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

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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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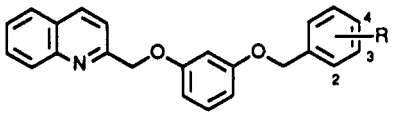
0022-2623/90/1833-1194$02.50/0

Table I. Carboxylic Acids vs Tetrazoles as LTD_4 Antagonist



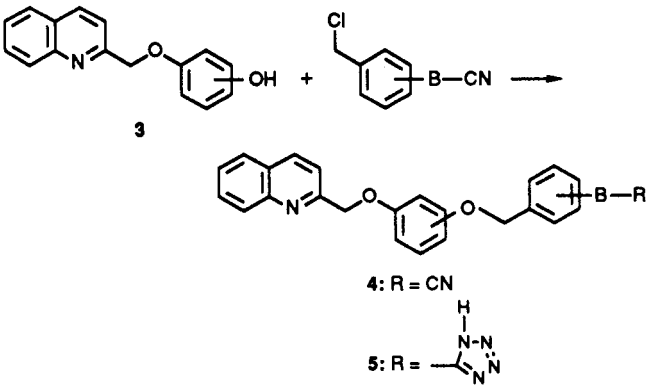
compd	R	K_i,[a] nM	IC_{50},[b] nM
12	4-CO_2H	90	75 ± 10 (2)
13	3-CO_2H	40	100 ± 30 (2)
14	3-(5-tetrazolyl)	16 ● 7 (2)	
15	4-(5-tetrazolyl)	10 ● 1 (2)	12 ± 7 (3)

[a] Radioligand binding assay on guinea pig lung membranes. Compounds were tested at multiple concentrations for competition with 0.2 nM [^{3}H]LTD_4 to calculate K_i values from the graphic determinations of IC_{50} values. Values are means ± SEM of (*N*) separate experiments. [b] Inhibition of induced contractions of peripheral lung stripes from guinea pigs induced with 0.2 nM LTC_4. The graphically determined IC_{50} values are means ± SEM of (*N*) separate experiments.

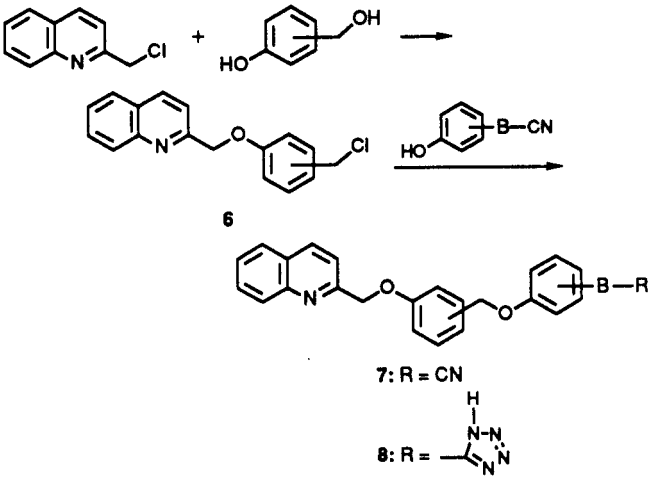
all contain the characteristic hydroxyacetophenone moiety. More recently, modification of the structure of the natural leukotriene moiety has led to the discovery of SKF 104353 as a high-affinity leukotriene antagonist.[6] In addition, other structures such as ONO-RS-411[7] and ICI 198,615[8] have been shown to be potent leukotriene antagonists. Aerosol formulations of SKF 104353[6a,b] and ICI 204,219,[9] an analogue of ICI 198,615, are presently being evaluated in the clinic for asthma. Preliminary communication has indicated that SKF 104353 has a relatively low oral bioavailability in guinea pigs and the dehydroxy analogue SKF 106203 is being studied for oral use.[6c,d]

Previously[1] we have described the initial structure–activity relationships for a series of (2-quinolinylmethoxy)phenyl-containing compounds as competitive receptor antagonists of LDT_4. In this series, we have demonstrated the importance of the quinoline nitrogen atom in the correct position in a hydrophobic region and an acidic

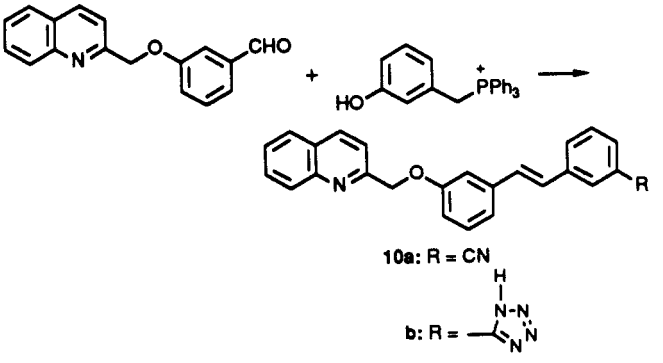
Scheme I



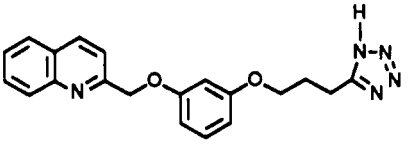
Scheme II



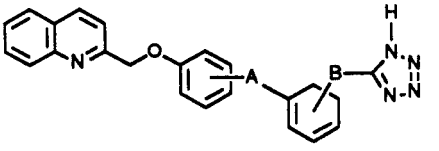
Scheme III



functional group with a specific geometric relationship to the quinoline. This led to the discovery of RG 7152 (1),



1



2

which was the first compound in this series to be selected for clinical studies as an antiasthmatic agent. Attempts

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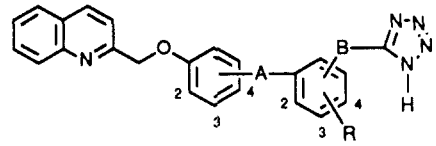
Table II. Radioligand Binding Assay on Guinea Pig Lung Membranes and Inhibition of LTC_4-Induced Contractions from Guinea Pig Lung Strip



compd	A	B	R	K_i,[a] nM	IC_{50},[a] nM
14	3-OCH_2	3-yl	H	16 ± 7 (2)	
15	3-OCH_2	4-yl	H	10 ± 1.4 (2)	12 ± 7 (3)
16	3-OCH_2	2-yl	H	20 ± 0.5 (2)	19 ± 2 (4)
17	3-OCH_2	3-yl	5-OCH_3	7 ± 1.4 (2)	6.3 ● 2.3 (3)
18	3-OCH_2	4-yl	2-OCH_3	4.3 ± 0.4 (2)	9 ± 1.4 (2)
19	3-OCH_2	3-CH_2	H	10 ± 2 (4)	12 ± 2 (3)
20	3-OCH_2	4-CH_2	H	7.3 ± 0.3 (3)	20 ± 4 (2)
21	3-OCH_2	2-CH_2	H	12 ± 2 (2)	9.5 ± 6.4 (2)
22	3-OCH_2	3-OCH_2	H	13 ± 2 (3)	24 ± 8 (4)
23	3-OCH_2	4-OCH_2	H	2.2 ± 0.3 (2)	8 ± 2 (6)
24	3-OCH_2	2-OCH_2	H	17 ± 5 (2)	27 ± 9 (3)
25	3-OCH_2	2-OCH_2	4-CO_2CH_3	8 ± 3 (2)	16 ± 6 (2)
26	4-OCH_2	3-yl	H	2.2 ± 0.3 (2)	2
27	4-OCH_2	2-CH_2	H	3.0 ± 0.3 (7)	2.7 ± 0.6 (7)
28	4-OCH_2	3-CH_2	H	8 ± 1.4 (2)	34 ± 1.4 (2)
29	4-OCH_2	4-CH_2	H	8.5 ± 0.7 (2)	12 ± 4 (6)
30	4-OCH_2	3-OCH_2	H	8 ± 3 (3)	9 ± 4 (4)
31	4-OCH_2	2-OCH_2	H	2.1 ± 0.1 (2)	4.2 ± 1.1 (5)
32	3-CH_2O	3-yl	H	5.3 ± 3 (3)	20 ± 7 (5)
33	3-CH_2O	4-yl	H	2.9 ± 0.2 (2)	14 ± 6 (2)
34	3-CH_2O	4-yl	2-OCH_3	16 ± 4 (2)	36 ± 20 (2)
35	3-CH_2O	3-yl	5-OCH_3	10 ± 2 (3)	
36	4-CH_2O	4-yl	H	31 ± 12 (2)	44 ± 15 (4)
37	4-CH_2O	4-yl	2-OCH_3	22 ± 2 (3)	
38	4-CH_2O	3-yl	5-OCH_3	7.5 ± 0.3 (3)	13
10	(*E*)-3-CH=CH	3-yl	H	8.5 ± 1 (2)	20
39	3-CH_2CH_2	3-yl	H	17 ± 3 (2)	20
FPL 55712				510 ± 130 (9)	940 ± 20 (3)

[a] See Table I.

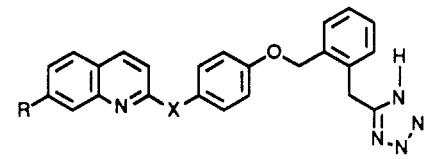
to further optimize the geometric relationships of the quinoline ring and the tetrazole moiety led to the studies of compounds with generic structure **2**. The addition of a phenyl ring also allowed us to examine the effects of different linkages between the two phenyl rings as well as the spatial orientation of the acidic functional group. Many of these compounds are high-affinity LTD_4 receptor antagonists with more than a 20-fold increase in intrinsic activity (receptor affinity) and in oral efficacy over **1**. One of these compounds, RG 12525 (**27**), has been selected for further evaluation on clinical studies.

Chemistry

The compounds listed in Tables I–III were prepared by the synthetic methods illustrated in Schemes I–III. The construction of the ether linkage between the aryl rings was achieved by simple coupling reactions between appropriately substituted benzyl halides and phenols. The synthesis of compounds with an oxygen–methylene (OCH_2) linkage between the phenyl rings is illustrated in Scheme I. Coupling of the key intermediates **3**[1] [(2-quinolinylmethoxy)phenols] with appropriately substituted benzyl chlorides gave **4**. Conversion of the nitrile group to the corresponding tetrazole was achieved by using NaN_3/NH_4Cl at 100 °C in DMF.

The synthesis of tetrazoles with a methylene–oxygen ($-CH_2O-$) linkage between the phenyl rings is shown in Scheme II. The key intermediate **6** was synthesized by the coupling of hydroxybenzyl alcohols with 2-(chloromethyl)quinoline. Further alkylation of **6** with appropriately substituted phenols gave **7**, which was subsequently converted to the desired tetrazoles as described above.

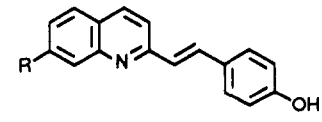
Table III. Effects of 7-Chloro Substitution on Quinoline, and Olefinic vs Ether Linkage between Quinoline and Phenyl Rings



compd	R	X	K_i,[a] nM
27	H	$-CH_2O-$	3.0 ± 0.3 (*N* = 7)
40	Cl	$-CH_2O-$	2.5
41	H	-CH=CH-	3.4 ± 0.8 (*N* = 3)
42	Cl	-CH=CH-	2.5

[a] See Table I. These four compounds were tested side by side in the same assay and the resulting K_i values were 2.5 nM for all four.

The synthesis of compounds with an olefinic linkage between the aryl rings is outlined in Scheme III. The olefinic bond in **10** was formed via a Wittig reaction from 3-(2-quinolinylmethoxy)benzaldehyde (**9**) and a ylide generated from 3-cyanobenzyl bromide. Compound **11**[10] was used for the synthesis of **41** and **42**, compounds with a double bond between the quinoline and phenyl rings.



11a: R = H
b: R = Cl

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Table IV. Oral in Vivo Activity of Selected Compounds

compd	LTD_4 wheal assay:[a] ED_{50}, mg/kg or % inhibn (mg/kg)	systemic anaphylaxis:[b] ED_{50} mg/kg or % inhibn (mg/kg)
13	7% (9)	60% (60)
14	45% (18)	83% (30)
15	6.5	10
17	38	17% (10)
18	22% (9)	45% (30)
19	1.8	10
20	6.8	30
21	17% (18)	75% (30)
22	37% (18)	64% (30)
23	59% (18)	82% (30)
24	42% (18)	10
25	29% (18)	9% (30)
26	2.0	33% (10)
27	4.9	2.2
28	3	64% (10)
29	34% (9)	30
30	2.8	27% (30)
31	45% (3)	61% (10)
32	28	45% (30)
33	ND[c]	-9% (30)
34	ND	9% (30)
36	8	64% (30)
38	26% (3)	ND
10	15% (3)	ND
39	44% (18)	24
41	ND	80% (10)

[a] Compounds were dosed orally 1 h prior to intradermal injections of 100 ng LTD_4. Five animals/dose were used and ED_{50} values were determined with at least three doses. [b] Compounds were dosed orally 1 h prior to aerosol exposure to antigen. Six animals/dose were used and ED_{50} values were determined with at least three doses. [c] ND = not determined.

Results and Discussion

The results from testing compounds for leukotriene antagonist activity in a radioligand binding assay and in the guinea pig parenchymal strip assay are summarized in Tables I and II. Although there is a good correlation between radioligand binding and tissue functional assays, the discussion of the structure–activity relationships is based on the K_i values obtained from the radioligand binding assay. This assay is a more direct measurement of receptor affinity. The more interesting compounds were tested in vivo in an LTD_4 induced wheal assay and in a systematic anaphylaxis assay, in which the leukotriene component was enhanced by pretreatment of the animals with a cycloxygenase inhibitor, an antihistamine, and a β-adrenergic antagonist. The results of the in vivo testing are summarized in Table IV.

We initially examined the benzoic acid derivatives, compounds **12** and **13**, as leukotriene antagonists. Interestingly, these compounds were approximately equipotent to **1**.[1] When the carboxylic acid functional group was replaced by bioisosteric tetrazolyl group, as in **14** and **15**, an additional 3–9-fold increase in receptor affinity was achieved (Table I). Although it is not obvious why the tetrazole group should make such a profound difference, a similar observation has been noted in other chemical series.[3]

In general, many of the newly synthesized tetrazoles described herein are high affinity LTD_4 antagonists with K_i values less than 10 nM. There are several structural features which contribute to receptor affinity for these compounds. The combined substitution patterns of the middle and terminal phenyl rings control the orientation of the acidic functional group, thereby exerting considerable influence upon biological activity (Table II). A clear and consistent trend can be discerned. In the series when the middle phenyl ring is meta substituted, para substitution of the terminal phenyl ring (meta–para configuration) seems to yield the most potent compounds. This appears to be independent of the position of attachment of the tetrazole functional group to the terminal phenyl ring; i.e., compounds **15**, **20**, and **23** are more potent than their corresponding isomers (**15** vs **14** and **16**; **20** vs **19** and **21**; **23** vs **22** and **24**). In the series when the middle phenyl ring is para substituted, ortho configuration of the terminal phenyl ring (para–ortho configuration) gives superior results (compare **27** vs **28** and **29**; **31** vs **30**). These results indicate the importance of the spatial orientations of the middle phenyl ring and the acidic functional group on receptor binding.

The choice of linkage between the two phenyl rings was also examined. The biological activity for compound **14** ($-OCH_2-$, K_i = 16 nM), **32** ($-CH_2O-$, K_i = 5 nM), **10** ($-CH{=}CH-$, K_i = 8 nM), and **39** ($-CH_2CH_2-$, K_i = 17 nM) illustrates the effect of the linkage between phenyl rings on receptor affinity. We have also examined the effect of replacing the ether linkage at the 2-position of the quinoline ring with an olefinic bond (Table III). The binding data indicate that compounds **27** and **41** are equipotent. Interestingly, chlorine atom substitution on the 7-position of the quinoline ring in both the ether and olefin series had no effect on potency (**27** vs **40**; **41** vs **42**). This result is in contrast to the observations reported by Merck with their latest series of LTD_4 antagonists which contain a 2-quinoline-styrene-phenyl moiety. In this series a significant increase in potency was reported when the 7-position of the quinoline was substituted with a halogen atom.[11a]

The type of linkage between the terminal phenyl ring and the tetrazole function also plays a role in receptor affinity in terms of placing the tetrazole into the correct spatial orientation with the quinoline and middle phenyl rings. In the series where the middle ring is meta substituted, the potency generally increases as the linkage is changed from a direct bond to a methylene or an oxymethylene spacer (**14** vs **19** or **22**; **15** vs **20** or **23**; **16** vs **21** or **24**). The greatest improvement in activity was observed in the meta–para series, where an oxymethylene linkage increased activity 4-fold (**23** vs **15**). However, similar comparison in the para–meta series indicates that this linkage decreases potency 3-fold (**30** vs **26**). These effects suggest that the absolute spatial orientation of the tetrazole to the quinoline ring is probably more important than the linkage.

Addition of a methoxy group to the terminal phenyl ring enhances potency about 2-fold (compare **14** and **17**, **15** and **18**) when the phenyl rings are connected with an oxymethylene bridge (Table II). However, when the linkage between the two phenyl rings is reversed to a $-CH_2O-$ bridge, substitution of the terminal phenyl ring with a methoxy group results in a 2-fold loss of potency (compare **33** and **34**, **32** and **35**).

From the drug development point of view, a critical issue is the translation of enhanced intrinsic potency (receptor affinity) into in vivo, oral activity. Many of these compounds were tested in two different animal models; one

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model tested antagonism of LTD_4 in the skin and one model tested antagonism of the systematic effects of endogenously generated leukotrienes. The results in Table IV indicate that in addition to intrinsic activity, pharmacokinetic parameters are affecting in vivo activity.

Although many of these compounds were active in vivo, minor structural modifications sometimes resulted in major differences in the in vivo activity even with compounds of similar receptor affinity. For example, the K_i values for compounds **23**, **26**, **27**, **31**, and **33** are between 2 and 3 nM. However, **27** had an ED_{50} of 2.2 mg/kg in the antigen induced anaphylaxis model while **33** was not active at 30 mg/kg in the same assay. In some cases, there were some discrepancies in the results between the two in vivo assays, suggesting differences in target organ distribution. For example, both **26** and **27** show good potency in the LTD_4 induced wheal assay but show different results in the antigen induced anaphylaxis model.

Compound **27** appears to have the best combination of all the required attributes, i.e. both intrinsic potency and appropriate pharmacokinetic parameters as reflected by in vivo activity. Therefore, compound **27** has been examined in greater detail.[12] It is a competitive inhibitor with a K_i of 3 nM, which represent more than a 300-fold increase in affinity for the LTD_4 receptor as compared to the affinities observed for RG 5901 and FPL-55712. Competitive antagonism was also demonstrated with a guinea pig lung strip assay in vitro (K_B vs $LTD_4 \approx 3$ nM) and an LTD_4 induced wheal assay in vivo ($ED_{50} = 5$ mg/kg).

In an antigen induced anaphylaxis assay, **27** was orally effective with an ED_{50} of 2.2 mg/kg, which represents at least a 30-fold increase in potency over a number of other reported LTD_4 antagonists, including LY-171883, L-649923, SC-39070, and ICI-198615 tested in this assay. Thus, **27** is a potent, competitive LTD_4 antagonist with good oral activity in our in vivo models.

In addition to the compounds described in these reports,[1] other quinoline-containing compounds related to RG 5901[13] have been reported to be competitive leukotriene antagonists.[14] However, they are not as potent as the compounds described in this paper nor were the structure–activity relationships developed with direct receptor measurements with [^{3}H]LTD_4. One of the more interesting compounds reported by this group[14c] is WY 48,252, which has a reported K_i value of 35 nM vs [^{3}H]LTD_4 binding but is also an inhibitor of both 5-lipoxygenase and cyclooxygenase. SR2640 is another compound with some structurally similarity to RG 5901 that has been recently reported.[15] SR2640 is reported to have an IC_{50} of 23 nM vs binding of [^{3}H]LTD_4 but the in vivo antagonist activity reported is via the iv route of administration. One of the most interesting quinoline-containing leukotriene antagonists recently reported is L-660,711.[11] It is a potent, competitive, and orally active LTD_4 receptor antagonist with a pA_2 value of 9.0 (guinea pig trachea).[11] This molecule has common structural elements of both RG 5901 (2-quinoline moiety linked to a phenyl group) and SKF 104353 (acidic functionality).

An additional benefit of having identified potent, highly selective LTD_4 antagonists will be that they can be used to not only to determine the extent of involvement of LTD_4 in diseases but the can be used to address the issue of multiple receptors for the leukotrienes. In some of the in vivo assays such as the parenchymal lung strip assay, LTC_4 can be converted to LTD_4, which may be the responsible contracting agent. Experiments using serine borate to prevent this conversion have not been totally satisfactory since borate complexes with and precipitates calcium and thus alters the responsiveness of all agonists. Studies with [^{3}H]ICI 198,615 have indicated multiple binding sites in guinea pig lung, which have been interpreted to indicate multiple LTD_4 receptors.[16] Competitive actions of these other potent antagonists need to be studied.

In summary, we have described the synthesis and structure–activity relationships of a novel class of high affinity, orally active, leukotriene D_4 receptor antagonists. Based on its overall in vitro and in vivo biological activity, compound **27** (RG 12525) has been selected for further evaluation and it may prove to be useful in the treatment of bronchial asthma and other diseases of immediate hypersensitivity.

Table V. Summary of Physical Data for Compounds Listed in Tables I–III

compd	mp, °C	formula	compd	mp, °C	formula
12	190–192	$C_{24}H_{19}NO_4 \cdot 0.5H_2O$	27	155–156	$C_{25}H_{21}N_5O_2$
			28	139–144	$C_{25}H_{21}N_5O_2$
13	149–151	$C_{24}H_{19}NO_4$[a]	29	167–171	$C_{25}H_{21}N_5O_2 \cdot H_2O$
14	115 dec	$C_{24}H_{19}N_5O_2 \cdot 1.25H_2O$	30	131–132	$C_{25}H_{21}N_5O_3 \cdot 1.5H_2O$
15	91–92	$C_{24}H_{19}N_5O_2 \cdot 1.75H_2O$	31	183–132	$C_{25}H_{21}N_5O_3 \cdot H_2O$
16	166–170	$C_{24}H_{19}N_5O_2 \cdot 4H_2O$	32	169–172	$C_{24}H_{19}N_5O_2 \cdot H_2O$
17	184–187	$C_{25}H_{21}N_5O_3 \cdot 0.5H_2O$	33	233–236	$C_{24}H_{19}N_5O_2$[e]
18	189–191	$C_{25}H_{21}N_5O_3 \cdot 0.5H_2O$	34	204–205	$C_{25}H_{21}N_5O_3$[f]
19	161–164	$C_{25}H_{21}N_5O_2$[b]	35	204–207	$C_{25}H_{21}N_5O_3 \cdot 0.5H_2O$
20	149–51.5	$C_{25}H_{21}N_5O_2 \cdot 0.5H_2O$	36	210–213	$C_{24}H_{19}N_5O_2$
21	145–147	$C_{25}H_{21}N_5O_2 \cdot 0.5H_2O$	37	195–197	$C_{25}H_{21}N_5O_3 \cdot 0.5H_2O$
22	135–137	$C_{25}H_{21}N_5O_3$	38	210–213	$C_{25}H_{21}N_5O_3$
23	154–156	$C_{25}H_{21}N_5O_3 \cdot H_2O$[c]	39	126–129	$C_{25}H_{21}N_5O \cdot 1.75H_2O$
24	118–120	$C_{25}H_{21}N_5O_3 \cdot H_2O$	40	159–163	$C_{25}H_{20}ClN_5O_2 \cdot 0.5H_2O$
25	159–162	$C_{27}H_{23}N_5O_5 \cdot 1.5H_2O$	41	191–196	$C_{25}H_{21}N_5O \cdot 0.5H_2O$
26	176–177	$C_{24}H_{19}N_5O_2$[d]	42	245 dec	$C_{26}H_{20}ClN_2O \cdot 3.5H_2O$

[a] C: calcd, 74.80; found, 73.80. [b] C: calcd, 70.84; found, 70.06. [c] C: calcd, 65.62; found, 65.07. [d] C: calcd, 70.40; found, 69.64 [e] C: calcd, 70.04; found, 69.59. [f] C: calcd, 68.32; found, 67.63.

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

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N within ±0.4% of the theoretical value unless otherwise indicated.

All tetrazoles were synthesized according to the examples described below. Physical data for new compounds are listed in Table V.

5-[[2-[[4-(2-Quinolinylmethoxy)phenoxy]methyl]phenyl]methyl]-1*H*-tetrazole (27). (a) 2-[[4-(2-Quinolinylmethoxy)phenoxy]methyl]benzyl Chloride (27a). A mixture of α,α'-dichloro-*o*-xylene (26.5 g, 0.152 mol) and the sodium salt of **5** [prepared from 9.5 g (0.038 mol) of **3b** and sodium hydride (1.48 g, 0.05 mol, of an 80% oil dispersion)] in 120 mL of THF was refluxed for 48 h. The solvent was removed and the residue was eluted through a silica gel plug (ca. 50 g of flash silica) with ethyl acetate to remove dark polymeric material. The ethyl acetate solution was evaporated to an oil, which crystallized rapidly upon cooling.

This material was a mixture of **27a** and excess dichloroxylene. To remove the excess dichloroxylene, the warmed oil was applied to 500 g of flash silica and eluted with ligroin. The compound crystallized on the silica gel column and was broken up with a spatula to allow for elution of the ligroin. After removal of the dichloro-*o*-xylene, the silica gel with impure **3b** adhering to it was ground up with a mortar and pestle, slurried with ligroin/ethyl acetate (1:1), and filtered. This solvent was removed to give a tan solid. Compound **3b** was finally isolated by dissolving the tan solid in chloroform and diluting the solution with enough hexane to achieve a 7:2 ratio of chloroform to hexane. This solution was filtered through a silica gel plug (ca. 200 g) and evaporated to give 9.65 g of purified **27a** (24.6 mmol, 65%). An analytically pure sample was crystallized from 6:1 hexane/ethyl acetate: mp 93–96 °C. Anal. ($C_{24}H_{20}ClNO_2$) C, H, N, Cl.

(b) 2-[[4-(2-Quinolinylmethoxy)phenoxy]methyl]benzyl Cyanide (27b). A biphasic mixture of **27a** (93.7 g, 240.6 mmol), potassium cyanide (31.3 g, 481.2 mmol) and Adogen phase-transfer catalyst (1.75 g) in 1:1 toluene/water (1.8 L) was heated at reflux for 48 h. The layers were separated, and the organic phase was washed with water (2 × 1 L), dried ($MgSO_4$), and concentrated to half of its volume. An equal volume of ether was added to initiate crystallization after which filtration gave 40.6 g of **27b**. The mother liquors were concentrated, and the crude product was triturated with ether/hexane (1:1) to give an additional 25.0 g of white solid. The total yield was 72% of the theoretical value. An analytical sample was prepared by crystallization from ethyl acetate/ligroin: mp 132–133 °C. Anal. ($C_{25}H_{20}N_2O_2$) C, H, N.

(c) Compound 27. A mixture of compound **27b** (13.53 g, 35.6 mmol), sodium azide (20.8 g, 320 mmol), and NH_4Cl (17.1 g, 320 mmol) in 70 mL of DMF was heated at 110 °C for 16 h. The reaction mixture was poured into 2% aqueous NaOH (500 mL). This suspension was swirled with ethyl ether (50 mL) and the ether layer was separated and discarded. This procedure was repeated until all yellow coloration was removed. The suspension was filtered and the crude, solid product was dissolved in water with the aid of EtOH. Acidification of the solution to pH 5–6 with 10% aqueous HCl solution caused a precipitation, and the product was collected on a filter and dried by suction. The crude product was recrystallized from ethyl acetate/hexane to give 10 g (66%) of tetrazole: mp 155–156 °C; ^{1}H NMR ($CDCl_3$) 4.4 (s, 2 H), 5.1 (s, 2 H), 5.3 (s, 2 H), 6.9 (q, 4 H), 7.3–7.45 (m, 4 H), 7.5–7.9 (m, 4 H), 8.1 (d, 1 H, J = 8.6 Hz), 8.2 (d, 1 H, J = 8.4 Hz). Anal. ($C_{25}H_{21}N_5O_2$) C, H, N.

Compounds **19–21**, **28**, **29**, and **40–42** were similarly prepared from the appropriate starting material.

5-[[2-[[4-(2-Quinolinylmethoxy)phenoxy]methyl]phenoxy]methyl]-1*H*-tetrazole (31). (a) [2-(Hydroxymethyl)phenoxy]acetonitrile (31a). A mixture of 2-hydroxybenzyl alcohol (10 g, 80.6 mmol), bromacetonitrile (5.6 mL, 80.6 mmol), and potassium carbonate (11.2 g, 80.6 mmol) in acetone (160 mL) with DMF (20 mL) was heated at reflux. After 72 h the reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate then washed with 10% NaOH solution and water. The ethyl acetate layer was dried ($MgSO_4$), treated with charcoal, filtered, and evaporated. This gave 8.9 g of crude product, which was suitable for further use. An analytical sample was prepared by crystallization from chloroform/heptane: mp 77–79 °C; ^{1}H NMR ($CDCl_3$) 2.5 (br s, 1 H), 4.7 (s, 2 H), 4.8 (s, 2 H), 6.9–7.6 (m, 4 H).

(b) [2-(Chloromethyl)phenoxy]acetonitrile (31b). To a solution of 8.3 g (51 mmol) of **31a** in 150 mL of CH_2Cl_2 was added 4.5 mL (61 mmol) of thionyl chloride and one drop of DMF. The reaction was stirred at ambient temperature for 16 h. After evaporation of the solvent, the residue was eluted through a silica gel plug with ligroin/ethyl acetate (1:1). Evaporation of this solution gave 8.5 g of **31b**: ^{1}H NMR ($CDCl_3$) 4.6 (s, 2 H), 4.8 (s, 2 H), 6.9–7.6 (m, 4 H).

(c) 2-[[4-(2-Quinolinylmethoxy)phenoxy]methyl]phenoxyacetonitrile (31c). A mixture of 5.5 g (22 mmol) of 4-(2-quinolinylmethoxy)phenol, 4.0 g (22 mmol) of **31b**, and 0.88 g (22 mmol) of NaOH in 25 mL of DMSO was stirred at room temperature for 16 h. The reaction mixtrure was poured into water (500 mL) and extracted with ethyl acetate (3 × 150 mL). The ethyl acetate solution was washed with water, dried ($MgSO_4$), and evaporated to give 5.5 g of crude product. The solid was chromatographed with ligroin/ethyl acetate (1.5:1) and 3.4 g (40%) of **31c** was obtained: mp 113–115 °C; ^{1}H NMR ($CDCl_3$) 4.7 (s, 2 H), 5.0 (s, 2 H), 5.3 (s, 2 H), 6.8–8.2 (m, 14 H). Anal. ($C_{25}H_{20}N_2O_3$) C, H, N.

(d) Compound 31. A mixture of compound **31c** (1.8 g, 4.5 mmol), NH_4Cl (0.73 g, 13.6 mmol), and NaN_3 (0.89 g, 13.6 mmol) in 10 mL of DMF was heated at 100–110 °C for 6 h. The mixture was cooled and 3 equiv of ammonium chloride (0.73, 13.6 mmol) and sodium azide (0.89 g, 13.6 mmol) were added. After 18 h of further heating at 100–110 °C, the reaction was poured into 200 mL of water and made basic with a 10% sodium hydroxide solution (pH 14). The aqueous solution was washed with ethyl acetate (5 × 100 mL) and then acidified with 10% HCl (pH 6). The cloudy solution was allowed to stand until crystallization was complete. The solid was filtered and allowed to air-dry to give 1.04 g (50%) of pure **31**: mp 183–185 °C; ^{1}H NMR (DMSO-d_6) 5.1 (s, 2 H), 5.3 (s, 2 H), 5.6 (s, 2 H), 7.0–8.5 (m, 14 H). Anal. ($C_{25}H_{21}N_5O_3 \cdot H_2O$) C, H, N.

Compounds **14–18**, **22–26**, and **30** were prepared similarly.

3-(2-Quinolinylmethoxy)benzyl Chloride (6b). (a) 3-(2-Quinolinylmethoxy)benzyl Alcohol (6a). A mixture of 2-(chloromethyl)quinoline hydrochloride (12.8 g, 60 mmol), 3-hydroxybenzyl alcohol (7.5 g, 60 mmol), and 18 g of K_2CO_3 in 50 mL of DMF was heated at 50 °C overnight. The reaction mixture was poured into water and the precipitated product was collected on a filter. Recrystallization from EtOAc/hexane gave 8 g (53%): mp 78–82 °C.

(b) Compound 6b. A solution of 5 g of the compound obtained above and 2.5 mL of $SOCl_2$ in 40 mL of $CHCl_3$ was stirred at room temperature overnight. The solvent was evaporated to give 5 g of crude product, which was used without further purification.

(c) 4-(2-Quinolinylmethoxy)benzyl chloride (6c) was similarly prepared according to above procedures and was used without further purification.

5-[3-[[3-(2-Quinolinylmethoxy)phenyl]methoxy]phenyl]-1*H*-tetrazole (32). (a) [[3-(2-Quinolinylmethoxy)phenyl]methoxy]benzonitrile (32a). A mixture of 0.65 g (5.4 mmol) of 3-hydroxybenzonitrile, 1.5 g (5.3 mmol) of 3-(2-quinolinylmethoxy)benzyl chloride, and K_2CO_3 (0.75 g, 5.4 mmol) in 15 mL of DMF was heated at 60 °C overnight. The reaction mixture was poured into water and the precipitated product was collected on a filter. The crude product was purified by flash chromatography eluted with EtOAc/hexane (1:3) to give 1.4 g (71%) of product (**32a**): mp 86–87 °C; ^{1}H NMR ($CDCl_3$) 9.1 (s, 2 H), 5.5 (s, 2 H), 7.1–8.3 (m, 14 H).

(b) Compound 32. A mixture of 1.2 g (3.28 mmol) of **32a**, 1.89 g (16.4 mmol) of pyridine hydrochloride, and 1.06 g (16.4 mmol) of NaN_3 in 10 mL of DMF was heated at 100 °C under nitrogen for 4 days. The reaction mixture was poured into water and the product was collected on a filter. Recrystallization from EtOAc gave 0.9 g (67%) of tetrazole **32**: mp 169–172 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) 5.0 (s, 2 H), 5.2 (s, 2 H), 6.9–8.1 (m, 14 H). Compounds **33–38** were prepared according to the methodology described above.

3-(2-Quinolinylmethoxy)benzaldehyde (9). A solution of 15 g (70 mmol) of 2-(chloromethyl)quinoline hydrochloride, 8.56 g (70 mmol) of 3-hydroxybenzaldehyde, and 20.36 g (147 mmol, 2.1 equiv) of K_2CO_3 in 120 mL of DMF was heated at 70 °C for 24 h. The reaction was poured into ice water and then extracted with EtOAc. The organic extract was dried and concentrated in

vacuo to give a brown oil. Purification by flash column chromatography through silica gel afforded 9.0 g (49% yield) of the desired aldehyde: mp 57–58 °C. Anal. ($C_{17}H_{13}NO_2$) C, H, N.

3-[[3-(2-Quinolinylmethoxy)phenyl]ethenyl]benzonitrile (10a). To a suspension of 8.18 g (17.85 mmol) of (3-cyanobenzyl)triphenylphosphonium bromide in 100 mL of DMF at 0 °C under an N_2 atmosphere was added 0.67 g (22.31 mmol, 1.25 equiv) of 80% NaH in oil dispersion. The mixture was stirred at 0 °C for 15 min followed by 1 h at room temperature. The reaction was recooled at 0 °C and 4.7 g (17.85 mmol) of aldehyde **9** in 20 mL of DMF was added dropwise over a period of 15 min. After addition, the reaction was stirred at 25 °C for 2 h and then poured into ice water. The precipitate that formed was filtered off, redissolved in CH_2Cl_2, dried, concentrated in vacuo, and then purified by flash column chromatography through silica gel to afford 4.73 g (73%) of the nitrile: mp 115–117 °C.

5-[[3-[3-(2-Quinolinylmethoxy)phenyl]ethenyl]phenyl]-1*H*-tetrazole (10). A solution of 1 g (2.76 mmol) of nitrile **10a**, 0.90 g (13.80 mmol, 5 equiv) of NaN_3, and 1.59 g (13.80 mmol, 5 equiv) of pyridine hydrochloride in 15 mL of DMF was heated at 100 °C for 48 h. The reaction mixture was poured into ice water and allowed to stand for 48 h. The precipitate that formed was filtered off and recrystallized from hot MeOH to afford 0.5 g (45% yield) of the desired tetrazole in the form of a beige, crystalline solid: mp 117–118 °C. Anal. ($C_{25}H_{19}N_5O$) C, H, N.

5-[3-[2-[3-(2-Quinolinylmethoxy)phenyl]ethyl]phenyl]-1*H*-tetrazole (39). (a) 3-[2-[3-(2-Quinolinylmethoxy)-phenyl]ethyl]benzonitrile (39a). A mixture of 2.0 g (5.52 mmol) of olefin **10a** and 0.2 g of 10% Pd/C in 50 mL of EtOH was hydrogenated at 30 psi for 4 h. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. Purification by flash column chromatography through silica gel gave a clear oil. Crystallization from Et_2O/hexane afforded 1.1 g (55%) of the desired nitrile in the form of a white, crystalline solid: mp 49–50 °C.

(b) Compound 39. To a solution of 1.07 g (2.94 mmol) of nitrile **39a** in 20 mL of DMF was added 0.95 g (14.68 mmol, 5 equiv) of NaN_3 and 0.78 g (14.68 mmol, 5 equiv) of NH_4Cl. The mixture was heated at 100 °C for 48 h, then poured into ice water. The resulting precipitate was filtered off, recrystallized from MeOH/H_2O, and finally recrystallized from CH_2Cl_2/Et_2O to afford 0.60 g (50%) of the desired tetrazole in the form of a white, crystalline solid: mp 126–129 °C. Anal. ($C_{25}H_{21}N_5O\cdot1.75H_2O$) C, H, N.

Biological Assays. All biological assays are described in the first paper of this series.[1]

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Registry No. **3a**, 107432-15-5; **3b**, 124993-40-4; **3b** (7-chloro derivative), 124993-50-6; **6a**, 123226-28-8; **6b**, 123226-29-9; **6c**, 124993-41-5; **9**, 103119-21-7; **10**, 124993-42-6; **10a**, 124993-54-0; **11a**, 4752-58-3; **11b**, 125023-19-0; **12**, 123225-66-1; **13**, 123225-67-2; **14**, 123225-63-8; **15**, 123225-57-0; **16**, 123225-64-9; **17**, 124993-43-7; **18**, 123225-76-3; **19**, 123225-81-0; **20**, 123225-82-1; **21**, 123225-80-9; **22**, 123225-69-4; **23**, 123247-25-6; **24**, 123225-72-9; **25**, 123225-73-0; **26**, 123225-95-6; **27**, 120128-20-3; **27a**, 124993-48-2; **27b**, 124993-49-3; **28**, 123225-97-8; **29**, 123225-98-9; **30**, 123247-23-4; **31**, 123226-00-6; **31a**, 123226-39-1; **31b**, 124993-51-7; **31c**, 124993-52-8; **32**, 123225-56-9; **32a**, 123225-79-6; **33**, 123226-27-7; **34**, 123225-58-1; **35**, 124993-44-8; **36**, 123225-60-5; **37**, 123225-96-7; **38**, 124993-45-9; **39**, 123692-28-4; **39a**, 124993-55-1; **40**, 123226-06-2; **41**, 124993-46-0; **42**, 124993-47-1; 3-HOC_6H_4CN, 873-62-1; 4-HOC_6H_4CN, 767-00-0; 2-$ClCH_2C_6H_4CH_2Cl$, 612-12-4; 3-$ClCH_2C_6H_4CH_2Cl$, 626-16-4; 4-$ClCH_2C_6H_4CH_2Cl$, 623-25-6; 2-$HOC_6H_4CH_2OH$, 90-01-7; $BrCH_2CN$, 590-17-0; 3-$HOC_6H_4CH_2OH$, 620-24-6; 4-$HOC_6H_4CH_2OH$, 623-05-2; 4-HO-2-$MeOC_6H_4CN$, 84224-29-3; 3-HO-5-$MeOC_6H_4CN$, 124993-53-9; 3-HOC_6H_4CHO, 100-83-4; 3-$NCC_6H_4CH_2P^+Ph_3\cdot Br^-$, 24722-19-8; 2-(chloromethyl)quinoline hydrochloride, 3747-74-8.

Synthesis and Biological Evaluation of 14-Alkoxymorphinans. 3.[1] Extensive Study on Cyprodime-Related Compounds

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A series of cyprodime-related compounds (**2**, **4–12**, and **26**) has been synthesized and evaluated for opioid agonist and antagonist activity with the mouse vas deferens and guinea pig ileum preparations. None of the changes to cyprodime, including the introduction of a 3-OMe group, increasing and decreasing the size of or completely removing the substituent in position 4, replacing the *N*-cyclopropylmethyl group with an *N*-allyl group, or replacing the 14-OMe with a 14-OEt substituent, resulted in an improved μ antagonist profile and most were detrimental either in terms of μ selectivity and potency or increased agonist activity. Increasing the length of the substituent in position 4 resulted in a compound (**6a**) with a very similar profile to that of cyprodime.

Cyprodime (**1**, Chart I) was found to be a pure opioid antagonist with high selectivity for μ receptors.[1,2] Since cyprodime has the highest μ selectivity of nonpeptide, competitive μ opioid antagonists reported, this ligand is of interest as a pharmacological tool in opioid research. In an attempt to enhance the μ potency and/or μ selectivity of cyprodime while retaining its antagonist purity and in order to further elaborate on structure–activity relationships of 14-alkoxymorphinans, we prepared the *N*-allyl analogue of cyprodime (compound **2**), its 4-hydroxy analogue **4** (a possible metabolite of cyprodime), aromatic unsubstituted derivative **5**, its 4-isopropyloxy analogue **6**, its 4-*n*-butoxy analogue **6a**, 3,4,14-trimethoxy derivatives

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(1) Part 2 of this series: Schmidhammer, H.; Burkard, W. P.; Eggstein-Aeppli, L.; Smith, C. F. C. *J. Med. Chem.* **1989**, *32*, 418.
(2) H. Schmidhammer In *Trends in Medicinal Chemistry '88*; van der Goot, H., Domany, G., Pallos, L., Timmerman, H., Eds.; Elsevier Science Publishers B. V.; Amsterdam, 1989.

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