eq 1-5, the figures in parentheses are the standard errors of the regression coefficients. For a given equation, n is the number of compounds, r is the correlation coefficient, F is a significance test, and s is the standard error of the estimate.

Molecular Modeling. Figure 2 was generated by using the SYBYL Molecular Modeling Package[9] running on a VAX 11/780.

Acknowledgment. We thank Robert F. Bruns and Gina H. Lu for performing the receptor binding assays.

Registry No. 1(X = CH_3), 5744-56-9; 2(X = CH_3), 3920-37-4; 2(X = CH_3, acid chloride), 37141-71-2; 3(X = CH_3), 78208-58-9; 4(X = CH_3), 59023-32-4; 4(X = C_2H_5), 89239-62-3; **5a**, 51222-27-6; **5b**, 104393-21-7; **5c**, 104393-30-8; **5d**, 104393-22-8; **5e**, 104393-44-4; **5f**, 104393-31-9; **5g**, 104393-23-9; **5h**, 104393-24-0; **5i**, 104393-37-5; **5j**, 104393-38-6; **5k**, 104393-40-0; **5l**, 104393-25-1; **5m**, 104393-32-0; **5n**, 104393-33-1; **5o**, 104393-41-1; **5p**, 104393-42-2; **5q**, 104393-43-3; **5r**, 104393-34-2; **5s**, 104393-26-2; **5t**, 104393-27-3; **5u**, 104393-39-7; **5v**, 104393-28-4; **5w**, 104393-29-5; **5x**, 104393-35-3; **5y**, 104393-36-4; **5z**, 104393-45-5; **6b**, 104393-46-6; **6d**, 104393-47-7; **6e**, 104393-53-5; **6g**, 104393-48-8; **6h**, 104393-49-9; **6l**, 104393-50-2; **6s**, 104393-51-3; **6t**, 104393-52-4; **6v**, 104393-54-6; **6w**, 104393-55-7; **7**, 13551-73-0; **8**, 32183-13-4; **9**, 32183-14-5; **10f**, 104393-59-1; **10i**, 104393-56-8; **10j**, 104421-41-2; **10u**, 104393-57-9; **II**(R_1 = CH_3, R_3 = CH_3, 8 = H), 58-55-9; **II**(R_1 = R_3 = CH_3, 8 = $CH_2C_6H_5$), 2879-15-4; **II**(R_1 = R_3 = CH_3, 8 = 4-pyridyl), 1088-64-8; **II**(R_1 = R_3 = CH_3, 8 = 3-pyridyl), 1029-62-5; **II**(R_1 = CH_3, R_3 = C_2H_5, 8 = C_6H_5), 104393-58-0; **II**(R_1 = R_3 = CH_3, 8 = C_6H_5), 961-45-5; **II**(R_1 = R_3 = CH_3, *p*-Cl), 29064-02-6; **II**(R_1 = R_3 = CH_3, *p*-CH_3), 57196-70-0; **II**(R_1 = R_3 = CH_3, *p*-NO_2), 1094-63-9; **II**(R_1 = R_3 = CH_3, *m*-NO_2), 78146-59-5; **II**(R_1 = R_3 = CH_3, *m*-NH_2), 85872-65-7; **II**(R_1 = R_3 = CH_3, o-OCH_3), 85872-55-5; **II**(R_1 = R_3 = CH_3, *m*-OCH_3, *p*-OCH_3), 93214-85-8; **II**(R_1 = R_3 = CH_3, o-OCH_3, *p*-OCH_3), 93214-92-7; **II**(R_1 = R_3 = CH_3, o-NH_2, *p*-Cl), 85872-60-2; **II**(R_1 = R_3 = CH_3, o-NH_2), 18830-58-5; **II**(R_1 = R_3 = CH_3, *p*-NH_2), 85872-66-8; **II**(R_1 = R_3 = CH_3, *p*-SO_3H), 80206-91-3; **II**(R_1 = R_3 = CH_3, *m*-Cl, *p*-Cl), 54013-58-0; **II**(R_1 = R_3 = CH_3, *m*-OCH_3, 5-OCH_3), 93214-89-2; **II**(R_1 = R_3 = CH_3, *m*-OCH_3), 85872-64-6; $C_6H_5CO_2H$, 65-85-0; 3,4-$(OCH_3)_2C_6H_3CO_2H$, 93-07-2; 2,4-$(OCH_3)_2C_6H_3CO_2H$, 91-52-1; 4-$H_3CC_6H_4CO_2H$, 99-94-5; 4-$HO_3SC_6H_4CO_2H$, 636-78-2; 2-$O_2NC_6H_4CO_2H$, 552-16-9; 2-O_2N-4-$ClC_6H_4C_6H_3CO_2H$, 6280-88-2; C_6H_5COCl, 98-88-4; $(H_3C)_2NCH_2CH_2NH_2$, 108-00-9; 4-pyridylbenzoic acid, 55-22-1.

(8) *SAS User's Guide: Statistics, 1982 Edition*; SAS Institute, Inc.: Cary, NC, 1982.
(9) Commercially available from Tripos Associates, Inc., St. Louis, MO 63117.
(10) We thank Dr. Horace DeWald for graciously supplying a sample of this compound.

Substituted Arylmethyl Phenyl Ethers. 1.[1] A Novel Series of 5-Lipoxygenase Inhibitors and Leukotriene Antagonists

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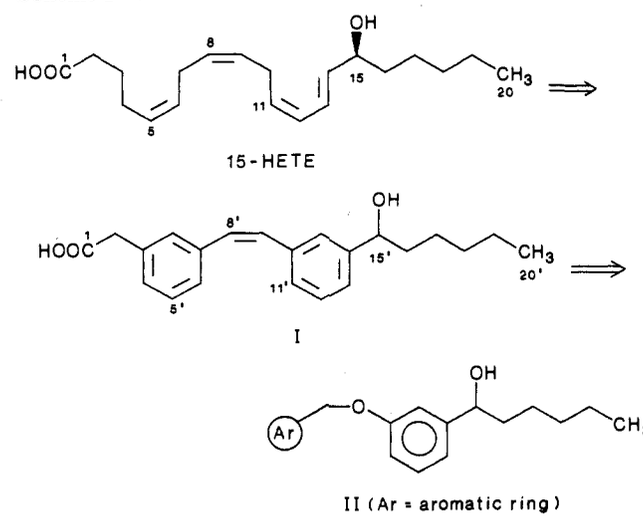
A series of new substituted arylmethyl phenyl ethers has been prepared. These compounds were tested as inhibitors of 5-lipoxygenase (5-LO) in rat neutrophils, in vitro antagonists of leukotriene-induced contraction of guinea pig (GP) lung parenchymal strips, and inhibitors of slow reacting substance of anaphylaxis (SRS-A) mediated bronchospasm in the GP in vivo. Most representatives of this new class of potential antiallergic/antiinflammatory agents showed potent inhibition of 5-LO activity in rat PMNs. The most potent compound, 2-[[3-(1-hydroxyhexyl)phenoxy]-methyl]quinoline (**33**), had an I_{50} of 0.12 μM in the rat PMN 5-LO assay and an I_{50} of 3.6 μM in the leukotriene-induced contraction of GP lung parenchymal strips, and it also showed 91% inhibition of SRS-A-mediated bronchospasm in the GP in vivo at 10 mg/kg, administered intraduodenally. Some of the compounds in this series were also leukotriene antagonists in vitro, and several of them showed in vivo activity against SRS-A-mediated bronchospasm in the GP.

The biosynthesis of prostaglandins (PG) from arachidonic acid (AA) is well-established.[2] Inhibition of this pathway may explain the therapeutic effects of nonsteroidal antiinflammatory agents in rheumatic diseases.[3] There is interest now in another aspect of the oxidative metabolism of arachidonic acid, i.e., the production of leukotrienes (LT) via the 5-lipoxygenase (LO) pathway.[4] Since LTC_4 and LTD_4 are potent bronchoconstrictors of human bronchi,[5] and LTB_4 is a powerful chemotactic factor for leukocytes,[6] inhibitors of 5-LO and/or antagonists of LTC_4 may be of therapeutic value in the treatment of asthma and inflammatory diseases.

Scheme I[a]



[a] ⟹ denotes stepwise structural evolution.

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(1) Preliminary accounts of this work were presented earlier. (a) Coutts, S.; Khandwala, A.; Van Inwegen, R.; Chakraborty, U.; Musser, J.; Bruens, J.; Jariwala, N.; Dalley-Meade, V.; Ingram, R.; Pruss, T.; Jones, H.; Neiss, E.; Weinryb, I. In *Prostaglandins, Leukotrienes, and Lipoxins*; Bailey, J. M., Ed.; Plenum: New York, 1985; p 627. (b) Gordon, R. J.; Travis, J.; Godfrey, H. R.; Sweeney, D.; Wolf, P. S.; Pruss, T. P.; Neiss, E.; Musser, J.; Chakraborty, U.; Jones, H.; Leibowitz, M. *Prostaglandins and Leukotrienes 1984*; Washington, DC, Abstr. 266.
(2) Samuelsson, B. *Fed. Proc. Am. Soc. Exp. Biol.* **1972**, *31*, 1442.
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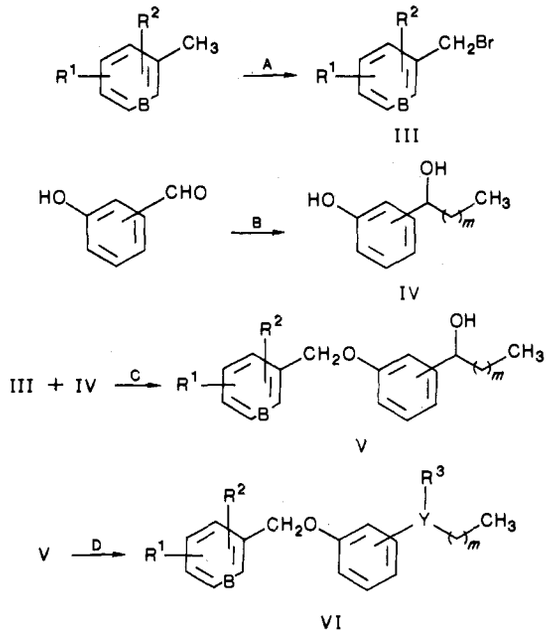
Scheme II[a]



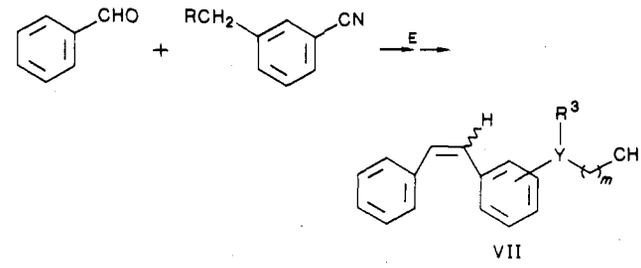
[a] B = CH, N; see Table I for R_1 and R_2.

There are several examples in the literature of rationally designed inhibitors of 5-LO. Common approaches involve the preparation of acetylenic,[7] allenic,[8] aryl,[9] or dimethyl[10] analogues of AA. Other approaches include the synthesis of analogues of 5-hydroperoxyeicosatetraenoic acid (HPETE)[11] or LTA_4.[12,13]

In 1980, Vanderhoek and co-workers reported that 15-hydroxyeicosatetraenoic acid (15-HETE) is an inhibitor of 5-LO.[14] We reasoned that analogues of 15-HETE, where the aliphatic double bonds are replaced by aromatic rings, might provide candidates for our biological studies on the inhibition of the biosynthesis of LTs.

When comparing computer-generated, space-filling models of 15-HETE with aromatic-ring-stabilized analogues, several features become apparent (Scheme I). The 11,13-cis,trans double bonds can easily be accommodated with a phenyl ring. However, substituting a ring for the remaining 5 or 8 double bond while retaining a good isosteric fit with 15-HETE is less straightforward. One of our approaches was to bridge C-3 to C-7 and to substitute a methyleneoxy group for the C-8–C-9 double bond. During the course of this study, it was realized that the phenylacetic acid moiety could also be substituted with various aromatic rings.

Scheme III[a]



[a] R = $PO(EtO)_2$, PPh_3.

We report herein the synthesis of substances of general structure II as rationally designed potent inhibitors of 5-LO. Several of these 5-LO inhibitors are also leukotriene antagonists. This observation has precedence in that the known LTD_4 antagonist, FPL 55712 (sodium 7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-4-oxo-8-propyl-4*H*-1-benzopyran-2-carboxylate), was recently reported as a specific 5-LO inhibitor.[15]

Chemistry. The synthetic pathway for the preparation of the compounds listed in Table I is shown in Scheme II and Scheme III. Bromination under photochemical conditions (procedure A) of various toluenes produced benzyl bromides III, and treatment of individual isomeric hydroxybenzaldehydes with 2.2 equiv of alkyl Grignard reagents (procedure B) gave the corresponding phenolic alcohols IV. The target benzyl ethers V were made by treating the intermediates III and IV under basic conditions (procedure C). These include (1) refluxing the intermediates in acetone with excess anhydrous potassium carbonate containing 0–10% cesium carbonate and 0–5% potassium or sodium iodide or (2) stirring the intermediates at room temperature in aqueous Me_2SO containing 1.1 equiv of sodium hydroxide. The presence of cesium carbonate often resulted in a shorter reaction time and occasionally a stoichiometric amount was used. This enhancement of reaction rate is probably due to the greater solubility of the cesium salts in acetone.[16]

The designation D used in Scheme II signifies a separately described sequence of reactions used to synthesize compounds of general structure VI (see Experimental Section). For example, oxidation of **22** with pyridinium chlorochromate gives compound **26**, and after methylation with iodomethane and sodium hydride, or reductive amination with methylamine, compoud **34** or **43**, respectively, was obtained.

To more closely approximate our original design of preparing aromatic 15-HETE analogues, we wanted to make the stilbenes VII (Scheme III), where the central double bond would be the equivalent of the C-8–C-9 double bond of 15-HETE. Reaction of diethyl 3-(cyanobenzyl)phosphonate with benzaldehyde, followed by treatment of the resulting trans olefin with *n*-pentylmagnesium bromide, and then hydrolysis gave the ketone **50**, which on reduction gave stilbene **44** (procedure E). The corresponding cis compounds **51** and **52** were prepared in the same manner except that the double-bond-forming

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(14) Vanderhoek, J. Y.; Bryant, R. W.; Bailey, J. M. *Biochem. Pharmacol.* **1982**, *31*, 3463.
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reaction was carried out with (3-cyanobenzylidene)triphenylphosphorane in Me_2SO.

Biological Results and Discussion

The results obtained for the [(1-hydroxyalkyl)phenoxy]methyl-substituted aryls as inhibitors of rat neutrophil 5-LO are listed in Table I. This assay utilizes an intact cell and therefore measures both intrinsic inhibitory activity as well as the ability of the compounds to cross the cellular membrane and partition into the cell. Some of the compounds presented in Table I were also screened against cell-free 5-LO from rat basophilic leukemia cells (data not shown)[1a] and showed 16–500-fold less activity against the cell-free preparation. This difference is probably due to the low aqueous solubility of these hydrophobic compounds as well as to their tendency to partition into cells and provide high intracellular concentrations. For example, compound **33** has an octanol–pH 7.4 phosphate buffer partition coefficient of 36 000 and an aqueous solubility of less than 0.006 mg/mL above pH 3. This compound was also concentrated up to 100-fold, compared to the concentration added to the incubation medium, in rat polymorphonuclear leukocytes (data not shown). In general, the esters **5–8** and **31** are more active than the corresponding carboxylic acids **1–4** and **32**, respectively. The ester **11** is an exception, being only equally active to the corresponding acid **10**. It is possible that the nonpolar esters are capable of crossing the cellular membrane of neutrophils in order to inhibit the cytosolic 5-LO. The more hydrophilic carboxylic acid derivatives, however, might not partition into the cell to the same extent as the esters and are, therefore, less potent inhibitors of the cellular enzyme. The position of the ester group in ring A was not found to be critical for 5-LO inhibitory activity (compare **5**, **6**, and **8**), although the 2- or 3-position appeared slightly preferable over the 4-position. When the simple carbomethoxy group in **5** was replaced by an acetic acid ester moiety as in **11**, a loss in the desired activity was observed. In fact, replacement of the ester group with other functionalities did not show significant improvement in the 5-LO inhibitory activity (compare **5** with **17–21** and **49** and **7** with **16**). However, complete removal of the ester group caused a slight loss of activity (compare **5** and **6** with **22**).

Replacement of the side-chain hydroxyl proton with acetyl, methyl, or tetrahydropyranyl groups lowered activity considerably (compare **5** with **12**, **13**, or **14** and **7** with **15**). Oxidation of this hydroxyl function to the carbonyl group did not cause a consistent change in the biological activity of these compounds (compare **20**, **22**, **30**, **33**, and **35** with **46**, **26**, **47**, **38**, and **34**, respectively), varying from a 5-fold *decrease* to a 3-fold *increase* in the I_{50} upon oxidation. When the secondary hydroxyl group was converted to a tertiary alcohol function (compare **22**, **28**, **33**, and **35** with **39**, **42**, **41**, and **40**, respectively), no significant change in the 5-LO I_{50} values occurred, with one exception (a 2.7-fold decrease, compare **22** with **39**). These observations indicated that the putative oxidative metabolism of the alkyl side chain of this series might yield active compounds and that stabilization of a hydroxyl functionality against oxidative metabolism via a tertiary alcohol would not destroy the desirable 5-LO activity in vitro. The analogues **35–37** were synthesized to impart protection against oxidation of the hydroxyl group, and when compared with their counterparts (**22** and **5**), it became clear that the modification could be achieved without loss of in vitro biological activity.

A limited study on analogues containing no oxygen atom in the benzylic position in the side chain (compare **45** with **33**) showed that dehydration of the alcohol to a double bond resulted in a greater than 80-fold loss of 5-LO activity. A preliminary assessment of the effect of bridge X on the activity of these molecules was also carried out. Although molecules containing X = CH_2O (**22**) and X = O (**48**) were comparable in activity and were both superior to that having X = OCH_2 (**23**), the linkage X = CH_2O was preferable to X = O because compounds containing the first linkage showed activity in *both* the 5-LO and SRS-A antagonism assays (compare **33** and **53**). When stilbene derivatives were examined (X = CH=CH, cis and trans), none showed a biological profile that warranted further synthesis of compounds having this type of linkage (compare **44** and **52** with **22** and **50** and **51** with **26**).

The incorporation of nitrogen within the A ring of VI (B = N) showed interesting effects on 5-LO inhibitory activity. In general, incorporation of this heteroatom had beneficial effects on the potency of 5-LO inhibition and anatagonism of leukotrienes. Some pyridine analogues (**28**, **32**, and **42**) showed an improved biological profile when compared with their carbocyclic (phenyl) counterparts **22**, **1** and **39**, respectively. However, the analogues **27**, **29**, **30**, and **31** had comparable activities when matched against their counterparts (**22**, **22**, **18**, and **5**, respectively). The same trend was also observed with a quinoline analogue: compound **33** possessed greater 5-LO and leukotriene antagonist activities than the corresponding carbocyclic naphthalene analogue **54**.

Especially interesting was the fact that these heterocyclic analogues showed a marked improvement in their biological activity when the nitrogen atom was in the 2-position with respect to the linkage X. The greater potency of 5-LO inhibition in rat PMN might be due to chelation of metal ions in the 5-LO enzyme.[17] For example, the 2-pyridinyl analogue **28** was over 5-fold more active than the phenyl analogue **22** and the isomeric pyridinyl analogues **27** (4-pyridinyl) and **29** (3-pyridinyl). The last two compounds behaved much like their non-nitrogen counterpart **22**, perhaps because the ring nitrogen in the 3- and 4-positions and the ether oxygen are sterically indisposed to form a chelating ligand.

As a representative of the phenolic compounds (IV), 1-(3-hydroxyphenyl)-1-hexanol was examined in the rat PMN 5-LO assay, and it was found to cause only 43% inhibition at 100 μM. Because it did not show a high level of inhibition of 5-LO in rat PMN, no other phenol (IV) was examined.

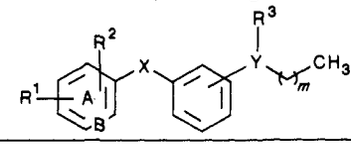
The most potent inhibitors of rat neutrophil 5-LO in Table I, 2-[[3-(1-hydroxyhexyl)phenoxy]methyl]quinoline (**33**) and its analogue **41**, with I_{50} values of 0.12 and 0.13 μM, respectively, are about 12 times more potent than 15-HETE (I_{50} = 1.45 ± 0.15 μM; mean ± half-range for two experiments) in the same system. Compound **33** has been investigated in detail and found to be a specific inhibitor of 5-LO.[1a]

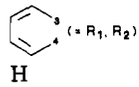
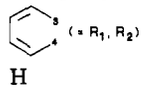
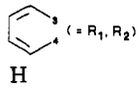
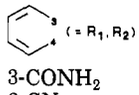
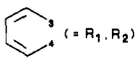
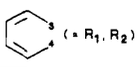
Thirty-six of the 54 compounds listed in Table I were also screened at 100 μM for inhibition of membrane-bound cyclooxygenase from rat PMN and cell-free 12-lipoxygenase from rat platelets (data not shown). None of the compounds demonstrated significant inhibition.

Most of the compounds in Table I were tested as antagonists of LTC_4-induced contraction of GP lung parenchymal strips (Table I). Some analogues showed dual

(17) For a possibility of the presence of metal ions in 5-LO enzyme, see Corey, E. J.; Cashman, J. R.; Eckrich, T. M.; Corey, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 713, and the references cited therein. A manuscript further supporting this observation is in preparation.

Table I. Arylmethyl Phenyl Ethers as 5-Lipoxygenase Inhibitors/LT Antagonists



no.	R^1	R^2	B	X	Y	R^3	m	5-LO[a] I_{50}, μM	LTC_4-induced contraction[a] % inhibn	LTC_4-induced contraction[a] concn, μM
1	3-CO_2H	H	C	CH_2O	3-$CHCH_2$	OH	3	20.5 ± 4.5 (N = 2)	30	30
2	2-CO_2H	H	C	CH_2O	3-$CHCH_2$	OH	3	30	50	20
3	2-CO_2H	H	C	CH_2O	3-$CHCH_2$	OH	2	10	50	19 ± 2 (2)
4	4-CO_2H	H	C	CH_2O	3-$CHCH_2$	OH	3	21	22	30
5	3-CO_2CH_3	H	C	CH_2O	3-$CHCH_2$	OH	3	1.0 ± 0.4 (N = 2)	20	30
6	2-CO_2CH_3	H	C	CH_2O	3-$CHCH_2$	OH	3	0.6	23	30
7	2-CO_2CH_3	H	C	CH_2O	3-$CHCH_2$	OH	2	2.5	35	30
8	4-CO_2CH_3	H	C	CH_2O	3-$CHCH_2$	OH	3	3.2	0	10
9	3-CO_2CH_3	H	C	CH_2O	2-$CHCH_2$	OH	3	3.2	50	20
10	3-CH_2CO_2H	H	C	CH_2O	3-$CHCH_2$	OH	3	2.5	50	40
11	3-$CH_2CO_2CH_3$	H	C	CH_2O	3-$CHCH_2$	OH	3	5.8	19	30
12	3-CO_2CH_3	H	C	CH_2O	3-$CHCH_2$	$OCOCH_3$	3	5.0	5	30
13	3-CO_2CH_3	H	C	CH_2O	3-$CHCH_2$	OCH_3	3	10	22	30
14	3-CO_2CH_3	H	C	CH_2O	3-$CHCH_2$	OTHP	3	23	0	30
15	2-CO_2CH_3	H	C	CH_2O	3-$CHCH_2$	OTHP	2	14		
16	2-CH_2OH	H	C	CH_2O	3-$CHCH_2$	OH	2	4 ± 0.45 (N = 2)	50	15 ± 4 (3)
17	3-CHO	H	C	CH_2O	3-$CHCH_2$	OH	3	4.0		
18	3-CN	H	C	CH_2O	3-$CHCH_2$	OH	3	17	3	10
19	3-CH_2NH_2	H	C	CH_2O	3-$CHCH_2$	OH	3	36	0	30
20	3-$CONH_2$	H	C	CH_2O	3-$CHCH_2$	OH	3	2.0	0	10
21	4-$OCH_2CO_2CH_3$	H	C	CH_2O	3-$CHCH_2$	OH	3	4.8		
22	H	H	C	CH_2O	3-$CHCH_2$	OH	3	2.7	10	100
23	H	H	C	OCH_2	3-$CHCH_2$	OH	3	6.7	19	30
24	3-CO_2CH_3	H	C	CH_2O	2-C=CH	CH_3	3	5.0	7	30
25	3-CO_2CH_3	H	C	CH_2O	4-C=CH	H	3	>100	26	30
26	H	H	C	CH_2O	3-C-CH_2	O	3	2.0	50	100
27	H	H	4-N	CH_2O	3-$CHCH_2$	OH	3	2.7	50	100
28	H	H	2-N	CH_2O	3-$CHCH_2$	OH	3	0.5	37	30
29	H	H	3-N	CH_2O	3-$CHCH_2$	OH	3	2.7	50	9 ± 1 (2)
30	3-CN	H	2-N	CH_2O	3-$CHCH_2$	OH	3	30	36	10
31	3-CO_2CH_3	H	2-N	CH_2O	3-$CHCH_2$	OH	3	1.9 ± 0.1 (N = 2)		
32	3-CO_2H	H	2-N	CH_2O	3-$CHCH_2$	OH	3	5.0 ± 4 (N = 2)	50	30
33			2-N	CH_2O	3-$CHCH_2$	OH	3	0.12 ± 0.041 (N = 6)	50	3.6 ± 0.5 (14)
34	H	H	C	CH_2O	3-$CCMe_2$	O	3	7.5 ± 2.5 (N = 2)	11	30
35	H	H	C	CH_2O	3-$CHCMe_2$	OH	3	2.5		
36	H	H	C	CH_2O	3-CHCHMe	OH	3	3.0	0	30
37	3-CO_2CH_3	H	C	CH_2O	3-$CHCMe_2$	OH	3	2.0 ± 0 (N = 2)	0	30
38			2-N	CH_2O	3-C-CH_2	O	3	0.37 ± 0.22 (N = 2)	50	20
39	H	H	C	CH_2O	3-$CMeCH_2$	OH	3	1.0	10	30
40	H	H	C	CH_2O	3-$CMeCMe_2$	OH	3	2.4	10	30
41			2-N	CH_2O	3-$CMeCH_2$	OH	3	0.13 ± 0 (N = 2)	50	8 ± 1.7 (4)
42	H	H	2-N	CH_2O	3-$CMeCH_2$	OH	3	0.43 ± 0.13 (N = 2)	50	22 ± 7 (3)
43	H	H	C	CH_2O	3-$CHCH_2$	$NHCH_3$	3	22	50	30
44	H	H	C	*trans*-CH=CH	3-$CHCH_2$	OH	3	4.5	12	30
45			2-N	CH_2O	3-C=CH	H	3	>10	50	12 ± 3 (3)
46	3-$CONH_2$	H	C	CH_2O	3-CCH_2	O	3	0.6	5	30
47	3-CN	H	C	CH_2O	3-CCH_2	O	3	6.0 ± 2 (N = 2)	-30	30
48	H	H	C	O	3-$CHCH_2$	OH	3	1.2	50	30
49	3-CF_3	H	C	CH_2O	3-$CHCH_2$	OH	3	4.0 ± 1 (N = 2)	10	30
50	H	H	C	*trans*-CH=CH	3-CCH_2	O	3	>100	0	30
51	H	H	C	*cis*-CH=CH	3-CCH_2	O	3	45	-20	30
52	H	H	C	*cis*-CH=CH	3-$CHCH_2$	OH	3	6.4	5	30
53			2-N	O	3-$CHCH_2$	OH	3	0.35	26	30
54			C	CH_2O	3-$CHCH_2$	OH	3	5.0	10	30

[a] Where applicable, the mean I_{50} (or percent inhibition) of multiple trials is given; when two trials were averaged, the mean ± half-range is presented. Othersise, the mean ± SE is indicated. Nordihydroguaiaretic acid (NDGA) used as a standard in 5-LO assay exhibited 60 ± 2.6% inhibition at 1 μM (N = 53), and FPL, 55712, a standard antagonist of LTC_4, had an I_{50} of 0.51 ± 0.13 μM (N = 9) against 0.2 nM LTC_4, in the guinea pig parenchymal strip test.

activities as LTC_4 antagonists and 5-LO inhibitors. The most potent compounds tested are **33** with an I_{50} of 3.6 ± 0.5 μM (N = 14) and **41** with an I_{50} of 6.6 ± 1.4 μM (N = 3). It should be noted that although contractions were induced by LTC_4, the tissues are probably converting LTC_4 to LTD_4,[18] and thus these compounds are possibly antagonizing LTD_4-induced contractions. Therefore, the general term of leukotriene antagonism is used for compounds inhibiting these contractions.

One of the compounds (**33**) was tested as an inhibitor of SRS-A-mediated bronchospasm in actively immunized guinea pigs.[1b] At 10 mg/kg (intraduodenal administration in PEG 400), it significantly inhibited bronchoconstriction (the maximum increase in airway resistance) following antigen challenge by 91% ($p < 0.05$, one-tailed Mann-Whitney test). Phenidone, 30 mg/kg ip, inhibited the bronchospastic response to antigen by 93% ($p < 0.01$, one-tailed Mann-Whitney test). Inhibition of this antigen-induced pulmonary response by **33** could be by inhibition of cellular 5-LO, by antagonism of leukotrienes, by a combination of these mechanisms, or by an unrelated mechanism(s). The in vitro data suggest, however, that one of the first three possibilities is more likely.

Experimental Section

Melting points were determined for all solids on a Thomas-Hoover apparatus and are uncorrected. Mass spectra were recorded on a Varian MAT-112 mass spectrometer for all compounds and were consistent with assigned structures. NMR spectra were recorded on either a Varian EM 390 spectrometer at 90 MHz or a JEOL JNM-FX 270 spectrometer at 270 MHz and were also consistent with assigned structures. IR spectra were recorded on a Perkin-Elmer Model 298 spectrophotometer. All compounds had elemental analysis within 0.4% of theoretical value unless otherwise indicated. However, compounds having an elemental analysis slightly outside of this range were found to be pure by both spectroscopic and chromatographic criteria. Melting points of all solids are given below. Where melting points are not indicated, the substance is a liquid at room temperature.

Procedure A. Substituted Benzyl Bromides (III). Methyl 3-(bromomethyl)benzoate, methyl 4-(bromomethyl)benzoate, and methyl 3-(bromomethyl)phenylacetate were prepared by the following general procedure as exemplified by the synthesis of methyl 2-(bromomethyl)benzoate.

Methyl 2-(Bromomethyl)benzoate. To a solution of methyl o-toluate (127 g, 0.847 mol) in carbon tetrachloride (1 L) was added a solution of bromine (43.5 mL, 0.849 mol) in carbon tetrachloride (400 mL). The reaction was heated to reflux and irradiated with a 600-W incandescent lamp. After the addition was complete, the solvent was removed in vacuo, giving an oil. The oil was crystallized from ethyl ether and hexanes (1:1) to give 119 g (61% yield) of product, mp 32–33 °C.[19]

Procedure B. Isomeric Diols (IV). The following general procedure, exemplified by the synthesis of 1-(3-hydroxyphenyl)-1-pentanol, was utilized to prepare compounds of type IV.

1-(3-Hydroxyphenyl)-1-pentanol. To a solution of butylmagnesium bromide (generated from magnesium (24.3 g, 1.0 mol) and 1-bromobutane (150 g, 1.1 mol)) in anhydrous ethyl ether at 0 °C was slowly added (1 h) a solution of 3-hydroxybenzaldehyde (38.0 g, 0.31 mol) in ethyl ether. After warming to room temperature, the reaction was neutralized with 5% aqueous HCl and extracted with ethyl acetate. The extract was washed with water, dried (sodium sulfate), and concentrated to a solid. The solid was crystallized from ethyl acetate to give 44.0 g (79% yield) of product, mp 120–122 °C.

In like manner as above, using the appropriate starting materials and reagents, 1-(3-hydroxyphenyl)-1-hexanol (mp 98–101 °C),[20] 1-(2-hydroxyphenyl)-1-hexanol, 2-(3-hydroxyphenyl)-2-heptene, 1-(4-hydroxyphenyl)-1-hexene, and 1-(3-phenoxyphenyl)-1-hexanol (**48**) were prepared.

Procedure C. Target Compounds (V). Compounds **5–9**, 11, **18**, **21**, **22**, **24**, **25**, **30**, **37**, **38**, **41**, **45**, **47**, and **49** in Table I were prepared by the following general procedure exemplified by the synthesis of compound **7**. The nitrogen-containing compounds **27–29** were prepared by the procedure exemplified by the synthesis of **28**.

Three of the compounds mentioned above (**24**, **25**, and **45**) contain olefinic bonds. The proton NMR spectra of these compounds in $CDCl_3$ can be used to ascertain their isomeric composition. Each of the compounds **24** and **25** contains only one isomer. The olefinic proton in **24** appears as a clean triplet (J = 7.5 Hz) at 5.8 ppm, which indicates an E configuration of the double bond (the Z isomer is expected to show a resonance absorption at 5.36 ppm according to the additivity rules for the chemical shifts of olefinic protons as postulated by Pascual, Meier, and Simon).[21] The proton NMR spectrum of **25** shows olefinic absorptions at 6.36 ppm (d, J = 15.5 Hz, α-H) and at 6.1 ppm (d of t, J = 15.5 Hz and 7.7 Hz, β-H). These values indicate that the stereochemistry of the double bond is trans (E configuration). Compound **45** is a mixture of isomers whose proton NMR spectrum shows absorptions for the β-protons at 5.62 ppm (d of t, J = 11.6 Hz and 7.7 Hz, Z isomer) and at 6.22 ppm (d of t, J = 17 Hz and 7.7 Hz, E isomer). The ratio of E–Z isomers can be estimated by NMR integration to be approximately 2:1. The α-protons absorb at 6.4 ppm as two overlapping doublets. The configurations of the double bonds in these compounds are what one would expect; the double-bond-forming reaction for compounds **24** and **25** was acid-catalyzed dehydration of the corresponding benzylic alcohols, which produced the thermodynamically more stable E isomers. The double bond in **45** was prepared via a Wittig reaction between an aromatic aldehyde and pentyl triphenylphosphorane in THF, which gave predominantly the Z isomer.

Methyl 2-[[3-(1-Hydroxypentyl)phenoxy]methyl]benzoate (7). A mixture of methyl 2-(bromomethyl)benzoate (45.2 g, 0.197 mol), 1-(3-hydroxyphenyl)-1-pentanol (35.5 g, 0.197 mol), sodium iodide (3.0 g, 0.020 mol), cesium carbonate (64.3 g, 0.198 mol), and acetone (500 mL) was refluxed for 18 h. After cooling, the suspension was filtered and the solvent removed in vacuo. The resulting oil was dissolved in ethyl acetate, washed with water, dried (sodium sulfate), and concentrated to an oil. Silica gel chromatography using hexane–chloroform (1:2) as an eluant afforded 54.7 g (85% yield) of product as an oil.

2-[[3-(1-Hydroxyhexyl)phenoxy]methyl]pyridine Hydrochloride (28). A suspension of 3.3 g (0.02 mol) of 2-picolyl chloride hydrochloride (Aldrich), 1-(3-hydroxyphenyl)-1-hexanol (3.9 g, 0.02 mol), cesium carbonate (16.3 g, 0.05 mol), cesium iodide (trace), and acetone was refluxed for 40 h. The reaction mixture was filtered through Celite and silica gel, and the solvent was removed in vacuo. The remaining oil was dissolved in ethyl ether, filtered through celite and silica gel, and treated with ethereal HCl. The resulting white precipitate was filtered, crystallized from ether–ethanol, and dried giving 4.2 g (66% yield) of solid, mp 164–165 °C.

By use of a similar procedure, compounds **27** (mp 160–165 °C) and **29** (mp 162–163 °C) were synthesized starting from 4-picolyl chloride hydrochloride and 3-picolyl chloride hydrochloride, respectively.

2-[[3-(1-Hydroxyhexyl)phenoxy]methyl]quinoline (33). A mixture of 2-(chloromethyl)quinoline hydrochloride (Aldrich, 15 g, 0.07 mol), 1-(3-hydroxyphenyl)-1-hexanol (14 g, 0.072 mol), finely powdered anhydrous potassium carbonate (22.5 g, 0.16 mol), cesium carbonate (4.7 g, 0.014 mol), and sodium iodide (2.2 g, 0.015 mol) in dry acetone (200 mL) was refluxed for 15 h. The mixture was poured into water (500 mL) and extracted with ethyl acetate. The organic extract was washed with NaOH solution (1 N), water, and brine and then dried over magnesium sulfate. After all

(18) Sautebin, L.; Vigano, T.; Grassi, E.; Crivellari, M. T.; Galli, G.; Berti, F.; Mezzetti, M.; Folco, G. *J. Pharmacol. Exp. Ther.* **1985**, *234*, 217.
(19) Eliel, E. L.; Rivard, D. E. *J. Org. Chem.* **1952**, *17*, 1252.
(20) McPhee, W. D.; Ball, F. J. *J. Am. Chem. Soc.* **1944**, *66*, 1636.
(21) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon: Oxford, 1972; Chapter 3-3.

volatiles were removed, the light-brown viscous liquid was dissolved in dry ether and then treated with dry ethereal HCl. The resulting gummy solid, on washing and triturating with dry ether and a solution of ether–petroleum ether (1:1), turned into an off-white powder (22.6 g, 87%). This solid was crystallized from ethanol–hexanes to give the desired hydrochloride salt as colorless needles, mp 118–119 °C. The free base was also prepared from the hydrochloride salt as white crystals, mp 68–69 °C.

By use of the above procedure, the naphthalene analogue **54** was synthesized from 2-(bromomethyl)naphthalene as a colorless liquid in 77% yield.

Methyl 3-[[3-(1-Hydroxy-2,2-dimethylhexyl)phenoxy]methyl]benzoate (37). A mixture of 3-(1-hydroxy-2,2-dimethylhexyl)phenol (0.7 g, 3.2 mmol) (prepared by hydrogenolysis (10% Pd–C in methanol) of **35**), methyl 3-(bromomethyl)benzoate (0.72 g, 3.1 mmol), potassium carbonate (0.45 g, 3.3 mmol), and sodium iodide (0.05 g, 0.3 mmol) in acetone (25 mL) was refluxed overnight. After cooling, the mixture was poured into water and extracted with ethyl acetate. The extract was dried (magnesium sulfate), concentrated to an oil, and purified by chromatography on silica gel using hexanes–ethyl acetate (82:18) as an eluant. The product was isolated as an oil (0.25 g, 21%).

2-[(3-Hexanoylphenoxy)methyl]quinoline (38). 1-(3-Hydroxyphenyl)-1-hexanol (made in the same manner as 1-(3-hydroxyphenyl)-1-pentanol) was oxidized using the same methodology as employed in the synthesis of **26**. The resulting ketone (1.2 g, 6.2 mmol) was reacted with 2-(chloromethyl)quinoline hydrochloride (1.3 g, 6.2 mmol) employing the same conditions used in the synthesis of **28**. The product was purified by chromatography on silica gel using hexanes–ethyl acetate (3:1) as an eluant to give the product as a solid, mp 52–55 °C (1.0 g, 49%).

2-[3-[2-(2-Hydroxyheptyl)phenoxy]methyl]quinoline Hydrochloride (41). A mixture of 2-(chloromethyl)quinoline hydrochloride (3.1 g, 14.4 mmol) and 2-(3-hydroxyphenyl)-2-heptanol (3 g, 14.4 mmol) (prepared in the same manner as described for compound **39**) in acetone (300 mL) containing potassium carbonate (20 g, 145.0 mmol) and potassium iodide (0.2 g, 1.2 mmol) was refluxed overnight. The solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. The solution was washed with 5% sodium hydroxide and brine, dried (magnesium sulfate), and concentrated. The resulting oil was purified by chromatography on silica gel using hexanes–ethyl acetate (80:20) as an eluant. The isolated free base was dissolved in ether and treated with HCl gas to give the product (1.3 g, 23%) as a solid, mp 133–134 °C dec. In like manner as above, using 2-(chloromethyl)pyridine hydrochloride, compound **42** was prepared, mp 160–161 °C (32%).

Procedure D. Carboxylic acids **1–4**, **10**, and **32** in Table I were prepared by the following general procedure exemplified by the synthesis of compound **2**. The remaining procedures are for the synthesis of compounds **12–14**, **16**, **17**, **19**, **20**, **23**, **26**, **31**, **34–36**, **40**, **42**, and **43**.

2-[[3-(1-Hydroxyhexyl)phenoxy]methyl]benzoic Acid (2). A solution of **6** (1.0 g, 2.9 mmol) in methanol (55 mL) was treated with 1 N aqueous sodium hydroxide (3 mL). The reaction was stirred for 1 h at room temperature. The mixture was washed with ethyl ether, neutralized with 5% aqueous HCl, and extracted with chloroform. The extract was dried (magnesium sulfate) and concentrated to give 0.7 g (73% yield) of product, mp 76–80 °C.

Methyl 3-[[3-(1-Acetoxyhexyl)phenoxy]methyl]benzoate (12). To a solution of **5** (1.7 g, 5.0 mmol) in pyridine at 0 °C was added acetic anhydride (2.7 mL, 29.0 mmol). The reaction was stirred for 4 days at room temperature. The solvent was removed in vacuo, and the remaining oil was purified by HPLC on silica gel using hexane–ethyl acetate (9:1) as an eluant to give 1.1 g (57% yield) of product as an oil.

Methyl 3-[[3-(1-Methoxyhexyl)phenoxy]methyl]benzoate (13). To a suspension of sodium hydride (0.5 g, 10.4 mmol) in ethyl ether at 0 °C was added **5** (1.7 g, 5.0 mmol) in ethyl ether. The mixture was allowed to warm to room temperature. Methyl iodide (0.6 g, 6.5 mmol) was added, and the reaction was stirred at room temperature for 3 days. The reaction was quenched with saturated ammonium chloride. The mixture was washed with water, dried (magnesium sulfate), and concentrated to an oil. The oil was purified by HPLC on silica gel using hexane–ethyl acetate (9:1) as an eluant to give 1.0 g (55% yield) of product as an oil.

Methyl 3-[[3-[1-(Tetrahydro-2*H*-pyran-2-yloxy)hexyl]phenoxy]methyl]benzoate (14). To a solution of **5** (2.2 g, 6.4 mmol), dihydropyran (2.3 mL, 25.5 mmol), and ethyl ether was added a catalytic amount of 4-toluene sulfonic acid. The reaction was stirred at room temperature for 4 days. The ethyl ether was removed in vacuo, and the remaining oil was purified on silica gel using hexane–ethyl acetate (93:7) as an eluant to give 1.8 g (67% yield) of oil. In like manner as above, using compound **7** (43.7 g) as starting material, compound **15** (48.3 g) was isolated in 88% yield after chromatography on silica gel using hexane–chloroform (2:1) as eluant.

2-[[3-(1-Hydroxypentyl)phenoxy]methyl]benzyl Alcohol (16). To a suspension of LAH (4.2 g, 0.11 mol) in dry ether (300 mL) was added a solution of **15** (44.2 g, 0.11 mol) in dry ether (150 mL) dropwise with vigorous stirring at room temperature over a period of 1 h. After the addition was complete, the slurry was refluxed overnight. The excess amount of LAH was destroyed by adding ethyl acetate (25 mL) to the cold suspension carefully. The organic layer was separated, washed with water and brine, and dried over anhydrous sodium sulfate. After removal of all volatiles, the crude residual liquid was passed through a column of silica gel using 1% methanol in chloroform as an eluant. The pure alcohol was obtained as a clear, colorless liquid in 89% yield (36.4 g).

The above alcohol with the THP protecting group (4.1 g, 11.0 mmol) was stirred with Amberlyst-15 (0.3 g) in methanol (40 mL) at 45 °C for 2 h. The liquid was decanted, and all methanol was removed to leave 3.2 g (100%) of the product, which was eluted with chloroform through a column of silica gel to yield the pure product **16** as a clear, colorless liquid (2.7 g, 82% yield).

3-[[3-(1-Hydroxyhexyl)phenoxy]methyl]benzaldehyde (17). To a solution of **18** (10.0 g, 32.4 mmol) in THF was added DIBAL (15 g, 105.6 mmol), and the reaction was refluxed overnight. Methanol (10.2 mL) was slowly added followed by water (85.7 mL). The mixture was filtered, and the filtrate was concentrated to an oil. The oil was dissolved in chloroform, washed with 5% aqueous HCl (5×), dried over magnesium sulfate, and flushed through a column of silica gel. The chloroform was evaporated to give 3.0 g (30% yield) of product as an oil.

3-[[3-(1-Hydroxyhexyl)phenoxy]methyl]benzylamine Hydrochloride (19). To a suspension of LAH (1.0 g, 26.3 mmol) in ethyl ether was added dropwise a solution of **18** (3.0 g, 10.0 mmol) in ethyl ether. After stirring for 2 h at room temperature, the reaction was quenched successively with 1 mL of water, 1 mL of 15% sodium hydroxide, and 3 mL of water. The mixture was filtered. The remaining solution was treated with ethereal HCl, and a precipitate formed which was filtered and dried to give 2.2 g (63% yield) of product, mp 90–94 °C.

3-[[3-(1-Hydroxyhexyl)phenoxy]methyl]benzamide (20). A mixture of **18** (5.0 g, 16.2 mmol) and 30% hydrogen peroxide (0.7 mL) was stirred at room temperature for 1 h. The reaction mixture was heated at 50 °C for 3 h. The solution was neutralized with 5% aqueous HCl and extracted with chloroform. The extract was dried (magnesium sulfate) and concentrated to a solid. The solid was crystallized from ethyl acetate to give 1.1 g (63% yield) of product, mp 97–98 °C.

1-[3-(Phenoxymethyl)phenyl]-1-hexanol (23). To a well-stirred suspension of NaH (1.35 g, 56 mmol) in dry THF (100 mL) was added a solution of phenol (5.3 g, 56 mmol) in dry THF (25 mL). After the anion formation was complete, a solution of 3-cyanobenzyl bromide (10 g, 51 mmol) in dry THF (50 mL) was added dropwise. After the addition was complete (30 min), the solution was refluxed for 4 h. All volatiles were removed, and the residue was dissolved in ethyl acetate. The organic extract was successively washed with 1 N NaOH solution, 1 N HCl solution, water, and brine. After drying over anhydrous magnesium sulfate, all solvent was removed. The desired ether was obtained as a liquid (10.7 g, 100% yield), which quickly solidified. This was pure enough to be used without further purification.

The cyano compound (10.7 g, 51 mmol) was dissolved in dry toluene (200 mL) and THF (35 mL), and to it was added a solution of DIBAL in toluene (63 mmol). The mixture was stirred at room temperature overnight (15 h) and then cooled in an ice bath. The reaction was quenched by adding cold water (25 mL) and a 5% solution of sulfuric acid (50 mL). After the mixture was stirred for 1 h at room temperature, the organic layer was separated and

dried over magnesium sulfate. Upon removal of all solvent, the desired aldehyde, 3-(phenoxymethyl)benzaldehyde, was obtained as a clear liquid (10.2 g, 95% yield), which also solidified readily on standing. This material was used without further purification.

Treatment of this aldehyde (10.2 g, 48 mmol) in dry THF (20 mL) and ether (50 mL) with pentylmagnesium bromide (60 mmol) in ether (50 mL) in the same manner as described under the synthetic procedure for 1-(3-hydroxyphenyl)-1-pentanol yielded the desired alcohol **23** as a clear liquid (13 g). This was purified chromatographically using a solution of 6.5% ethyl acetate in hexanes on a silica gel column to get 6.5 g of pure **23** as a clear, colorless liquid (47.5% yield).

Benzyl 3-(Hexanoyl)phenyl Ether (26). To a suspension of pyridinium chlorochromate (32.3 g, 0.14 mol) in methylene chloride (200 mL) was added a solution of **22** (28.4 g, 0.1 mol) in methylene chloride (25 mL). The reaction was stirred at room temperature for 1.5 h. The excess methylene chloride was decanted, and the residual black solid was triturated with ethyl ether (4×). The combined organic extracts were purified on Flurosil using ethyl ether as an eluant to give 27.8 g (98% yield) of product as an oil.

Methyl 6-[[3-(1-Hydroxyhexyl)phenoxy]methyl]picolinate (31). A solution of **30** (7.0 g, 22.6 mmol), methanol (50 mL), and cesium carbonate was stirred at room temperature overnight. The reaction was diluted with 0.1 N HCl. After stirring for 3 h, the methanol was removed in vacuo and the remaining suspension was extracted with chloroform. The organic extract was dried (magnesium sulfate) and concentrated to give 7.6 g (94% yield) of product as an oil.

Benzyl 3-[1-(*N*-Methylamino)hexyl]phenyl Ether (43). A solution of **26** (4.6 g, 16.3 mmol) and methylamine hydrochloride (3.0 g, 44.4 mmol) in anhydrous methanol (50 mL) was treated with sodium cyanoborohydride (0.64 g, 10.2 mmol). The pH was adjusted to about 5 (wet pH paper) with dry HCl gas dissolved in methanol. This solution was refluxed over molecular sieves (3A) for 2 days. An aqueous solution of hydrochloric acid was added to the reaction mixture, and then most of the methanol was removed at the rotary evaporator. The aqueous solution was extracted thoroughly with chloroform. The organic extract was dried over magnesium sulfate, and then all volatiles were removed to leave the crude product, as the hydrochloride salt, as a white solid. This was crystallized from ether–ethanol to obtain the hydrochloride salt of the desired amine as white needles, mp 147–149 °C (2.0 g, 41%).

Benzyl 3-(1-Hydroxy-2,2-dimethylhexyl)phenyl Ether (35). To a refluxing suspension of sodium hydride (3.6 g, 0.15 mol) and methyl iodide (28.0 g, 0.197 mol) in dry THF (50 mL) was added dropwise a solution of **26** (13.0 g, 0.046 mol) in dry THF (150 mL) over a period of 90 min. After the addition was complete, the mixture was refluxed for 3 h. Any excess of NaH was destroyed by adding cold methanol (50 mL) to the ice-cold reaction mixture. Most of the volatiles were removed at the rotary evaporator. The residue was taken up in ethyl acetate, and the organic extract was washed with dilute HCl (1 N), water, and brine. After drying over $MgSO_4$, all volatiles were removed to leave the crude product (13.7 g) as a pale-yellow liquid. This was chromatographed on silica gel using 5% ethyl acetate in hexanes as eluant to obtain the pure product **34** (7.7 g, 54%) as a colorless liquid.

When pure **34** (4 g, 13 mmol) was reduced with LAH (0.18 g, 4.8 mmol) in dry ether (35 mL) in the same manner as compound **16**, the crude alcohol **35** was obtained as an oil, which was chromatographed on silica gel using 5% ethyl acetate in hexanes as eluant. The pure product **35** was isolated as a colorless liquid (2.1 g, 52%).

When the NMR spectrum of the crude alkylated product **34** was examined, it could be seen that there was a monoalkylated ketone (10–15%). The monoalkylated alcohol **36** was obtained as a sideproduct in an overall yield of 8% from a two-step sequence starting from **26**. The alcohol **36** could be isolated in the same manner as **35** when a crude sample of **34** was reduced with LAH.

2-[3-(Benzyloxy)phenyl]-2-heptanol (39). To an ethereal solution of **26** (3.0 g, 10.6 mmol) was added slowly an excess of methylmagnesium bromide (2.5 g, 21.2 mmol; 7.0 mL of a 3 M solution in ether). The reaction mixture was stirred overnight at room temperature. The reaction was quenched with ammonium chloride and filtered. The ethereal layer was separated, washed with brine, dried (magnesium sulfate), and concentrated to an oil. The oil was purified by chromatography on silica gel using hexane–ethyl acetate (96:4) as an eluant to give the product (1.5 g, 47%) as an oil. In like manner as above using ketone **34** (6.5 g), compound **40** (4.0 g, 58%) was prepared.

2-[3-(1-Hydroxyhexyl)phenoxy]quinoline (53). To a well-stirred mixture of 2-chloroquinoline (20 g, 0.134 mol) and sodium hydride (3.25 g, 0.135 mol) in dry DMF (100 mL) was added a solution of 3-hydroxybenzaldehyde (16.4 g, 0.134 mol) in dry DMF (100 mL) dropwise over a period of 45 min. This reaction mixture was heated at 120 °C for 18 h. Most of the DMF was removed at the rotary evaporator, and the residue was treated with ethyl acetate. The organics were washed with water and brine and dried over magnesium sulfate. All volatiles were removed, and the residual light-brown liquid was washed and triturated with petroleum ether a few times, whereupon it solidified into a beige solid, weighing 19 g (62%). This solid, 3-(2-quinolinyloxy)benzaldehyde, was found to be pure enough to be used in the next step.

A solution of the Grignard reagent, *n*-pentylmagnesium bromide, prepared from magnesium turnings (2 g, 0.08 mol) and *n*-pentyl bromide (12.43 g, 0.08 mol) in dry THF (75 mL), was added dropwise to an ice-cold solution of the above-mentioned aldehyde (19 g, 0.076 mol) in dry THF (100 mL). After the addition was complete (ca. 45 min), the solution was allowed to warm up to room temperature and was stirred for 3 h. The reaction mixture was poured into saturated ammonium chloride solution, and the THF layer was separated and dried over magnesium sulfate. All volatiles were removed in vacuo to obtain the crude product as a yellow liquid, which was chromatographed on silica gel using 15% ethyl acetate in hexanes as eluant. The pure alcohol **53** was obtained as a white solid, mp 54–57 °C, weighing 10 g (41%).

Procedure E. Stilbenes **44** and **50–52** in Table I were prepared by the following procedures. The configurations of these stilbene derivatives were determined from their proton NMR spectra. It is well-known that the olefinic protons in the *trans*-stilbenes resonate at a lower field than the corresponding protons in the cis derivatives (e.g., *trans*-stilbene, 7.05 ppm; *cis*-stilbene, 6.5 ppm). This large difference in the chemical shift in *cis*- and *trans*-stilbene analogues has also been observed in the present case. The olefinic protons in the *cis*-stilbene derivative **52** absorbed at 6.6 ppm, whereas the corresponding protons in the trans isomer **44** resonated at 7.16 ppm. The trans ketone **50** exhibited the vinyl absorptions at 7.2 ppm, whereas the cis isomer **51** showed olefinic signals at 6.7 ppm. Interestingly, only in the cis ketone **51** are the olefinic protons coupled to each other (d of d, J = 11.6 Hz). In all other isomers, these protons appear as either one single, sharp absorption (as in **44** and **52**) or two very closely spaced (ca. 3–4 Hz at 270 MHz) sharp absorptions (as in **50**). This variation in the splitting pattern in cis and trans stilbene derivatives is known. It has been reported that the olefinic protons in 3-methoxy-*trans*-stilbene absorb at 7.1 ppm as a singlet, whereas the corresponding cis isomer showed resonance at 6.6 ppm as a doublet of doublet with J = 12.5 Hz.[22]

***trans*-3-Hexanoylstilbene (50).** To a suspension of sodium hydride (4.2 g, 87.5 mmol, 50% in oil) in THF was added a solution of diethyl 3-(cyanobenzyl)phosphonate (22 g, 87.0 mmol) (generated from 3-cyanobenzyl bromide and triethyl phosphite followed by distillation (bp 152–154 °C at 0.02 mm)) in THF. After stirring at room temperature for 1 h, the mixture was cooled to 0 °C and treated with a solution of benzaldehyde (9.2 g, 87.0 mmol) in THF. The reaction was allowed to warm to room temperature and was stirred overnight. The reaction was quenched with methanol and concentrated. The residue was dissolved in ethyl acetate, washed with 5% HCl, water, and brine, dried (sodium sulfate), and concentrated to give 18 g (87.8 mmol) of *trans*-3-cyanostilbene (100%), mp 69–71 °C.

To a solution of *n*-pentylmagnesium bromide (prepared from 1-bromopentane (7.3 g, 48.3 mmol) and magnesium turnings (1.2 g, 50 mmol)) in THF was added a solution of the above cyano compound (9 g, 43.9 mmol) in THF. The reaction was refluxed for 8 h. After cooling to 0 °C, a solution of 6 N HCl (24 mL, 145

(22) Gusten, H.; Salzwedel, M. *Tetrahedron* **1967**, *23*, 173, 187.

mmol) was added and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate, washed with saturated sodium bicarbonate and brine, dried (magnesium sulfate), and concentrated. The product was purified by chromatography on silica gel using hexanes–ethyl acetate (97:3) as eluant to give a solid, mp 54–56 °C (9.5 g, 75%).

***trans*-3-(1-Hydroxyhexyl)stilbene (44).** To a solution of compound **50** (1 g, 3.6 mmol) in ethanol was added sodium borohydride (0.2 g, 7.0 mmol), and the reaction was stirred overnight. The excess borohydride was destroyed with dilute HCl, and the mixture was extracted with ethyl ether. The extract was washed with brine, dried (magnesium sulfate), and concentrated to an oil (0.7 g, 69%).

***cis*-3-Hexanoylstilbene (51).** To a solution of (3-cyanobenzyl)triphenylphosphonium bromide (15 g, 32.9 mmol) (prepared from triphenylphosphine and 3-cyanobenzyl bromide) in Me_2SO at 0 °C was added a solution of *n*-butyllithium (49.3 mmol) in hexane. The mixture turned red. It was allowed to warm to room temperature at which point it turned clear. After cooling to 0 °C, a solution of benzaldehyde (3.8 g, 36.2 mmol) in Me_2SO was added. The reaction was stirred overnight at room temperature. The solvent was removed in vacuo, and the residue was dissolved in ethyl ether. The ethereal solution was washed with water and brine, dried (magnesium sulfate), and concentrated to an oil. The oil was purified on silica gel using hexanes–ethyl acetate (95:5) as an eluant. *cis*-3-cyanostilbene was separated from the minor product, which was the trans isomer. Pure *cis*-3-cyanostilbene was isolated as a white solid weighing 7.6 g, which was converted to the ketone **51**, in a fashion similar to that described for the trans isomer **50**, as a colorless liquid (5 g, 48%).

***cis*-3-(1-Hydroxyhexyl)stilbene (52).** This compound was synthesized from the corresponding pure ketone **51** (3.2 g, 11.5, mmol) in the same manner as **44**, to give the pure alcohol (1.0 g, 31%) as a clear, colorless liquid.

Rat Neutrophil 5-LO Test. A suspension of ca. 2×10^6 glycogen-elicited rat neutrophils[23] in buffer is incubated for 3 min at 3 °C with 4 μM [^{14}C]AA and 0.8 μM calcium ionophore A23187. Citric acid (2 M) is used to quench the reaction. Following the addition of a trace amount of [^{3}H]-5-HETE (ca. 10 000 dpm) together with an excess of unlabeled 5-HETE to each tube, the mixture is extracted with chloroform–methanol. The organic layer is washed with dilute HCl, and an aliquot is transferred to glass tubes and dried in vacuo at room temperature. The residue is dissolved in a small volume of chloroform, and an aliquot is spotted on silica gel TLC sheets, which are developed with an ethyl acetate–isooctane–water–acetic acid solvent system. The 5-HETE spots are visualized with iodine, cut out, and placed in scintillation vials for counting. After adjusting for the extraction efficiency, the amount (pmol) of [^{14}C]-5-HETE in each tube is quantitated. The net picomoles of 5-HETE is obtained by subtracting the picomoles of 5-HETE in the tubes containing buffer alone (blank) from the picomoles of 5-HETE in the tubes containing buffer and cells (control). The ability of the test compounds to modulate the activity of this enzyme is determined by a decrease or increase in the net amount of 5-HETE produced. In Table I the third from last column shows the concentration required for 50% inhibition of the 5-LO pathway.

All assays were performed in triplicate. In results from 162 experiments with this protocol, a mean of 79 ± 1.7 pmol of 5-HETE/1 × 10^6 neutrophils (mean ± SE) was produced in control samples. The average error, expresed as a percent of the mean value of picomoles in the triplicates, was just 4.0%. In trials where the I_{50} values for inhibitors were determined twice (for 12 of the 44 compounds presented in Table I), the mean half-range of the two values, expressed as a percent of the mean I_{50}, was 28 ± 7% (mean ± SE). Values of I_{50} differing by a factor of 2 or more may be regarded as significantly different.

GP Lung Parenchymal Strip Test. Parenchymal strips of GP lungs are prepared and suspended in tissue baths according to a published procedure.[24] The tissues are allowed to equilibrate in the tissue bath and are challenged with 1 μM histamine. After maximum contractions have been obtained, the tissues are washed and allowed to relax back to base-line tension. This histamine challenge is repeated to obtain a reproducible control response. The average response of 1 μM histamine for each tissue is used to normalize all other challenges. Responses of each tissue to 0.2 nM LTC_4 are then obtained. Usually test compounds are examined initially at 30 μM without agonist or antagonist to determine if the compound has any intrinsic activity on lung parenchyma. The LTC_4 is added after the desired preincubation time (usually 5 min). Compounds causing 20% or less inhibition are to be considered as ineffective at the concentrations tested. The values noted in Table I as causing 50% inhibition have been retested at several concentrations to obtain the graphically determined I_{50} values. Compounds having I_{50} values of less than 20 μM were retested, and, as indicated in Table I, the I_{50} values were reproducible within an error of less than 30%.

SRS-A-Mediated Bronchospasm in the GP in Vivo. This test is based on a published procedure[25] and is performed with GPs actively immunized 14 days earlier with ovalbumin (2.7 mg/kg, intraperitoneal (ip)) and *B. pertussis* as an adjuvant. Prior to challenge with antigen, the animals are anesthetized and prepared for monitoring pulmonary dynamics by whole-body plethysmography. They are treated with methapyrilene (2 mg/kg, iv) and indomethacin (10 mg/kg, ip) in order to enhance the SRS-A component of anaphylactic bronchoconstriction. Bronchoconstriction is quantified as the maximum increase in airway resistance following antigen challenge. The drug is administered either ip 10 min before challenge or id in PEG 400 15 min before challenge.

Acknowledgment. We thank Dr. C. Rehm and his staff in the Departments of Analytical Chemistry and Pharmacy for mass spectral, elemental analysis, and solubility data, Dr. T. Hudec for preliminary work, and C. Jackson and T. Consavage for typing the manuscript.

Registry No. 1, 103119-30-8; **2**, 92532-06-4; **3**, 103119-31-9; **4**, 92532-08-6; **5**, 92532-11-1; **6**, 92532-07-5; **7**, 92532-05-3; **8**, 103119-32-0; **9**, 103119-33-1; **10**, 103119-34-2; **11**, 103119-35-3; **12**, 92532-10-0; **13**, 92532-12-2; **14**, 92532-13-3; **15**, 103119-36-4; **15** (alcohol), 104508-26-1; **16**, 103119-04-6; **17**, 92532-14-4; **18**, 92532-15-5; **19**·HCl, 92532-16-6; **20**, 92532-17-7; **21**, 103119-38-6; **22**, 92532-19-9; **23**, 103119-39-7; **24**, 104508-13-6; (*E*)-**25**, 104508-14-7; **26**, 92532-18-8; **27**, 103119-28-4; **28**·HCl, 92532-20-2; **29**, 103119-27-3; **30**, 92532-26-8; **31**, 92532-25-7; **32**, 92532-09-7; **33**, 101910-24-1; **33**·HCl, 92532-23-5; **34**, 103119-42-2; **35**, 103119-05-7; **36**, 103119-43-3; **36** (ketone), 104508-28-3; **37**, 103119-10-4; **38**, 103119-12-6; **39**, 103119-14-8; **40**, 103119-44-4; **41**·HCl, 104508-15-8; **42**, 103119-45-5; **43**, 92532-27-9; **44**, 103119-19-3; (*E*)-**45**, 104508-16-9; (*Z*)-**45**, 104508-21-6; **46**, 103119-46-6; **47**, 103119-47-7; **48**, 64628-95-1; **49**, 103119-48-8; **50**, 103119-18-2; **51**, 104508-17-0; **52**, 104508-18-1; **53**, 104508-19-2; **54**, 104325-75-9; **III** (B = C, R_1 = 3-CO_2CH_3, R_2 = H), 1129-28-8; **III** (B = C, R_1 = 2-CO_2CH_3, R_2 = H), 2417-73-4; **III** (B = C, R_1 = 4-CO_2CH_3, R_2 = H), 2417-72-3; **III** (B = C, R_1 = 3-$CH_2CO_2CH_3$, R_2 = H), 104508-22-7; **III** (B = C, R_1 = 3-CN, R_2 = H), 28188-41-2; **III** (B = C, R_1 = 4-$OCH_2CO_2CH_3$, R_2 = H), 104508-23-8; **III** (B = C, R_1 = R_2 = H), 100-39-0; **III** (B = N, R_1 = 3-CN, R_2 = H), 104508-24-9; **III** (B = N, R_1 = R_2 = 3,4-CHCH=CHCH=CHCH), 5632-15-5; **III** (B = C, R_1 = 3-CF_3, R_2 = H), 402-23-3; **IV** (m = 4, *m*-OH), 92532-21-3; IV (m = 3, *m*-OH), 92532-04-2; **IV** (m = 4, o-OH), 59648-34-9; **IV** (m = $C(CH_3)_2(CH_2)_3$, *m*-OH), 103119-11-5; **IV** (m = $C(CH_3)_2(CH_2)_3$, *m*-OH, ketone), 104508-25-0; **IV** (m = 5, *m*-OH), 103119-16-0; 2-$H_3CC_6H_4CO_2CH_3$, 89-71-4; $H_3C(CH_2)_3Br$, 109-65-9; 3-HOC_6H_4CHO, 100-83-4; 3-$HOC_6H_4C(CH_3)$=$CH(CH_2)_3CH_3$, 104508-20-5; 4-HOC_6H_4CH=$CH(CH_2)_3CH_3$, 103493-57-8; 3-$NCC_6H_4CH_2Br$, 28188-41-2; 3-$NCC_6H_4CH_2OC_6H_5$, 57928-72-0; 3-$C_6H_5OCH_2C_6H_4CHO$, 104508-27-2; $H_3C(CH_2)_4Br$, 110-53-2; 3-HOC_6H_4CHO, 100-83-4; 3-$NCC_6H_4CH_2OP(OCH_2CH_3)_2$, 104508-30-7; $(H_3CCH_2O)_3P$, 122-52-1; C_6H_5CHO, 100-52-7; (*E*)-NCC_6H_4CH=CHC_6H_5, 14064-35-8; 3-$(C_6H_5)_3PCH_2C_6H_4CN^+Br^-$, 24722-19-8; $(C_6H_5)_3P$, 603-35-0;

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(*Z*)-$NCC_6H_4CH{=}CHC_6H_5$, 19466-33-2; 2-HOC_6H_4CHO, 90-02-8; 3-$C_6H_5OC_6H_4CHO$, 39515-51-0; 3-$HOC_6H_4CO(CH_2)_4CH_3$, 103119-13-7; 2-picolyl chloride hydrochloride, 6959-47-3; 4-picolyl chloride hydrochloride, 1822-51-1; 3-picolyl chloride hydrochloride, 6959-48-4; 2-(chloromethyl)quinoline hydrochloride, 3747-74-8; 2-bromomethylnaphthalene, 939-26-4; 2-chloroquinoline, 612-62-4; 3-(2-quinolinyloxy)benzaldehyde, 104508-29-4; 5-lipoxygenase, 80619-02-9.

Synthesis of *N*-(3,6-Dihydro-1(2*H*)-pyridinyl)benzamides with Hyperglycemic–Hypoglycemic Activity

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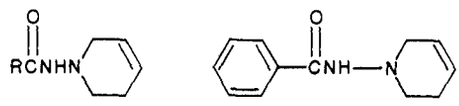
Received April 2, 1986

A group of *N*-(3,6-dihydro-1(2*H*)-pyridinyl)benzamides **7** were synthesized to determine the effect that the position and physicochemical properties of substituents attached to the heterocyclic ring have on blood glucose levels. 5-Methyl-*N*-(3,6-dihydro-1(2*H*)-pyridinyl)benzamide **7b** was the most active hyperglycemic agent, elevating blood glucose 124% and 116% at 2 and 4 h, respectively, after a 100 mg/kg po dose. The most active hypoglycemic agent was the 4-acetyl analogue **7o**, which was about 50% as active as chlorpropamide, lowering blood glucose 19% at 4 h after a 100 mg/kg po dose. A correlation between blood glucose levels and the partition coefficient *P* was not observed.

In earlier studies we described a facile method for the synthesis of *N*-(3,6-dihydro-1(2*H*)-pyridinyl) amides **1** via the sodium borohydride reduction of *N*-(carbonylimino)-pyridinium ylides,[1] which exhibited significant hyperglycemic activities.[2,3] The lead compound **2** elevated blood



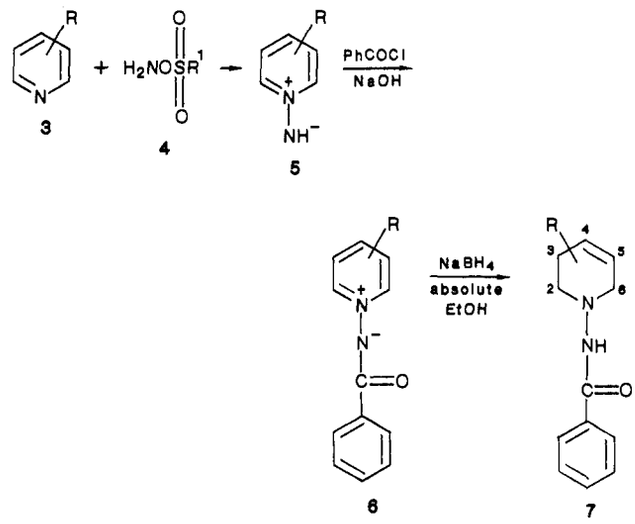
1 **2**

R = alkyl, cycloalkyl, arylalkyl, alkyloxy, arylalkyloxy, aryl, heteroaryl, heteroarylalkyl

glucose 78% and 50% at 2 and 4 h, respectively, after a 100 mg/kg po dose. The nature and position of substituents attached to a phenyl moiety of **1** were determinants of blood glucose concentration. It was therefore of interest to determine the effect of substituents on the 3,6-dihydro-1(2*H*)-pyridinyl ring of **1**, with regard to substituent position and physicochemical properties, upon hyperglycemic activity. Hyperglycemic agents such as **1** may have potential for the treatment of hypoglycemia. We now describe the synthesis and hyperglycemic–hypoglycemic activities of functionalized *N*-(3,6-dihydro-1(2*H*)-pyridinyl)benzamides **7**.

Chemistry. *N*-[(Phenylcarbonyl)imino]pyridinium ylides **6** were prepared via two synthetic procedures. Reaction of the nonisolable *N*-iminopyridinium ylides **5a–d**, obtained by amination of pyridines **3a–d** with hydroxylamine-*O*-sulfonic acid (**4**, R^1 = OH), with benzoyl chloride in the presence of 10% aqueous sodium hydroxide afforded ylides **6a–d**. On the other hand, pyridinium ylides **6e–f,h–k** were prepared more efficiently by amination of **3e–f,h–k** with use of the more reactive *O*-(mesitylenesulfonyl)hydroxylamine (**4**, R^1 = 2,4,6-trimethylphenyl) followed by reaction of **5** with benzoyl chloride (Scheme I). Alternatively, reaction of 1-(2,4-dinitrophenyl)-pyridinium chlorides **8g,l–o** with benzoic acid hydrazide yielded the respective 5-(2,4-dinitroanilino)-penta-2,4-dienal benzoic acid hydrazones **9**, which on heating cyclized to afford the respective *N*-[(phenylcarbonyl)imino]-pyridinium ylides **6g,l–o** as illustrated in Scheme II and summarized in Table I. The sodium borohydride reduction of ylides **6a–o** in absolute ethanol at 0 °C for 5 h, unless otherwise noted, afforded the respective *N*-(3,6-dihydro-1(2)-pyridinyl)benzamides **7a–o** as illustrated in Scheme I and summarized in Table II. The formation of the C-3 *exo*-methylene product **7h** from **6h** likely arises via a reductive elimination reaction[4] following initial attack by hydride anion at C-2 and/or C-6 (see Scheme III). The 200-MHz ^{1}H NMR spectrum of **7h** (Me_2SO-d_6) exhibited two 1 H singlets at δ 4.89 and 4.93 assigned to the exocyclic methylene protons.[5] The structure assigned to **7h** was confirmed by unambiguous chemical methods since catalytic hydrogenation of **7h** and **7b** using 10% palladium-

Scheme I



a, R = 2-CH_3; **b**, R = 3-CH_3; **c**, R = 4-CH_3; **d**, R = 3,4-$(CH_3)_2$; **e**, R = 3-F; **f**, R = 3-$CH_2CH_2CH_2OH$; **g**, R = 4-$CH_2CH_2CH_2OH$; **3-6h**, R = 3-CH_2OCOCH_3; **7h**, R = 3 = CH_2; **3-6l**, R = 4-CH_2OCOCH_3; **7i**, R = 4-CH_2OH; **j**, R = 3-$CH_2CH_2CO_2CH_3$; **k**, R = 4-$CH_2CH_2CO_2CH_3$

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