were sacrificed in groups of five animals. The brain of each animal was immediately excised, and the striatum and cerebellum were dissected over an ice-cold plate.[68] A blood sample was obtained via cardiac puncture immediately preceeding decapitation. The femur was also dissected from each test animal following sacrifice. The tissue samples were weighed, and the radioactivity content assayed by counting in a NaI(Tl) well-type γ scintillation counter. The results were calculated in terms of percent injected dose per gram of tissue by comparison of the data to that of a standard sample of the injectate.

Acknowledgment. The authors are grateful to C. J. Mathias and D. Robbins for assistance with the animal biodistribution experiments. We also thank Astra Läkemedel AB, Södertäjle, Sweden for the gift of raclopride. This work was supported by NIH FIRST Award NS-26788, NIH Grant HL-13851, and by the Animal Resources Program, University of Washington Regional Primate Center Grant RR00166.

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A Novel Series of Selective Leukotriene Antagonists: Exploration and Optimization of the Acidic Region in 1,6-Disubstituted Indoles and Indazoles[1]

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A systematic structure–activity exploration of the carboxylic acid region in a series of indole- or indazole-derived leukotriene antagonists 1 led to several discoveries. Use of the 3-methoxy-*p*-tolyl fragment (illustrated in acid 1) for connecting the indole and the acidic site provides the most potent carboxylic acids 1, tetrazoles **20**, and aryl sulfonimides **21** (Figure 1). The aryl sulfonimides are 5–500 times more potent (in vitro and/or in vivo) than the corresponding carboxylic acids 1. The *o*-tolyl sulfonimides such as **114** (Table VII) show greater oral potency than the phenyl sulfonimides at a given level of in vitro activity. Acidic keto sulfone derivatives **10** (Nu = $CH(CO_2CH_3)SO_2Ph$) mimic the activity of the sulfonimides.

The peptidoleukotrienes (LTC_4, LTD_4, and LTE_4) have been the focus of intense research efforts for the past 10 years,[2] following the discovery by Samuelsson,[3] that the leukotrienes were the active components of the "slow reacting substance of anaphylaxis" (SRS-A). SRS-A is believed to be an important biological mediator in several disorders, especially human allergic diseases. A major pharmaceutical goal has been the discovery and development of novel, selective antagonists of the leukotrienes as potential therapeutic agents for the treatment of asthma. An earlier paper from these laboratories described the discovery of a novel series of indole and indazole carboxylic acids 1 which are leukotriene antagonists.[4] Herein we describe the detailed exploration of the carboxylic acid region in this series of antagonists. These efforts led to novel aryl sulfonimides **21** which show increased potency both in vitro (pK_B up to 10.9 against LTE_4 on guinea pig trachea)[5] and in vivo (oral $ED_{50} < 1$ mg/kg against LTD_4 induced labored abdominal breathing in the guinea pig) (Figure 1).[5]

Chemistry

General Routes and Syntheses of the Aryl Acids 8. The general synthetic routes to the indole/indazole carboxylic acids **8**, sulfonimides **10** (Nu = $-NHSO_2R''$) and many of the acid mimics **3**[6] listed in Tables I, II, and III are presented in Schemes I and II. Our first route (1.a, Scheme I) began with 6-aminoindazole **2a** or with catalytic hydrogenation of 6-nitroindole **32b** to afford 6-aminoindole **2b**. The amines **2** were acylated by treatment either with a carboxylic acid or water soluble carbodiimide (WSCDI, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) and with an acid chloride and triethylamine.[7] These reactions provided amides and urethanes **3** which retained a reactive hydrogen at position N-1′ in the indole/indazole fragment. Therefore, compounds **3** were convenient intermediates for series of acids **8** in which only the acidic region was to be varied (e.g. Tables I and II).

Alkylation of the acylated intermediates **3** to afford esters **4** was achieved by sequential treatment with sodium hydride and halo-ester **7** in dimethylformamide.[8] The halo esters **7** were prepared by bromination of toluate esters.[9,10]

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(1) Portions of this work have been previously presented: (a) Matassa, V. G.; Bernstein, P. R.; Brown, F. J.; Hesp, B.; Yee, Y. K.; Krell, R. D.; Giles, R. E.; Snyder, D. W. *Abstracts of Papers*, 193rd National Meeting of the American Chemical Society, Division of Medicinal Chemistry, Denver, CO, April, 1987; American Chemical Society: Washington, DC, 1987; Abstract 87. (b) Yee, Y. K.; Bernstein, P. R.; Brown, F. J.; Matassa, V. G. *Ibid.* Abstract 88.
(2) Chakrin, L. W., Bailey, D. M., Eds. *The Leukotrienes, Chemistry and Biology*; Academic: Orlando, FL, 1984.
(3) Hammarstrom, S.; Murphy, R. C.; Clark, D. A.; Mioskowski, C.; Corey, E. J. *Biochem. Biophys. Res. Commun.* **1979**, *91*, 1266.
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(5) The biological tests are described in the Experimental Section of the text and have been discussed in refs 4 and 10.
(6) These synthetic sequences, where the halo ester **7** was methyl 4-(bromomethyl)-3-methoxybenzoate, have been described in ref 4.
(7) As exemplified in the Experimental Section in the preparation of tetrazole **80** by the conversion of 5-nitroindole (**32b**) to 6-aminoindole (**2b**) and its subsequent acylation to 6-hexanamidoindole (**3b**, R = pentyl).
(8) As exemplified in the Experimental Section under acid **42** by conversion of 6-hexanamidoindole (**3b**, R = pentyl) to ester **4b** (R = pentyl, C and D = hydrogen, CO_2R_1 is at position C-1 and R_1 = methyl).
(9) The syntheses of all the benzylic bromides utilized in this paper are described: (a) Bernstein, P. R.; Willard, A. K. U.S. Patent 4,499,299, 1985. (b) Brown, F. J.; Bernstein, P. R.; Yee, Y. K. European Patent Application, Publication Number 0179 619 A1, published April 30, 1986. (c) Reference 10.

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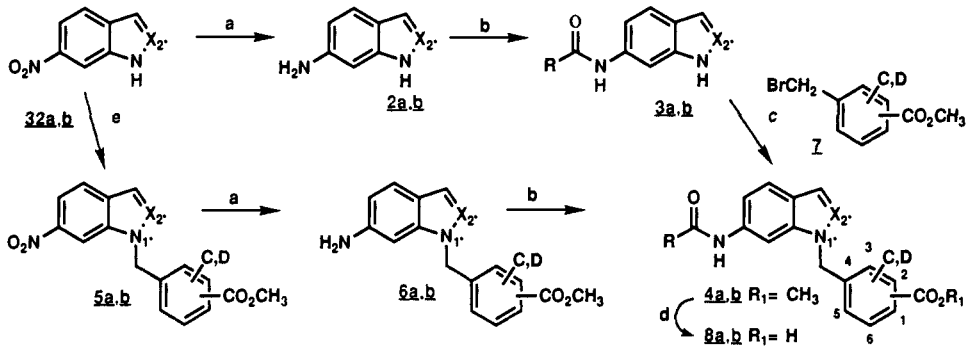
Scheme I

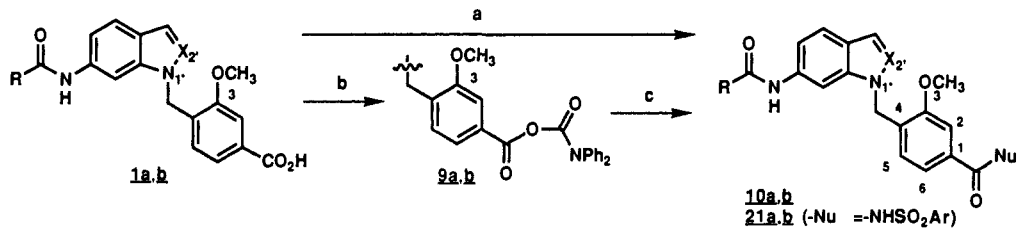


a) H_2, Pd/C, EtOAc; b) RCO_2H, DMAP, WSCDI/THF-CH_2Cl_2 or RCOCl, Et_3N/CH_2Cl_2; c) I. NaH/DMF, II. (7); d) LiOH/methanol-water; e) for 32a, I. NaOH, II. $ArCH_2Br$ (7)/ solvent: for 32b, K_2CO_3, $ArCH_2Br$ (7)/acetone.

#a X = N, #b X = CH; R = alkyl, alkoxy; C, D = hydrogen, alkyl, alkoxy, halogen;
WSCDI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

Route 1.a 32->2->3->4->8
Route 1.b 32->5->6->4->8

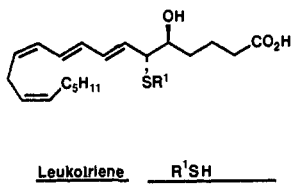
Scheme II



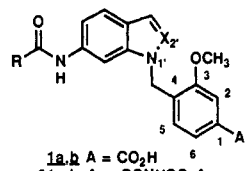
a) WSCDI, DMAP, NuH/ CH_2Cl_2-THF; b) N,N-diphenylcarbamoyl pyridinium chloride, Et_3N/methanol; c) NuH or Nu^-/ solvent as in text

#a X=N, #b X = CH; R= Alkyl, Alkoxy

Route 2.a 1->10
Route 2.b 1->9->10



Leukotriene	R^1SH
C_4	glutathione
D_4	cysteinylglycine
E_4	cysteine



1a,b A = CO_2H
21a,b A = $CONHSO_2Ar$

R = alkyl, alkoxy, alkylamino
1a, 21a X = N, 1b, 21b X = CH

Since most of these compounds have a carbonyl group at position 1 we used the illustrated numbering sequence for purposes of discussion

Figure 1.

In the case of the N-1′ alkylated indazole esters **4a** it was usually necessary to remove a minor amount of the N-2′ alkylated esters via chromatography.

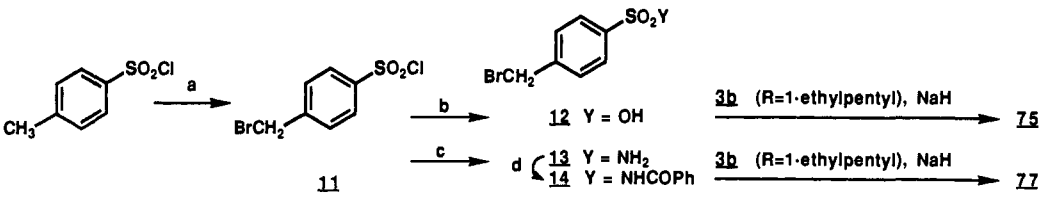
An alternate route (1.b) to esters **4** is also shown in Scheme I. In this approach, the first step was alkylation of 6-nitroindazole **32a** or 6-nitroindole **32b** with halo ester **7** to afford nitro ester **5**. In particular, for the indazoles, the salt of 6-nitroindazole was made with sodium hydroxide according to the protocol of Granger.[11] This salt was then allowed to react with halo ester **7** in acetone.[12] The indazole ester **5a** produced in this alkylation was accompanied by the N-2′ alkylated analogue and purification usually required chromatography. In contrast, 6-nitroindole **32b** was cleanly N-alkylated to afford esters **5b** by treatment with potassium carbonate and the appropriate halo ester **7** in refluxing acetone.[12] Catalytic reduction of the nitro group in esters **5** with hydrogen and palladium on carbon afforded amino esters **6**.[12] The amino esters **6** were convenient intermediates for series of acids

(10) Brown, F. J.; Bernstein, P. R.; Cronk, L. A.; Dosset, D. L.; Hebbel, K. C.; Maduskuie, T. P.; Shapiro, H. S.; Vacek, E. P.; Yee, Y. K.; Willard, A. K.; Krell, R. D.; Snyder, D. W. *J. Med. Chem.* **1989**, *32*, 807.

(11) Granger, R.; Koeberle, J.; Hao-Dong, L.; Boucard, M.; Giroux, J. J.; Mizoule, J.; Yavordis, D. *Chim. Ther.* **1970**, *5*, 24. (Although this paper reported the use of "dilute sodium hydroxide", we found that formation of the sodium salt of 6-nitroindazole required 6 N NaOH.)

(12) This general reaction has not been exemplified in the Experimental Section. It is very similar to the corresponding sequence that uses halo nitrile **19** instead of halo ester **7** and which is included in the Experimental Section in the preparations of tetrazoles **80** and **81**. Furthermore this general sequence has been reported in full detail, along with the structure proof for the N-1′ versus N-2′ products, in ref 4 for sequences in which halo ester **7** is methyl 4-(bromomethyl)-3-methoxybenzoate.

Scheme III



a) NBS/CCl_4; b) Ethanol-water; c) NH_3/ solvent; d) benzoyl chloride

Route 3.a 11->12->75
Route 3.b 11->13->14->77

8 in which we wanted to vary the amide/urethane group (R in **36**, Table III). Acylation of amino esters **6**, as previously described for amines **2**, produced the esters **4**.

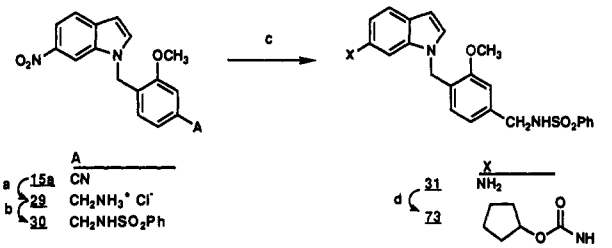
Hydrolysis of the esters **4** with aqueous lithium hydroxide provided the corresponding carboxylic acids **8**.[13] Preparation of tetrazole carboxylic acid **55** required an additional step. It was synthesized from cyano acid **53** by reaction with sodium azide and triethylamine hydrochloride in DMF.[14]

Aryl Acid Mimics, Excluding Tetrazoles (Compounds in Tables II and III). The sulfonimides **21** were formed (see Scheme II) from the appropriate sulfonamide and carboxylic acid **1**. This conversion could be accomplished directly by using WSCDI as the coupling agent (method 2.a),[15] or it also be done via the intermediacy of a mixed carbamic anhydride **9** (method 2.b).[16] Carbamic anhydride **9** was formed by reaction of carboxylic acid **1** and (*N*,*N*-diphenylcarbamoyl)pyridinium chloride[17] in methanolic base.[18] To prevent formation of the corresponding methyl ester **4** it was necessary to isolate anhydride **9** after a short reaction period, either by filtration or by extractive work up.

The carbamic anhydride **9** was also useful as a precursor for several other acid mimics (listed in Table II). In particular, reaction of anhydride **9b** (R = 1-ethylpentyl) and the following nucleophiles (in the indicated solvent), afforded the indicated acid mimic (designated by their compound number): lithiomethyl(phenylsulfonyl)acetate (THF), **59**; lithio(phenylsulfonyl)acetonitrile (THF), **60**; sodium 2-aminobenzoate (DMF), **61**; sodium glycinate (DMSO), **62**; 5-aminotetrazole (DMF), **63**; hydroxylamine (methanol–DMF), **64**; benzenesulfinamide (DMF), **65**; and lithiomethyl phenyl sulfone (THF), **72**.[19]

The sulfonic acid **75** and the transposed sulfonimide **77** analogues were both prepared from *p*-toluenesulfonyl chloride as outlined in Scheme III. Reaction of *p*-toluenesulfonyl chloride with *N*-bromosuccinimide followed by solvolysis in aqueous ethanol according to the protocol of Blangey[20] afforded 4-(bromomethyl)benzenesulfonic acid (**12**). Treatment of the intermediate 4-(bromomethyl)benzenesulfonyl chloride (**11**) with ammonia afforded bromo sulfonamide **13** which was further converted to sulfonimide **14** by acylation with benzoyl chloride. Alkylation of indole **3b** (R = 1-ethylpentyl) by sequential treatment with sodium hydride and either bromide **14** (route 3.b) or bromide **12** (route 3.a) afforded **77** (37%) and the sodium salt of sulfonic acid **75** (20%), respectively. It was necessary to isolate **75** as the sodium salt because the sulfonic acid rapidly decomposed after isolation.[21]

Scheme IV



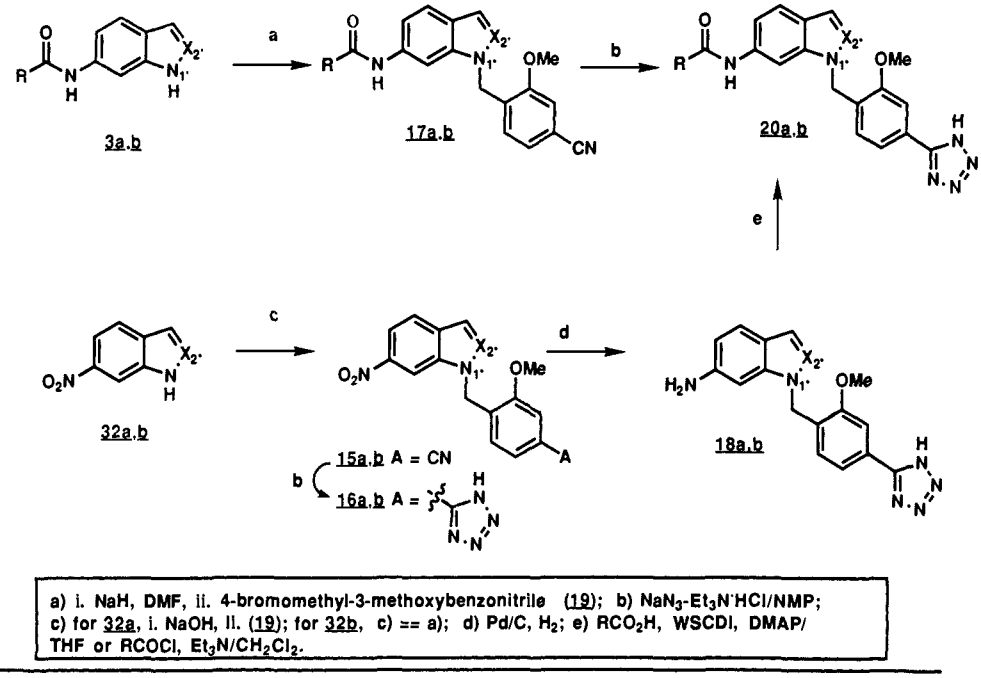
a) I. BH_3/THF, II. HCl; b) $PhSO_2Cl$, lutidine/DMF; c) H_2/Pt; d) $ClCO_2CH(CH_2)_4$

The preparation of sulfonamide **73** from nitrile **15a**[22] is illustrated in Scheme IV. Reduction of nitrile **15a** with borane–tetrahydrofuran and acidic workup afforded amine hydrochloride **29** which was converted to sulfonamide **30** by treatment with benzenesulfonyl chloride and 2,6-lutidine in DMF. Catalytic reduction of nitro sulfonamide **30** with hydrogen and platinum black gave amine sulfonamide **31** which upon treatment with cyclopentyl chloroformate gave **73**.

Aryl Tetrazoles. The general syntheses of the aryl tetrazoles **20** (R = alkyl or alkoxy) is given in Scheme V. The tetrazole amides **20** (R = alkyl) were made via route 5.a. This route began with alkylation of indoles/indazoles **3**, by treatment with sodium hydride and 4-(bromomethyl)-3-methoxybenzonitrile **19**[9b] in dimethylformamide, to afford nitriles **17**.[23] These nitriles were then converted

(13) As exemplified in the Experimental Section by the preparation of carboxylic acid **42** from ester **4b** (R = 1-ethylpentyl, C and D = hydrogen, CO_2R_1 is at position C-1 and R_1 = methyl).
(14) Finnegan, W. G.; Henry, R. A.; Lofquist, R. J. *J. Am. Chem. Soc.* **1958**, *80*, 3908.
(15) As exemplified in the Experimental Section by the preparation of sulfonimide **92** by the coupling of *o*-toluenesulfonamide with carboxylic acid **1a** (R = cyclopentyloxy).
(16) As exemplified in the Experimental Section in the preparation of sulfonimide **58** by the conversion of carboxylic acid **1b** (R = 1-ethylpentyl) to anhydride **9b** (R = 1-ethylpentyl) and its subsequent coupling with benzenesulfonamide.
(17) Shephard, K. L.; Halczenko, W. *J. Heterocycl. Chem.* **1979**, *16*, 321.
(18) As exemplified in the Experimental Section by the preparation of sulfonimide **58** by the conversion of carboxylic acid **1b** (R = 1-ethylpentyl) to anhydride **9b** (R = 1-ethylpentyl).
(19) As exemplified in the Experimental Section by the preparation of acid mimics **59**, **60**, **65**, and **72**.
(20) Blangey, L.; Fierz-David, H. E.; Stamm, G. *Helv. Chim. Acta* **1942**, *25*, 1162.
(21) The decomposition presumably occurs since indoles are unstable to exposure to strong acids, see page 7 in: Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, NY, 1970.
(22) For preparation of nitrile **15a**, see Scheme V and the discussion on the preparation of aryl tetrazoles.
(23) As exemplified in the Experimental Section in the preparation of tetrazole **80**, part d, by the conversion of 6-hexanamidoindole **3b** (R = pentyl) to nitrile **17b** (R = pentyl).

Scheme V



to tetrazole amides **20** (R = alkyl) by reaction with sodium azide and triethylamine hydrochloride in *N*-methylpyrrolidone at 150 °C.[24,25] The analogous cyanourethanes (**17**, R = alkoxy) decomposed under either the standard[14] or the alternate[24] tetrazole forming conditions. Because of this problem, the tetrazole urethanes **20** (R = alkoxy) were prepared via route 5.b. In this route 6-nitroindole **32b** or 6-nitroindazole **32a** was alkylated with nitrile **19**.[26] The conditions utilized were identical with that described above in route 1.b, in the section General Routes and Syntheses of the Aryl Acids **8**, for alkylation of **32** with halo ester **7**. The product nitronitriles **15** were converted to nitrotetrazoles **16** by reaction with sodium azide and triethylamine hydrochloride in *N*-methylpyrrolidone at 150 °C.[24,27] Catalytic reduction of nitrotetrazoles **16** with hydrogen and palladium on carbon, as a solution in methanolic base, produced the amines **18**.[28] These amines were directly acylated with the appropriate alkyl chloroformates to afford the urethane tetrazoles **20** (R = alkoxy).[29]

Results and Discussion

During the initial exploration of this series of leukotriene antagonists only three variants in the benzoic acid region had been explored.[4] These were the 3-methoxy-*p*-toluic acid derivative **1** (Figure 1) and the less potent *o*- or *p*-toluic acid analogues (not illustrated, carboxyl group at positions 3 and 1, respectively). Acid **1** had been prepared because of a perceived correlation between the original *o*- and *p*-toluic acids and a series of hydroxyacetophenone (HAP) derived antagonists **26** which were prepared in these laboratories (see Figure 2).[4,10] In the HAP series the 3-methoxy group was important for optimal activity.[10] It was unknown how well the structure–activity relationships, of the HAP and indole/indazole series would correlate. To determine if the 3-methoxy-*p*-toluic acid fragment was also optimal in this series we chose to explore the indoles (**1b**). We initially focused on substituted *p*- and *m*-toluic acids. Concurrent with these studies, exploration of the amide region (R in acids **1**) was resulting in significant increases in potency.[4] Because of this, most of our early acid-region studies were done on a series in which the original hexanamide group in **1** (R = pentyl) was replaced with the more potent 2-ethylhexanamide group (R = 1-ethylpentyl). As our exploration of the acid-region progressed better amide derivatives were incorporated.[4]

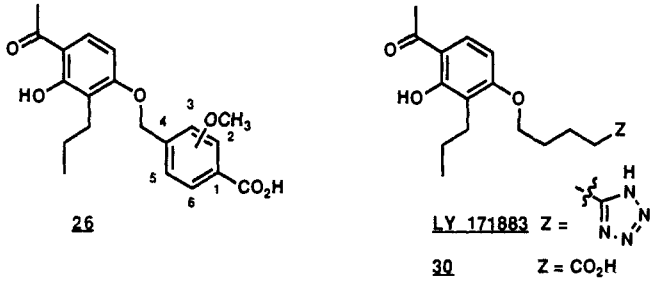
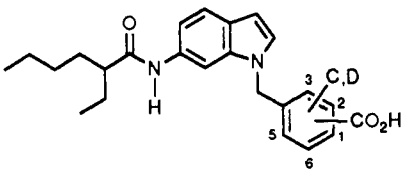


Figure 2. Hydroxyacetophenone-based antagonists.

The compounds were tested in several in vitro and in vivo assays.[5] We originally used an in vitro assay that measured inhibition of an LTE_4-induced contraction in guinea pig tracheal spirals.[30] The selectivity of some of

(24) Bernstein, P. R.; Vacek, E. P. *Synthesis* **1987**, 1133.
(25) As exemplified in the Experimental Section by the preparation of tetrazole **80** by the conversion of nitrile **17b** (R = pentyl) to tetrazole **80**.
(26) As exemplified in the Experimental Section in the preparation of tetrazole **81**, part a, by the alkylation of 6-nitroindole **32b** to afford nitrile **15b**.
(27) As exemplified in the Experimental Section in the preparation of tetrazole **81**, part b, by the conversion of nitrile **15b** to nitrotetrazole **16b**.
(28) As exemplified in the Experimental Section in the preparation of tetrazole **81**, part c, by the conversion of nitrotetrazole **16b** to aminotetrazole **18b**.
(29) As exemplified in the Experimental Section by the preparation of tetrazole **81** by the acylation of aminotetrazole **18b** with butyl chloroformate.

Table I. Toluic Acid Variations



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entry	C	D	CO_2H substitution	test concn, 10^{-7} M	% antagonism of LTE_4[a]	mp, °C	microanalysis	% yield[b]
41	3-MeO		1	33	100	234–5	$C_{25}H_{30}N_2O_4 \cdot 0.4H_2O$	ref 4
				10	59			
42			1	100	44	208–10	$C_{24}H_{28}N_2O_3 \cdot 0.25H_2O$	46
43	3-MeO	5-MeO	1	10	63	274–5 dec	$C_{26}H_{32}N_2O_5$[c]	83
44	3-Me		1	100	91	239–40	$C_{25}H_{30}N_2O_3$	91
				33	21			
45	3-Cl		1	100	44	222–32 dec	$C_{24}H_{27}ClN_2O_3$	45
46	3-F		1	100	86	215–6.5	$C_{24}H_{27}FN_2O_3$	96
47	2-MeO		1	10	15	189–90	$C_{25}H_{30}N_2O_4$	69
48			2	100	31	216–8	$C_{24}H_{28}N_2O_3 \cdot 0.25H_2O$	98
49	1-MeO		2	100	28	171–4	$C_{25}H_{30}N_2O_4$	69
50	3-MeO		2	100	38	200–1	$C_{25}H_{30}N_2O_4$	64
51	2-Br		1	33	33	186–7	$C_{24}H_{27}BrN_2O_3$	43
52	3-BuO		1	100	83	197–9	$C_{28}H_{36}N_2O_4$	70
				33	44			
53	$3\text{-}O(CH_2)_3CN$		1	100	84	175–6	$C_{28}H_{33}N_3O_4$	82
				33	33			
54	$3\text{-}O(CH_2)_3Ph$		1	100	18NS[d]	167–72	$C_{33}H_{38}N_2O_5$	98
55	$3\text{-}O(CH_2)_3Tet$[e]		1	10	32	187–8	$C_{28}H_{34}N_6O_4$	50[f]

[a] Percent antagonism of 8 nM of LTE_4 induced contraction of guinea pig tracheal spirals by antagonists at the indicated test concentration. All tests run on a minimum of four tracheal spirals. Reproducibility was, in general, ≤ 20% of the mean. Results are statistically significant ($p < 0.05$) from control unless otherwise indicated. [b] Yield on ester hydrolysis. [c] Nitrogen: calcd 6.19; found 5.72. [d] NS = not significant. [e] Tet = 1*H*-tetrazol-5-yl. [f] Experimental included, yield for tetrazole formation.

these compounds was checked in a similar assay in which the LTE_4 was replaced with the nonspecific spasmogen $BaCl_2$. For compounds which were of greater interest, K_B values were determined,[31] also by using LTE_4 and guinea pig tracheal spirals. More recently a LTD_4-binding assay on isolated guinea pig lung membrane was developed by Dr. D. Aharony, in these laboratories.[32] Several of these compounds have been tested in this newer assay,[33] and the high potency of **92** ($K_i = 0.28 \pm 0.03$ nM) in it has already been reported.[32] The activity of these compounds in this assay confirms that their mode of action is by blocking the binding of leukotrienes at specific receptors in a competitive manner.

Only selected compounds were checked in vivo. Oral activity was determined in a guinea pig dyspnea model with aerosolized LTD_4 as the agonist.[34]

Toluic Acids (Table I). None of the series of toluic acids **34** (Table I) were more potent, in vitro, than the 3-methoxy-*p*-toluic acid derivative **41**. This finding was similar to the result that had been obtained, with a similar series of toluic acids, in the hydroxyacetophenone derived antagonists **26**.[10] The desmethoxy analogue **42** was 5–10-fold less potent than reference acid **41**. Since one methoxy group was beneficial we decided to determine if a second symmetrically placed methoxy would further increase potency. The resultant 3,5-dimethoxy analogue **43** was equipotent with acid **41**. The 3-methyl **44**, 3-chloro **45**, and 3-fluoro **46** analogues were 3–10-fold less potent. Removal of the 3-methoxy group and substitution at the 2-position with either methoxy or bromine were equally detrimental, see **47** and **51**. Both the 3-oxybutyronitrile analogue **53**

(30) LTE_4 was used in this assay instead of LTC_4 or LTD_4 for the following reasons: Guinea pig trachea contains multiple receptors for the leukotrienes which have different affinities for LTC_4, LTD_4, and LTE_4 as described in: (a) Snyder, D. W.; Krell, R. D. *J. Pharmacol. Exp. Ther.* **1984**, *231*, 616. (b) Aharony, D.; Catanese, C. A.; Falcon, R. C. *J. Pharmacol. Exp. Ther.* **1989**, *248*, 581. In the absence of metabolic inhibitors there is rapid metabolic conversion of LTC_4 to LTD_4 and of LTD_4 to LTE_4 in guinea pig tracheal smooth muscle. Therefore if either LTC_4 or LTD_4 is used instead of LTE_4, which agonist is being inhibited at which receptor will remain unknown, unless metabolic inhibitors are used as described in ref 30a above. We felt it was important to do testing in the presence of only the minimum number of extra drugs. Isolated human airways do not contain this multiplicity of receptors. Furthermore of the receptors in guinea pig lung, the receptors which appear to have the most similar response characteristics to the human airways receptors are the LTE_4 subtype as described: (c) Buckner, C. K.; Krell, R. D.; Laravuso, R. B.; Coursin, D. B.; Bernstein, P. R.; Will, J. A. *J. Pharmacol. Exp. Ther.* **1986**, *237*, 558.

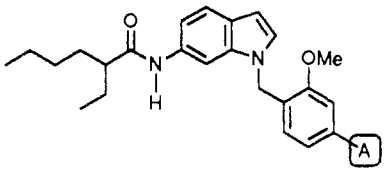
(31) To make it easier to compare the activity of these compounds over the wide potency range reported in this paper we have reported pK_B values in the tables. As described in the Biological Evaluation Procedures section of the Experimental Section these pK_B values are all statistically significant ($p < 0.05$) from control and are derived from the average K_B. The average K_B, the ± SEM from the average value, and the number of determinations (n) are listed as Appendix A in the supplementary materials.

(32) Aharony, D.; Falcon, R. C.; Krell, R. D. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 921.

(33) The available pK_i values are reported in the supplementary materials as Appendix A. Although there is a general linear correlation between the pK_i and pK_B values (see ref 32), the relative potencies of these compounds are not always the same using the two screens. As a result the SAR interpretations are not identical. This should not be surprising since these two screens were done with different leukotrienes (LTD_4 and LTE_4) and different tissues, parenchyma and trachea, respectively, wich are known to contain heterogeneous populations of leukotriene receptors as described in ref 30a.

(34) Snyder, D. W.; Liberati, N. J.; McCarthy, M. M. *J. Pharmacol. Meth.* **1988**, *19*, 219.

Table II. Indole Acid Replacements



35

entry	A	test concn, 10^{-7}M	% antagonism of LTE_4[a]	pK_B[b]	mp, °C	microanalysis	method of synthesis	% yield[c]
41	CO_2H	33	100	6.6	234–5	$C_{25}H_{30}N_2O_4 \cdot 0.4H_2O$	ref 4	
		10	59					
42[d]	CO_2H	100	44		208–10	$C_{24}H_{28}N_2O_3 \cdot 0.25H_2O$	ref 4	
56	Tet[e]	10	50	6.6	211–2	$C_{25}H_{30}N_6O_2$	5.a[f]	56
		3.3	31					
57	$CONHSO_2Me$	100	100		214–5.5	$C_{26}H_{33}N_3O_5S$	2.b	55
		10	60					
58	$CONHSO_2Ph$	1	100	8.6	216.5–8	$C_{31}H_{35}N_3O_5S$	2.b[f]	79
		0.1	27					
59	$COCH(CO_2Me)SO_2Ph$	0.1	65	8.5	148–9	$C_{34}H_{38}N_2O_7S$	2.b[f]	17
60	$COCH(CN)SO_2Ph$	1	73	8.1	184 dec	$C_{33}H_{35}N_3O_5S \cdot 0.25H_2O$[g]	2.b[f]	85
61	$2\text{-}CONHC_6H_4CO_2H$	100	34		212–5 dec	$C_{32}H_{35}N_3O_5$	2.b[f]	70
62	$CONHCH_2CO_2H$	100	43		176–8 dec	$C_{27}H_{33}N_3O_5$	2.b[f]	81
63	CONH-Tet[e]	100	62		284–5.5 dec	$C_{26}H_{31}N_7O_3 \cdot 0.25H_2O$	2.b[f]	70
		10	20					
64	CONH(OH)	100	38		205–8	$C_{25}H_{31}N_3O_4 \cdot 0.4CH_3OH$	2.b[f]	55
65	CONHS(O)Ph	33	34		122–6	$C_{31}H_{35}N_3O_4S \cdot 0.25H_2O$[g]	2.b	17
66	$CONHSO_2iPr$	10	47		206–7	$C_{28}H_{37}N_3O_5S$	2.b	32
67	$CONHSO_2nBu$	10	100		157–9	$C_{29}H_{39}N_3O_5S$	2.b	20
		3	63					
68	$CONHSO_2CH_2Ph$	100	89		212–3.5	$C_{32}H_{37}N_3O_5S$	2.b	73
69		100	31		202–5	$C_{27}H_{32}N_2O_4$	1.a	75
70[h]	$CON(CH_3)SO_2Ph$	1	42		205–7.5	$C_{31}H_{33}N_3O_5S \cdot 0.25H_2O$	2.b	50
71[h]	CO_2H	1	34	7.7		—	ref 4	
72	$COCH_2SO_2Ph$	10	59		131–3	$C_{32}H_{36}N_2O_5S$	2.b[f]	44
73[i]	CH_2NHSO_2Ph	100[j]	NA[k]		194–5	$C_{29}H_{31}N_3O_5S$	see text	38
74[i]	CO_2H	1	61	7.8	237–8	$C_{23}H_{24}N_2O_5$	ref 4	
75[i]	SO_3H	100	48		203–7 dec	$C_{23}H_{27}N_2O_4S \cdot 1.75H_2O$	see text	20
76[i]	$CONHSO_2Ph$	1	42	6.8	166–74	$C_{30}H_{33}N_3O_4S \cdot 1.5H_2O$	2.b	37
77[i]	$SO_2NHCOPh$	100	37		180–5	$C_{30}H_{33}N_3O_4S \cdot 0.25H_2O$	see text	37

[a] Results are significant ($p < 0.05$) from control unless otherwise indicated. [b] See ref 31. K_B determined in guinea pig tracheal spirals with LTE_4 as agonist. As an example of K_B variability, the K_B of 58 is 2.50 ± 0.52 ± 10^{-9} M. [c] Yield on final step. [d] Tet = 1*H*-tetrazol-5-yl. [e] Experimental included. [f] Hydrogen: calcd 6.39; found 5.91. [g] Carbon: calcd 68.23; found 67.61. [h] In 6-[cyclopentylacetamido]indole series instead of 6-[2-ethylhexanamido]indole series. [i] In 6-[cyclopentyloxycarbonylamino]indole series instead of 6-[2-ethylhexanamido]indole series. [j] Not soluble at 10^{-5} M. [k] NA = not active. [l] Des-3-methoxy series.

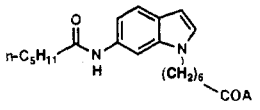
and the more lipophilic 3-butoxy analogue **52** were about 5-fold weaker as antagonists. Further increases in the lipophilicity and steric bulk of the substituent, as in the terminal phenyl substituted analogue **54**, resulted in a greater than 20-fold decrease in potency. The doubly acidic tetrazole **55** also showed a large decrease in potency.

The importance of the *p*-toluic framework was confirmed by the three *m*-toluic acid analogues **48**, **49**, and **50** which were about 20-fold weaker. It was interesting to note that methoxy substitution did not affect the potency of these *m*-toluic acid derivatives.

In addition to the above aryl-linked acids we explored replacement of the 3-methoxy-*p*-toluic acid region with a polymethylene-linked acid. All of these polymethylene-linked acids ($[CH_2]_n$, n = 3–8) were much less potent than the reference acid **41**.[35]

Carboxylic Acid Replacements (Table II). Despite these efforts and the fairly intensive effort which had gone into optimizing the amide/urethane substituent (R), the most potent indole carboxylic acids **1** only had pK_B values of ~8.[4] Furthermore these acids had oral ED_{50} values > 100 μmol/kg in the guinea pig dyspnea model.[4] As part of our continuing study of this series we then decided to explore replacement of the carboxylic acid group in the indoles **1** with mimics. This approach had been employed previously to improve the potency of carboxylic acids.[36,37] At about this time a group at Eli Lilly announced that they had discovered a tetrazole[38] substituted leukotriene antagonist, LY-171883[39] (Figure 2), which is 30 time more potent in vitro than the corresponding carboxylic acid **30**.

(35) For example, 10 μM of 7-[6-hexanamidoindol-1-yl]heptanoic acid i or the corresponding phenylsulfonimide ii, respectively, afforded 53% and 58% antagonism of the 8 nM LTE_4 induced contraction. Unpublished results of Drs. P. Bernstein and D. Snyder.



i. A = OH
ii. A = $NHSO_2Ph$

(36) Schaaf, T. K.; Hess, H.-J. *J. Med. Chem.* **1979**, *22*, 1340.
(37) Thornber, C. W. *Chem. Soc. Rev.* **1979**, 8, 563.
(38) (a) Singh, H.; Singh, A.; Kapoor, V. K.; Paul, D.; Malhotra, R. K.; Medicinal Chemistry of Tetrazoles. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; Elsevier: New York, 1980; Vol. 17, Chapter 4. (b) Butler, R. N. Recent Advances in Tetrazole Chemistry. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1977; Vol. 21, pp 323–435.
(39) Fleisch, J. H.; Rinkema, L. E.; Haisch, K. D.; Swanson-Bean, D.; Goodson, T.; Ho, P. P. K.; Marshall, W. S. *J. Pharmacol. Exp. Ther.* **1985**, *233*(*1*), 148.

Most of the acid mimics in Table II have the 3-methoxy substituent and are in the 2-ethylhexanamide series (e.g. **1b**, R = 1-ethylpentyl). However for synthetic convenience, three of the mimics, **75–77**, vary from this general structure by being desmethoxy analogues. Also entries **70** and **73** are respectively in the more potent cyclopentylacetamide (**1b**, R = c-$C_5H_{11}CH_2$) and cyclopentylurethane (**1b**, R = c-$C_5H_{11}O$) series instead of the 2-ethylhexanamide series.

The most significant discovery in the acid mimic series (see Table II) was the finding that phenyl sulfonimide **58** is 100 times more potent in vitro than the parent carboxylic acid **41**. In contrast, tetrazole **56** is equipotent in vitro to carboxylic acid **41**. The desmethoxy sulfonic acid analogue **75** was also equipotent with the corresponding desmethoxy carboxylic acid **42**. The less acidic hydroxamic acid **64** (pK_a ~8.9[40]), has less than one-tenth the potency of carboxylic acid **41** (pK_a ~4.8[36]). Insertion of several amide-derived groups (-CONHX-) between the 3-methoxytolyl group and the acidic site were all detrimental to potency, see entries **61** (X = *o*-Ph), **62** (X = CH_2), **63** (X = -). Similarly the cinnamic acid derivative **69** was also much weaker. Both methyl sulfonimide **57** and phenyl sulfonimide **58** have pK_a values[36] similar to that of carboxylic acid **41**. However methyl sulfonimide **57** is only equipotent with acid **41** whereas phenyl sulfonimide **58** is 100 times more potent.

The unique increase in potency obtained with phenyl sulfonimide **58** prompted us to view it as a new lead. We decided to prepare analogues of it to probe what structural features were resulting in the increased potency. A few of the initial structural probes had the same level of in vitro activity as the corresponding carboxylic acids. These included the less acidic phenyl sulfinimide **65** (pK_a ~6.5[41]) and the nonacidic N-methylated sulfonimide **70**. Removal of the sulfonimide carbonyl group afforded sulfonamide **73**. This structural change both decreases the acidity of the NH and changes the orientation of the pendant phenylsulfonyl group. Sulfonamide **73** was more than 100-fold less potent than the corresponding carboxylic acid **74**.

It seemed possible to us that, in part, the increased potency with the pendant phenyl group might be due to the increased lipophilicity (log *P*) of a phenyl as compared to a methyl group. To check this we prepared several other sulfonimides. Comparison of the in vitro potency of these analogues with either the carboxylic acid **41** or the equipotent methyl sulfonimide **57** shows that the isopropyl analogue **66** is about as potent, the *n*-butyl analogue **67** is approximately 3 times more potent, and the benzyl analogue **68** is less than one-tenth as potent as the two reference compounds. Thus variation of lipophilicity cannot be the key reason for the increased activity of the phenyl sulfonimide, rather there may be a region of the receptor which specifically binds an aromatic ring.

Transposition of the carbonyl and sulfonyl groups, as in (desmethoxy) sulfonimide **77**, also resulted in activity at the level of the corresponding acid **42** rather than the 100-fold greater level of sulfonimide **76**. This result in conjunction with the earlier findings implied to us that the spatial relationship between the pendant phenyl group and the sulfonimide group is important for the increased potency of phenyl sulfonimide **58**.

The keto sulfone **72** is equipotent to carboxylic acid **41** and is 100-fold less potent than sulfonimide **58**. In a structural sense keto sulfone **72** is removed by two variations from sulfonimide **58**. The first difference is its much lower acidity (pK_a ~9–11[42]). The second change is geometric in nature. The keto sulfone methylene exists predominantly in an sp^3 hybridized form (keto tautomer).[43] In contrast the sulfonimide nitrogen is expected to be predominantly in an sp^2 hybridized state.[44] Given the above results we hypothesized that both an acidic hydrogen and a specific orientation of the phenyl sulfone were required for the potency of the sulfonimides. We then reasoned that a bioisostere for the sulfonimide might be found if we could increase the acidity of the keto sulfone methylene hydrogens and the percentage of enolic tautomer (i.e. change the hybridization of the methylene to sp^2). Replacement of one of the keto sulfone methylene hydrogens with an electron withdrawing group (e.g. cyano, nitro, acyl) was expected to induce both of these desired effects. The keto sulfone nitrile **60** and keto sulfone ester **59** (pK_a ~6[42]) were approximately equipotent to sulfonimide **58**. The high potency of these two compounds supported our hypothesis.

Comparison of the Structure–Activity Relationships in Carboxylic Acids, Tetrazoles, Keto Sulfone Esters, and Sulfonimides (Tables III and IV). Several examples of the correlations which can be made between changes in in vitro potency and variation of the different segments of these antagonists can be found in Tables III and IV. A key finding was that most of the structure–activity relationships which had been discovered in one series proved to be directly related to the structure–activity relationships of the other species. This discovery allowed us to mix and match the most potent groups which had been found for different segments of these molecules.

Notably the indole tetrazoles **56**, **81**, and **82** are approximately equipotent to the corresponding indazoles **84**, **85**, and **86**. The two keto sulfone esters, indole **94** and indazole **95**, are also equipotent. These findings are similar to what had previously been found when the indole and indazole segments has been interchanged in the carboxylic acid series.[4] However, in contrast to this relationship the indole phenyl sulfonimides **87**, **88**, and **89** had between one-fourth and one-tenth the potency of the corresponding indazoles **90**, **92**, and **93**.

An additional correlation is that the rank order of potency as a function of the amide/urethane substituent which was found for phenyl sulfonimides (**58** ≤ **88** < **89** or **91** < **92** ≤ **93**), tetrazoles (**80** < **56** < **81** ≤ **82** < **83** or **84** < **85** < **86**), and keto sulfone esters (**59** < **94**) was similar to what had been previously determined for the carboxylic acids.[4]

The increase in potency that resulted from conversion of a carboxylic acid to a phenyl sulfonimide also occurred if the 3-methoxy-*p*-toluic acid was replaced by other *p*-toluic acids, e.g. compare sulfonimides **76** (Table II), **96** and **97** (Table IV) to their respective acids **42**, **47**, and **43** (Table I). In contrast to these results there was no change in potency upon conversion of a polymethylene-linked acid

(40) Abbasi, S. A.; Ahmed, J. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2013.

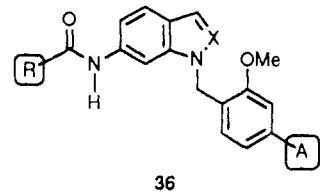
(41) The pK_a of sulfinimide **65** was measured as 6.5 in aqueous ethanol by P. Parhami, ICI Pharmaceuticals group, personal communication.

(42) Poot, A.; Delzenne, G.; Pollet, R.; Laridon, U. *J. Photogr. Sci.* **1971**, *19*, 88.

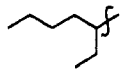
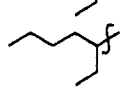
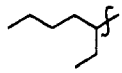
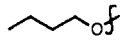
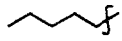
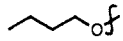
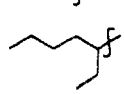
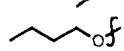
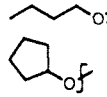
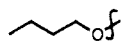
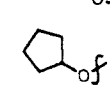
(43) The ^1H NMR ($CDCl_3$) of keto sulfone **72** shows the SO_2-C-H_2-CO as a 2H singlet at 4.6 δ which is consistent with the non-enolized (sp^3) tautomer. The ^1H NMR (DMSO) of keto sulfone ester **59** shows the SO_2-C*H*-CO as a ~0.5 H singlet at 7.13 δ which is consistent with rapid equilibration of the keto and enol forms and predominance of the enolic (sp^2) tautomer.

(44) The X-ray crystallographic structure of compound **92** (ICI-198615) shows the sulfonimide nitrogen as planar. Unpublished results of Drs. Y. K. Yee and P. J. Carroll (University of Pennsylvania).

Table III. Indole and Indazole Acid Replacements SAR

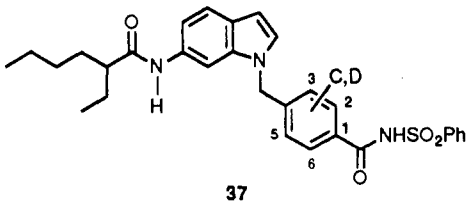


36

entry	R	X	A	test concn, 10^{-7} M	% antagonism[a] of LTE_4	pK_B[b]	In vivo[c,d] po, μmol/Kg	In vivo[c,d] % prot[a]/±SEM (n[e])	mp, °C	microanalysis	method of synthesis	% yield[f]
56		CH	Tet[h]	10 3.3	50 31	6.6			211–2	$C_{25}H_{30}N_6O_2$	5.a[i]	56
58		CH	$C(O)NHSO_2Ph$	1 0.1	100 27	8.6	100 30	40/17 (15) 24/7 (9)	216.5–8	$C_{31}H_{35}N_3O_5S$	2.b[i] 2.a	42 79
59		CH	$COCH(CO_2Me)$-SO_2Ph	1 0.1	100 65	8.5			148–9	$C_{34}H_{38}N_2O_7S$	2.b[i]	17
71		CH	CO_2H	1	34	7.7			218–20	$C_{24}H_{26}N_6O_2 \cdot 0.25H_2O$	ref 4	
74		CH	CO_2H	33 1	100 61	7.8	100[g]	23/6 (10)	237–8		ref 4	
78		N	CO_2H	3.3	30	7.1	113[g]	14/4 (12)	244–5 dec		ref 4	
79		N	CO_2H	3.3	56	6.7	126[g]	33/5 (14)	213.5–4 dec		ref 4	
80		CH	Tet[h]	33 10	86 32				210–2 dec	$C_{23}H_{26}N_6O_2$	5.a[i]	48
81		CH	Tet[h]	10 3.3	68 42	7.2	120[g] 120[k]	17NS[j]/7 (8) -4NS[j]/4 (8)	197–8.5	$C_{22}H_{24}N_6O_3$	5.b[i]	54
82		CH	Tet[h]	10	62	7.6	100[g] 100[k]	45/11 (10) 31/12 (10)	216–8	$C_{23}H_{24}N_6O_3$	5.b	57
83		CH	Tet[h]	10 3.3 1	100 79 42				218–20	$C_{24}H_{26}N_6O_2 \cdot 0.25H_2O$	5.a	29
84		N	Tet[h]	10 3.3	100 49	7.1			203–4	$C_{24}H_{29}N_7O_2$	5.b	56
85		N	Tet[h]	3.3	55	7.1			210.5–1.5 dec	$C_{21}H_{23}N_7O_3$	5.b[i]	40
86		N	Tet[h]	10 1	100 58	7.7	100[g] 100[k]	42/5 (6) 3NS[j]/2 (6)	203.5–4.5 dec	$C_{22}H_{23}N_7O_3$	5.b	66
87		CH	$C(O)NHSO_2Ph$	0.1	33	8.4			214–6	$C_{33}H_{31}N_3O_5S \cdot 1.0H_2O$	2.6	41
88		CH	$C(O)NHSO_2Ph$	0.33 0.033	100 61	9.5	30[g] 30	48/12 (9) 67/11 (6)	209–10	$C_{29}H_{29}N_3O_6S$	2.b	34
89		CH	$C(O)NHSO_2Ph$	0.033 0.01	92 50	9.6	30	43/7 (6)	208–9	$C_{30}H_{31}N_3O_5S$	2.a	42
90		N	$C(O)NHSO_2Ph$	0.033	43	9.0	30[g] 30	29NS[j]/15 (9) 42NS[j]/19 (6)	142–4.5	$C_{32}H_{30}N_4O_5S$	2.a	69
91		N	$C(O)NHSO_2Ph$	0.1 0.033	100 77	9.2	30[g] 30	29/5 (6) 27/4 (9)	153–4	$C_{27}H_{28}N_4O_6S$	2.b	35
92 (ICI-198,615)		N	$C(O)NHSO_2Ph$	0.033 0.01	100 69	10.3	30 10	89/8 (6) 37/8 (16)	189–90	$C_{28}H_{28}N_4O_6S$	2.a[i]	67
93		N	$C(O)NHSO_2Ph$	0.01 0.001	100 23	10.5	10	56/13 (8)	167–9	$C_{29}H_{30}N_4O_5S$	2.a	48
94		CH	$COCH(CO_2Me)$-SO_2Ph	0.033 0.01	94 63	10.1	3 1	83/12 (6) 30/8 (8)	93–5	$C_{33}H_{34}N_2O_7S$	2.b	10
95		N	$COCH(CO_2Me)$-SO_2Ph	0.033 0.01	78 53	9.9	30	88/5 (6)	95–100	$C_{31}H_{31}N_3O_8S \cdot 0.33MTBE$[l]	2.b	27

[a] Results are statistically significant ($p < 0.05$) from control unless otherwise indicated. [b] See ref 31. As an example of K_B variability, the K_B of **58** is $2.50 \pm 0.52 \times 10^{-9}$ M. [c] Protection (% prot) against aerosolized LTD_4 induced dypsnea in guinea pig. Model is described in Experimental Section and in ref 34. [d] 180 min post oral dosing unless otherwise indicated. [e] Number of animals = n. [f] Yield for final step. [g] 60 min post oral dosing. [h] Tet = 1*H*-tetrazol-5-yl. [i] Experimental included. [j] NS = not significant. [k] 120 min post oral dosing. [l] MTBE = methyl *tert*-butyl ether.

Table IV. Additional Sulfonimides



37

entry	C	D	test concn, 10^{-7} M	% antagonism of LTE_4[a]	pK_B[b]	mp, °C	microanalysis	method of synthesis	% yield[c]
96	2-MeO		1	52		134-6	$C_{31}H_{35}N_3O_5S$	2.b	71
97	3-MeO	5-MeO	1	72	8.0	220-1.5	$C_{32}H_{37}N_3O_6S$[d]	2.b	39

[a] Results are statistically significant ($p < 0.05$) from control. [b] See ref 31. As an example of K_B variability, the K_B of **97** is $9.96 \pm 1.29 \times 10^{-9}$ M. [c] Yield on hydrolysis. [d] Nitrogen: calcd 7.10; found 6.53.

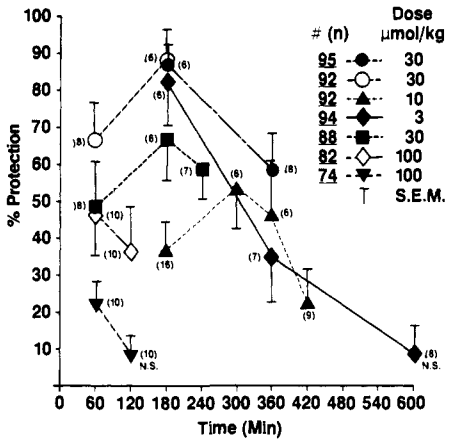


Figure 3. Determination of po activity in the guinea pig dyspnea model as a function of time postdosing.

to a phenyl sulfonimide (e.g. an analogue in which the 3-methoxy-*p*-toluoyl group was replaced with $-[CH_2]_6-$).[35]

Several of these findings were especially important. For example, after the more potent amide/urethane substituents (R) had been discovered in the indole carboxylic acid series **1**[4] application of these R groups to the indole phenyl sulfonimides led to analogues **88** and **89**. Incorporation of these groups into the more potent indazoles led to sulfonimides **92** and **93**. With pK_B values of 10.1 and 10.5 these were for a time the two most potent leukotriene antagonists of which we were aware.

Discussion of in Vivo Results (Table III and Figure 3)

Limited po in vivo data was obtained for several of these compounds (Table III). Direct comparison of any two compounds in any single acid (mimic) series is straightforward. However the time lag postdosing for maximal efficacy appeared to vary as a function of the acid group (see Figure 3 and discussion below) and this makes comparison between series more difficult. The most striking finding was although the phenyl sulfonimides did show increases in in vivo potency relative to the carboxylic acid the increases were not as great as we had anticipated from the in vitro results.

In particular, the ca. 100-fold increase in in vitro potency which sulfonimides **90** and **91** had shown as compared to carboxylic acids **78** and **79** only translated to an ca. 5-fold increase in vivo (when both were assayed at 60 min postdosing). At 60 min postdosing the tetrazoles tended to be equal to the carboxylic acids (e.g. indole tetrazole **81** vs indazole carboxylic acid **79**, indole tetrazole **82** vs indole carboxylic acid **74**). At 120 min postdosing indole tetrazole **82** retained more activity than did indole carboxylic acid **74** or indazole tetrazole **86**.

The phenyl sulfonimides and keto sulfone esters showed an extended duration of action (see Figure 3) as compared to either the carboxylic acids or tetrazoles. Indeed, rather than a steady decrease in activity, the sulfonimides (**92** and **88**) showed maximal efficacy about 3–5 h postdose (the keto sulfone esters were not checked at shorter timepoints). Indazole keto sulfone ester **95** and indazole sulfonimide **92** were equiactive at the 3 h timepoint. However the indole keto sulfone ester **94** was 20 times more potent than the corresponding indole sulfonimide **89**.

The large difference between the increase in potencies in vitro and in vivo in comparing the phenyl sulfonimides and the carboxylic acids served as a warning for us of a potential problem with either bioavailability or metabolism/rapid elimination. Much of our attention then turned to possible solutions. Initially keto sulfone esters looked like they might be the answer to these concerns. This was because comparison of the in vivo and in vitro potencies of indole keto sulfone ester **94** and indole sulfonimide **89** had shown keto sulfone ester **94** to be 5–10 times more potent orally than we had anticipated based on sulfonimide **89**. However the keto sulfone esters were dropped from further consideration when they proved unstable to strong light or prolonged storage at room temperature.

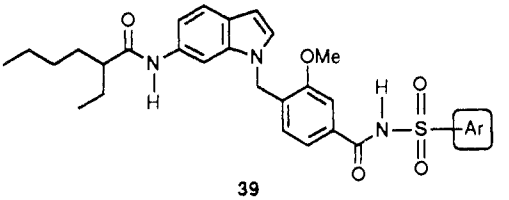
As a way of further exploring the biological properties of the sulfonimide series, phenyl sulfonimide **92** was chosen for very broad pharmacological evaluation. Most of these pharmacologic studies have been reported.[32,45] In summary, they confirmed that **92** is very selective (in vitro, it is at least 5000 times less potent against a wide variety of other agonists).[45a,c,d] They also showed that **92** suffered from poor and variable absorption in dogs after oral administration.[45b] Additional studies have shown <0.3% bioavailability in dogs and revealed very low blood levels in rats following oral administration.[46]

Aryl Sulfonimides (Tables V, VI, and VII). We then turned to investigation of the effects on in vitro and in vivo potency of replacement of the terminal phenyl group with other aryl groups in the phenyl sulfonimides. Like our study of different aryl acids, this exploration was initially based on the 2-ethylhexanamide indole series (**39**, Table V).[47] We succeeded in finding other, more potent, aryl

(45) The pharmacological profile of ICI-198615 has been extensively reported: (a) Krell, R. D.; Giles, R. E.; Yee, Y. K.; Snyder, D. W. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 557. (b) Snyder, D. W.; Giles, R. E.; Keith, R. A.; Yee, Y. K.; Krell, R. D. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 548. (c) Aharony, D. A.; Falcone, R. C.; Yee, Y. K.; Hesp, B.; Giles, R. E.; Krell, R. D. *Ann. N.Y. Acad. Sci.* **1988**, *524*, 162. (d) Krell, R. D.; Kusner, E. J.; Aharony, D.; Giles, R. E. *Eur. J. Pharmacol.* **1989**, *159*, 73.

(46) Personal communication from L. S. Tutak, Toxicology Section, ICI Pharmaceuticals Group.

Table V. SAR of Substituted Phenyl Sulfonimides (Part 1)

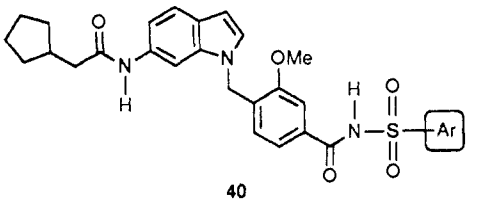


39

entry	Ar	pK_B[a]	mp, °C	microanalysis	method of synthesis	% yield[b]
58	Ph	8.6	216.5–8	$C_{31}H_{35}N_3O_5S$	2.b	42
98	4-ClC_6H_4	7.8	182.5–4	$C_{31}H_{34}ClN_3O_5S$	2.b	64
99	4-FC_6H_4	7.7	182.5–4	$C_{31}H_{34}FN_3O_5S$	2.b	65
100	4-$MeOC_6H_4$	7.4	197–9	$C_{32}H_{37}N_3O_6S \cdot 0.25H_2O$	2.b	18
101	4-$NO_2C_6H_4$	7.7	212–4	$C_{31}H_{34}N_4O_7S$	2.b	45
102	4-MeC_6H_4	8.4	228–9	$C_{32}H_{37}N_3O_5S$	2.b	48
103	2-MeC_6H_4	8.9	221–2	$C_{32}H_{37}N_3O_5S$	2.b	27

[a] See ref 31. As an example of K_B variability, the K_B of 58 is $2.50 \pm 0.52 \times 10^{-9}$ M. [b] Yield for final step.

Table VI. SAR of Substituted Phenyl Sulfonimides (Part 2)



40

entry	Ar	pK_B[a]	in vivo[b,c] po, μmol/Kg	in vivo[b,c] % prot[d]/ ±SEM (n)[e]	mp, °C	microanalysis	method of synthesis	% yield[f]
89	Ph	9.6	30	43/7 (6)	208–9	$C_{30}H_{31}N_3O_5S$	2.a	42
104	2-MeC_6H_4	9.9	1	40/6 (8)	218–20	$C_{31}H_{33}N_3O_5S$	2.a	63
105	2-NHC_6H_4	9.9			140–55	$C_{30}H_{32}N_4O_5S$	2.a	30
106	2-ClC_6H_4	9.8	3	52/13 (7)	139–140	$C_{30}H_{30}ClN_3O_5S \cdot 0.5H_2O$	2.a	53
107	2-$MeOC_6H_4$	9.7	30	68/9 (7)	222–4	$C_{31}H_{33}N_3O_6S \cdot 1.25H_2O$	2.a	39
108	2-Thienyl	9.6	30	10/4 (8)	144–8	$C_{28}H_{29}N_3O_5S \cdot 0.25H_2O$	2.a	64
109	2-Pyridyl	8.9	30	20NS[g]/16 (7)	184–6 dec	$C_{29}H_{30}N_4O_5S \cdot 0.25H_2O$[h]	2.a	61
110	2,5-$(Me)_2C_6H_3$	8.4			228–30 dec	$C_{32}H_{35}N_3O_5S \cdot 0.25H_2O$	2.a	10
111	2,5-$(OMe)_2C_6H_3$	9.1	30	21/4 (10)	216–8	$C_{32}H_{35}N_3O_7S$	2.a	52
112	2-Naphthyl	8.3			144–7	$C_{34}H_{33}N_3O_5S$	2.a	60
113	2,6-(Cl,Me)C_6H_3	8.8	30	99/1 (9)	214–6 dec	$C_{31}H_{32}ClN_3O_5S \cdot 0.25H_2O$	2.a	66
			10	95/3 (10)				
			3	48/9 (10)				

[a] See ref 31. As an example of K_B variability, the K_B of 89 is $0.243 \pm 0.086 \times 10^{-9}$ M. [b] Model is described in Experimental Section and in ref 34. [c] 180 min post oral dosing. [d] Results are statistically significant ($p < 0.05$) from control unless otherwise indicated. [e] Number of animals = n. [f] Yield for final step. [g] NS = not significant. [h] Nitrogen: calcd 10.16; found 9.61.

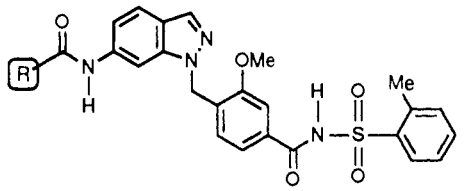
sulfonimides. However, the most significant finding in this area was that some substituent patterns resulted in much greater improvements in potency in vivo than in vitro.

The 2-methyl analogue **103** showed a 2-fold improvement in in vitro potency compared to the parent phenyl sulfonimide **58**. This result contrasted with the decreased potency shown by several 4-substituted phenyl analogues, **98–102**.

The 2-fold increase in in vitro potency induced by a 2-methyl substituent was confirmed by preparation of analogue **104** in the more potent cyclopentylacetamide indole series (Table VI).[4] However, the more striking result with analogue **104** was the 30-fold improvement in oral potency. Further study of the structure–activity relationships of the pendant aryl group of these antagonists was then carried out in this series. The 2-methoxy analogue **107** was approximately equipotent both in vitro and in vivo to the parent compound. The 2-amino analogue **105** and the 2-chloro analogue **106** were, respectively, 2 times and 1.5 times more potent in vitro than the unsubstituted phenyl analogue **89**. Only the latter analogue was checked in vivo and the 10-fold increase in oral potency which it showed was also much greater than the increase in potency in vitro. An attempt to obtain a beneficial additive effect by combining the chloro and methyl substituents into a single molecule, the 2-methyl-6-chloro analogue **113**, resulted in an 8-fold decrease in vitro potency. In contrast this compound shows a 10-fold improvement in oral potency. Thus, analogue **113** serves as particularly good example of the divergence in structure–activity relationships between in vitro and oral potencies. Two other disubstituted analogues, **110** and **111**, also showed decreased in vitro potency. One heterocyclic replacement for the phenyl group, the (bioisosteric[37]) 2-thienyl analogue **108**, resulted in no change in in vitro potency but showed a significant decrease in oral potency. Two other replacements for the phenyl group, the 2-pyridyl **109** and 2-naphthyl **112** analogues, were, respectively, 5-

(47) Preliminary results on some sulfonimides have been disclosed: Yee, Y. K.; Brown, F. J.; Hebbel, K. C.; Cronk, L. A.; Snyder, D. W.; Krell, R. D. *Ann. N.Y. Acad. Sci.* **1988**, *524*, 458.

Table VII. Indazole 2-Methylphenylsulfonimides



entry	R	pK_B°	in vivo[b,c] po, μmol/Kg	in vivo[b,c] % prot[d]/ ±SEM (n)[e]	mp, °C	microanalysis	method of synthesis	% yield[f]
114		10.9	3	90/10 (10)	183.5–5	$C_{30}H_{32}N_4O_5S$	2.a	60
			1	29/7 (27)				
115		10.2	3	90/10 (9)	211–2	$C_{29}H_{30}N_4O_6S$	2.a	62
			0.3	56/15 (9)				

[a] See ref 31. As an example of K_B variability, the K_B of 114 is 0.0126 ± 0.0033 × 10^{-9} M. [b] Model is described in Experimental Section and in ref 34. [c] 180 min post oral dosing. [d] Results are statistically significant ($p < 0.05$) from control. [e] Number of animals = n. [f] Yield for final step.

and 20-fold less potent in vitro.

Extension of these findings to the more potent indazole series led to two especially exciting compounds (Table VII). The cyclopentylacetamide indazole **114** has the highest in vitro potency (pK_B = 10.9) of any leukotriene antagonist reported to date. Also it was only the second compound in this series to show oral activity at 1 μmol/kg (its corresponding indole analogue **104** was the first). The cyclopentyl urethane indazole **115**, has the greatest oral potency (an ED_{50} of approximately 0.3 μmol/kg ≈ 0.2 mg/kg) of any of these compounds. This value establishes it as one of the most orally potent of the reported leukotriene antagonists.

Conclusion

This paper describes the in vivo and in vitro effects of modifications of the acidic grouping in the benzoic acid **41**, a structurally novel leukotriene antagonist. Replacement of the carboxylic acid with a variety of acid mimics generally did not afford improvement in the profile of the compound. However a substantial increase in potency was seen when the carboxylic acid was replaced by a phenyl sulfonimide (e.g. **58**). Keto sulfone based mimics (e.g. **59**) of these phenyl sulfonimides proved to be intellectually interesting, but inherently unstable and impractical as alternates. Further improvement in the in vivo profile and the potency of these compounds was obtained by substitution of the phenyl sulfonimides with an *o*-chloro or *o*-methyl group (e.g. **103**).

Although none of the compounds reported in this manuscript were chosen for clinical evaluation, the results obtained are important. For example, ICI-198615 (**92**), which was discovered in the course of this study, has proven to be a valuable pharmacological tool.[32,45] Also the aryl sulfonimides have been applied in newer related series. Several compounds derived from these newer series, including ICI-204219,[48] have been selected for further evaluation as antiasthma drugs and they should help delineate the role of leukotrienes in asthma.

Experimental Section

Synthetic Procedures. Analytical samples were homogeneous by TLC and afforded spectroscopic results consistent with the assigned structures. Analytical thin-layer chromatography (TLC) was conducted on either normal-phase on prelayered silica gel GHLF plates (Analtech, Newark, DE) or in reverse-phase mode (RP-TLC) on Whatman MKC 18 reversed-phase TLC plates. Visualization of the plates was accomplished by using UV light and/or phosphomolybdic acid–sulfuric acid charring. Infrared spectra (IR) were taken on either a Perkin-Elmer 727B or 781 spectrophotometer; band locations are reported in frequency (cm^{-1}). Proton nuclear magnetic resonance spectra (^1H NMR) were obtained by the ICI Pharmaceuticals Group, Structural Chemistry Section with use of either a Bruker WM-250, an IBM NR-80, or a Varian EM-360 spectrometer. Peak positions are reported in parts per million (δ), with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded by the Structural Chemistry Section on a Kratos MS-80 operating either in the electron impact (EI) or chemical ionization (CI) mode as indicated. Elemental analyses for carbon, hydrogen, and nitrogen were determined by the Analytical Department, ICI Americas Inc., on a Perkin-Elmer 241 elemental analyzer and are within ±0.4% of the theoretical values unless otherwise indicated. Melting points were taken on either a Fisher-Johns or a Thomas-Hoover melting point apparatus and are uncorrected. Flash chromatography[49] was done either, normal phase on Kieselgel 60, 230–400 mesh (E. Merck, Darmstadt, West Germany), or reversed phase on J.T. Baker Octadecyl Silyl (ODS) packing material, 40 μm. High-pressure liquid chromatography (HPLC) was done on a Beckmann Model 334 HPLC. The water soluble carbodiimide (WSCDI, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) was obtained from Sigma Chemicals and stored in the freezer over desicant until used. All other organic starting materials and reagents were obtained from Aldrich Chemicals and were used without any additional purification unless otherwise indicated. Solvents used were either reagent or HPLC grade and were obtained from either Fisher Scientific or J.T. Baker Chemical Co. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl directly prior to use. Triethylamine (TEA) was distilled from CaH_2 and stored over KOH pellets under nitrogen. Lithium diisopropylamide (LDA) solutions were prepared in THF from *n*-BuLi and diisopropylamine directly prior to use. Unless otherwise indicated, all reactions were carried out under an inert atmosphere of nitrogen with vigorous magnetic stirring.

4-[[6-(2-Ethylheptanamido)indol-1-yl]methyl]benzoic Acid (42). General Example of Aryl Acid Synthesis: Scheme I. To a solution of 130 mg of methyl 4-[[6-(2-ethylheptanamido)-

(48) (a) Krell, R. D.; Buckner, C. K.; Keith, R. A.; Snyder, D. W.; Bernstein, P. R.; Brown, F. J.; Matassa, V. G.; Yee, Y. K.; Hesp, B.; Giles, R. E. *Am. Acad. Allergy Immunol.* **1988**, *81*, 276. (b) Buckner, C.; Fedyna, J.; Krell, R.; Robertson, J.; Keith, R.; Matassa, V.; Brown, F.; Bernstein, P.; Yee, Y.; Will, J.; Fishleder, R.; Saban, R.; Hesp, B.; Giles, R. *FASEB J.* **1988**, *47*, A1264. (c) Matassa, V. G.; Maduskuie, T. P.; Shapiro, H. S.; Hesp, B.; Snyder, D. W.; Aharony, D.; Krell, R. D.; Keith, R. A. *J. Med. Chem.* **1990**, *33*, 1781.

(49) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

indol-1-yl]methyl]benzoate, 4.4 mL of methanol, and 3.0 mL of tetrahydrofuran was added 52 mg of lithium hydroxide monohydrate in 1.5 mL of water. The mixture was stirred under nitrogen for 16 h and then diluted with water and extracted with ethyl ether. The aqueous layer was acidified to pH 1 with 1 N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was recrystallized from ethyl acetate and ethyl ether to give 58 mg (46%) of acid **42** as a colorless solid: mp 208–210 °C; MS-DCI *m/e* 393 (p + 1).

The starting ester, **methyl 4-[[6-(2-ethylheptanamido)indol-1-yl]methyl]benzoate**, was synthesized by using a similar procedure to that described for tetrazole **80** but with 6-(2-ethylhexanamido)indole (**3b**, R = 1-ethylpentyl) in place of 6-hexanamidoindole (**3b**, R = pentyl) and methyl 4-(bromomethyl)benzoate in place of 4-(bromomethyl)-3-methoxybenzonitrile (**19**) and was obtained as a white solid in 32% yield, mp 139–141 °C. The starting indole (**3b**, R = 1-ethylpentyl) was obtained in an analogous manner to that described for 6-(hexanamido)indole (**3b**, R = pentyl) in part b of the preparation of tetrazole **80** but with 2-ethylhexanoyl chloride in place of hexanoyl chloride and was obtained as a light brown powder in 56% yield, mp 154–156 °C.

4-[[6-(2-Ethylhexanamido)indol-1-yl]methyl]-3-(3-cyanopropoxy)benzoic Acid (53). By using a similar procedure described for acid **42** but with methyl 3-(3-cyanopropoxy)-4-(bromomethyl)benzoate as the starting material, acid **53** was obtained as a white solid in 82% yield, mp 175–176 °C. Anal. ($C_{28}H_{33}N_3O_4$) C, H, N. Intermediate, methyl 4-[[6-(2-ethylhexanamido)indol-1-yl]methyl]-3-(3-cyanopropoxy)benzoate, was obtained, as an oil, in 56% yield, MS-DCI 490 (p + 1).

4-[[6-(2-Ethylhexanamido)indol-1-yl]methyl]-3-(3-tetrazolylpropoxy)benzoic Acid (55). A mixture of 4-[[6-(2-ethylhexanamido)indol-1-yl]methyl]-3-(cyanopropoxy)benzoic acid (**53**) (334 mg, 0.7 mmol), triethylamine (0.1 mL, 0.7 mmol) in 1.5 mL of DMF was added to triethylamine hydrochloride (145 mg, 1.05 mmol) and sodium azide (137 mg, 2.1 mmol). The reaction was heated to 125 °C for 42 h under a nitrogen atmosphere. After cooling, water (3 mL) was added and the mixture was acidified with 1 N HCl. The extractions from 2 × 25 mL of ethyl acetate were combined, washed with water (3 × 10 mL) and brine (10 mL), and dried ($MgSO_4$). After evaporation of solvent, the residue was flash chromatographed (50 g of silica gel, 1% acetic acid in 1:1 methylene chloride/ethyl acetate as eluent) to give acid **55** as a white solid in 50% yield: mp 175–176 °C; ^{1}H NMR (DMSO) 2.29 (m, 1 H), 3.15 (t, *J* = 7.5 Hz, 2 H), 4.25 (t, *J* = 6.4 Hz, 2 H), 5.32 (s, 2 H, indole-CH_2-Ar), 9.71 (s, 1 H, -CONH-); MS-DCI *m/e* 519 (p + 1, 100). Anal. ($C_{28}H_{33}N_3O_4$) C, H, N.

6-(2-Ethylhexanamido)-1-[2-methoxy-4-(1*H*-tetrazol-5-yl)benzyl]indole (56). By using a similar procedure to that described for tetrazole **80** but with 1-(4-cyano-2-methoxybenzyl)-6-(2-ethylhexanamido)indole (**17b**, R = 1-ethylpentyl) as the starting material, there was obtained tetrazole **56** in 73% yield as a solid, mp 211–212 °C. The starting nitrile **17b** (R = 1-ethylpentyl) was obtained in 53% yield as a white solid, mp 177–178 °C, by sodium hydride alkylation of 6-(2-ethylhexanamido)indole (**3b**, R = 1-ethylpentyl) with 4-(bromomethyl)-3-methoxybenzonitrile **19** and by using the general method described for tetrazole **80**. The starting indole **3b** (R = 1-ethylpentyl) was obtained in an analogous manner to that described for 6-hexanamidoindole (**3b**, R = pentyl) in part b of the preparation of tetrazole **80** but with use of 2-ethylhexanoyl chloride in place of hexanoyl chloride and was obtained as a light brown powder in 56% yield: mp 154–156 °C; ^{1}H NMR (DMSO) 0.80 (m, 6 H), 1.38 (m, 8 H), 2.25 (m, 1 H), 4.02 (s, 3 H, OCH_3), 5.35 (s, 2 H, indole-CH_2-Ar), 6.44 (d, *J* = 2 Hz, 1 H), 6.74 (d, *J* = 8 Hz, 1 H), 7.13 (d, *J* = 8.5 Hz, 1 H), 7.40 (d, *J* = 3.5 Hz, 1 H), 7.48 (m, 2 H), 7.67 (s, 1 H), 7.89 (s, 1 H), 9.75 (s, 1 H); MS-DCI (isobutane) *m/e* 447 (p + 1, 17.3), 259 (100). Anal. ($C_{25}H_{30}N_6O_2$) C, H, N.

***N*-(4-[[6-(2-Ethylhexanamido)indol-1-yl]methyl]-3-methoxybenzoyl)benzenesulfonamide (58). General Example of Synthesis of Sulfonimides via Mixed Carbonic Anhydride.** Sodium hydride, 99 mg (50% w/w dispersion in mineral oil), was washed twice with hexane and suspended in 1 mL of dry dimethylformamide (DMF). The suspension was stirred and a solution of 355 mg of benzenesulfonamide in 1 mL of DMF was added. The mixture was stirred for 1 h until effervescence had stopped. A solution of 253 mg of 4-[[6-(2-ethylhexanamido)indol-1-yl]methyl]-3-methoxybenzoic *N*,*N*-diphenylcarbamic anhydride (**9b**) (R = 1-ethylpentyl) in 0.5 mL of DMF was added. The mixture was stirred for a further 1 h and poured into 20 mL of water. The aqueous mixture was acidified to pH 6 with acetic acid and extracted with ethyl acetate. The extracts were washed with water and then with saturated brine, dried ($MgSO_4$), and evaporated. The resultant residue was purified by flash chromatography (using 8% v/v ethyl acetate in toluene containing 1% v/v acetic acid), followed by recrystallization [from ethyl acetate/petroleum ether (bp 60–80 °C)] to give 130 mg (57%) of sulfonamide **58** as a white solid: mp 216.5–218 °C; ^{1}H NMR (DMSO) 2.24 (m, 1 H), 3.95 (s, 3 H, OCH_3), 5.32 (s, 2 H, indole-CH_2-Ar), 9.73 (s, 1 H, CONH), 12.04 (s, 1 H, -$NHSO_2$-); MS-DCI *m/e* 562 (p + 1, 75), 405 (85), 143 (100). Anal. ($C_{31}H_{35}N_3O_5S$) C, H, N.

The starting diphenylcarbamic anhydride **9b** (R = 1-ethylpentyl) was obtained as follows. A solution of 3.1 g of 4-[[6-(2-ethylhexanamido)indol-1-yl]methyl]-3-methoxybenzoic acid[4] and 1.0 mL of triethylamine in 30 mL of methanol was treated with a solution of 2.5 g of (*N*,*N*-diphenylcarbamoyl)pyridinium chloride in 30 mL of methanol. The resultant precipitate was collected by filtration, washed with methanol, and dried under vacuum to give 3.54 g (79%) of 4-[[6-(2-ethylhexanamido)indol-1-yl]methyl]-3-methoxybenzoic *N*,*N*-diphenylcarbamic anhydride (**9b**) (R = 1-ethylpentyl) as a white solid, mp 159–162 °C. Anal. ($C_{38}H_{39}N_3O_5$) C, H, N.

Methyl 2-[4-[[6-(2-Ethylhexanamido)indol-1-yl]methyl]-3-methoxybenzoyl]-2-(phenylsulfonyl)acetate (59). To a solution of 650 mg of methyl 2-(phenylsulfonyl)acetate in 5.0 mL of THF at −78 °C was added 6.0 mL of a 0.5 M solution of lithium diisopropylamide in THF. To this was then added a solution of 617 mg of carbamic anhydride **9b** (R = 1-ethylpentyl) the reaction mixture was allowed to slowly warm to room temperature overnight. Saturated sodium diacid phosphate was added, the THF was removed in vacuo, and the residue was partitioned between ethyl acetate and water. The ethyl acetate solution was dried, filtered, and concentrated in vacuo to afford a yellow oil. This was chromatographed on 42 g silica gel by utilizing a gradient eluent going from pure methylene chloride up to 5% ethyl ether/methylene chloride. Combination of the appropriate fractions and concentration in vacuo afforded a clear oil that crystallized from methyl *tert*-butyl ether, affording 172 mg (17% yield) of keto sulfone ester **59** as an ivory powder: mp 148–149 °C; ^{1}H NMR (DMSO) 0.82 (m, 6 H, CH_3), 1.38 (m, 8 H), 2.27 (m, 1 H), 3.33 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 5.35 (s, 2 H, indole-CH_2-Ar), 6.47 (d, *J* = 3.0 Hz, 1 H), 6.54 (d, *J* = 7.8 Hz, 1 H), 7.13 (s, 0.5 H), 7.16 (d, *J* = 8.3 Hz, 1 H), 7.39 (d, *J* = 3.0 Hz, 1 H), 7.52 (m, 6 H), 7.67 (m, 1 H), 7.87 (m, 3 H), 9.77 (s, 1 H, CON*H*Ar); MS-DCI (isobutane) *m/e* 619 (p + 1, 17), 165 (100). Anal. ($C_{34}H_{38}N_2O_7S$) C, H, N.

6-(2-Ethylhexanamido)-1-[2-methoxy-4-[2-(phenylsulfonyl)-2-cyanoacetyl]benzyl]indole (60). Via a procedure similar to that used for preparation of keto sulfone **59**, but by using (phenylsulfonyl)acetonitrile instead of methyl 2-(phenylsulfonyl)acetate and by using ethyl acetate in chloroform instead of ethyl ether in methylene chloride as eluent, there was obtained **60** in 85% yield as an off-white powder: mp 184 °C dec, hydrate; ^{1}H NMR (DMSO) 0.83 (m, 6 H), 1.36 (m, 8 H), 2.27 (m, 1 H), 3.86 (s, 3 H, OCH_3), 5.27 (s, 2 H), 6.41 (d, *J* = 3 Hz, 1 H), 6.52 (d, *J* = 7.8 Hz, 1 H), 7.02 (d, *J* = 10 Hz, 1 H), 7.18 (m, 2 H), 7.34 (d, *J* = 3 Hz, 1 H), 7.48 (m, 4 H), 7.80 (s, 1 H), 7.86 (d, *J* = 6.5 Hz, 2 H), 9.79 (s, 1 H). Anal. ($C_{33}H_{35}N_3O_5S\cdot 2.5H_2O$) C, H, N; H: calcd, 6.36; found 5.91.

***N*-[4-[[6-(2-Ethylhexanamido)indol-1-yl]methyl]-3-methoxybenzoyl]benzenesulfinamide (65).** Via a similar procedure to that described in example **58** but with benzenesulfinamide as starting material, there was obtained sulfinamide **65** in 28% as a solid: mp 122–126 °C; ^{1}H NMR (DMSO) 2.25 (m, 1 H), 3.94 (s, 3 H, OCH_3), 5.33 (s, 2 H, indole-CH_2-Ar), 9.74 (s, 1 H, -CONH-), 11.58 (s, 1 H, -$NHSO_2$-); MS-DCI *m/e* 562 (p + 1, 3.0), 530 (24), 422 (100). Anal. ($C_{31}H_{35}N_3O_4S$) C, H, N; C: calcd, 68.23; found, 67.61. Benzenesulfinamide was prepared by reacting benzenesulfinyl chloride with ammonia in ethyl ether initially at −78 °C and finally at ambient temperature and was isolated in

17% yield as a solid, mp 112–115 °C.

6-(2-Ethylhexanamido)-1-[2-methoxy-4-[2-(phenylsulfonyl)acetyl]benzyl]indole (72). To a solution of 312 mg of methyl phenyl sulfone in 5.0 mL of dry THF at −78 °C was added 0.86 mL of a 2.3 M solution of *n*-butyllithium in hexanes. After ~15 min a white suspension had formed. To this was added a solution of 500 mg of 4-[6-(2-ethylhexanamido)indol-1-yl]-methyl]-3-methoxybenzoic *N,N*-diphenylcarbamic anhydride **9b** (R = 1-ethylpentyl) in 4.0 mL of THF. After 2 h the solution was allowed to warm to room temperature, and a saturated solution of potassium diacid phosphate was added. The THF was removed in vacuo, the residue was partitioned between water and ethyl acetate, and the organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a gum. This was chromatographed on 20 g of silica gel by eluting with 2% ethyl ether in methylene chloride. Combination of the appropriate fractions and concentration in vacuo afforded in 44% yield, 200 mg of keto sulfone **72** as a white solid: mp 131–133 °C; ^{1}H NMR ($CDCl_3$) 0.86 (t, J = 6.6 Hz, 3 H), 0.94 (t, J = 7.4 Hz, 3 H), 1.29 (m, 4 H), 1.54 (m, 2 H), 1.71 (m, 3 H), 2.07 (m, 1 H), 3.94 (s, 3 H, OCH_3), 4.65 (s, 2 H), 5.33 (s, 2 H), 6.52 (d, J = 3.1 Hz, 1 H), 6.58 (d, J = 7.9 Hz, 1 H), 6.85 (d, J = 12.7 Hz, 1 H), 7.08 (d, J = 3.1 Hz, 1 H), 7.42 (s, 1 H), 7.53 (m, 3 H), 7.85 (m, 2 H), 8.09 (s, 1 H); MS-DCI m/e 561 (p + 1, 100). Anal. ($C_{32}H_{36}N_2O_5S$) C, H, N.

The synthesis of the required starting material **9b** (R = 1-ethylpentyl) is described for the preparation of sulfonimide **58**.

***N*-[4-[[6-(2-Ethylhexanamido)indol-1-yl]methyl]-3-methoxybenzyl]benzenesulfonamide (73).** To a solution of amine **31** (307 mg, 0.73 mmol) and 2,6-lutidine (0.83 mg, 0.77 mmol) in dry dichloromethane was added cyclopentyl chloroformate (110 mg, 0.74 mmol), and the reaction was warmed to room temperature overnight. The dichloromethane was removed by evaporation, and the residue was dissolved in ethyl acetate. The ethyl acetate was washed with dilute aqueous acid, water and saturated brine and dried ($MgSO_4$). The residue was purified by chromatography and the appropriate fractions were combined and recrystallized from methanol/water to give sulfonamide **73** as a white solid in 38% yield: mp 194–195.0 °C; ^{1}H NMR (DMSO) 1.75 (m, 8 H), 3.78 (s, 3 H, OCH_3), 3.96 (d, J = 6 Hz, 2 H), 5.07 (m, 1 H), 5.17 (s, 2 H), 6.36 (d, J = 3 Hz, 1 H), 6.55 (d, J = 8.5 Hz, 1 H), 6.60 (d, J = 10 Hz, 1 H), 6.83 (s, 1 H), 7.00 (d, J = 10 Hz, 1 H), 7.27 (d, J = 3 Hz, 1 H), 7.45 (d, J = 16.5 Hz, 1 H), 7.51 (m, 3 H), 7.71 (m, 3 H), 8.14 (t, 6.8 Hz, 1 H, $NHSO_2$), 9.41 (s, 1 H, CONH); MS-DCI (isobutane) m/e 534 (p + 1, 14), 448 (100). Anal. ($C_{29}H_{31}N_3O_5S$) C, H, N.

The starting amine **31** was prepared as follows: (a) A solution of nitrile **15a** (1.2 g, 3.9 mmol) in THF (10 mL) was added dropwise to a 0 °C solution of borane in THF (15 mL of 1.0 M solution) over 10 min. The reaction was refluxed for 1 h, allowed to stand at room temperature for 1 h, and cooled to 0 °C, and then 6 mL of 12 N HCl was added. The resulting suspension was refluxed for 1 h, stirred at room temperature overnight, cooled to 0 °C, and made basic by the addition of 50% aqueous sodium hydroxide. The THF was removed by evaporation, and the aqueous residue was extracted with dichloromethane. The combined organic layers were washed with water and saturated brine, dried (K_2CO_3), and evaporated. The residue was dissolved in ethanol, saturated HCl in ethyl ether was added, and the mixture was stirred 30 min and filtered to give amine hydrochloride **29** in 76% yield: ^{1}H NMR (DMSO) 3.64 (m, 2 H, CH_2NH_3), 3.89 (s, 3 H, OCH_3), 5.51 (s, 2 H, indole–CH_2–), 7.75 (m, 11 H, aromatic and NH_3^+).

(b) To a 0 °C solution of amine hydrochloride **29** (1.0 g, 2.9 mmol) and 2,6-lutidine in THF (15 mL) was added benzenesulfonyl chloride (511 mg, 2.9 mmol), and the mixture was stirred for 1 h at 0 °C. The reaction was warmed to room temperature, and DMF (15 mL) was added, and the reaction was stirred for 24 h. Over the course of the next 2.5 h, 80 mg of sodium hydride was added, and the reaction was stirred an additional 3 h. The THF was removed by evaporation, and the reaction was partitioned between ethyl ether and water. The aqueous layer was extracted with ethyl ether, and the combined organic was washed with water and saturated brine and evaporated. The residue was purified by chromatography (silica 32 g) by using gradient elution of ethyl acetate/toluene 1:15, 1:10, 1:5 (v/v) to give sulfonamide **30** in 25% yield: ^{1}H NMR ($CDCl_3$) 3.81 (s, 3 H, OCH_3), 4.12 (d, 2 H, CH_2NH), 4.68 (bt, 1 H, NH), 5.31 (s, 2 H, indole–CH_2–Ar), 6.86 (m, 4 H, aromatic), 7.87 (m, 9 H, aromatic).

(c) To a Paar bottle containing preadsorbed hydrogen on 33 mg of 10% Pd/C in ethyl acetate was added sulfonamide **30** (330 mg, 0.73 mmol). After 3.5 h, 64 mg of 10% Pd/C was added, and after 16 h an additional 34.5 mg was added. Three hours after the last addition of catalyst, the reaction was filtered through Celite, the solvent was evaporated, and the product amine **31** was used directly for the next reaction.

6-Hexanamido-1-[2-methoxy-4-(1*H*-tetrazol-5-yl)benzyl]-indole (80). General Example of Route 5.a: Synthesis of Tetrazole Amides 20 (R = Alkyl). A mixture of 189 mg of 6-hexanamido-1-(4-cyano-2-methoxybenzyl)indole (**17b**, R = pentyl), 99 mg of sodium azide, 105 mg of triethylamine hydrochloride, and 3.7 mL *N*-methylpyrrolidone was stirred at 150 °C under nitrogen for 3.5 h. After cooling, the reaction mixture was diluted with 20 mL of water, acidified to pH 1 with 10% v/v hydrochloric acid, and extracted with ethyl acetate. The organic layer was extracted with 10% w/v sodium hydroxide. The alkaline extract was washed with ethyl ether and then acidified. Ethyl acetate extraction of this acidified aqueous layer gave, upon evaporation, a solid which was recrystallized from aqueous methanol to yield 90 mg (43%) of tetrazole **80**: mp 210–212 °C; ^{1}H NMR (DMSO) 0.84 (t, J = 7.5 Hz, 3 H, CH_3), 1.30 (m, 4 H), 1.56 (m, 2 H), 2.27 (t, J = 7.5 Hz, 2 H, $-CH_2CO-$), 4.01 (s, 3 H, OCH_3), 5.36 (s, 2 H, indole–CH_2–Ar), 6.44 (d, J = 4.5 Hz, 1 H), 6.74 (d, J = 7.5 Hz, 1 H), 7.10 (d, J = 7.5 Hz, 1 H), 7.41 (d, J = 4.5 Hz, 1 H), 7.48 (m, 2 H), 7.68 (s, 1 H), 7.86 (s, 1 H), 9.77 (s, 1 H); MS-DCI (isobutane) m/e 419 (p + 1, 24.1), 231 (100). Anal. ($C_{23}H_{26}N_6O_2$) C, H, N.

The starting amido nitrile **17b** (R = pentyl) was prepared as follows: (a) A yellow solution of 5.2 g of 6-nitroindole (**32b**) in 150 mL of ethyl acetate was added to 1.25 g of prereduced 10% w/w palladium on charcoal in 50 mL of ethyl acetate. The mixture was shaken under 3.45 bar of hydrogen overnight and then filtered through diatomaceous earth. The residue was washed with 150 mL of hot chloroform, and the combined colorless filtrate and washings were evaporated to give a quantitative yield of 6-aminoindole (**2b**) as a dark oil; ^{1}H NMR 3.5 (br s, 2 H, NH_2), 6.4 (m, 1 H, H^3), 6.5 (m, 2 H, H^5 + H^7), 7.0 (dd, 1 H, H^2), 7.4 (d, 1 H, H^4), 7.8 (br, 1 H, NH).

(b) A solution of 4.24 g of 6-aminoindole (**2b**) in 300 mL of methylene chloride was stirred at 0 °C, and 5.4 mL of triethylamine followed by 4.2 mL of hexanoyl chloride was then added. The dark mixture was stirred for 1 h and then filtered to remove a white precipitate. The filtrate was diluted with methylene chloride, washed sequentially with 10% w/v sodium hydrogen sulfate water, and brine, dried ($MgSO_4$), and evaporated. The residue was crystallized from ethyl acetate and hexane to give 6-hexanamidoindole (**3b**, R = pentyl) as a white solid. Partial evaporation of the mother liquor gave a second crop of solid, giving a combined yield of 4.5 g (65%): ^{1}H NMR 0.9 (t, 3 H, CH_3), 1.4 (m, 4 H, $CH_3CH_2CH_2$), 1.8 (m, 2 H, $COCH_2CH_2$), 2.4 (t, 2 H, $COCH_2$), 6.5 (m, 1 H, H^3), 6.8 (dd, 1 H, H^5), 7.2 (m, 2 H, CON*H* + H^2), 7.5 (d, 1 H, H^4), 8.1 (bs, 1 H, H^7), 8.3 (br, 1 H, NH).

The starting bromo nitrile **19** was prepared as follows:

(c) To a stirred suspension of 9.97 g of 3-methoxy-4-methylbenzoic acid in 18 mL of methylene chloride heated to reflux under nitrogen was added dropwise over 45 min a solution of 5.35 mL of chlorosulfonyl isocyanate (1.025 equiv) in 3 mL of methylene chloride. The resulting homogeneous, bright red solution was heated under reflux for 45 min, chilled in an ice bath, and treated dropwise with 9.5 mL of dimethylformamide over 15 min. After stirring for 30 min at 0 °C, the orange solution was poured onto ice. The organic layer was separated, washed five times with 20 mL of water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a Waters 500 HPLC (SiO_2, 10% (v/v) hexane in toluene) to give 5.28 g (60%) of 3-methoxy-4-methylbenzonitrile (i2) as a white solid, mp 51–52.5 °C.

(d) A solution of 2.65 g of 3-methoxy-4-methylbenzonitrile (i2) in 90 mL of dry carbon tetrachloride was treated with 3.20 g of *N*-bromosuccinimide and 5 mg of benzoyl peroxide. The mixture was then heated to reflux for 15 min with a 250-W tungsten lamp. The cooled reaction mixture was diluted with 90 mL of petroleum ether (bp 60–80 °C), insoluble material was removed by filtration, and the filtrate was evaporated. The solid residue was recrys-

tallized from methylene chloride/petroleum ether to give 2.64 g (65%) of 4-(bromomethyl)-3-methoxybenzonitrile (**19**) as a white solid, mp 87–91 °C.

(e) To a stirred slurry of 24 mg of sodium hydride (hexane washed) in dry dimethylformamide (DMF) (1 mL) at 0 °C was added a solution of 200 mg of 6-hexanamidoindole (**3b**, R = pentyl) in dry DMF (2 mL) and the mixture was stirred 15 min at 0 °C and then 30 min at room temperature. After the mixture was cooled to 0 °C, 216 mg of 4-(bromomethyl)-3-methoxybenzonitrile (**19**) in 3 mL of DMF was added, and the reaction was stirred for 15 minutes at 0 °C and then warmed to room temperature. After the reaction was stirred for 3.5 h at room temperature, an additional 6 mg of sodium hydride was added and stirring continued for 45 min. The reaction was quenched by addition of saturated ammonium chloride, poured into water, and extracted with ethyl ether. The combined extracts were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by chromatography on 16 g of silica gel by eluting with dichloromethane to give 196 mg (60% yield) of 6-hexanamido-1-(4-cyano-2-methoxybenzyl) indole (**17b**, R = pentyl) as a solid, mp 136–138 °C.

6-[(Butoxycarbonyl)amino]-1-[2-methoxy-4-(1*H*-tetrazol-5-yl)benzyl]indole (81). General Example of Route 5.b: Synthesis of Tetrazole Urethanes 20b (R = Alkoxy). A solution of 4.0 g of 6-amino-1-[2-methoxy-4-(1*H*-tetrazol-5-yl)-benzyl]indole (**18b**) in a mixture of 10 mL of *N*-methylpyrrolidone, 10 mL of tetrahydrofuran, and 2.2 mL of 2,6-lutidine was added dropwise to a stirred, ice-cooled solution of 2.57 g of butyl chloroformate in 10 mL of tetrahydrofuran, maintained under a nitrogen atmosphere. The mixture was allowed to attain room temperature during 2 h and then left for 14 h. Solid was removed by filtration, and the filtrate was concentrated under reduced pressure. The oily residue was dissolved in 35 mL of 20% w/v potassium carbonate solution, basified to pH 10 with 10% w/v sodium hydroxide solution, and extracted with ethyl acetate. These extracts were discarded. The aqueous phase was acidified to pH 1 with 6 M hydrochloric acid and reextracted with ethyl acetate. These extracts were combined, washed with water and then with saturated brine, dried ($MgSO_4$), and evaporated. The solid residue was recrystallized from ethyl acetate to give 2.8 g (54%) of tetrazole **81** as a yellow powder: mp 194–195 °C; ^{1}H NMR (DMSO) 0.86 (t, J = 5.5 Hz, 3 H), 1.35 (m, 2 H), 1.56 (m, 2 H), 4.00 (s, 3 H, OCH_3), 4.04 (t, J = 7.5 Hz, 2 H, OCH_2), 5.33 (s, 2 H, indole-CH_2-Ar), 6.42 (d, J = 4 Hz, 1 H), 6.78 (d, J = 9 Hz, 1 H), 7.03 (d, J = 9 Hz, 1 H), 7.38 (d, J = 3 Hz, 1 H), 7.44 (d, J = 9 Hz, 1 H), 7.50 (d, J = 7.5 Hz, 1 H), 7.65 (s, 1 H), 7.68 (s, 1 H), 9.46 (s, 1 H); MS-DCI (isobutane) m/e 421 (p + 1, 30), 161 (100). Anal. ($C_{22}H_{24}N_6O_3$) C, H, N.

The starting material **18b** was obtained as follows: (a) A slurry of 6-nitroindole **32b** (510 mg, 3.1 mmol), 4-(bromomethyl)-3-methoxybenzonitrile **19** (771 mg, 3.4 mmol), and potassium carbonate (474 mg, 3.4 mmol) in dry acetone (10 mL) was refluxed overnight. The reaction was diluted with ethyl acetate and filtered, and the solvent was evaporated. The residue was purified by chromatography (100 g silica) by eluting with 90/10 v/v chloroform/hexanes to give 1-(4-cyano-2-methoxybenzyl)-6-nitroindole (**15b**) as a solid 90% yield, mp 190.5–191 °C.

(b) The nitrile **15b** was converted to the corresponding tetrazole, 1-[2-methoxy-4-(1*H*-tetrazol-5-yl)benzyl]-6-nitroindole (**16b**), obtained in 86% yield as a yellow-green solid, mp 258–260 °C dec, via the general procedure described for tetrazole **80**.

(c) A solution of 4.76 g of indole **16b** in 2.3 mL of 6 M potassium hydroxide solution and 180 mL of methanol was treated with 480 mg of 10% w/w palladium on charcoal and then hydrogenated at a pressure of 3.45 bar for 2 h. Catalyst was removed by filtration through diatomaceous earth, and the filtrate was evaporated. Treatment of the residual oil with saturated monobasic sodium phosphate solution produced a precipitate which was collected and dried to give 6-amino-1-[2-methoxy-4-(1*H*-tetrazol-5-yl)-benzyl]indole (**18b**) in quantitative yield as a grey powder: ^{1}H NMR 4.0 (s, 3 H, OCH_3), 5.2 (s, 2 H, NCH_2), 6.3 (d, 1 H, H^3-indole), 6.4 (d, 1 H, H^5-indole), 6.5 (s, 1 aromatic H), 6.7 (d, 1 aromatic H), 7.1 (d, 1 H, H^2-indole), 7.2 (d, 1 H, H^4-indole), 7.5 (d, 1 aromatic H), 7.7 (s, 1 H, H^7-indole).

6-[(Butyloxycarbonyl)amino]-1-[2-methoxy-4-(1*H*-tetrazol-5-yl)benzyl]indazole (85). General Example of Route 5.b: Synthesis of Tetrazole Urethanes 20a (R = Alkoxy). 6-Amino-[2-methoxy-4-(1*H*-tetrazol-5-yl)benzyl]indazole (**18a**) was acylated with butyl chloroformate via the procedure described for tetrazole **81** to give tetrazole **85** in 40% yield as a white solid: mp 210.5–211.5 °C dec: ^{1}H NMR (DMSO) 3.98 (s, 3 H, OCH_3), 4.09 (t, J = 6.0 Hz, 2 H, -OCH_2-), 5.50 (s, 2 H, indazole-CH_2-Ar), 9.83 (s, 1 H); MS-DCI m/e 422 (p + 1, 7), 348 (78), 160 (100).

The starting material **18a** was obtained as follows: (a) 4-[(6-Nitroindazol-1-yl)methyl]-3-methoxybenzonitrile (**15a**) was obtained in 24% yield as a solid, mp 207–208 °C, from sodium 6-nitroindazolide and 4-(bromomethyl)-3-methoxybenzonitrile **19** via an analogous procedure to that described for **17b** in the preparation of tetrazole **80**.

(b) 1-[2-Methoxy-4-(1*H*-tetrazol-5-yl)benzyl]-6-nitroindazole (**16a**) was obtained in 98% yield as a solid, mp 152–153.5 °C dec, by reaction of benzonitrile **15a** with sodium azide and triethylamine hydrochloride in *N*-methylpyrrolidone at 150 °C for 3 h under an atmosphere of nitrogen by using the procedure described for tetrazole **80**.

(c) 6-Amino-1-[2-methoxy-4-(1*H*-tetrazol-5-yl)benzyl]indazole (**18a**) was obtained in 79% yield as a pale yellow solid, mp 247–248 °C dec, by 10% w/w palladium-on-charcoal catalyst hydrogenation (1.1 bar for 2 h) of the nitro compound (**16a**), via the procedure described for **18b** in the preparation of tetrazole **81**.

***N*-[4-[[6-(2-Phenylbutanamido)indazol-1-yl]methyl]-3-methoxybenzoyl]benzenesulfonamide (90).** Sodium hydride, 48 mg, (50% w/w dispersion in mineral oil) was washed twice with petroleum ether (bp 40–60 °C) and suspended in 2 mL of dry dimethylformamide (DMF). The reaction vessel was flushed with nitrogen and 188 mg benzenesulfonamide added. The mixture was stirred for 30 minutes until effervescence had stopped. A solution of 260 mg of 3-methoxy-4-[[6-(2-phenylbutanamido)-indazol-1-yl]methyl]benzoic *N,N*-diphenylcarbamic anhydride (**9a**) (R = 1-phenylpropyl) in 1 mL of DMF was then added and the mixture stirred for 30 min. The reaction mixture was diluted with 30 mL of ethyl acetate and washed successively with 5 mL of 1 M hydrochloric acid, 5 mL of water (2×), and 5 mL of saturated brine, then dried ($MgSO_4$), and evaporated. The residue obtained was purified by flash chromatography, by using 30% v/v ethyl acetate in toluene containing 1% v/v acetic acid as eluent, to give a solid which was recrystallized from ethyl acetate/petroleum ether (bp 60–8 °C). There was thus obtained 161 mg (69%) of sulfonamide **90** as a white solid: mp 140–141 °C; ^{1}H NMR (DMSO) 3.57 (t, 1 H), 3.92 (s, 3 H, OCH_3), 5.51 (s, 2 H, indazole-CH_2-Ar) 8.12 (s, 1 H, -CONH-), 10.26 (s, 1 H, -$NHSO_2$-); MS-DCI m/e 583 (p + 1, 46), 426 (86), 143 (100). Anal. ($C_{32}H_{30}N_4O_5S$) C, H, N.

The starting *N,N*-diphenylcarbamic anhydride was obtained as follows:

A mixture of 177 mg of 3-methoxy-4-[[6-(2-phenylbutanamido)indazol-1-yl]methyl]benzoic acid,[4] 2.5 mL of methanol, and 0.4 mL of 1 M sodium hydroxide solution was added to a solution of 149 mg of (*N,N*-diphenylcarbamoyl)pyridinium chloride in 0.8 mL of methanol. The reaction mixture was stirred for 20 min and diluted with 30 mL of ethyl acetate. The mixture was then washed with 5 mL of water and then with 5 mL of brine, dried ($MgSO_4$), and evaporated to give 260 mg of 3-methoxy-4-[[6-(2-phenylbutanamido)indazol-1-yl]methyl]benzoic *N,N*-diphenylcarbamic anhydride (**9a**) (R = 1-phenylpropyl) as a yellow oil, essentially pure by TLC (retention factor value = 0.8 on SiO_2; eluent 50% v/v ethyl acetate/toluene containing 2% acetic acid) and which was used without further purification or characterization.

***N*-(4-[[6-[(Cyclopentyloxycarbonyl)amino]indazol-1-yl]-methyl]-3-methoxybenzoyl)benzenesulfonamide (92) (ICI-198615). General Example of Synthesis of Sulfonamides from Carboxylic Acids by Using Water Soluble Carbodiimide.** 4-[[6-[(Cyclopentyloxy)carbonyl)amino]indazol-1-yl]-methyl]-3-methoxybenzoic acid,[4] 204 mg, was added to a stirred solution of 79 mg of benzenesulfonamide, 4-(dimethylamino)-pyridine, and 96 mg of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride in 5 mL of dry methylene chloride. After 15 min the mixture became homogeneous. It was stirred for a further 18 h, then diluted with 20 mL of methylene chloride and washed successively with 20-mL portions of 1 M hydrochloric acid, water, and saturated brine. The solution was then dried ($MgSO_4$) and evaporated to give 278 mg of amorphous solid. This

was crystallized from a mixture of methylene chloride, ethyl ether, and petroleum ether (bp 40–60 °C) to give 184 mg (67%) sulfonamide **92** as a white solid: mp 181–182.5 °C; ^{1}H NMR (DMSO) 3.93 (s, 3 H, OCH_3), 5.08 (m, 1 H), 5.50 (s, 2 H, indazole-CH_2–Ar), 9.75 (s, 1 H, -$NHSO_2$–); MS-DCI *m/e* 549 (p + 1, 20), 463 (22), 184 (100). Anal. ($C_{28}H_{28}N_4O_6S$) C, H, N.

Biological Evaluation Procedures. In vitro activity was assessed on guinea pig tracheal strips. Guinea pigs were killed by a sharp blow to the head, followed by exsanguination, and the trachea was removed and cut into spiral strips. Each trachea was divided into two sections for paired experiments. Each section was placed in a jacketed, 10-mL, tissue bath maintained at 37 °C and bathed with modified Kreb's buffer which was bubbled with 95% O_2 and 5% CO_2. The Kreb's buffer consisted of the following composition (mM); NaCl (119), KCl (4.6), $CaCl_2$ (1.8), $MgCl_2$ (0.5), $NaHCO_3$ (24.9), NaH_2PO_4 (1.0), and glucose (11.1). The bath fluid also contained indomethacin (5 μM). Isometric tension was monitored via a Grass Force Displacement Transducer and displayed on a Beckman Dynograph (Model R 612). Resting tension was set at 2 g, and the tissues were allowed to stabilize for 60 min during which time the bath fluid was changed every 15 min.

The ability of test compounds to inhibit the LTE_4 (8 nM) contractile response was assessed as follows: After a 60-min equilibration period, the tissues were challenged with 8 nM LTE_4 for 10 min, and the responses were recorded. Following washout and reequilibration (25 min) the tissues were again exposed to 8 nM LTE_4, and the response was recorded. After reproducible control responses to 8 nM LTE_4 were obtained, the test compound was added to the bath at selected concentrations for 10 min. Any significant change in resting tension after the 10-min incubation period was noted. In the presence of test compounds the tissues were challenged with 8 nM LTE_4, and the contractile response was recorded. The paired sections of trachea received vehicle to serve as control. Percent inhibition was determined by the following equation:

$$\% \text{ inhibition} = [(2\text{nd } LTE_4 - 3\text{rd } LTE_4)/2\text{nd } LTE_4] \times 100$$

An adjusted % inhibition was determined by subtracting the % inhibition obtained with the vehicle treated tissues from that obtained with the drug treated tissues. Significant differences ($p < 0.05$) between the contractile response of the second and third LTE_4 challenges were determined by using the Student's paired *t* test.[50] All tests were run on a minimum of four tracheal spirals. Reproducibility was, in general, ≤ 20% of the mean. To determine specificity of these compounds as leukotriene antagonists, a similar protocol was established where $BaCl_2$ (1.5 mM) was substituted for LTE_4 as the agonist.

In vitro potencies of the more active compounds were evaluated further in isolated guinea pig tracheal strips by using cumulative concentration–response curves to determine dissociation constants (K_B) for the antagonists. LTE_4 concentration–response curves were obtained by addition of the agonist to the tissue bath to establish log increments of bath agonist concentration over a particular range according to the method of van Rossum.[51] Each successive concentration was added only after the plateau of the contraction, due to the preceding agonist concentration, was reached. Contractile responses were expressed as a percentage of the response obtainable to a maximally effective concentration of carbachol (30 μM) which was added to the bath after the 60-min stabilization period. Following the carbachol challenge, the tissues were washed and allowed 60 min to restabilize to baseline tension before the LTE_4 concentration–response curves were begun. EC_{50} values, the molar concentration of agonist required to produce a contraction equal to 50% of the maximal response, were derived by linear regression.[50] The test compound was incubated for 30 min prior to starting the curves. Paired control tissues received vehicle. EC_{50} values were determined in the absence and presence of test compound and significance ($p < 0.05$) was established with the Student's paired *t* test. Dissociation constants for the receptor–antagonist complex were calculated by the method of Furchgott[52] by using the equation: K_B = [antagonist]/(dose ratio - 1). The dose ratio (DR) represents the EC_{50} value in the presence of antagonist divided by the EC_{50} value in the absence of antagonist. Only one concentration–response curve was obtained from each tissue.

In vivo activity of selected compounds was evaluated in spontaneously breathing, conscious guinea pigs challenged with aerosolized LTD_4 as described by Snyder.[34] Six guinea pigs were secured in a circular, plexiglass chamber via neck yokes. The head of each guinea pig was enclosed in separate exposure chambers fitted with a glass tube for delivery of aerosolized solutions of the agonist. Aerosolization was accomplished with either a Monaghan (Model 650) or a Pulmosonic (Devilbis, Model 25) ultrasonic nebulizer. Air flowing at a rate of 2 L per min carried the agonist to each exposure chamber. The median droplet size produced in the exposure chamber by either nebulizer was 5.55 ± 0.43 μm, as measured with a Malvern 2600C Droplet and Particle Sizer. The guinea pigs were pretreated with indomethacin (10 mg/kg, ip) and propranolol (5 mg/kg, ip) and then positioned in the chamber for a 30-min acclimation period prior to the aerosol challenge.

The challenge consisted of an aerosolized solution of LTD_4 (60 μM) delivered for a maximum time of 5 min during which time changes in the breathing patterns of the guinea pigs were visually monitored. The end point was defined as a consistent, slow, deep, deliberate respiratory pattern with marked involvement of the abdominal muscles. Time, in seconds, to reach the end point was determined for each guinea pig, and percent protection was calculated using the following equation:

$$\% \text{ protection} = [(\text{drug time} - \text{mean control time})/(\text{maximal aerosol time} - \text{mean control time})] \times 100$$

Mean control time was the time to dyspnea for all vehicle-treated animals run concomitantly with a given compound. The animals in each run were pretreated with compound or vehicle at the indicated times prior to LTD_4 challenge. At least two vehicle-treated animals were contained in each test run and the experimenter was blind as to treatment groups. Differences in means between the drug group and vehicle group were compared using Student's unpaired *t* test with $p < 0.05$ considered significant.

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Supplementary Material Available: Appendix A: Tables for K_B and pK_i values (3 pages). Ordering information is given on any current masthead page.

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