For AA8 and UV4 cultures, drug exposure was terminated after 18 h by washing three times with fresh medium. Cultures were grown for a further 72 h before determining cell density by staining with methylene blue.[36]

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Registry No. **2**, 305-03-3; **4**, 72667-33-5; **7**, 1448-52-8; **8**, 1204-68-8; **9**, 64977-17-9; **10**, 1215-16-3; **11**, 122567-50-4; **12**, 20805-66-7; **13**, 1669-15-4; **14**, 125173-74-2; **14**·2HCl, 125173-81-1; **15**, 125173-75-3; **15**·2HCl, 125173-92-4; **16**, 125173-76-4; **16**·HCl, 125173-99-1; **17**, 125173-77-5; **17**·2HCl, 125174-11-0; **18**, 125173-78-6; **18**·2HCl, 125174-17-6; **19**, 125173-79-7; **19**·2HCl, 125174-07-4; **20**, 125173-80-0; **20**·HCl, 125174-20-1; **21**, 38968-78-4; **22**, 125174-00-7; **23**, 125174-01-8; **24a**, 106275-33-6; **24b**, 125173-87-7; **24c**, 125173-93-5; **25a**, 125173-82-2; **25b**, 125173-88-8; **25c**, 125173-94-6; **25d**, 125174-02-9; **26a**, 125173-83-3; **26b**, 125173-89-9; **26c**, 125173-95-7; **26d**, 125174-03-0; **27a**, 125173-84-4; **27c**, 125173-96-8; **27d**, 125174-05-2; **28a**, 125173-85-5; **28b**, 125173-90-2; **28c**, 125173-97-9; **28d**, 125174-06-3; **29a**, 125173-86-6; **29b**, 125173-91-3; **29c**, 125173-98-0; **30**, 125174-12-1; **31a**, 125174-08-5; **31b**, 125174-13-2; **32a**, 125174-09-6; **32b**, 125174-14-3; **33a**, 125174-10-9; **33b**, 125174-16-5; **34**, 125174-18-7; **35**, 125174-19-8; **36**, 125197-02-6; p-$NO_2C_6H_4(CH_2)_6CO_2H$, 66147-99-7; p-$NO_2C_6H_4SH$, 13113-79-6; $MeOCO(CH_2)_5Br$, 14273-90-6; p-$MeO_2C(CH_2)_5COC_6H_4N(CH_2CH_2OSO_2Me)_2$, 125174-04-1; $HO_2C(CH_2)_4NHCO_2CH_2Ph$, 23135-50-4; p-$NH_2C_6H_4N(CH_2CH_2OH)_2$, 7575-35-1; p-$MeO_2CC_6H_4N(CH_2CH_2OH)_2$, 91645-48-6; p-$HO_2CC_6H_4N(CH_2CH_2OH)_2$, 117821-33-7; p-$HO_2CC_6H_4N(CH_2CH_2OAc)_2$, 87971-61-7; $H_2N(CH_2)_4NHCO_2CH_2Ph$, 62146-62-7; p-$PhCH_2OCONH(CH_2)_4NHCOC_6H_4N(CH_2CH_2OSO_2Me)_2$, 125174-15-4; oxirane, 75-21-8; 9-methoxyacridine, 10228-90-7.

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Development of a Novel Series of (2-Quinolinylmethoxy)phenyl-Containing Compounds as High-Affinity Leukotriene Receptor Antagonists. 1. Initial Structure–Activity Relationships

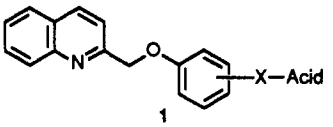
Raymond D. Youssefyeh, Ernest Magnien, Thomas D. Y. Lee,† Wan-Kit Chan, Clara J. Lin, Robert A. Galemmo, Jr., William H. Johnson, Jr., Jenny Tan, Henry F. Campbell, Fu-Chih Huang,* George W. Nuss, Gilbert W. Carnathan, Charles A. Sutherland, and Richard G. Van Inwegen

Rorer Central Research, 800 Business Center Drive, Horsham, Pennsylvania 19044. *Received June 12, 1989*

This series of reports describes the development of orally active, highly potent, specific antagonists of the peptidoleukotrienes containing a (2-quinolinylmethoxy)phenyl moiety. Described in this first report are the structure–activity relationships that led to more than a 20-fold improvement of the potency and selectivity of the initial chemical lead (RG 5901). From this series of compounds, RG 7152 (**16**) was identified and selected for further evaluation in the clinic as an antiasthmatic agent. Compound **16** competitively inhibits [^{3}H]LTD_4 binding to membranes from guinea pig lung (K_i = 38 ± 6 nM) and the spasmogenic activity of LTC_4, LTD_4, and LTE_4 in parenchymal lung strips from guinea pigs. Unlike the original lead (RG 5901), compound **16** does not inhibit 5-lipoxygenase from guinea pig PMNs. Following oral administration to guinea pigs, **16** blocks LTD_4-induced dermal permeability (ED_{50} = 6.9 mg/kg), LTD_4-induced bronchoconstriction (ED_{50} = 1.1 mg/kg), antigen-induced bronchoconstriction (ED_{50} = 2.5 mg/kg), and anaphylactic-induced mortality (ED_{50} = 16 mg/kg). These studies on structure–activity relationships indicate that there is a requirement for an acidic function and the presence of the (2-quinolinylmethoxy)phenyl moiety in a specific geometric arrangement.

Several lines of evidence have suggested that the sulfidopeptide leukotrienes (LTC_4, LTD_4, and LTE_4) play a pathophysiological role in hypersensitivity diseases.[1] Several laboratories[2-7] have been searching for potent and selective antagonists of these leukotrienes for the potential therapeutic use in treating diseases such as asthma. Some of the earlier reported leukotriene antagonists were evaluated in clinical studies, but the results have been disappointing.[8] However, it is highly possible that the antagonists under evaluation in the clinic have lacked sufficient potency and/or the appropriate pharmacokinetic profile to determine if this pharmaceutical approach has therapeutic utility. In this series of papers, we describe the development of a chemical series containing a (2-quinolinylmethoxy)phenyl moiety into high-affinity, orally active leukotriene receptor antagonists.

Initially, we concentrated on structure–activity studies of a series of compounds represented by generic structure



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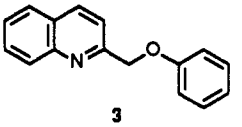

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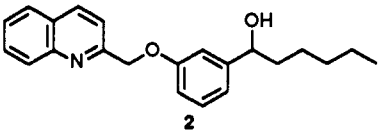

2

the observations that RG 5901 (**2**) is not only a competitive

* To whom correspondence should be sent.
† Present address: T.D.Y.L. General Food Corp., Tarrytown, NY 10591.

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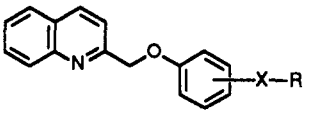
Table I. Effect of Different Linkages and Acidic Functions

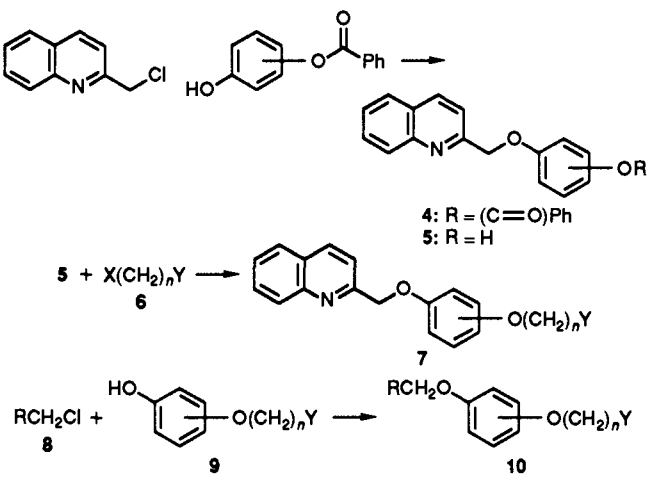


compd	position of X on phenyl Ring	X	R	binding assay:[a] K_i, nM, or % inhibn	spasmolytic assay:[a] IC_{50}, nM, or % inhibn
2[b]	–	–	–	1500	ND[c]
3[b]	–	–	–	1000	800
11	3	–[d]	tet[e]	115 ± 7 (2)	200
12	4	CH_2	tet	275 ± 35 (2)	1000
13	3	OCH_2	tet	85	140 ± 20 (2)
14	4	$(CH_2)_2$	tet	160	280
15	4	$(CH_2)_4$	tet	18 ± 4 (2)	36 ± 10 (5)
16	3	$O(CH_2)_3$	tet	42 ± 5 (5)	79 ± 12 (18)
17	4	$S(CH_2)_3$	tet	31	25 ± 3 (3)
18	3	$O(CH_2)_4$	tet	75 ± 15 (2)	120
19	4	$O(CH_2)_3$	tet	69 ± 15 (3)	250 ± 80 (3)
20	2	$O(CH_2)_3$	tet	3300	10% (10 μM)
21	3	$O(CH_2)_3$	COOEt	160 ± 0 (2)	600 ± 100 (2)
22	3	$O(CH_2)_3$	COOH	130 ± 15 (2)	240 ± 30 (2)
23	4	$O(CH_2)_3$	$CONHSO_2Ph$	31 ± 8 (3)	19 ± 2 (3)
24	4	$O(CH_2)_3$	COOH	1200	800
25	4	$O(CH_2)_3$	COOEt	500	2000
51	3	$O(CH_2)_3$	CH_3	3800 ± 300 (3)	2000 ± 200 (2)
FPL 55712	–	–		940 ± 20 (3)	510 ± 130 (9)

[a] Mean values ± SEM with (N) separate experiments or % inhibition at indicated concentration. For the binding assay, [^{3}H]LTD_4 = 0.2 nM. For the spasmolytic assay, LTC_4 = 0.2 nM. [b] The structure is shown in the text. [c] ND = not determined. [d] A direct carbon–carbon bond. [e] 5-Tetrazolyl.

inhibitor of neutrophil 5-lipoxygenase but is also a competitive antagonist of [^{3}H]LTD_4 binding with a K_i of 700 nM.[9] A structural similarity between **2** and arachidonic acid could explain these two distinct activities since arachidonic acid is the substrate for 5-lipoxygenase and a structural component of the peptidoleukotrienes. The fact that the unsubstituted compound (2-quinolinylmethoxy)benzene (**3**) also displays competitive interactions with the LTD_4 receptors seems to support this notion. The structure–activity relationships reported in this paper show that we can independently enhance the LTD_4 antagonist activity. The most significant improvement of LTD_4 antagonist activity resulted from the addition of an acidic

Scheme I



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functional group (i.e., a carboxylic acid or a tetrazole) to 2. The rationale for the addition of an acidic function is based on the chemical attributes of the LTD_4 molecule. Besides discussing the structure–activity relationships for this series, we have also described the pharmacological profile of RG 7152 (16). Compound 16 is the first compound in the series to be selected for clinical evaluation as an antiasthmatic agent.

Chemistry

Synthetic methods for the compounds listed in Tables I–III are illustrated in Scheme I. Two methods were used to form the phenolic ether linkage. The key intermediates, (2-quinolinylmethoxy)phenols (5), were prepared by reacting 2-chloromethylquinoline with hydroxyphenyl benzoates followed by hydrolysis of the ester group. Similarly, 3 was prepared by reacting 2-(chloromethyl)quinoline with phenol. Reaction of 5 with appropriately substituted haloalkyl derivatives (6, where Y = CN or COOEt) in the presence of K_2CO_3 in acetone or DMF gave good yields of the desired products 7. The carboxylic acid derivatives were usually obtained from the hydrolysis of their corresponding esters. Reaction of the nitriles with NaN_3/NH_4Cl in DMF at elevated temperature gave the 5-tetrazolyl compounds.

The compounds listed in Table II, in which other heterocyclic groups have replaced the quinoline moiety, were usually prepared by reacting phenol 9 with the appropriate halo compounds (8). The synthesis of most of these desired halo compounds is well-known. Compounds with an amide linkage between the quinoline and the phenyl ring (Table III) were synthesized by N-alkylation of the appropriate amides with halo compounds as described in the Experimental Section.

Results and Discussion

The affinities of the compounds listed in Tables I–III for LTD_4 receptors in membranes from guinea pig lung were determined with a radioligand binding assay. Since this assay does not necessarily differentiate between an agonist and antagonist, most of these compounds were also tested for their ability to inhibit the spasmogenic activity of leukotrienes on guinea pig parenchymal strips. In general, there is an excellent correlation between the two assays. However, for those discussions on structure–activity relationships involving receptor affinity, only the data from the binding assay are used.

The effect of adding an acidic functional group to the phenyl ring of 2 was examined first. As shown in Table I, the addition of a tetrazolyl function (as noted in LY 171,883[3]) resulted in a 6-fold increase in potency over the initial lead (compare 11 vs 2) and a 10-fold increase in potency over the corresponding unsubstituted compound 3. A greater enhancement of potency was seen with extended alkyl chain lengths, e.g. compare 16 vs 51. The requirement for an acidic function is consistent with the chemical attributes of the LTD_4 molecule. Based on this result, we prepared a series of compounds in which the tetrazolyl and the phenyl groups were separated by connecting groups of varying length. The data initially suggested that receptor affinity is optimal when the connecting group is lengthened to four atoms (compounds 15–17). Further synthetic work, discussed in the subsequent paper of this series, indicates that receptor binding affinity can be enhanced by different modifications of this side chain.

Having modified the chain length separating the phenyl and tetrazolyl rings, we then synthesized compounds to determine the effects of modifying the relative orientation of the quinoline ring and the acidic function by altering the substitution pattern of the phenyl ring. The ortho-substituted compound (20) is 40–60-fold less potent than the meta- or para-substituted isomers (16 and 19). The effect of different acidic functional groups was also examined. Results in Table I show that compounds with a tetrazolyl group (16 or 19) or an *N*-sulfonylacyl group (23) have a 3–10-fold greater receptor affinity than compounds with a carboxyl functional group (22 or 24).

To determine if the quinolinyl moiety is essential for high affinity to the leukotriene receptors, we evaluated compounds with different ring systems (Table II). Surprisingly, all replacements including phenyl (34), naphthyl (36), pyridyl (35), substituted pyridyl (37–41), and several benzoheterocycles (31–33) were significantly less potent than the 2-quinolinyl-containing compounds. It is interesting to note that the 3-quinolinyl compound is significantly less potent than the 2-quinolinyl isomer (16). The dramatic effect of this 2-quinolinyl moiety makes it intriguing to speculate that the nitrogen atom plays an important role in a hydrophobic region. (The *N*-oxide analogue of compound 2 was devoid of antagonist activity; data not shown.) Not only did other nitrogen-containing heterocyclic compounds have much lower receptor affinity, but the addition of a second nitrogen into this ring system also diminished activity. Therefore, the proper orientation of the fused benzene ring (compare 16, 27, and 28) and the presence of a nitrogen atom in this position appear to play critical roles for activity in this series. Possibly this nitrogen is involved in hydrogen bonding in an area of the receptor which also requires hydrophobic interaction. Recently, there have been some reports of other leukotriene D_4 antagonists that also contain this 2-quinolinyl group linked to a phenyl ring.[10,11]

Several different linkages between the phenyl and quinoline rings were also examined (Table III). The results show the importance of an ether linkage. Compounds with other connecting groups such as an amide (42, 43, and 45) are much less potent. The compound with a sulfide linkage (46) is slightly less potent than the corresponding ether (16).

Finally, we studied the effect of additional substitution on the phenyl ring (Table III). All four compounds studied are less potent than the corresponding unsubstituted compound (i.e., 16 or 18).

For drug development, it is important that compounds also have the appropriate pharmacokinetic profile so that

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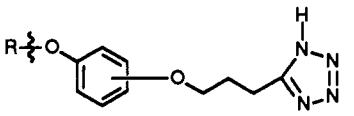
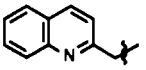
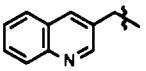
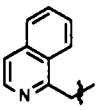
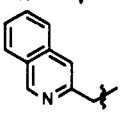
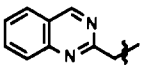
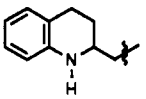
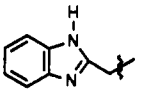
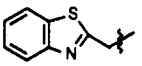
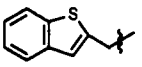
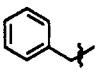
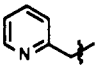
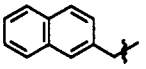
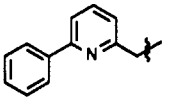
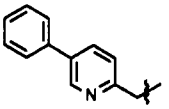
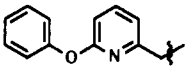
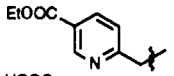
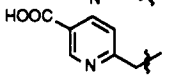
Table II. Variation of Different R Groups



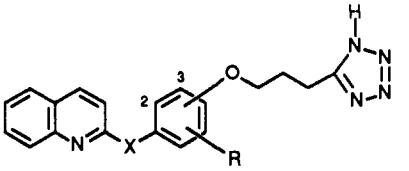
compd	R	position of subst	binding assay:[a] K_i, nM, or % inhibn (μM)	spasmolytic assay:[a] IC_{50}, nM, or % inhibn (μM)
16		3	42 ± 5 (5)	79 ± 12 (18)
26		3	15% (10 μM)	-10% (10 μM)
27		4	7% (1 μM)	
28		3	45% (10 μM)	68% (10 μM)
29		4	500	75% (10 μM)
30		4		22% (10 μM)[b]
31		4	28% (10 μM)	42% (10 μM)
32		4	240	59% (10 μM)
33		4	9% (10 μM)	36% (10 μM)
34		3	12% (10 μM)	9% (10 μM)
35		3	10% (10 μM)	18% (10 μM)
36		3	0% (10 μM)	12% (10 μM)
37		4	48% (10 μM)	50% (10 μM)
38		3	58% (10 μM)	22% (10 μM)
39		3	48% (10 μM)	9% (10 μM)
40		4	35% (10 μM)	41% (10 μM)
41		4	30% (10 μM)	22% (10 μM)

[a] See Table I. [b] Compound **30** gave variable results with some agonistlike activity at high concentrations.

potent intrinsic activity (receptor affinity and selectivity) translates into in vivo activity. Thus, selected compounds in this series were initially tested orally in two animal models. A wheal and flare assay was used to test antagonism of exogenously administered LTD_4 and a systemic anaphylactic assay was used to test antagonism of the systemic effects of endogenously generated leukotrienes. Since compounds **16**, **19**, and **22** demonstrated oral activity at reasonable doses in both of these initial assays (Table IV), they were selected for additional pharmacological studies.

Analysis of the concentration–response curves of the inhibition of [^{3}H]LTD_4 binding with the Ligand Program from Biosoft (Milltown, NJ) showed that **16** is a compe-

Table III. Effects of Variation of the Linkage between the Quinoline and Phenyl Rings and Substitution on the Phenyl Ring



compd	X	position of oxygen	R	binding assay:[a] K_i, nM, or % inhibn (μM)	spasmolytic assay:[a] IC_{50}, nM, or % inhibn (μM)
42	$-CH_2NHC(=O)-$	4	H	18% (10 μM)	-3% (10 μM)
43	$-NHC(=O)-$	4	H	33% (10 μM)	43% (10 μM)
44	$-CH_2OCH_2-$	4	H	1200	50% (10 μM)
45	$-C(=O)NH-$	4	H	25% (10 μM)	4% (10 μM)
46	$-CH_2S-$	4	H	540	400
47	$-CH_2O-$	4	3-CH_3	170	275 ± 30 (2)
48	$-CH_2O-$	3	4-C_2H_5	240	250
49	$-CH_2O-$	3	5-CH_3	640 ± 160 (2)	20% (1 μM)[b]
50	$-CH_2O-$	3	6-BnO[c]	57% (10 μM)	44% (10 μM)

[a] See Table I. [b] Agonistlike activity at high concentration. [c] BnO = benzyloxy.

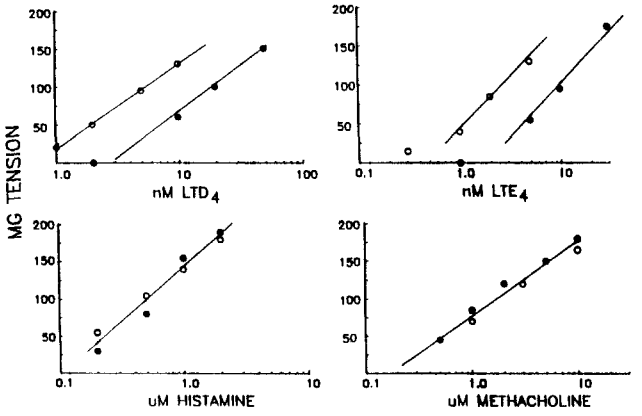


Figure 1. Representative effects of 16 on spasmogen-induced contractions of peripherial lung strips. Open circles = contractions in absence of 16. Closed circles = contractions due to LTD_4 or LTE_4 in the presence of 0.5 μM 16 or contractions due to histamine or methacholine in the presence of 50 μM 16.

titive inhibitor of [^{3}H]LTD_4 binding with a K_i of 38 ± 6 nM. Additional experiments with Scatchard[13] analysis yielded similar results and interpretation (data not shown). Figure 1 shows that **16** causes parallel shifts in the concentration–response curves of LTD_4- and LTE_4-induced contractions of the peripheral lung strips. From these types of experiments, K_B values of approximately 90 nM were obtained for all three leukotrienes (C_4, D_4, and E_4). Schild[14] plot analyses of these data indicate competitive activity against all three leukotrienes (data not shown). Against histamine-, methacholine-, and $PGF_{2\alpha}$-induced contractions of these peripheral lung strips, **16** had no significant effect up to 50 μM (Figure 1). This indicates a selectivity of at least 1000-fold for leukotriene receptors over other types of receptors. This selectivity has been confirmed by other radioligand binding studies which showed a lack of affinity for α- and β-adrenergic receptors as well as chloinergic and dopaminergic receptors (G. Gessner, Pharmacology Department, Rorer Central Research, personal communication). Furthermore, up to 50 μM **16** had no effect on base-line tension of these lung strips, which indicates a lack of partial agonist activity. Although slightly less potent, compounds **19** and **22** show similar results, indicating specific and competitive activity (data not shown).

Table IV. Oral Activity of Selected Compounds

compd	wheal assay: ED_{50} (mg/kg) or % inhibn[b] (mg/kg)	anaphylaxis assay:[a] ED_{50} (mg/kg) or % inhibn[b] (mg/kg)
11	ND[c]	145
13	18% (18)	67% (60)
15	35% (10)	ND
16	6.9	16
17	23% (10)	ND
18	ND	64% (60)
19	7.0	50
22	7.2	20
21	15	83% (30)
23	24% (9)	64% (60)

[a] Anaphylaxis assay = systemic anaphylaxis with pretreated guinea pigs challenged with aerosolized ovalbumin with mortality being the end point. [b] % inhibn (mg/kg) = % inhibition at the indicated mg/kg dose. ED_{50} values were determined as described in the methods. [c] ND = not determined.

Although very similar K_B values were against all three leukotrienes, it is difficult with only the present data to differentiate between the possibility that these compounds are selectively interacting with LTD_4 receptors or that they are nonselectively interacting at multiple subtypes of leukotriene receptors. With the spasmolytic assay conditions used, LTC_4 could be converted to LTD_4. As we have discussed[11] previously, these compounds will have to be studied with several different tissues (e.g. trachea, arteries, etc.) to differentiate between these two possibilities. However, it is quite interesting to note that there is an excellent correlation with the activities of these compounds in both the [^{3}H]LTD_4 binding assay and the spasmolytic assay using LTC_4. Considering the compounds in this and the subsequent paper in this series, this correlation occurs over 7 log orders of potency. In some of the cases where the correlation does not hold up, the compounds show partial agonist profiles of activities.

In contrast to the activity profile of the initial chemical lead (**2**), **16** does not significantly inhibit 5-lipoxygenase

(13) Scatchard, G. *Ann. N. Y. Acad. Sci.* **1949**, *51*, 660.
(14) Tallarida, R. J.; Murray, R. B. *Manual of Pharmacological Calculations*; Springer-Verlag: New York, 1987; pp 38–60.
(15) (a) 3-(Chloromethyl)quinoline: Aloup, S. C.; Bouchadon, J.; Farge, D.; James, C. Eur. Pat. Appl. EP 46, 417, 1982. (b) 3-(Chloromethyl)isoquinoline: *Chem. Abstr.* **1982**, *102*, 132055*f*. (c) 1-(Chloromethyl)isoquinoline: Newton, G. R.; Kiefeer, C. E.; Xia, Y. J.; Gupta, V. K. *Synthesis* **1984**, 679. (d) 2-(Chloromethyl)-6-phenoxypyridine: Whittle, A. S. Eur. Pat. Appl. EP 227, 369, 1987. (e) 2-(Chloromethyl)-6-phenylpyridine: Crossley, R. Eur. Pat. Appl. EP 146, 370, 1985.

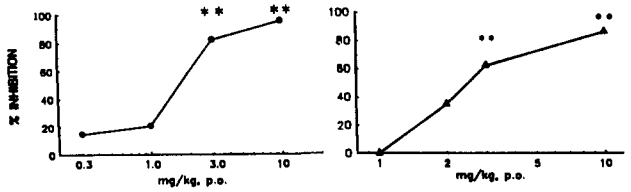


Figure 2. Inhibition of LTD_4-induced bronchoconstriction by oral administration of **16**. Left panel: inhibition of 0.8 μg/kg (iv) LTD_4. Right panel: inhibition of bronchoconstriction caused by endogenously generated LTD_4. Pharmacologically pretreated animals (indomethacin, pyrilamine, and propranolol) were challenged with ovalbumin iv as described.[5h] The asterisks denote significant difference from controls at $p < 0.01$.

from guinea pig PMNs.[12] At 30 μM, **16** caused only 9 ± 2% inhibition ($N = 5$) in this assay, whereas **2** and NDGA had IC_{50} values of 3.0 and 0.16 μM, respectively, which are consistent with published data.[4a]

When tested in the wheal assay 60 min prior to the LTD_4 challenge, compounds **16**, **19**, and **22** are approximately equipotent (Table IV). However, when tested at various time intervals prior to the LTD_4 challenge, both **16** and **19** have a pharmacological $T_{1/2}$ of approximately 4 h, whereas compound **22** has a $T_{1/2}$ of approximately 2 h (data not shown). When compound **16** is administered iv 5 min prior to the LTD_4 challenge, it inhibits the wheal formation with an ED_{50} (95% CI) of 2.2 (1.4–3.5) mg/kg. This excellent po to iv ratio suggests good bioavailability. This has been substantiated by pharmacokinetic studies that show almost 100% bioavailability (V. Kheterpal, Drug Disposition Department, Rorer Central Research, personal communication). In contrast to the effect on LTD_4 induced wheals, 30 mg/kg of **16** has no significant effect on changes in dermal permeability due to intradermal injection of histamine or serotonin (data not shown). These results confirm the selectivity observed with the in vitro data.

Figure 2 shows that intraduodenal administration of compound **16** effectively antagonizes the bronchoconstrictive response to 0.8 μg/kg (iv) of LTD_4 with an ED_{50} (95% CI) of 1.1 (0.6–2.0) mg/kg. Similarly, intraduodenal administration of **16** antagonizes the bronchoconstriction induced by iv administration of antigen in actively sensitized guinea pigs with an ED_{50} (95% CI) of 2.5 (2.0–3.2) mg/kg (Figure 2). One of the more dramatic effects of these compounds is their ability to prevent mortality due to systemic anaphylaxis in an animal model where the effects of leukotrienes have been pharmacologically enhanced by an antihistamine, a β-receptor antagonist, and an inhibitor of cyclooxygenase. Compounds **16** and **22** are approximately 2-fold more potent than **19** (Table IV). Significant protection in this systemic anaphylaxis model was observed within 15 min after oral administration of 60 mg/kg of **16** and it lasted as long as 8 h (Figure 3).

In summary, we have described the structure–activity relationships that led to the discovery of compound **16**, a specific orally active sulfidopeptide leukotriene receptor antagonist. In comparison to the initial lead compound (**2**), the activity of **16** represents a 20-fold improvement in receptor affinity and a concomitant loss of 5-lipoxygenase inhibitory activity. The structure–activity relationships show that the addition of an acidic functional group in the appropriate spatial relationship to the required (2-quinolinylmethoxy)phenyl group is important for activity. The implication is that the nitrogen plays a critical role, possibly for hydrogen bonding in a hydrophobic region of the receptor. Of clinical importance is that the increase in leukotriene receptor antagonist activity

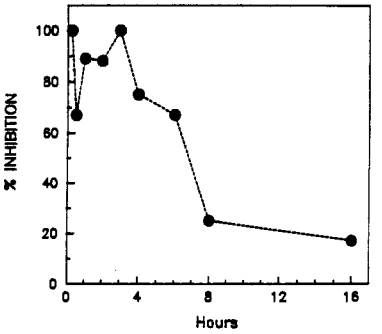


Figure 3. Oral duration of action of **16** (60 mg/kg) as an inhibitor of systemic anaphylaxis. χ^2 analysis comparison to controls: $p < 0.001$ for 0.25–4 h; $p < 0.01$ for 6 h; $p < 0.05$ for 8 h.

is also translated into increased in vivo activity with this series of compounds. The efficacy of **16** as an in vivo antagonist of LTD_4 is demonstrated by its blockade of exogenously administered LTD_4 in a wheal and flare model and a bronchoconstriction assay. Compound **16** also antagonizes the effects of endogenously generated leukotrienes in an antigen induced bronchoconstriction model and a systemic anaphylaxis model in which the effects of leukotrienes are pharmacologically enhanced. Finally, the specificity of **16** as a leukotriene antagonist, devoid of agonist activity, was demonstrated both in vitro and in vivo.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with the assigned structure. Proton NMR were recorded on a Varian EM-390 spectrometer at 90 MHz. IR spectra were recorded on a Perkin-Elmer Model 298 spectrophotometer. All compounds had elemental analyses for C, H, and N within ±0.4% of the theoretical values unless otherwise indicated. General methods of synthesis, structural formulas, and melting points of all compounds discussed are in Table V.

4-(2-Quinolinylmethoxy)phenyl Benzoate (4a). A mixture of 106.2 g (0.5 mol) of 2-(chloromethyl)quinoline and 88.5 g (0.41 mol) of 4-hydroxyphenyl benzoate were heated at reflux in 8:1 acetone/DMF (900 mL) with 68.5 g (0.5 mol) of K_2CO_3 for 48 h. The reaction mixture was filtered hot to remove the inorganic material. The addition of an equal volume of ligroin to the filtered solution completed the crystallization of 105 g (76%) of product. Recrystallization gave a pure analytical sample: mp 159–160 °C. Anal. ($C_{23}H_{17}NO_3$) C, H, N.

Compounds **3** and **51** were prepared by the same method as above with phenol or 3-(pentyloxy)phenol instead of 4-hydroxyphenyl benzoate.

4-(2-Quinolinylmethoxy)phenol (5a). To a solution of sodium ethoxide [prepared from 8.8 g (380 mmol) of sodium and 300 mL of EtOH] were added 107 g (317 mmol) of **3a** and 1.5 L of EtOH. The reaction mixture was heated at reflux for 2 h, after which a dialkylated impurity precipitated from the solution then was removed by filtration. The filtrate was evaporated to dryness and the residue was dissolved in 10% aqueous NaOH solution. The insoluble material was removed by filtration. The filtrate was acidified to pH 5 and the crystallized product was collected on a filter and air-dried to yield 50 g of **5a** (198 mmol, 63%): mp 175–177 °C. Anal. ($C_{16}H_{13}NO_2$) C, H, N.

3-(2-Quinolinylmethoxy)phenol (5b) was similarly prepared as **5a**: mp 152–153 °C. Anal. ($C_{16}H_{13}NO_2$) C, H, N.

4-[(2-Quinolinylmethyl)thio]phenol (5c). A mixture of 4-hydroxythiophenol (2.5 g, 0.02 mol), 2-(chloromethyl)quinoline hydrochloride (4.3 g, 0.02 mol), and triethylamine (5 g, 0.05 mol) in 50 mL of methylene chloride was stirred at room temperature for 2 h and then refluxed overnight. The organic solvent was removed and water was added to the residue. The crude solid product was collected on a filter (4 g, 75%) and used in the synthesis of **47a** without further purification.

4-(3-Hydroxyphenoxy)butyronitrile (9a). A solution of 15.8

Table V. Summary of Physical Data

compd	mp, °C	formula	method of preparation
3	80–81	$C_{18}H_{13}NO$	
11	214–216	$C_{17}H_{13}N_5O$[a]	A
12	173–175	$C_{18}H_{15}N_5O$	A
13	188–190	$C_{18}H_{15}N_5O_2 \cdot 2.5H_2O$	A
14	154–162 dec	$C_{19}H_{17}N_5O$[b]	A
15	124–127	$C_{21}H_{21}N_5O \cdot 0.5H_2O$	A
16	147–149	$C_{20}H_{19}N_5O_2$	A
17	122–124	$C_{20}H_{19}N_5OS$[c]	A
18	129–130	$C_{21}H_{21}N_5O_2$	D[d]
19	158–160	$C_{20}H_{19}N_5O_2$	A
20	137–140	$C_{20}H_{19}N_5O_2$	A
21	61–63	$C_{22}H_{23}NO_4$	A
22	135–137	$C_{20}H_{19}NO_4$	A
23	142–143	$C_{26}H_{24}N_2O_5S$	D
24	132–133	$C_{20}H_{19}NO_4$[e]	A
25	72–73	$C_{22}H_{23}NO_4$	A
26	215–218 dec	$C_{20}H_{19}N_5O_2$	B[f]
27	154–155	$C_{20}H_{19}N_5O_2$	B[f]
28	165–166	$C_{20}H_{19}N_5O_2$[g]	B[f]
29	156–157	$C_{19}H_{18}N_8O_2 \cdot H_2O$	B
30	147–149	$C_{20}H_{23}N_5O_2$[h]	D
31	225 dec	$C_{18}H_{18}N_8O_2$	B
32	179–180	$C_{18}H_{17}N_5O_2S$	B
33	211–212	$C_{19}H_{18}N_4O_2S$	B
34	113–114	$C_{17}H_{18}N_4O_2$[i]	B
35	102–103	$C_{18}H_{17}N_5O_2$	B
36	137–138	$C_{21}H_{20}N_4O_2$	B
37	125–126	$C_{22}H_{21}N_5O_2$	B[f]
38	131–133	$C_{22}H_{21}N_5O_2$	B[f]
39	91–92	$C_{22}H_{21}NO_5$	B[f]
40	150–151	$C_{19}H_{21}N_5O_4$	B
41	224–225	$C_{17}H_{17}N_5O_4$	B
42	180 dec	$C_{21}H_{20}N_8O_2$	C
43	215 dec	$C_{20}H_{18}N_8O_2$	C
44	114–116	$C_{21}H_{21}N_5O_2$[j]	B
45	218–219	$C_{20}H_{18}N_6O_2$	C
46	141–143	$C_{20}H_{19}N_5OS$	A
47	72–73	$C_{21}H_{21}N_5O_2$	B
48	139–140	$C_{22}H_{23}N_5O_2$	B
49	108–112	$C_{21}H_{21}N_5O_2$	B
50	44–46	$C_{30}H_{31}NO_4$	B
51	74–75	$C_{20}H_{21}NO$	

[a] C: calcd, 67.32; found, 66.86. [b] C: calcd, 68.87; found, 67.96. [c] C: calcd, 63.64; found, 63.11. [d] See the Experimental Section for details of synthesis. [e] C: calcd, 71.20; found, 70.75. [f] See ref 15 for the synthesis of the starting material. [g] C: calcd, 66.47; found, 65.49. [h] C: calcd, 65.73; found, 65.17. [i] C: calcd, 65.79; found, 65.21. [j] C: calcd, 67.18; found, 66.74.

g (0.08 mol) of 4-benzyloxyphenol, 11.7 g (0.08 mol) of 4-bromobutyronitrile, and 6 g (0.04 mol) of K_2CO_3 in 50 mL of acetone and 15 mL of DMF was refluxed for 24 h. The reaction mixture was filtered and the filtrate was concentrated and extracted with ethyl acetate. The organic solution was washed well with water, dried, and evaporated to give 22 g (96%) of crude product. The crude product thus obtained was added to 3 g of 10% Pd/C in 200 mL of ethanol and hydrogenated at 45 psi for 7 h. After filtration through Celite, the filtrate was concentrated to give 13 g (92%) of **9a** as an oil: ^{1}H NMR ($CDCl_3$) 2.1 (m, 2 H), 2.5 (t, 2 H), 3.9 (t, 2 H), 6.7 (s, 4 H).

3-(3-Hydroxyphenoxy)butyronitrile (9b). A mixture of 42.8 g (0.2 mol) of resorcinol monobenzoate, 29.6 g (0.2 mol) of 4-bromobutyronitrile, and K_2CO_3 (41.4 g, 0.3 mol) in 100 mL of DMF was heated at 50–55 °C for 6 h. The reaction mixture was poured into 400 mL of water and allowed to settle. The oily layer was separated and suspended in 100 mL of water and then treated with a methanolic NaOH solution (16 g in 160 mL of CH_3OH) for 0.5 h. After concentration under reduced pressure to remove the methanol, the aqueous solution was washed with toluene (2 × 35 mL) and poured into 100 g of ice. The product was precipitated from solution by careful neutralization with concentrated HCl and was collected on a filter and washed well with water. The product was air-dried to give 17 g (48%): mp 72–74 °C; ^{1}H NMR ($CDCl_3$) 2.2 (m, 2 H), 2.5 (t, 2 H), 3.9 (t, 2 H), 6.4–7.2 (m, 4 H). Anal. ($C_{10}H_{11}N_2$) C, H, N.

4-(4-Hydroxy-2-methylphenoxy)butyronitrile (9c). A mixture of (4-hydroxy-3-methylphenyl)benzoate (10 g, 0.044 mol), 4-bromobutyronitrile (6 g, 0.041 mol), and K_2CO_3 (7 g, 0.051 mol) in 50 mL of DMF was heated at 55–60 °C for 4 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic solution was washed well with water, dried, and evaporated. The crude product was eluted through a silica gel dry column with EtOAc/hexane (1:6) to give 5 g of an oily product. This oil was stirred with 50 mL of methanol and 20 mL of 1 N NaOH solution at room temperature for 2 h. The mixture was acidified to pH ~5–6 with 1 N HCl solution and extracted with ethyl acetate. The organic solution was dried and evaporated. Purification by dry-column chromatography gave 2 g (24%) of oil, which was used for the synthesis of **48**: ^{1}H NMR ($CDCl_3$) 2.1 (s, 3 H), 1.9–2.2 (m, 2 H), 2.4–2.6 (m, 2 H), 3.8–4.1 (m, 2 H), 6.5 (m, 3 H).

Intermediates 4-(6-ethyl-3-hydroxyphenoxy)butyronitrile (**9d**), 4-(4-hydroxy-2-methylphenoxy)butyronitrile (**9e**), and 4-[3-hydroxy-4-(benzyloxy)phenoxy]butyronitrile (**9f**) were prepared similarly from appropriate starting material and were used for the synthesis of **47**, **49**, and **50**, respectively.

4-[(4-Hydroxyphenyl)thio]butyronitrile (9g). 4-Bromobutyronitrile (6 g, 0.041 mol) was added to a mixture of 5 g (0.04 mol) of 4-hydroxythiophenol and 3.5 g (0.042 mol) of $NaHCO_3$ in 25 mL of DMF and stirred for 20 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed with water, dried, and evaporated to give 6.3 g (81%) of **9g**. This was used in the synthesis of **17** without further purification.

Method A. 4-[3-(2-Quinolinylmethoxy)phenoxy]butyronitrile (16a). A solution of 14.8 g (0.0835 mol) of **9b** and 17.9 g (0.0835 mol) of 2-(chloromethyl)quinoline hydrochloride in 100 mL of DMSO was treated with a 50% aqueous NaOH solution (prepared from 6.7 g of NaOH and 6.7 mL of water) for 15 min. The reaction mixture was stirred at 40–50 °C for 30 min followed at 60 °C for 1 h. It was then diluted with 85 mL of ice-cold water and filtered. The filter cake was washed with 100 mL of water. The crude product in a mixture of 100 mL of methanol and 25 mL of water was heated to reflux, treated with charcoal, and then filtered hot. The filtrate was cooled to 5 °C and the precipitated product was collected by filtration. The filter cake was washed with 40 mL of methanol and dried to give 17 g (71%) of **16a**: mp 86–87 °C; ^{1}H NMR ($CDCl_3$) 2.1 (m, 2 H), 2.5 (t, 2 H), 3.9 (t, 2 H), 5.4 (s, 2 H), 6.5–8.3 (m, 10 H). Anal. ($C_{20}H_{18}N_2O_2$) C, H, N.

5-[3-[3-(2-Quinolinylmethoxy)phenoxy]propyl]-1*H*-tetrazole (16). A mixture of 16 g (0.05 mol) of **16a**, 9.75 g (0.15 mol) of sodium azide, and 8.0 g (0.15 mol) of ammonium chloride in 150 mL of DMF was stirred at 140 °C for 20 h. The reaction mixture was then cooled and poured into ice water. The resulting suspension was extracted with ethyl acetate and the extract was washed with water, dried, and evaporated under vacuum to yield 15 g of crude oil which solidified upon standing. The product was recrystallized twice, first from ethyl acetate to give 10 g of material and then from acetonitrile to give 7.3 g (40%) of pure **16**: mp 150–151 °C; ^{1}H NMR (DMSO-d_6) 2.2 (m, 2 H), 2.5 (t, 2 H), 3.9 (t, 2 H), 5.3 (s, 2 H), 6.5–8.2 (m, 10 H). Anal. ($C_{20}H_{19}N_5O_2$) C, H, N.

Ethyl 4-[3-(2-Quinolinylmethoxy)phenoxy]butyrate (21). A mixture of 3.9 g (0.016 mol) of 3-(2-quinolinylmethoxy)phenol, 3 g (0.022 mol) of K_2CO_3, and 3.95 g (0.02 mol) of ethyl 4-bromobutyrate in 30 mL of DMF was heated at 60 °C for 18 h. It was then diluted with water and extracted with ethyl acetate. The extract was washed twice with water, dried, and evaporated to dryness. The oily residue was crystallized from ether/hexane to give 4.3 g (76%) of **21**: mp 61–63 °C; ^{1}H NMR ($CDCl_3$) 1.3 (t, 3 H), 2.1 (m, 2 H), 2.4 (m, 2 H), 3.9 (t, 2 H), 4.1 (q, 2 H), 5.3 (s, 2 H), 6.6 (m, 3 H), 7.0–8.1 (m, 7 H). Anal. ($C_{22}H_{23}NO_4$) C, H, N. Compound **25** was prepared similarly from appropriate starting material.

4-[3-(2-Quinolinylmethoxy)phenoxy]butyric Acid (22). A mixture of 2.6 g (7 mmol) of **21**, 150 mL of 1 N NaOH solution, and 50 mL of ethanol was stirred at 70 °C for 16 h. It was then cooled, acidified with 10% acetic acid, and filtered to give 2.1 g of crude product, which was recrystallized from acetonitrile to

give 1.3 g (55%) of acid **22**: mp 135–137 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) 2.0 (m, 2 H), 2.4 (m, 2 H), 3.9 (t, 2 H), 5.3 (s, 2 H), 6.5 (m, 3 H), 6.9–8.1 (m, 7 H). Anal. ($C_{20}H_{19}NO_4$) C, H, N.

Method B. 4-[3-[(5-Phenylpyridin-2-yl)methoxy]phenoxy]butyronitrile (38a). A mixture of 2-(chloromethyl)-5-phenylpyridine hydrochloride (2.86 g, 11.9 mmol), 4-(3-hydroxyphenoxy)butyronitrile (2.0 g, 11.3 mmol), and 0.9 g (22.6 mmol) of solid NaOH in 6.5 mL of DMF was stirred at room temperature for 24 h. The reaction mixture was diluted with water and extracted with ether (3 × 50 mL). The combined extracts were washed with water, dried, and evaporated to give 3.4 g of an impure oil. The crude product was purified by flash silica gel (100 g) and eluted with ligroin/ether to give 2.9 g (75%) of desired product: mp 70–75 °C; ^{1}H NMR ($CDCl_3$) 2.5 (t, J = 5 Hz, 2 H), 4.0 (t, J = 5 Hz, 2 H), 5.2 (s, 2 H), 6.2–8.0 (m, 11 H), 8.8 (s, 1 H), and 2.1 (q, 2 H). M^+ for $C_{22}H_{20}N_2O_2$: calcd 344.1524, obs 344.1532.

5-[3-[3-[(5-Phenylpyridin-2-yl)methoxy]phenoxy]propyl]-1*H*-tetrazole (38). A mixture of the nitrile obtained above (2.9 g, 8.43 mmol), sodium azide (1.6 g, 24.6 mmol), and ammonium chloride (1.3 g, 24.6 mmol) in 22 mL of DMF was heated at 140 °C for 18 h. The reaction mixture was poured into 100 mL of 1 N NaOH solution and the solution was extracted with EtOAc (2 × 50 mL). The crude product was precipitated from the basic layer by acidification with 1 N HCl solution to pH 5. Recrystallization from EtOAc gave 1.37 g (42%) of product: mp 131–133 °C; ^{1}H NMR (DMSO-d_6) 2.2 (m, 2 H), 3.0 (t, 2 H), 4.0 (t, 2 H), 5.2 (s, 2 H), 8.5–8.9 (m, 12 H). Anal. ($C_{22}H_{21}N_5O_2$) C, H, N.

***N*-(Phenylsulfonyl)-4-[4-(2-quinolinylmethoxy)phenoxy]butyroamide (23).** A mixture of the carboxylic acid **24** (350 mg, 1.04 mmol), benzenesulfonamide (310 mg, 2 mmol), 4-(dimethylamino)pyridine (12 mg, 0.1 mmol), and 1-(3-(dimethylamino)propyl)-3-ethylcarbodimide (310 mg, 1.04 mmol) in 15 mL of methylene chloride was stirred at room temperature overnight. The reaction mixture was diluted with 50 mL of methylene chloride, washed with water, dried and evaporated to give 650 mg of crude product. Purification with flash chromatography on silica gel (50 g) followed by recrystallization from ligroin/chloroform gave 230 mg (46%) of **23**: mp 142–143 °C. Anal. ($C_{26}H_{24}N_2O_5S$) C, H, N.

4-[4-[(2-Quinolinylmethyl)thio]phenoxy]butyronitrile (46a). A mixture of **5c** (3.5 g, 0.013 mol), 4-bromobutyronitrile (2.0 g, 0.0135 mol), and K_2CO_3 (2.1 g, 0.015 mol) in 20 mL of DMF was heated at 65–70 °C for 4 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic solution was washed well with water, dried, and evaporated to dryness. Recrystallization from EtOH gave 2.8 g (65%) of **46a**: mp 75–76 °C; ^{1}H NMR ($CDCl_3$) 1.9–2.2 (m, 2 H), 2.4–2.6 (m, 2 H), 3.8–4.1 (m, 2 H), 4.3 (s, 2 H), 6.6 (d, 2 H, J = 9 Hz), 7.2 (d, 2 H, J = 9 Hz), 7.3–8.1 (m, 6 H). Anal. ($C_{20}H_{18}N_2OS$) C, H, N.

5-[3-[4-[(2-Quinolinylmethyl)thio]phenoxy]propyl]-1*H*-tetrazole (46). A mixture of the nitrile **46a** (2.7 g, 0.0081 mol), NaN_3 (1.5 g, 0.024 mol), and NH_4Cl (1.3 g, 0.024 mol) in 20 mL of DMF was heated at 130–135 °C overnight. The reaction mixture was poured into water and basified to pH 11 with 1 N NaOH solution. The aqueous solution was washed with ethyl acetate and the organic solution was discarded. The aqueous solution was then acidified to pH 5 and extracted with ethyl acetate, and the organic solution was dried and evaporated to dryness. Recrystallization from ethyl acetate gave 1.3 g (43%) of **46**: mp 141–143 °C. ^{1}H NMR ($CDCl_3$/DMSO-d_6) 2.0–2.3 (m, 2 H), 3.0 (t, 2 H), 6.6 (d, 2 H). Anal. ($C_{20}H_{19}N_5O_5 \cdot 5H_2O$) C, H, N.

4-[4-(1,2,3,4-Tetrahydroquinolin-2-ylmethoxy)phenoxy]butyronitrile (30a). A mixture of 4-[4-(2-quinolinylmethoxy)-phenoxy]butyronitrile (1.4 g, 4.4 mmol) and 10% Pd/C (1 g) in 200 mL of ethanolk was shaken in a Parr apparatus under 40 psi of hydrogen for 4 h. TLC indicated the starting material was not present in the reaction mixture. After filtration to remove the catalyst, the crude product was purified by a silica gel dry column (solvent system: 20% ethyl acetate in hexane) to give 0.6 g of **30a** and 0.3 g of 4-(4-hydroxyphenoxy)butyronitrile. Compound **30a** was converted to tetrazole **30** as usual.

4-[4-(2-Benzimidazolylmethyl)phenoxy]butyronitrile (31a). A mixture of 4-(4-hydroxyphenoxy)butyronitrile (1.77 g, 10 mmol) and NaOH (0.5 g, 12.5 mmol) in 125 mL of ethanol was stirred at room temperature for 1.5 h and a solution of 2-(chloromethyl)benzimidazole in 50 mL of ethanol was added. The resulting mixture was stirred at room temperature for 18 h and heated to reflux for 45 min. After cooling to room temperature, ethanol was removed in vacuo to give an oily substance. The crude product was purified by a silica gel dry column (solvent system: ethyl acetate/hexane, 2:1, v/v) to give 0.4 g of pure product as white powder: mp 130–132 °C. This compound was used for the synthesis of **31**.

Method C. 4-[(3-Cyanopropyl)oxy]benzamide (42a). To a solution of 4-[(3-cyanopropyl)oxy]benzoic acid (2.05 g, 10 mmol) in 25 mL of anhydrous CH_2Cl_2, stirred under nitrogen in an ice bath, was added dropwise 2.18 mL (3.17 g, 25 mmol) of oxalyl chloride, followed by a few drops of DMF. The resulting mixture was stirred for 3 h while the temperature was allowed to rise to room temperature. After concentration under reduced pressure, the residue was dissolved in 10 mL of anhydrous CH_2Cl_2. This solution was added dropwise to a stirred mixture of NH_3 (0.4 mL, 20 mmol) and pyridine (3 mL) in 15 mL of anhydrous CH_2Cl_2 at −78 °C. The resulting mixture was stirred for several hours at room temperature and poured into an ice/water mixture. About 150 mL of ethyl acetate was added, and the layers were separated. The organic layer was washed with water and 5% aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated to give a beige, solid substance. The crude product was triturated in diethyl ether to give 1.8 g of **42a** as an off-white powder.

***N*-(2-Quinolinylmethyl)-4-[(3-cyanopropyl)oxy]benzamide (42b).** To a suspension of 0.4 g (60% suspension in oil, 10 mmol) of NaH in 7 mL of DMSO was added dropwise at room temperature a solution of **42a** (1.9 g, 9.3 mmol) in 10 mL of THF. The mixture was stirred for 3 h and a solution of 2-(chloromethyl)quinoline (1.7 g, 9.3 mmol) in 5 mL of THF was added. The resulting mixture was stirred overnight at room temperature. The reaction mixture was poured into an ice/water mixture and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and concentrated to give an oily residue, which was purified by a silica gel dry column, using a solvent system of ethyl acetate/hexane (2:1, v/v) as eluent to give 1.4 g of **42b** as a white powder. This compound was converted to tetrazole **42** without further purification.

4-[4-[(2-Quinolinylmethoxy)methyl]phenoxy]butyronitrile (44a). To a suspension of NaH (0.54 g, 60% suspension in mineral oil, 13.6 mmol) in 10 mL of DMF, stirred under N_2 in an ice bath, was added dropwise a solution of 4-[4-(hydroxymethyl)phenoxy]butyronitrile in 10 mL of DMF. The resulting mixture was stirred at room temperature for 1 h and 2.42 g (13.6 mmol) of 2-(chloromethyl)quinoline was added in one portion. The mixture was stirred overnight at room temperature, poured into an ice/water mixture and extracted with ethyl acetate. The combined organic layer was washed with brine and dried over $MgSO_4$. Removal of solvent in vacuo afforded a solid substance, which was purified on a silica gel dry column (eluent: 25% ethyl acetate in hexane) to give 2.5 g of the pure product as an off-white powder. This compound was used for the synthesis of **44**.

Biological Assays. Leukotriene D_4 Binding Assay. Measurements of specific binding of [^{3}H]LTD_4 to receptors in membranes from guinea pig lungs was done as previously described.[4b,11] LTD_4 had a K_d of 0.2 ± 0.1 nM (N = 3) in this assay, and the standard leukotriene antagonist FPL 55712 gave a K_i of 0.94 ± 0.02 μM (N = 3). K_i values for compounds were calculated from a graphic determination of the IC_{50} vs 0.2 nM [^{3}H]LTD_4 with at least four concentrations in duplicate.

Spasmolytic Assay. Parenchymal strips were cut from guinea pig lungs and suspended in tissue bath as described.[4b,11] IC_{50} values were graphically determined with at least four concentrations. The standard FPL 55712 had an IC_{50} of 0.51 ± 0.13 μM (mean ± SD, N = 9) vs 0.2 nM LTC_4. Specificity of compounds was measured by their relative potency vs the leukotrienes to other spasmogenic agents such as 1 μM histamine, 3 μM methacholine, and 10 μM $PGF_{2\alpha}$.

LTD_4 Wheal Assay. The LTD_4-induced wheal assay was done as previously described.[4b,11] ID_{50} values were graphically determined with a linear regression analysis using at least three concentrations of compounds. At least five animals were used for each data point.

Leukotriene Mediated Anaphylaxis Assays in Guinea Pigs. As previously described,[11] immunized guinea pigs were pharmacologically pretreated with pyrilamine, propranolol, and indomethacin and then challenged with ovalbumin either by aerosol or iv. ID_{50} values were graphically determined with at least three doses using at least six animals per dose.

LTD_4-Induced Bronchoconstriction. As previously described,[4b,11] animals were challenged with LTD_4 (0.4 μg/kg, iv). Compound or vehicle (PEG 400) was administered intraduodenally (id) and the animals were rechallenged with LTD_4.

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Registry No. **3**, 107813-49-0; **4a**, 125439-41-0; **5a**, 125439-42-1; **5b**, 107432-15-5; **5c**, 125439-43-2; **9a**, 40232-81-3; **9b**, 40232-81-3; **9c**, 125439-44-3; **9d**, 125439-45-4; **9e**, 125451-73-2; **9f**, 125439-46-5; **9g**, 125439-47-6; **11**, 107813-59-2; **12**, 107813-83-2; **13**, 114497-48-2; **14**, 114497-45-9; **15**, 114497-46-0; **16**, 107813-63-8; **16a**, 107813-64-9; **17**, 114516-61-9; **18**, 107813-81-0; **19**, 107813-78-5; **20**, 107813-79-6; **21**, 125439-16-9; **22**, 125439-17-0; **23**, 125439-18-1; **24**, 125439-19-2; **25**, 125439-20-5; **26**, 125439-21-6; **27**, 125439-22-7; **28**, 125439-23-8; **29**, 125439-24-9; **30**, 125439-25-0; **30a**, 125439-51-2; **31**, 125439-26-1; **32**, 125439-27-2; **33**, 125439-28-3; **34**, 125439-29-4; **35**, 125439-30-7; **36**, 125439-31-8; **37**, 125439-32-9; **38**, 125439-33-0; **38a**, 125439-48-7; **39**, 125439-34-1; **40**, 125439-35-2; **41**, 125439-36-3; **42**, 125439-37-4; **42a**, 125439-52-3; **42b**, 125439-54-5; **43**, 125439-38-5; **44**, 114497-52-8; **44a**, 125439-55-6; **45**, 125439-39-6; **46**, 114497-44-8; **46a**, 125439-50-1; **47**, 114497-40-4; **48**, 125439-40-9; **49**, 114497-41-5; **50**, 125451-72-1; **51**, 107813-90-1; LTC_4, 72025-60-6; LTD_4, 73836-78-9; LTE_4, 75715-89-8; 2-(chloromethyl)quinoline, 4377-41-7; 4-hydroxyphenyl benzoate, 2444-19-1; phenol, 108-95-2; 3-(pentyloxy)phenol, 20056-66-0; 4-hydroxythiophenol, 637-89-8; 2-(chloromethyl)quinoline hydrochloride, 3747-74-8; 4-(benzyloxy)phenol, 103-16-2; 4-bromobutyronitrile, 5332-06-9; resorcinol monobenzoate, 136-36-7; 4-hydroxy-3-methylphenyl benzoate, 71528-84-2; ethyl 4-bromobutyrate, 2969-81-5; 2-(chloromethyl)-5-phenylpyridine hydrochloride, 125439-49-8; 4-(dimethylamino)pyridine, 1122-58-3; 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide, 1892-57-5; benzenesulfonamide, 98-10-2; 4-[4-(2-quinolinylmethoxy)phenoxy]butyronitrile, 114497-65-3; 4-(4-hydroxyphenoxy)butyronitrile, 43232-83-5; 2-(chloromethyl)benzimidazole, 4857-04-9; 4-[(3-cyanopropyl)oxy]benzoic acid, 125439-53-4; 4-[4-(hydroxymethyl)phenoxy]butyronitrile, 125439-56-7.

Development of a Novel Series of (2-Quinolinylmethoxy)phenyl-Containing Compounds as High-Affinity Leukotriene D_4 Receptor Antagonists. 2. Effects of an Additional Phenyl Ring on Receptor Affinity

Fu-Chih Huang,* Robert A. Galemmo, Jr., William H. Johnson, Jr., Gregory B. Poli, Matthew M. Morrissette, James J. Mencel, James D. Warus, Henry F. Campbell, George W. Nuss, Gilbert W. Carnathan, and Richard G. Van Inwegen

Rorer Central Research, 800 Business Center Drive, Horsham, Pennsylvania 19044. *Received June 12, 1989*

This series of reports describe the development of orally active, highly potent, specific antagonists of the peptidoleukotrienes containing a (2-quinolinylmethoxy)phenyl moiety. The compounds reported in this paper contain an additional phenyl ring, which has significantly improved the receptor affinity. The effect of changes in the linkage between the two phenyl rings as well as the orientation of the acidic functional group on biological activity are discussed. Many of these compounds have high affinity to the sulfidopeptide leukotriene D_4 receptors with K_i values ranging between 2 and 20 nM and are orally active. Compound **27** [RG 12525, 5-[[2-[[4-(2-quinolinylmethoxy)phenoxy]methyl]phenyl]methyl]-1*H*-tetrazole] represents the best combination of in vitro and in vivo biological activity in this series and has been selected for further evaluation in clinical studies of asthma.

The development of a potent, specific leukotriene receptor antagonist with a favorable pharmacokinetic profile has been the goal of several laboratories (see references cited in ref 1). Such a compound would not only permit the study of the role of leukotrienes in human diseases but may also provide novel and effective therapy for hypersensitivity diseases. The leukotriene antagonists initially studied in the clinic appear to lack sufficient potency, specificity, and/or appropriate bioavailability to allow a satisfactory evaluation of the potential benefits obtained by specifically antagonizing the sulfidopeptide leukotrienes.

A number of the previously reported leukotriene antagonists are chemically similar to FPL-55712.[2] For example, LY 171883,[3] LY 163443,[3] SC 39070,[4] and L649,923,[5]

* To whom all correspondence should be sent.

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