol) was hydrolyzed by the general procedure described above for the preparation of compound **15**. The crude acid was converted to the sodium salt as described above for the preparation of compound **16** to provide 291 mg (64%) product as a fluffy yellow solid: ^{1}H NMR (DMSO-d_6) 8.36 (d, J = 8.6 Hz, 1 H), 8.09 (s, 1 H), 7.83–8.04 (m, 5 H), 7.67–7.78 (m, 2 H), 7.64 (t, J = 7.6 Hz, 1 H), 7.51–7.59 (m, 2 H), 7.45 (s, 1 H), 7.39 (d, J = 7.4 Hz, 1 H), 6.97 (d, J = 7.7 Hz, 1 H), 5.70 (s, 2 H), 3.59 (s, 3 H); MS-FAB m/e 487 (p + 1, 3); IR ($CHCl_3$, cm^{-1}) 3400 (b), 2977, 1601, 1565, 1413, 1224. Anal. ($C_{27}H_{20}N_5O_3Na$) C, H, N.

2-[[5-[3-(Quinolin-2-ylmethoxy)phenyl]-2*H*-tetrazol-2-yl]methyl]benzeneacetic Acid (24). (a) Methyl [2-(Iodomethyl)phenyl]acetate (24a). To a suspension of [2-(bromomethyl)phenyl]acetic acid (21.25 g, 93.6 mmol, prepared in 93% yield by the treatment of 3-isochromanone with 33% HBr/acetic acid) in hexane (250 mL) was added oxalyl chloride (11.9 g, 93.8 mmol) followed by dimethylformamide (~3 drops). The mixture was stirred for 4 h at which time gas evolution had ceased. The mixture was concentrated in vacuo and dissolved in excess methanol. The resulting solution was stirred at room temperature for 1 h then concentrated in vacuo. The resulting oil was dissolved in acetone (100 mL) and treated with potassium iodide (17.1 g, 103 mmol) at room temperature for 2 h. The mixture was filtered and concentrated in vacuo. Chromatography (LC-500) of the resulting residue provided 13.0 g (48%) product as an unstable tan crystalline material: mp 39–41 °C; ^{1}H NMR ($CDCl_3$) 7.37 (d, J = 2.7 Hz, 1 H), 7.25 (m, 3 H), 4.53 (s, 2 H), 3.77 (s, 2 H), 3.73 (s, 3 H); MS-EI m/e (no parent ion), 231 (17), 163 (100), 131 (36), 105 (67), 104 (66), 103 (56); IR ($CHCl_3$, cm^{-1}) 3010, 1735, 1437, 1263, 1155. Anal. ($C_{10}H_{11}O_2I$) C, H.

(b) 2-[[5-[3-(Quinolin-2-ylmethoxy)phenyl]-2*H*-tetrazol-2-yl]methyl]benzeneacetic Acid Methyl Ester (24b). Compound **2**[4j] (3.00 g, 9.90 mmol) was alkylated with compound **24a** according to the general tetrazole alkylation procedure described above for the preparation of compound **25a** except potassium iodide was omitted. Chromatography (LC-500) provided 2.54 g (55%) product: ^{1}H NMR (DMSO-d_6) 8.40 (d, J = 9 Hz, 1 H), 8.02 (d, J = 9 Hz, 1 H), 7.97 (d, J = 9 Hz, 1 H), 7.76 (t, J = 9 Hz, 1 H), 7.68 (m, 2 H), 7.60 (m, 2 H), 7.47 (t, J = 9 Hz, 1 H), 7.30 (m, 4 H), 7.23 (d, J = 8 Hz, 1 H), 6.00 (s, 2 H), 5.44 (s, 2 H), 3.91 (s, 2 H), 3.45 (s, 3 H).

(c) Compound 24. Compound **24b** (2.50 g, 5.38 mmol) was hydrolyzed by the general procedure described above for the preparation of compound **15**. The resulting precipitate was collected via suction filtration and washed well with deionized water. Further drying in a vacuum oven at 60 °C provided 1.43 g (59%) product as a white crystalline material: mp 166–168 °C; ^{1}H NMR (DMSO-d_6) 8.40 (d, J = 8.6 Hz, 1 H), 8.01 (d, J = 9.2 Hz, 1 H), 7.98 (d, J = 9.5 Hz, 1 H), 7.77 (t, J = 8 Hz, 1 H), 7.70 (m, 2 H), 7.60 (m, 2 H), 7.45 (t, J = 8.1 Hz, 1 H), 7.18–7.37 (m, 5 H), 6.01 (s, 2 H), 5.44 (s, 2 H), 3.80 (s, 2 H); MS-FD m/e 452 (p + 1); IR (KBr, cm^{-1}) 1711, 1602, 1454, 1249, 1187. Anal. ($C_{28}H_{21}N_5O_3\cdot0.5H_2O$) C, H, N.

2-[[5-[3-(2-Quinolin-2-ylethenyl)phenyl]-2*H*-tetrazol-2-yl]methyl]benzeneacetic Acid Sodium Salt (25). (a) 2-[[5-[3-(2-Quinolin-2-ylethenyl)phenyl]-2*H*-tetrazol-2-yl]methyl]benzeneacetic Acid Methyl Ester (25a). Compound **3** (5.00 g, 16.8 mmol) was alkylated with compound **24a** according to the general tetrazole alkylation procedure described above for the preparation of compound **15a** except potassium iodide was omitted. Chromatography (LC-500) provided 4.42 g (57%) product as fluffy pale yellow needles: mp 122–124 °C; ^{1}H NMR (DMSO-d_6) 8.36 (d, J = 9 Hz, 1 H), 8.32 (s, 1 H), 7.95 (m, 6 H), 7.73 (t, J = 8 Hz, 1 H), 7.58 (m, 3 H), 7.31 (m, 4 H), 6.05 (s, 2 H), 4.94 (s, 2 H), 3.49 (s, 3 H); MS-FD m/e 461 (p); IR ($CHCl_3$, cm^{-1}) 3010, 1736, 1597, 1437, 1225. Anal. ($C_{28}H_{23}N_5O_2$) C, H, N.

(b) Compound 25. Compound **25a** (1.00 g, 2.17 mmol) was hydrolyzed by the general procedure described above for the preparation of compound **15**. The crude acid was converted to the sodium salt and purified as described above for the preparation of compound **16** to provide 755 mg (74%) product as a fluffy pale yellow solid: ^{1}H NMR (DMSO-d_6) 8.36 (d, J = 8.9 Hz, 1 H), 8.34 (s, 1 H), 7.94 (m, 6 H), 7.73 (t, J = 8 Hz, 1 H), 7.58 (m, 3 H), 7.14 (m, 3 H), 7.04 (d, J = 9 Hz, 1 H), 6.22 (s, 2 H), 3.42 (s, 2 H); MS-FAB m/e (no parent ion); IR ($CHCl_3$, cm^{-1}) 3019, 1598, 1390, 1050. Anal. ($C_{27}H_{20}N_5O_2Na\cdot1.5H_2O$) C, H, N.

2-[[5-[3-(Benzothiazol-2-ylmethoxy)phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid Sodium Salt (26). (a) 2-[(3-Cyanophenoxy)methyl]benzothiazole (26a). 3-Cyanophenol (14.2 g, 119 mmol) was alkylated with 2-(bromomethyl)benzothiazole[19] (prepared by the bromination of 2-methylbenzothiazole as described above for the preparation of compound **10**) according to the general phenol alkylation procedure described above for the preparation of compound **4b**. This protocol provided 9.21 g (30%) product which was used directly in the next step: ^{1}H NMR ($CDCl_3$) 8.08 (d, J = 9 Hz, 1 H), 7.94 (d, J = 9 Hz, 1 H), 7.53 (t, J = 9 Hz, 1 H), 7.44 (m, 2 H), 7.32 (m, 2 H), 7.28 (s, 1 H), 5.52 (s, 2 H).

(b) 2-[[3-(2*H*-Tetrazol-5-yl)phenoxy]methyl]benzothiazole (26b). Compound **26a** (9.10 g, 34.2 mmol) was submitted to the general tetrazole formation method 1 as described above for the preparation of compound **3**. This protocol provided 6.16 g (58%) product: mp 190 °C dec; ^{1}H NMR (DMSO-d_6) 8.09 (d, J = 9 Hz, 1 H), 8.00 (d, J = 9 Hz, 1 H), 7.69 (s, 1 H), 7.64 (d, J = 9 Hz, 1 H), 7.49 (t, J = 8 Hz, 1 H), 7.45 (t, J = 9 Hz, 1 H), 7.37 (t, J = 8 Hz, 1 H), 7.19 (dd, J = 9, 1 Hz, 1 H), 5.64 (s, 2 H); MS-FD m/e 309 (p); IR ($CHCl_3$, cm^{-1}) 3369 (b), 2924, 2855, 1685, 1457, 1377, 1254. Anal. ($C_{15}H_{11}N_5O_5\cdot1.3H_2O$) C, H, N.

(c) Compound 26. Compound **26b** (6.10 g, 19.8 mmol) was alkylated with methyl 2-(bromomethyl)benzoate according to the general tetrazole alkylation procedure described above for the preparation of compound **15a**. The crude reaction product was hydrolyzed directly by the general procedure described above for the preparation of compound **15**. The crude acid was converted to the sodium salt and purified as described above for the preparation of compound **16** to provide 2.30 g (25%) product as a fluffy white solid: ^{1}H NMR (DMSO-d_6) 8.10 (d, J = 8.2 Hz, 1 H), 8.01 (d, J = 7.9 Hz, 1 H), 7.81 (d, J = 7.4 Hz, 1 H), 7.70 (s, 1 H), 7.68 (d, J = 9.5 Hz, 1 H), 7.48 (m, 3 H), 7.23 (m, 3 H), 6.74 (d, J = 7.3 Hz, 1 H), 6.48 (s, 2 H), 5.69 (s, 2 H); MS-FAB m/e 466 (p + 1, 15); IR (neat, cm^{-1}) 3300, 2932, 1612, 1590, 1571, 1459, 1377. Anal. ($C_{23}H_{16}N_5O_3SNa\cdot3.5H_2O$) C, H, N.

2-[[5-[3-[(7-Chloroquinolin-2-yl)methoxy]phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid Sodium Salt (27). (a) 2-[[5-[3-[(7-Chloroquinolin-2-yl)methoxy]phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid Methyl Ester (27a). Compound **4** (2.00 g, 5.95 mmol) was alkylated with methyl 2-(bromomethyl)benzoate according to the general tetrazole alkylation procedure described above for the preparation of compound **15a**. Chromatography (LC-500) provided 1.94 g (67%) product as a fibrous white solid: mp 139 °C; ^{1}H NMR (DMSO-d_6) 8.43 (d, J = 9 Hz, 1 H), 8.05 (s, 2 H), 8.02 (d, J = 9 Hz, 1 H), 7.94 (d, J = 8 Hz, 1 H), 7.70 (d, J = 9 Hz, 1 H), 7.61 (m, 4 H), 7.51 (t, J = 7 Hz, 1 H), 7.46 (t, J = 9 Hz, 1 H), 7.29 (d, J = 8 Hz, 1 H), 7.22 (dd, J = 8, 1 Hz, 1 H), 6.24 (s, 2 H), 5.43 (s, 2 H), 3.75 (s, 3 H); MS-FD m/e 488 (p + 2, 56), 487 (p + 1, 46), 486 (p, 100); IR ($CHCl_3$, cm^{-1}) 3010, 1719, 1615, 1284, 1268, 1092, 1073. Anal. ($C_{26}H_{20}N_5O_3Cl$) H, N; C: calcd, 64.27; found, 65.45.

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(b) Compound 27. Compound **27a** (1.00 g, 2.02 mmol) was hydrolyzed by the general procedure described above for the preparation of compound **15**. The crude acid was converted to the sodium salt and purified as described above for the preparation of compound **16** to provide 830 mg (82%) product as a fluffy white solid: ^{1}H NMR (DMSO-d_6) 8.46 (d, J = 8.5 Hz, 1 H), 8.06 (s, 1 H), 8.05 (d, J = 11.5 Hz, 1 H), 7.80 (d, J = 7.4 Hz, 1 H), 7.74 (d, J = 8.5 Hz, 1 H), 7.69 (s, 1 H), 7.64 (m, 2 H), 7.46 (t, J = 9 Hz, 1 H), 7.20 (m, 3 H), 6.75 (d, J = 8 Hz, 1 H), 6.47 (s, 2 H), 5.45 (s, 2 H); MS-FAB m/e 494 (p + 1, 59), 472 (17); IR (KBr, cm^{-1}) 3450, 1613, 1595, 1571, 1473, 1400, 1324, 1260. Anal. ($C_{25}H_{17}N_5O_3ClNa$) C, H, N.

2-[[5-[3-[2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid Sodium Salt (28). (a) 2-[[5-[3-[2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-2*H*-tetrazol-2-yl]methyl]benzoic Acid Methyl Ester (28a). Compound **5** (5.00 g, 15.0 mmol) was alkylated with methyl 2-(bromomethyl)benzoate according to the general tetrazole alkylation procedure described above for the preparation of compound **15a**. Chromatography (LC-500) provided 2.82 g (39%) product: mp 146–149 °C; ^{1}H NMR (DMSO-d_6) 8.38 (d, J = 8 Hz, 1 H), 8.30 (s, 1 H), 7.97–8.05 (m, 7 H), 7.64 (t, J = 8 Hz, 1 H), 7.48–7.59 (m, 4 H), 7.33 (d, J = 8 Hz, 1 H), 6.31 (s, 2 H), 3.81 (s, 3 H); MS-FD m/e 483 (p + 1, 38), 482 (p, 38), 481 (p - 1, 100); IR ($CHCl_3$, cm^{-1}) 3000, 1719, 1610, 1595, 1498, 1284, 1268. Anal. ($C_{27}H_{20}N_5O_2Cl$) C, H, N.

(b) Compound 28. Compound **28a** (1.80 g, 3.74 mmol) was hydrolyzed by the general procedure described above for the preparation of compound **15**. The crude acid was converted to the sodium salt and purified as described above for the preparation of compound **16** to provide 1.31 g (72%) product as a fluffy white solid: ^{1}H NMR (DMSO-d_6) 8.37 (d, J = 8.5 Hz, 1 H), 8.33 (s, 1 H), 7.87–8.08 (m, 6 H), 7.83 (dd, J = 7, 1 Hz, 1 H), 7.50–7.65 (m, 3 H), 7.24 (t, J = 7 Hz, 1 H), 7.23 (dt, J = 8, 1 Hz, 1 H), 6.77 (d, J = 7 Hz, 1 H), 6.50 (s, 2 H); MS-FAB m/e 492 (2), 490 (p, 4), 470 (1.5), 468 (3); IR (KBr, cm^{-1}) 3450, 1610, 1594, 1570, 1498, 1397. Anal. ($C_{28}H_{17}N_5O_2ClNa$) C, H, N.

2-[[5-[3-(2-Quinolin-2-ylethenyl)phenyl]-2*H*-tetrazol-2-yl]methyl]-3-furancarboxylic Acid Sodium Salt (29). (a) 2-[[5-[3-(2-Quinolin-2-ylethenyl)phenyl]-2*H*-tetrazol-2-yl]methyl]-3-furancarboxylic Acid Methyl Ester (29a). Compound **3** (1.49 g, 5.00 mmol) was alkylated with methyl 2-(bromomethyl)furan-3-carboxylate (**12**)[20] according to the general tetrazole alkylation procedure described above for the preparation of compound **15a**. Chromatography (LC-500) provided 1.57 g (72%) product as a white powder: ^{1}H NMR (DMSO-d_6) 8.15 (d, J = 9 Hz, 1 H), 8.09 (d, J = 9 Hz, 1 H), 7.91 (s, 1 H), 7.60–7.85 (m, 6 H), 7.50 (m, 3 H), 7.37 (d, J = 1 Hz, 1 H), 6.69 (d, J = 1 Hz, 1 H), 6.05 (s, 2 H), 3.73 (s, 3 H); MS-FD m/e 437 (p); IR ($CHCl_3$, cm^{-1}) 3012, 1725, 1597, 1506, 1428, 1315. Anal. ($C_{25}H_{19}N_5O_3$) H, N; C: calcd, 68.64; found, 67.98.

(b) Compound 29. Compound **29a** (300 mg, 0.683 mmol) was hydrolyzed by the general procedure described above for the preparation of compound **15**. The crude acid was converted to the sodium salt and purified as described above for the preparation of compound **16** to provide 160 mg (52%) product as a fluffy pale yellow solid: ^{1}H NMR (DMSO-d_6) 8.32 (d, J = 9 Hz, 1 H), 8.31 (s, 1 H), 7.97–8.08 (m, 6 H), 7.69 (t, J = 8 Hz, 1 H), 7.50–7.63 (m, 3 H), 7.48 (d, J = 1 Hz, 1 H), 6.55 (d, J = 1 Hz, 1 H), 6.49 (s, 2 H); MS-FAB m/e 447 (p + 1, 1.7); IR ($CHCl_3$, cm1-^{1}) 1635, 1616, 1597, 1506, 1430, 1221. Anal. ($C_{24}H_{16}N_5O_3Na\cdot1.1H_2O$) C, H, N.

3-[[5-[3-[2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-2*H*-tetrazol-2-yl]methyl]-2-thiophenecarboxylic Acid Sodium Salt (30). (a) 3-[[5-[3-[2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-2*H*-tetrazol-2-yl]methyl]-2-thiophenecarboxylic Acid Methyl Ester (30a). Compound **4** (3.33 g, 10.0 mmol) was alkylated with methyl 3-(bromomethyl)thiophene-2-carboxylate (**13**)[21] according to the general tetrazole alkylation procedure described above for the preparation of compound **15a**. Chromatography (LC-500) provided 1.11 g (23%) product as yellow crystals: mp 134–136 °C; ^{1}H NMR (DMSO-d_6) 8.48 (s, 1 H), 8.13 (m, 3 H), 7.75 (m, 3 H), 7.68 (d, J = 9 Hz, 1 H), 7.54 (t, J = 8 Hz, 1 H), 7.50 (m, 3 H), 6.88 (d, J = 6 Hz, 1 H), 6.37 (s, 2 H), 3.98 (s, 3 H); MS-FD m/e 489 (p + 1, 38), 488 (p, 28), 487 (p - 1, 100); IR ($CHCl_3$, cm^{-1}) 3011, 1725, 1598, 1506, 1315, 1141, 1068, 1046.

(b) Compound 30. Compound **30a** (1.00 g, 2.15 mmol) was hydrolyzed by the general procedure described above for the preparation of compound **15**. The crude acid was converted to the sodium salt and purified as described above for the preparation of compound **16** to provide 641 mg (64%) product as a white powder: ^{1}H NMR (DMSO-d_6) 8.39 (d, J = 9 Hz, 1 H), 8.34 (s, 1 H), 7.90–8.10 (m, 6 H), 7.57 (m, 3 H), 7.24 (d, J = 6 Hz, 1 H), 6.71 (d, J = 6 Hz, 1 H), 6.50 (s, 2 H); MS-FAB m/e (no parent ion), 309 (32); IR ($CHCl_3$, cm^{-1}) 3450 (b), 1610, 1594, 1496, 1430, 1373. Anal. ($C_{24}H_{15}N_5O_2ClS\cdot0.3H_2O$) C, H, N.

2-[2-[5-[3-[2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-2*H*-tetrazol-2-yl]ethyl]benzoic Acid Sodium Salt (31). Compound **5** (1.33 g, 3.99 mmol) was dissolved in dimethylformamide (25 mL) and carefully treated at room temperature with 95% sodium hydride (111 mg, 4.40 mmol) in four equal portions. After stirring the mixture for 5 minutes, compound **14** (methyl 2-(2-bromoethyl)benzoate,[22] 970 mg, 3.99 mmol) was added. The resulting mixture was stirred overnight and then diluted with water (25 mL). The resulting precipitate was collected via vacuum filtration and washed well with cold water. The crude product was hydrolyzed by the general procedure described above for the preparation of compound **15**. The crude acid was converted to the sodium salt and purified as described above for the preparation of compound **16** to provide 280 mg (14%) product as a fluffy white solid: ^{1}H NMR (DMSO-d_6) 8.41 (d, J = 8.6 Hz, 1 H), 8.36 (s, 1 H), 7.95 (m, 6 H), 7.59 (m, 4 H), 7.10 (t, J = 7.3 Hz, 1 H), 7.02 (t, J = 7.4 Hz, 1 H), 6.84 (d, J = 7.3 Hz, 1 H), 5.07 (t, J = 7.0 Hz, 2 H), 3.60 (t, J = 7.0 Hz, 2 H); MS-FAB m/e 505 (p + 1, 3), 331 (8), 329 (9), 309 (11); IR (KBr, cm^{-1}) 3435 (b), 1608, 1562, 1517, 1498, 1392. Anal. ($C_{27}H_{19}N_5O_2ClNa\cdot2H_2O$) C, H, N.

2-[[5-[3-[2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-2*H*-tetrazol-2-yl]methyl]-5-fluorobenzoic Acid Sodium Salt (32). (a) Methyl 2-(Bromomethyl)-5-fluorobenzoate (32a). A mixture of 5-fluoro-2-methylbenzoic acid (5.00 g, 32.5 mmol) and concentrated sulfuric acid (1 mL) in methanol (25 mL) was refluxed for 24 h. The mixture was cooled to room temperature and excess sodium bicarbonate was carefully added. When gas evolution had ceased the mixture was diluted with ether and washed with water (1×), dried (sodium sulfate), filtered, and concentrated in vacuo to provide an orange oil (3.42 g). This material was dissolved in carbon tetrachloride (50 mL) and treated with *N*-bromosuccinimide (3.60 g, 20.2 mmol) and benzoyl peroxide (50 mg). The mixture was irradiated briefly with a heat lamp and then gently refluxed for 3 h. The reaction mixture was diluted with methylene chloride and washed with water (1×), dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (LC-500) provided 2.20 g (27%) product as an unstable golden oil: ^{1}H NMR ($CDCl_3$) 7.68 (dd, J = 9.3, 2.8 Hz, 1 H), 7.46 (dd, J = 8.5, 5.4 Hz, 1 H), 7.20 (dt, J = 2.6, 8.2 Hz, 1 H), 4.95 (s, 2 H), 3.95 (s, 3 H); MS-EI m/s 248 (p + 1, 1.5), 246 (p - 1, 1.5), 217 (5), 215 (5), 167 (88), 137 (27), 109 (29), 108 (27), 107 (19), 85 (70), 83 (100); IR ($CHCl_3$, cm^{-1}) 2955, 1727, 1438, 1282, 1225, 1069.

(b) Compound 32. Compound **5** (670 mg, 2.01 mmol) was alkylated with compound **32a** according to the general tetrazole alkylation procedure described above for the preparation of compound **15a**. The crude ester (700 mg) was hydrolyzed directly by the general procedure described above for the preparation of compound **15**. The crude acid was converted to the sodium salt and purified as described above for the preparation of compound **16** to provide 408 mg (40%) product as a fluffy white solid: ^{1}H NMR (DMSO-d_6) 8.39 (d, J = 8.6 Hz, 1 H), 8.32 (s, 1 H), 7.88–8.04 (m, 6 H), 7.51–7.64 (m, 4 H), 7.07 (m, 1 H), 6.96 (m, 1 H), 6.48

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(s, 2 H); MS-FAB *m/e* (no parent ion), 309 (100); IR (KBr, cm^{-1}) 3436 (b), 1595, 1578, 1424, 1386, 1234. Anal. ($C_{25}H_{16}N_5O_2ClF$-Na·0.4H_2O) C, H, N.

Biological Assays. Experimental details for the determination of LTD_4 antagonist activity in the isolated guinea pig ileum are as reported in ref. 1a and 4o.

Acknowledgment. We thank the members of the Physical Chemistry Department for providing analytical data.

Registry No. **2**, 107813-59-2; **3**, 138813-28-2; **3a**, 138786-13-7; **4**, 138786-14-8; **4a**, 138786-15-9; **5**, 138786-16-0; **5a**, 138786-17-1; **10**, 78265-34-6; **11**, 22115-41-9; **12**, 53020-08-9; **13**, 59961-15-8; **14**, 25109-86-8; **15**, 138786-18-2; **15a**, 138786-19-3; **16**, 138786-20-6; **17**, 138786-21-7; **17**·Na, 138786-22-8; **17a**, 138786-23-9; **18**, 138786-24-0; **18**·Na, 138786-25-1; **18a**, 138786-26-2; **19**, 138786-27-3; **19**·Na, 138786-28-4; **19a**, 138786-29-5; **20**, 138786-30-8; **20**·Na, 138786-31-9; **20a**, 138786-32-0; **21**, 138786-33-1; **21**·Na, 138786-34-2; **21a**, 138786-35-3; **22**, 138786-36-4; **22**·Na, 138786-37-5; **22a**, 138786-38-6; **23**, 138786-39-7; **23**·Na, 138786-40-0; **23a**, 138786-41-1; **24**, 138786-42-2; **24**·Na, 138786-43-3; **24a**, 138786-43-3; **24b**, 138813-29-3; **25**, 138786-45-5; **25**·Na, 138786-46-6; **25a**, 138786-47-7; **26**, 138786-48-8; **26**·Na, 138786-49-9; **26a**, 138786-50-2; **26b**, 138786-51-3; **27**, 138786-52-4; **27**·Na, 138786-53-5; **27a**, 138786-54-6; **28**, 138786-55-7; **28**·Na, 138786-56-8; **28a**, 138813-30-6; **29**, 138786-57-9; **29**·Na, 138786-58-0; **29a**, 138813-31-7; **30**, 138786-59-1; **30**·Na, 138786-60-4; **30a**, 138786-61-5; **31**, 138786-62-6; **31**·Na, 138813-32-8; **32**, 138786-63-7; **32**·Na, 138786-64-8; **32a**, 138786-65-9; 2-[(triphenylphosphonio)methyl]quinoline chloride, 99651-30-6; 3-cyanobenzaldehyde, 24964-64-5; 3-cyanophenol, 873-62-1; 2-(bromomethyl)-7-chloroquinoline, 115104-25-1; 7-chloroquinaldine, 4965-33-7; methyl 2-(bromomethyl)benzoate, 2417-73-4; 2-(3-methoxy-2-methylphenyl)-4,4-dimethyl-2-oxazoline, 72623-17-7; methyl 4-(bromomethyl)-3-methoxybenzoate, 70264-94-7; 3-isochromanone, 4385-35-7; 2-(bromomethyl)benzothiazole, 106086-78-6; 5-fluoro-2-methylbenzoic acid, 33184-16-6; methyl 2-[(3-cyanophenyl)methyl]-5-fluorobenzoate, 138786-66-0; [2-(bromomethyl)phenyl]acetic acid, 13737-35-4.

Analogues of Natural Phloroglucinols as Antagonists against Both Thromboxane A_2 and Leukotriene D_4

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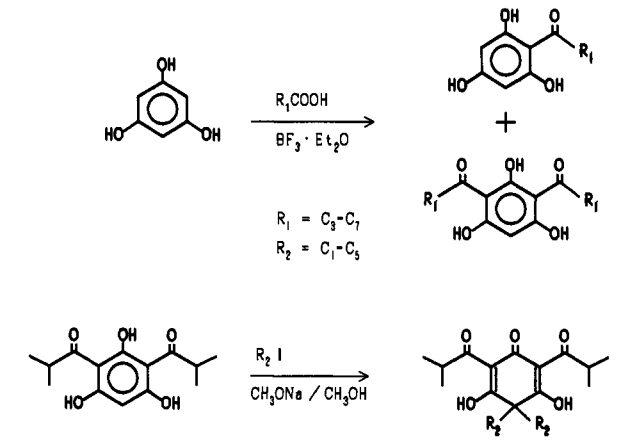
Antagonists against both thromboxane A_2 and leukotriene D_4 were prepared from phloroglucinol. These compounds showed almost the same activity as the chinesins which were isolated from *Hypericum chinense* L. The correlation between the structures and activity was studied in the synthesized and naturally occurring phloroglucinol derivatives.

Introduction

The plants belonging to the Guttiferae family are well-known folk medicines in Japan, having anodynic, staunching, and antiphlogistic properties. Previously, we found new antibacterial compounds, chinesin I (1), chinesin II (2),[1] otogirin (3), and otogirone (4)[2] from these plants (Figure 1). Compounds 1 and 2 were isolated from flowers of *Hypericum chinense* L. Compounds 3 and 4 were found in roots and flowers of *Hypericum erectum*, respectively. These compounds are derivatives of phloroglucinol, showing antimicrobial activity against Gram-positive microorganisms.[3] They also showed marked antiviral activity against both an RNA virus with envelope (vesicular stomatitis virus) and a DNA virus with envelope (herpes simplex virus type I).[3] Furthermore, we found that these compounds showed antagonistic activity against both thromboxane A_2 (TxA_2) and leukotriene D_4 (LTD_4) as evaluated by measuring the contraction of guinia pig trachea smooth muscle.[2] Especially, chinesins (a 3:1 mixture of 1 and 2) and 4 showed strong activity in comparison with 3.

Some allergic diseases involved with the IgE antibody are developed with chemical mediators such as histamine, leukotriene, and thromboxane. Leukotoriene mediates asthma,[4] psoriasis,[5] myocardial infarction,[6] endotoxin shock,[7] and heart anaphylaxis,[8] and thromboxane promotes platelet aggregation, blood vessel contraction, and bronchial contraction.[9,10] Antagonists against these chemical mediators are expected to be possible antiallergic agents.

Scheme I



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0022-2623/92/1835-1209$03.00/0