Evolution of a Series of Peptidoleukotriene Antagonists: Synthesis and Structure-Activity Relationships of 1,6-Disubstituted Indoles and Indazoles

Frederick J. Brown,* Ying K. Yee,* Laura A. Cronk, Kevin C. Hebbel, Robert D. Krell,† and David W. Snyder†,‡

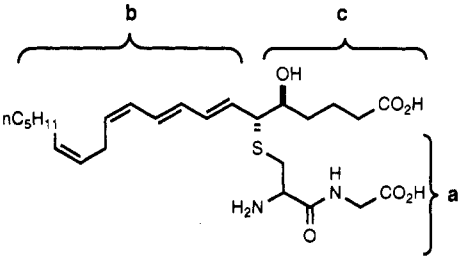
Departments of Medicinal Chemistry and Pharmacology, ICI Pharmaceuticals Group, A Business Unit of ICI Americas Inc., Wilmington, Delaware 19897. *Received October 16, 1989*

A perception of structural similarities between two independent series of leukotriene antagonists (one emanating from FPL 55712 and one based upon the leukotrienes themselves) led to the discovery of a novel class of indole and indazole derived antagonists of peptidoleukotrienes. A systematic exploration of C-6 substituted 4-(indol-1-ylmethyl)-3-methoxybenzoic acids identified cyclopentylacetamide and cyclopentylurethane as preferred substituents. The corresponding indazoles were equipotent. These compounds are selective leukotriene antagonists with pK_B values of 7.5-7.8 vs LTE_4 on guinea pig trachea.

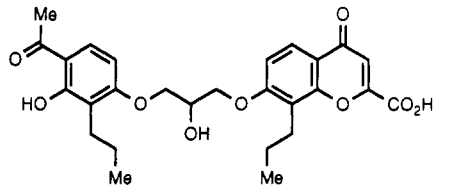
The peptidyl leukotrienes (LTC_4, LTD_4, and LTE_4), collectively known as the slow-reacting substance of anaphylaxis (SRS-A), exert profound pharmacological effects on respiratory smooth muscle contractility[1] and microvascular permeability.[2] These potential pathophysiological agents have been implicated in several human disorders, one of the more prominent ones being asthma.[3] Indeed, the administration of leukotrienes to human volunteers has evoked asthmatic symptoms.[4] The identification of leukotriene receptors in human lung tissue[5] has spurred interest in the development of leukotriene antagonists as potential therapeutic agents for combating the asthmatic condition.[6]

A report of the discovery of a SRS-A antagonist at Fisons Corp. in 1977[7] and the subsequent elucidation of the structures of the leukotrienes (Chart I) in 1980[8] set the stage for further developments in the leukotriene field. The ensuing chemical designs for better antagonists have evolved from these two structural leads. Fisons' prototypical antagonist FPL 55712 (Chart I), a hydroxyacetophenone-chromone, never advanced beyond the stage of a valuable pharmaceutical tool, primarily because of a short biological half-life. However, over the past decade many other hydroxyacetophenones derived from FPL 55712 have been evaluated as leukotriene antagonists.[9] Other investigators have made structural modifications to the leukotrienes themselves so as to develop more stable analogues exhibiting antagonist properties.[10] We report herein how elements from these two distinct approaches to the design of leukotriene antagonists were combined in a series of indazoles and indoles to generate novel and selective antagonists.

Chart I. Leads from Which Leukotriene Antagonists Have Evolved



LTD_4, 1



FPL 55712

Biological Evaluation Procedures

The biological activity of the leukotriene antagonists described herein was determined by their ability to inhibit LTE_4-induced contractions of guinea pig tracheal strips. LTE_4 was favored as the agonist because of its selectivity for one of the two LTD_4 receptors found in guinea pig trachea[5c] and the apparent pharmacological similarity of this receptor to the single human airway peptidoleukotriene receptor.[5a]

For compounds of special interest, selectivity for antagonism of the leukotriene-induced contraction was determined by comparison with the concentration required to inhibit contractions induced by the nonspecific agonist barium chloride. The in vitro potency of selected compounds was further defined by the construction of cumulative concentration-response curves (guinea pig tracheal strips, LTE_4 as agonist) to determine dissociation constants (K_B) for the antagonists.

Preliminary in vivo evaluation of selected antagonists was carried out in spontaneously breathing, conscious

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(5) (a) Lewis, M. A.; Mong, S.; Vessella, R. L.; Hogaboom, G. K.; Wu, H.-L.; Crooke, S. T. *Prostaglandins* **1984**, *27*, 961. (b) Buckner, C. K.; Krell, R. D.; Laravuso, R. B.; Coursin, D. B.; Bernstein, P. R.; Will, J. A. *Pharmacol. Exp. Ther.* **1986**, *237*, 558. (c) Krell, R. D.; Tsai, B. S.; Berdoulay, A.; Barone, M.; Giles, R. E. *Prostaglandins* **1983**, *25*, 171.
(6) (a) Krell, R. D.; Brown, F. J.; Willard, A. K.; Giles, R. E. *The Leukotrienes, Chemistry, and Biology*; Chakrin, L. W., Bailey, D. M., Eds.; Academic: Orlando, FL, 1984; Chapter 11. (b) Brooks, D. W.; Bell, R. L.; Carter, G. W. *Annu. Rep. Med. Chem.* **1988**, *23*, 69.
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(8) Hammarstrom, S.; Samuelsson, B.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Corey, E. J. *Biochem. Biophys. Res. Commun.* **1980**, *92*, 946.
(9) For some prominent examples, see: (a) Fleisch, J. H.; Rinkema, L. E.; Haisch, D. D.; Swanson-Bean, D.; Goodson, T.; Ho, P. P. K.; Marshall, W. S. *J. Pharm. Exp. Ther.* **1985**, *233*, 148. (b) Young, R. N.; Belanger, P.; Champion, E.; DeHaven, R. N.; Denis, D.; Ford-Hutchinson, A. W.; Fortin, R.; Frenette, R.; Gauthier, J. Y.; Gillard, J.; Guindon, Y.; Jones, T. R.; Kakushima, M.; Masson, P.; Maycock, A.; McFarlane, C. S.; Piechuta, H.; Pong, S. S.; Rokach, J.; Williams, H. W. R.; Yoakim, C.; Zamboni, R. *J. Med. Chem.* **1986**, *29*, 1573.

† Department of Pharmacology.
‡ Present address: Lily Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285.

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Scheme I. The Discovery of Indazole and Indole Leukotriene Antagonists

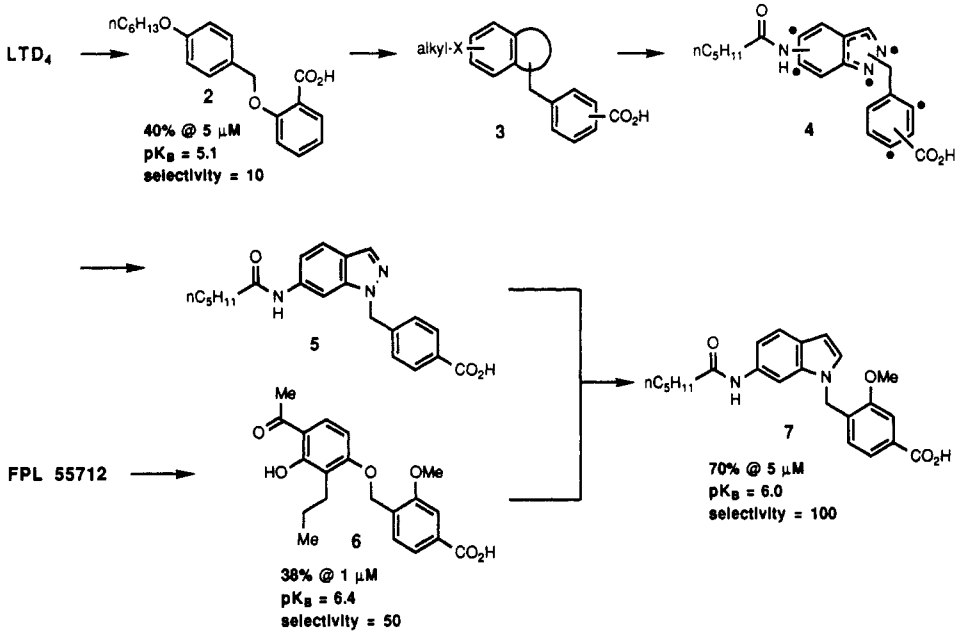
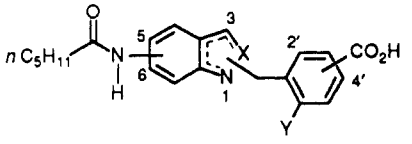


Table I. (Hexanamidoheterocyclyl)toluic Acids[a]



no.	amide position	X	toluic acid position	CO_2H position	Y	% inhibition/ concentration, μM[b]	mp, °C	microanalysis[c]
13	5	N	1	2′	H	NS[d]/10	207–8	$C_{21}H_{23}N_3O_3$
14	5	N	1	4′	H	NS/10	226.5–8 dec	$C_{21}H_{23}N_3O_3$
15	5	N	2	2′	H	13/10	205.5–7	$C_{21}H_{23}N_3O_3$
16	5	N	2	4′	H	NS/10	226.5-7.5	$C_{21}H_{23}N_3O_3 \cdot 0.25H_2O$
17	6	N	1	2′	H	NS/10	209.5–10.5	$C_{21}H_{23}N_3O_3$
5	6	N	1	4′	H	62/10	215–215.5	$C_{21}H_{23}N_3O_3$
18	6	N	2	2′	H	NS/10	203.5–4.5	$C_{21}H_{23}N_3O_3$[f]
19	6	N	2	4′	H	NS/10	182–5	$C_{21}H_{23}N_3O_3 \cdot 0.25H_2O$
20	7	N	1	4′	OCH_3	NS/10	234–5	$C_{22}H_{25}N_3O_4 \cdot 0.75H_2O$
7[e]	6	CH	1	4′	OCH_3	70/5	221–3 dec	$C_{23}H_{26}N_2O_4$
21	4	CH	1	4′	OCH_3	29/10	204–5	$C_{23}H_{26}N_2O_4$

[a] These compounds were prepared via synthetic method 1 (see Scheme II). [b] Percent inhibition of the LTE_4-induced contraction of guinea pig tracheal spirals by antagonist at the indicated concentration as compared to that of paired control tissues. Results are statistically significant ($p < 0.05$, $n \geq 4$) unless otherwise indicated. Details of the test are provided in the Experimental Section. [c] Elemental analyses for carbon, hydrogen, and nitrogen are within ±0.4% of the theoretical values for the formula indicated. [d] NS indicates the percent inhibition was low and not statistically significant ($p > 0.05$) at the indicated concentration. [e] Synthetic details for the intermediates leading to this compound appear in the Experimental Section. [f] N: calcd, 11.50; found, 12.17.

guinea pigs challenged with aerosolized LTD_4. Percent protection at a given dose and pretreatment time was determined by comparison of the time required for the challenged animals to exhibit labored abdominal breathing in the presence and absence of the compounds.

All of these biological procedures are described more fully in the Experimental Section.

Origins of the Indazole/Indole Series

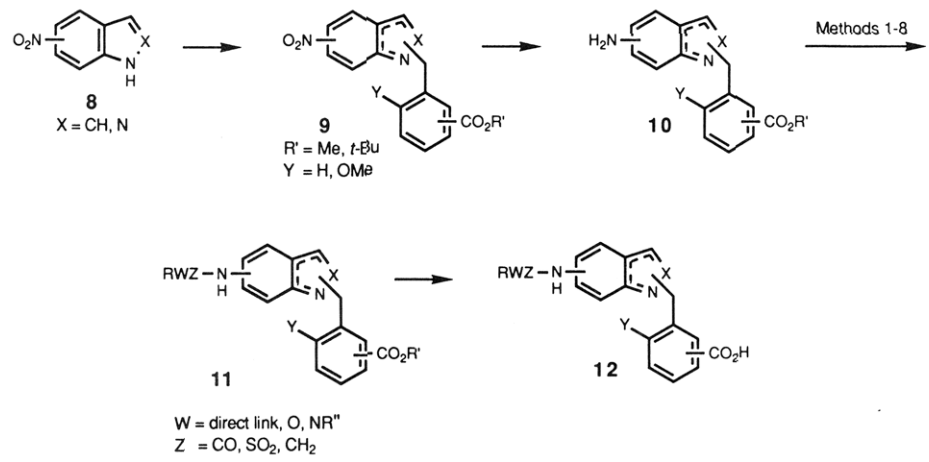
The molecular structure of LTD_4 (1) can be dissected into three distinct domains: the peptide fragment (**1a**), the lipophilic tetraene portion (**1b**), and the C-1 to C-6 acid-bearing segment (**1c**). In conjunction with an investigation of leukotriene analogues,[11a] a series of antagonists was designed to mimic just the lipophilic tetraene and carboxylic acid portions of the leukotrienes. Structure–activity optimization[11b] led to benzyl ether **2** (Scheme I). In an effort to increase the potency of compound **2**, we decided to restrict the conformational freedom of the benzylic ether group.[12] One of several approaches envi-

(10) For a clinical candidate, see: Gleason, J. G.; Hall, R. F.; Perchonock, C. C.; Erhard, K. F.; Frazee, J. S.; Ku, T. W.; Kondrad, K.; McCarthy, M. E.; Mong, S.; Crooke, S. T.; Chi-Rosso, G.; Wasserman, M. A.; Torphy, T. J.; Muccitelli, R. M.; Hay, D. W.; Tucker, S. S.; Lynne, V.-C. *J. Med. Chem.* **1987**, *30*, 959.

(11) (a) Bernstein, P. R.; Snyder, D. W.; Adams, E. J.; Krell, R. D.; Vacek, E. P.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 2477. (b) Brown, F. J.; Bernstein, P. R.; Hesp, B.; Willard, A. K.; Yee, Y. K.; Krell, R. D.; Giles, R. E.; Snyder, D. W. *A Novel Class of Peptidoleukotriene Antagonists: Discovery and Initial Structure–Activity Characterization.* 193rd National ACS Meeting, Denver, CO, April 5–10, 1987.

(12) For some recent examples of the use of conformational constraints to achieve increased binding affinities, see: (a) Van Wijngaarden, I.; Kruse, C. G.; Van Hes, R.; Van der Heyden, J. A. M.; Tulp, M. T. M. *J. Med. Chem.* **1987**, *30*, 2099. (b) Jaycox, G. D.; Gribble, G. W.; Hacker, M. P. *J. Heterocycl. Chem.* **1987**, *24*, 1405.

Scheme II. Synthetic Methodology



Method. 1. RCOCl, Et_3N
2. RCO_2H, N,N'-carbonyldiimidazole
3. RNCO
4. ROCOCl, Et_3N
5. a) $Cl_3COCOCl$; b) ROH or RR"NH, Et_3N
6. RCO_2H, carbodiimide, 4-(dimethylamino)pyridine
7. RCH_2Br, K_2CO_3
8. RSO_2Cl, Et_3N

sioned incorporating the benzylic carbon of benzyl ether **2** into a fused ring. Thus, we sought a bicyclic framework to which both a lipophilic chain and a benzoic acid group could be readily appended to generate molecules of the general form **3**. Indazoles were chosen as appropriate templates since the toluic acid moiety could be attached at either N-1 or N-2. The availability of nitroindazoles suggested an amide group as a synthetically convenient way of appending the lipophilic moiety.

Eight regioisomeric indazoles **4** were prepared (Table I, **5**, **13**–**19**) in order to provide an assessment of the benefits of introducing conformational rigidity and to define the optimal spatial orientation of the lipophilic and acidic groups. On the basis of the structure–activity relationships which had highlighted ether **2**, it was anticipated that the analogous 1,5-disubstituted indazole isomer with an ortho-substituted benzoic acid (**13**) would be the most active indazole. However, out of the series of eight isomeric indazoles the only compound which exhibited noteworthy activity at 10 μM was the 1,6-disubstituted indazole with a para-substituted benzoic acid (**5**). Indazole **5** possesses a quite different spatial orientation of the lipophilic and acidic appendages compared to that in the original lead **2**. We were intrigued by the singular activity of indazole **5** and sought a rationalization for the unexpected structure–activity relationship.

Concurrently, extensive modifications of the chromone portion of FPL 55712 had led us to a series of hydroxyacetophenone toluic acids in which the 3-methoxy-4-toluic acid moiety of compound **6** proved to be a preferred acidic group.[13] Examination of the structure of the active indazole **5** suggested some possible similarities between the indazole and hydroxyacetophenone series. Of the eight isomeric indazoles, active compound **5** achieved the best atom-for-atom overlap with **6** such that the indicated electron lone pairs of the carbonyl oxygens and the toluic acid moieties of both molecules coincided (Figure 1).

This analysis of a possible relationship between the two different series implied that the incorporation of the important 3-methoxy group from the hydroxyacetophenone series into the toluic acid of indazole **5** might improve

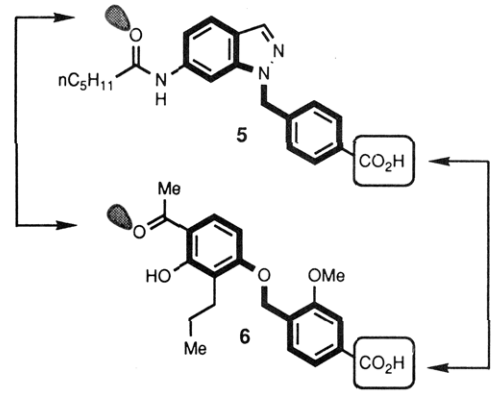


Figure 1. Similarities between indazole **5** and hydroxyacetophenone **6**.

potency. Since the N-2 alkylated isomers **15**, **16**, **18**, and **19** had been inactive, the indazole nucleus was simultaneously replaced by an indole.[14] Indeed, the activity of indazole **5** was surpassed by that of indole **7** (Scheme I). Although indole **7** was still a less potent antagonist than hydroxyacetophenone **6**, its selectivity for the leukotriene receptor was greatly improved over that seen for any of our previous compounds. For example, hydroxyacetophenone **6** blocked contractions of guinea pig trachea induced by the nonspecific spasmogen barium chloride at a concentration only 50 times greater than that required to block LTE_4. In contrast, the corresponding selectivity ratio for indole **7** was 100. It was this superior selectivity, combined with the structural novelty of indole **7**, that encouraged us to undertake an extensive investigation of this new structural class of leukotriene antagonists.

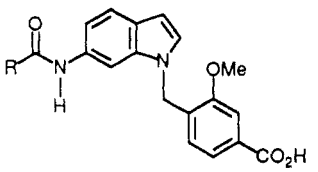
Chemistry

The generalized synthetic route to the substituted indoles and indazoles listed in Tables I–IX is presented in Scheme II. A nitroindole or nitroindazole **8** was alkylated with an ester derived from toluic acid. The nitro group was then hydrogenated to provide amino derivatives **10**, which were convenient intermediates for a variety of

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

(14) For an example of indole–indazole bioisosterism, see: Pawel, F.; Evard, D. A.; Bloomquist, W. E.; Lacefield, W. B.; Pfeifer, W.; Jones, N. D.; Deeter, J.; Cohen, M. L. *J. Med. Chem.* **1987**, *30*, 1535.

Table II. 6-Amidoindoles: Effect of Chain Length[a]



no.	R	% inhibition/ concentration, μM	mp, °C	microanalysis
22	CH_3	NS/0	223–4	$C_{19}H_{18}N_2O_4$
23	$CH_3(CH_2)_2$	42/5	225–8	$C_{21}H_{22}N_2O_4$
24	$CH_3(CH_2)_6$	53/5	200–1	$C_{25}H_{30}N_2O_4 \cdot 0.2H_2O$
25	$CH_3(CH_2)_8$	NS/10	194–6	$C_{27}H_{34}N_2O_4$
26	$CH_3(CH_2)_{10}$	NS/5	194–6	$C_{29}H_{38}N_2O_4$
27	Ph	14/10	231–3 dec	$C_{24}H_{20}N_2O_4$
28	$PhCH_2$	71/5	249–250	$C_{25}H_{22}N_2O_4$
29	$Ph(CH_2)_2$	62/10	225–227	$C_{26}H_{24}N_2O_4$
30	$Ph(CH_2)_3$	73/10	186–8	$C_{27}H_{26}N_2O_4$

[a] These compounds were prepared via synthetic method 1 (see Scheme II).

products (11). Ester hydrolysis provided the desired carboxylic acids 12.

Nitroindazoles were alkylated by the method of Granger,[15] to give N-alkylated products. Both the N-1 and N-2 alkylated isomers 9 were obtained and were separated by chromatography. The isomers could be identified on the basis of their ^{13}C NMR spectra, by analogy with the reported spectra of the two *N*-methyl-6-nitroindazole isomers.[16] The C-3 carbon signal for the N-1 alkylated isomer appears at lower field than the corresponding signal for the N-2 isomer.

Nitroindole alkylation was achieved with potassium carbonate in refluxing acetone. The coupling of 6-nitroindole with bromotoluic esters occurred exclusively on nitrogen. The regiochemistry was apparent from NMR analysis—both the C-2 and C-3 proton resonances were clearly distinguishable at approximately 7.4 and 6.6 ppm, respectively, in deuterated chloroform.

Catalytic hydrogenation of the nitro groups of compounds 9 was often surprisingly sluggish. Prereduction of the catalyst and the use of a 50 psi hydrogen atmosphere ensured complete conversion to amines 10.

The various methodologies used to prepare precursors 11 are presented in Scheme II, and an example of each method is provided in the Experimental Section. The particular method utilized for each compound is identified in Tables I–IX.

The in situ preparation of acid chlorides with thionyl chloride proved troublesome with some of the carboxylic acid reagents required for the synthesis of acylamino compounds 11. Therefore, it was generally more convenient to activate the acids with carbonyldiimidazole. At reaction concentrations of 0.3 M products 11 often precipitated from the reaction solution. The carbonyldiimidazole methodology was used to prepare the two enantiomers of 43 (Table IV). Acylation of methyl 4-[(6-aminoindol-1-yl)methyl]-3-methoxybenzoate with (*R*)-(−)-2-phenylbutanoic acid[17] led to 51 ($[\alpha]_D = -143°$) while acylation with (*S*)-(+)-2-phenylbutanoic acid[17] led to 52 ($[\alpha]_D = +145°$). Chiral shift NMR studies verified that the optical purity of these compounds was >95%.

A number of ureas and urethanes were prepared via acylations of amines 10 with isocyanates and chloroformates, respectively. However, a more versatile route was desired, so the in situ preparation of isocyanate analogues of 10 was investigated (method 5). Direct application of the trichloromethyl chloroformate (TCF) methodology of Kurita[18] (0.5 equiv of TCF, 80 °C) gave predominantly a bis-indole urea. However, good yields were obtained by utilizing 1 equiv of TCF at room temperature.

In most cases the methyl ester of 4-(bromomethyl)-3-methoxybenzoic acid was used to alkylate the nitroindoles and nitroindazoles. The desired acid 12 was then liberated by alkaline hydrolysis. However, in the case of compound 58 (Table V) it was suspected that the acylamino group might not withstand the alkaline conditions, so the *tert*-butyl ester was employed. The indole ring proved to be sensitive to the trifluoroacetic acid conditions traditionally employed for *tert*-butyl ester hydrolysis. Therefore, the nonacidic, (trimethylsilyl)triflate methodology of Bernauer[19] was utilized.

Structure–Activity Relationships

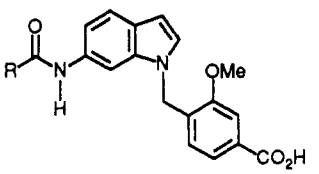
Our exploration of the structure–activity relationships around the novel leukotriene antagonist 7 (Scheme I) initially focused on the acylamino portion of the molecule. We established preferred amidic chains for both an alkyl and an arylalkyl series and then demonstrated that ureas and urethanes were viable alternatives to amides. The cyclopentyl moiety was subsequently found to be a particularly favorable lipophilic group in both the urethane and amide series. These structure–activity relationships were duplicated nicely in the indazole series. Thus, four equipotent compounds—cyclopentyl urethanes 74 and 87 and cyclopentyl acetamides 79 and 88 in the indole and indazole series, respectively—emerged with activity at submicromolar concentrations. A more detailed explanation of this stepwise progression of the structure–activity relationships is presented in the following sections.

Amides. It was established that the optimal position for attachment of the lipophilic amide moiety was C-6 of the indazole/indole (Table I: compare 14, 5, 7, 21, and 20). An investigation of amide chain length (Table II) in an alkyl series (22–26) and a phenylalkyl series (27–30) established the hexanamide (7) and phenylacetamide (28) groups as the better amide appendages. Next the effect of incorporating various groups in the alkanamide and phenylacetamide chains was explored (Table III). In all cases these amides were less potent than their unfunctionalized progenitors 7 and 28, which suggested that the amide chains were binding to a relatively well-defined, hydrophobic pocket of the receptor.

A series of branched amides was prepared (Table IV) to delineate the shape and size of this hydrophobic portion of the receptor. The initial compound in this series (43) was designed to determine whether the terminal ethyl group of 23 (Table II) and the phenyl group of 28 were binding to the same or different subsites of the receptor. The 5-fold increase in potency of hybrid 43 over its progenitors 23 and 28 hinted at the existence of two distinct pockets in the acylamino-accomodating portion of the receptor. Other variations of the phenylacetamide α-substituent (44–48) resulted in diminished activity compared to that of 2-phenylbutyramide 43. Two branched

(15) Granger, R.; Koeberle, J.; Hao-Dong, L.; Boucard, M.; Giroux, J. J.; Mizoule, J.; Yavordis, D. *Chim. Ther.* **1970**, *5*, 24.
(16) Bouchet, P.; Furchier, A.; Joncheray, G.; Elquero, J. *Org. Magn. Res.* **1977**, *9*, 716.
(17) (a) Pettersson, *Ark. Kemi* **1957**, *10*, 283, 291; *Beilstein* E IV 9, 1815. (b) Klyne, W.; Buckingham, J. *Atlas of Stereochemistry*; Oxford University Press: New York, 1978; Vols. 1 and 2, p 45.
(18) Kurita, K.; Matsumura, T.; Iwakura, Y. *J. Org. Chem.* **1976**, *41*, 2070.
(19) Bogulya, J.; Bernauer, K. *Synthesis* **1980**, 545.

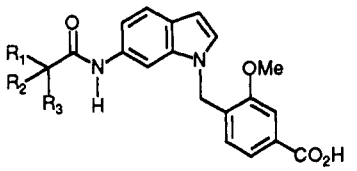
Table III. Functionalized Amides



no.	R	% inhibition/ concentration, μM	mp, °C	microanalysis	method of synthesis
31	$HO_2C(CH_2)_6$	NS/10	217–8	$C_{25}H_{28}N_2O_6 \cdot 0.1H_2O$	1
32	$CH_3C(O)NH(CH_2)_5$	NS/10	188–90 dec	$C_{25}H_{29}N_3O_5$	2
33	$CH_3C(O)(CH_2)_3$	NS/10	171–2 dec	$C_{23}H_{24}N_2O_5$	2
34	$CH{\equiv}C(CH_2)_2$	47/10	230–1	$C_{22}H_{20}N_2O_4$	2
35	$CH_3CH{=}CHCH{=}CH$[a]	28/5	238–40 dec	$C_{23}H_{22}N_2O_4$	1
36	$4\text{-}CH_3C_6H_4CH_2$	29/10	254–5	$C_{26}H_{24}N_2O_4$	2
37	$4\text{-}ClC_6H_4CH_2$	44/10	>255	$C_{25}H_{21}ClN_2O_4$	2
38	$4\text{-}CF_3C_6H_4CH_2$	13/10	>250	$C_{26}H_{21}F_3N_2O_4$	2
39	$4\text{-}PhC_6H_4CH_2$	NS/10	243–4	$C_{31}H_{26}N_2O_4$	2
40	$3,4\text{-}(CH_3O)_2C_6H_3CH_2$	NS/10	206–7	$C_{27}H_{26}N_2O_6$	1
41	2-naphthyl-CH_2	NS/10	237–8	$C_{29}H_{24}N_2O_4$	2
42	2-thienyl-CH_2	77/10	244-5	$C_{23}H_{20}N_2O_4S \cdot 0.2H_2O$	2

[a] *trans*-Olefin geometries.

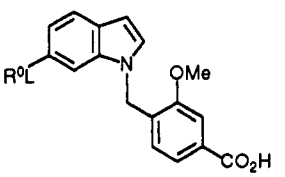
Table IV. Branched Amides[a]



no.	R^1	R^2	R^3	% inhibition/ concentration, μM	$K_B \pm SEM$[b] $\times 10^{-7}$ M (*n*)	mp, °C	microanalysis	method of synthesis
43	Et	Ph	H	65/1	1.77 ± 0.33 (8)	212–4	$C_{27}H_{26}N_2O_4$	2[c]
44	OMe	Ph	H	52/3.3		193–4	$C_{26}H_{24}N_2O_5$	6
45	Me	Ph	H	59/3.3		209–10	$C_{26}H_{24}N_2O_4 \cdot 0.2H_2O$	2
46	Me	Ph	Me	23/3.3		209–10	$C_{27}H_{26}N_2O_4$	6
47	$CH_3(CH_2)_3$	Ph	H	34/10		230–1	$C_{29}H_{30}N_2O_4$	2
48	Ph	Ph	H	38/3.3		262–3	$C_{31}H_{26}N_2O_4$	2
49	CH_3CH_2	$CH_3(CH_2)_3$	H	59/1	2.55 ± 1.03 (6)	234–5	$C_{25}H_{30}N_2O_4$	2
50	$-(CH_2)_4-$		H	58/1		271–2	$C_{23}H_{24}N_2O_4 \cdot 0.1H_2O$	2
51[d]	Et	Ph	H	NS/1	6.95 ± 2.29 (4)	230–1	$C_{27}H_{26}N_2O_4$	2
52[e]	Et	Ph	H	35/1	1.79 ± 0.33 (4)	230–1	$C_{27}H_{26}N_2O_4$	2

[a] All compounds with chiral centers are racemates except for **51** and **52**. [b] Dissociation constants vs LTE_4 on guinea pig trachea. *n* = the number of concentration–response curves. [c] Synthetic details appear in the Experimental Section to exemplify this method of synthesis. [d] *R* (−)-enantiomer. [e] *S* (+)-enantiomer.

Table V. Alternatives to the Amide Linkage

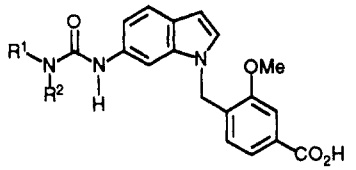


no.	R^0	L	% inhibition/ concentration, μM	$K_B \pm SEM$ $\times 10^{-7}$ M (*n*)	mp, °C	microanalysis	method of synthesis
53	*n*-Bu	CH_2CONMe	NS/10		166–8	$C_{24}H_{28}N_2O_4$	1
54	*n*-Bu	CH_2CH_2NH	52/10		136–8	$C_{23}H_{28}N_2O_3 \cdot 0.5HCl$	7[a]
55	*n*-Bu	NHCSNH	18/10		200–1	$C_{22}H_{25}N_3O_3S$	3
56	*n*-Bu	NHCONH	39/1	6.7 ± 1.6 (11)	193–4	$C_{22}H_{25}N_3O_4$	3[a]
57	*n*-Bu	OCONH	54/0.5	1.55 ± 0.43 (8)	174–5	$C_{22}H_{24}N_2O_5$	4[a]
58	CF_3CF_2	CF_2CONH	40/10		213–5	$C_{21}H_{15}N_2O_4F_7$	1[b]
59	Ph	CH_2SO_2NH	NS/10		196–8	$C_{24}H_{22}N_2O_5S$	8[a]

[a] Synthetic details appear in the Experimental Section to exemplify this method of synthesis. [b] Prepared from the *tert*-butyl ester.

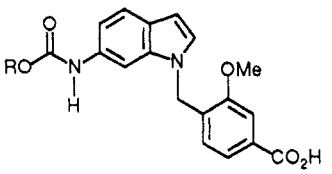
alkyl amides, **49** and **50**, proved to be approximately equipotent with **43**. Since the potency of the initial branched amide (**43**) remained unsurpassed, the two enantiomers **51** and **52** were prepared as a further assessment of the importance of α-branching. The failure to achieve enhanced potency with either enantiomer suggested that α-branched amides might not be the best substrates for the receptor. Therefore, we turned to an exploration of

Table VI. Ureas



no.	R^1	R^2	% inhibition/ concentration, μM	mp, °C	microanalysis	method of synthesis
60	*n*-Bu	Me	NS/10	184–5	$C_{23}H_{27}N_3O_4$	5
61	Et	Et	19/10	230–1	$C_{22}H_{25}N_3O_4$	1
62	Ph	H	NS/10	>240	$C_{24}N_{21}N_3O_4$	3
63	2-$CF_3C_6H_4$	H	42/10	223–5	$C_{25}H_{20}N_3O_4F_3 \cdot 0.5H_2O$	3
64	$PhCH_2$	H	57/10	204–5	$C_{25}H_{23}N_3O_4 \cdot 0.4H_2O$	3
65	*t*-Bu	H	24/3.3	181–2	$C_{22}H_{25}N_3O_4$	3
66	*n*-C_6H_{13}	H	51/3.3	204–5	$C_{24}H_{29}N_3O_4$	3
67	cyclohexyl	H	34/3.3	252–4	$C_{24}H_{27}N_3O_4$	3
68	cyclopentyl	H	73/1	247–8	$C_{23}H_{25}N_3O_4$	5

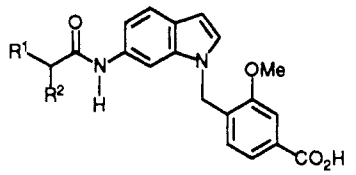
Table VII. Urethanes



no.	R	% inhibition/ concentration, μM	K_B + SEM × 10^{-8} M (*n*)	mp, °C	microanalysis	method of synthesis
69	Me	NS/10		198–200	$C_{19}H_{18}N_2O_5$	4
70	*t*-Bu	10/3.3		200–1	$C_{22}H_{24}N_2O_5$	5
71	*n*-C_6H_{13}	30/1.0		172–4	$C_{24}H_{28}N_2O_5$	4
72	*i*-Pr	24/0.33		235–6	$C_{21}H_{22}N_2O_5 \cdot 0.5H_2O$	5
73	Et_2CH	31/0.33	10.7 ± 2.1 (7)	232–3	$C_{23}H_{26}N_2O_5$	5
74	cyclopentyl	61/0.1	1.57 ± 0.15 (8)	236–7	$C_{23}H_{24}N_2O_5$	5[a]
75	cyclobutyl	27/0.1	5.87 ± 1.07 (8)	238–9	$C_{22}H_{22}N_2O_5$	5
76	cyclohexyl	NS/1.0		242–3	$C_{24}H_{26}N_2O_5$	5
77	3-cyclohexenyl	47/1.0		236–7	$C_{24}H_{24}N_2O_5$	5
78	3-tetrahydrofuranyl	70/3.3		214–5	$C_{22}H_{22}N_2O_6$	5

[a] See footnote *a* in Table V.

Table VIII. Amides Revisited



no.	R^1	R^2	% inhibition/ concentration, μM	K_B ± SEM × 10^{-8} M (*n*)	mp, °C	microanalysis	method of synthesis
79	cyclopentyl	H	34/0.1	2.07 ± 0.46 (8)	259–60	$C_{24}H_{26}N_2O_4$	2
80	cyclopentyl	Pr	62/1.0		268–9	$C_{27}H_{32}N_2O_4$	6
81	cyclopentyl	Ph	27/1.0		236–7	$C_{30}H_{30}N_2O_4$	6[a]
82	cyclohexyl	H	53/0.33		252–3	$C_{25}H_{28}N_2O_4$	2
83	cyclohexyl	Et	18/0.33		277–8	$C_{27}H_{32}N_2O_4$	6

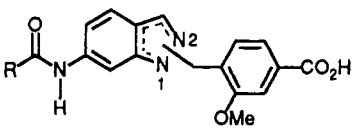
[a] Synthetic details appear in the Experimental Section to exemplify this method of synthesis.

alternatives to the amide group in an attempt to gain increased potency.

Ureas and Urethanes. A series of closely related derivatives of **7** was evaluated as part of an investigation of alternatives for the amide linking group (Table V). *N*-Methyl amide **53**, amine **54**, and thiourea **55** were all less potent than **7**. However, urea **56** was an improvement. Urethane **57** was even better, being approximately 6 times more active than **7**. Perfluoroamide **58** and sulfonamide **59** were both less active than the corresponding amides **23** and **28** (Table II), respectively.

The increased potency observed with urea **56** and urethane **57** prompted a more detailed investigation of the lipophilic substituent in these series. Table VI lists some of the ureas which were explored. Activity dropped precipitously with the *N*,*N*-dialkylated compounds **60** and **61**. Phenylurea **62** was inactive at 10 μM, which was surprising given the close structural relationship to the active phenylacetamide **28**. Some activity could be regained by negating the propensity for the aromatic ring to adopt a conformation in which it was coplanar with the urea functionality (**63** and **64**). Several alkyl substituents were

Table IX. Indazoles



no.	R	toluic acid position	% inhibition/ concentration, μM	K_B ± SEM × 10^{-8} M (n)	$BaCl_2$[a] % inhibition (100 μM)	mp, °C	microanalysis	method of synthesis
84	$CH_3(CH_2)_3CH(Et)$	1	56/0.33	13.1 ± 3.2 (8)	NS	249–50.5	$C_{24}H_{29}N_3O_4 \cdot 0.25H_2O$	1
85	PhCH(Et)	1	30/0.33	7.37 ± 2.54 (6)	NS	244–5	$C_{26}H_{25}N_3O_4$	2
86	$CH_3(CH_2)_3O$	1	56/0.33	20.4 ± 6.5 (7)	41	207–11	$C_{21}H_{23}N_3O_5 \cdot 0.1H_2O$	4
87	c-C_5H_9O	1	65/0.1	3.20 ± 0.98 (8)	44	233.5–5.0	$C_{22}H_{23}N_3O_5$[b]	4
88	c-$C_5H_9CH_2$	1	83/0.1	1.63 ± 0.22 (4)		254–6	$C_{23}H_{25}N_3O_4$	6
89	PhCH(Et)	2	22/10			195–7	$C_{26}H_{25}N_3O_4$	2
90	$CH_3(CH_2)_3O$	2	50/10			173–4	$C_{21}H_{23}N_3O_5$	4

[a] Percent inhibition of the $BaCl_2$-induced contraction of guinea pig trachea engendered by a 100 μM concentration of the indicated compound. [b] N: calcd, 10.26; found, 10.72.

tried as replacements for the butyl chain of **56**, but it proved difficult to obtain any enhancement of the potency. The cyclopentyl analogue **68** was more active than **56**.

Greater advances were made with the urethane series shown in Table VII. The methyl (**69**), *tert*-butyl (**70**), and *n*-hexyl (**71**) analogues were all less potent than their butyl progenitor **57**. However, the isopropyl (**72**) and 3-pentyl (**73**) derivatives were approximately equiactive with **57**. The simple transition from 3-pentyl (**73**) to the more constrained cyclopentylurethane (**74**) provided approximately a 6-fold gain in potency. Cyclobutyl analogue **75** was 3 times less active than cyclopentyl compound **74**, and the cyclohexyl derivative **76** was substantially less active. Incorporation of a heteroatom into the cyclopentyl framework (**78**) also diminished activity. Cyclopentylurethane **74** surpassed the potency of the original hexanamidoindole **7** by a factor of 60 and was 30 times more active than FPL 55712.

Amides Revisited. The emergence of cyclopentyl as a preferred group in the urethane series prompted us to incorporate that moiety into the amide series. Cyclopentylacetamide **79** (Table VIII) was equipotent with its urethane counterpart **74**. This result was surprising since hexanamide **7** was 6 times less active than the isosteric *n*-butylurethane **57**. *The cyclopentylacetamide **79** and cyclopentylurethane **74** provided leukotriene antagonists with pK_B values approaching 8.0.*

At an earlier stage in the project the activity of an amide series had been enhanced by α-branching (Table IV). With the discovery of the potent cyclopentylacetamide we decided to determine if substitution α to the carbonyl of that moiety would provide any further increases in potency (Table VIII). In fact, activity was diminished by this strategy in both a cyclopentyl- and a cyclohexylacetamide series.

Indazoles. The initial compound in this novel structural class of leukotriene antagonists had been an indazole. As the improved acylamino groups were discovered in the indole series, they were incorporated into indazoles (Table IX). A comparison of the K_B values in Table IX (compounds **84–88**) with those for the corresponding indoles (**49**, **43**, **57**, **74**, and **79**) illustrates the excellent concordance of activity existing between the indole and indazole series. The deleterious effect of attaching the methoxytoluic acid moiety to N-2 rather than N-1 was reconfirmed with indazoles **89** and **90**. The concentration of cyclopentylurethane **87** required to attenuate smooth muscle response to a barium chloride challenge was 100 μmol, giving this compound a selectivity ratio of 1000 as a leukotriene antagonist.

Oral Activity. Selected antagonists were evaluated for oral activity in a conscious guinea pig model[20] wherein dyspnea is induced by aerosol administration of LTD_4. Compounds were administered orally as solutions in poly(ethylene glycol) 60 min prior to the leukotriene challenge.[21] Percent protection engendered by the compound was calculated from the time delay to the onset of dyspnea compared to that for the control animals. Some compounds were active at doses of 50 mg/kg. For example, butylurethane indazole **86** provided 33 ± 5% protection ($n = 14$, $p < 0.01$) at a dose of 126 μmol/kg (50 mg/kg). Cyclopentylurethane indole **74** gave 23 ± 6% protection ($n = 10$, $p < 0.05$) at a dose of 100 μmol/kg (41 mg/kg).

Conclusions

The structure–activity relationships delineated above permit some speculation about the nature of the leukotriene receptor in the region which binds the acylamino portion of these antagonists. The data in Table II suggest the presence of a hydrophobic pocket. Such a view is supported by the potency losses which resulted from the introduction of polar functionalities (Table III). Given the 50-fold increase in potency achieved with cyclopentylacetamide **79** over hexanamide **7**, the hydrophobic pocket would appear to be quite discriminating. The fact that in both the urea and urethane series a *tert*-butyl group was less potent than the corresponding *n*-butyl group (**65** vs **56** and **70** vs **57**) supports the idea that the pocket is not simply a large hole into which any lipophilic moiety will fit. There also appears to be a preference on the part of this portion of the receptor for a ligand with some degree of planarity. For example, potency increased by a factor of 7 upon substituting cyclopentyl for 3-pentyl in the urethane series (**73** vs **74**). Furthermore, while the cyclopentyl- and cyclobutylurethanes were potent compounds, the cyclohexyl analogue was considerably weaker. Some of the potency lost with the cyclohexylurethane could be regained by the introduction of a double bond into the cyclohexyl ring (**77** vs **76**).

These data imply the existence of a narrow hydrophobic cleft in the receptor which prefers to see relatively planar, lipophilic groups. On this basis, aromatic rings might appear to be good substitutes for the cyclopentyl group. However, aryl moieties proved to be consistently less potent than their cycloaliphatic counterparts. In the acet-

(20) Snyder, D. W.; Liberati, N. J.; McCarthy, M. M. *J. Pharmacol. Methods* **1988**, *19*, 219.
(21) See the Experimental Section for details of the testing protocol.

amide series, phenyl **28** vs cyclohexyl **82** and thienyl **42** vs cyclopentyl **79** can be compared. In the urea series phenyl **62** can be compared to cyclohexyl **67**. One explanation for these findings is that the hydrophobic cleft may be oriented relative to the rest of the receptor such that the ligand must have tetrahedral geometry β to the carbonyl. Alternatively, an electron π cloud may interfere with binding.

The structure–activity relationship established for the acylamino chain in the indole series transferred exceedingly well to the indazole series. Thus, the cyclopentyl group emerged as the preferred lipophilic moiety for both the indoles and indazoles, generating four approximately equipotent compounds (acetamides **79** and **88** and urethanes **74** and **87**) active at submicromolar concentrations.

These compounds represent a novel series of selective leukotriene antagonists which possess oral activity. This new class arose from a combination of structural features from two quite different series of leukotriene antagonists: a series derived from the prototypical antagonist hydroxyacetophenone FPL 55712 and a series derived from the leukotrienes themselves.

The leukotriene antagonists described here provided a good foundation for other chemical modifications, which have expanded the structural scope of this class and have given dramatic increases in potency. The following paper[22] describes some of those modifications and highlights the selection of a clinical candidate for evaluation in asthma.

Experimental Section

General Methods. Analytical samples were homogeneous by TLC and afforded spectroscopic results consistent with the assigned structures. Melting points were determined on either a Fisher-Johns hot stage or a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were obtained by using either a Bruker WM-250, an IBM NR-80, or a Varian EM-360 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as an internal standard. Mass spectra (MS) were recorded on a Kratos MS-80 instrument 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 ICIA Analytical Department on a Perkin-Elmer 241 elemental analyzer and are within ±0.4% of the theoretical value for the given formulae. Infrared spectra (IR) were taken on Perkin-Elmer 727B or 781 spectrometers; band locations are reported in cm^{-1}. Analytical thin-layer chromatography (TLC) was conducted either on prelayered silica gel GHLF plates (Analtech, Newark, DE) or on Whatman MKC 18F reversed-phase TLC plates (RP-TLC). Visualization of the plates was accomplished by using UV light and/or phosphomolybdic acid–sulfuric acid charring. Flash chromatography was conducted on Kieselgel 60, 230–400 mesh (E. Merck, Darmstadt, West Germany) or on J. T. Baker octadecylsilyl (ODS) packing material (40 μm). Reactions were run at ambient temperature and under a nitrogen atmosphere unless otherwise noted. Solvents were either reagent or HPLC grade. Solvent mixtures are expressed as volume/volume ratios. Solutions were evaporated under reduced pressure with a rotary evaporator. Starting materials were commercially available and were used as received unless otherwise indicated.

The method of synthesis for each of the final compounds is indicated in Tables I–IX. The general synthetic route is illustrated in Scheme II, and a detailed experimental protocol for a specific example of each method is provided below. The majority of the carboxylic acids (**12**) described herein were prepared by alkaline hydrolyses of the corresponding methyl esters according to the protocol exemplified for **5**.

(Bromomethyl)benzoate Starting Materials. *tert*-Butyl 3-Methoxy-4-methylbenzoate (114). A solution of 3-methoxy-4-methylbenzoic acid (10 g; 60.2 mmol), concentrated H_2SO_4 (1 mL), and condensed isobutylene (200 mL) in CH_2Cl_2 (200 mL) was prepared in a pressure vessel and stirred for 16 h. The vessel was then opened to vent unreacted isobutylene. The remaining liquid was poured into 10% w/v aqueous NaOH (150 mL) and extracted twice with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (690 mL) using EtOAc–hexane (1:9) as the eluent to give **114** as a colorless oil (9.1 g; 70%). ^1H NMR (80 MHz, $CDCl_3$): 1.6 [s, 9 H, $C(CH_3)_3$], 2.27 (s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 7.11 (d, 1 H), 7.49 (m, 2 H).

***tert*-Butyl 4-(Bromomethyl)-3-methoxybenzoate (115).** A suspension of ester **114** (8.92 g; 40.2 mmol), *N*-bromosuccinimide (8.57 g; 48.1 mmol), and benzoyl peroxide (0.1 g; 0.4 mmol) in CCl_4 (150 mL) was heated to reflux and irradiated with a sunlamp for 1 h. After cooling to room temperature, solids were removed from the suspension by filtration. The filtrate was evaporated. The resultant residue was purified by flash chromatography on silica gel (690 mL) using EtOAc–hexane (1:19) as the eluent to give **115** as a pale yellow oil (11.52 g; 95%). ^1H NMR (80 MHz, $CDCl_3$): 1.5 [s, 9 H, $C(CH_3)_3$], 3.9 (s, 3 H, OCH_3), 4.5 (s, 2 H, CH_2Br), 7.15 (d, 1 H), 7.4 (m, 2 H).

Methyl 3-Methoxy-4-methylbenzoate (116). A solution of 3-methoxy-4-methylbenzoic acid (6.0 g; 36.1 mmol) in MeOH (120 mL) was treated with acetyl chloride (6 mL; 84.4 mmol) and stirred for 36 h. The solution was evaporated. The residue was dissolved in methanol (100 mL) and the solution was evaporated. This procedure was repeated to give **116** as a colorless solid (6.34 g; 98%). Mp: 46–47 °C. ^1H NMR (250 MHz, $CDCl_3$): 2.2 (s, 3 H, CH_3), 3.9 (2 s, 6 H, OCH_3), 7.1 (d, 1 H), 7.5 (m, 2 H).

Methyl 4-(Bromomethyl)-3-methoxybenzoate (117). A stirred solution of ester **116** (121.2 g; 673.3 mmol) in CCl_4 (1.4 L) was heated under gentle reflux with a 350-W tungsten lamp and subjected to an air purge by means of a T-tube attached to a water aspirator. A solution of bromine (107.2 g; 670.8 mmol) in CCl_4 (500 mL) was added dropwise over 4 h. Evaporation of the solvent gave a yellow residue which was triturated with Et_2O–hexane (1:1; 500 mL). The residue was collected by filtration to give **117** as a pale yellow solid (111.7 g; 64%). Mp: 92–93 °C. ^1H NMR (250 MHz, $CDCl_3$): 3.9 (2 s, 6 H, OCH_3), 4.5 (s, 2 H, $BrCH_2$), 7.4 (m, 3 H, ArH).

Aminoindazole and Aminoindole Intermediates (10). Methyl 4-[(6-Nitroindazol-1-yl)methyl]benzoate (118). A mixture of sodium 6-nitroindazolide (3.7 g; 20 mmol), methyl 4-(bromomethyl)benzoate (4.58 g; 20 mmol), and acetone (120 mL) was heated under reflux for 54 h and then diluted with EtOAc (250 mL) and brine (40 mL). The organic layer was separated, washed with brine, dried ($MgSO_4$), and evaporated to give a brown solid, which was purified by HPLC on a Waters 500 machine. Elution with EtOAc–hexane (1:3) gave a yellow solid, which was crystallized from EtOAc to give **118** as pale yellow needles (1.71 g; 28%). Mp: 171–172.5 °C. Partial ^{13}C NMR: 134.10 (C-3). ^1H NMR (80 MHz, $CDCl_3$): 3.9 (s, 3 H, OMe), 5.7 (s, 2 H, NCH_2), 7.3 (d, J = 9 Hz, 1 H, ArH), 7.8–8.1 (m, 3 H, ArH), 8.2 (d, J = 0.5 Hz, 1 H, ArH), 8.3 (d, J = 0.5 Hz, 1 H, H^7-indazole). IR (Nujol): 1705. MS (EI, m/z): 311. Subsequent fractions provided a pale brown solid, which was crystallized from EtOAc to give **methyl 4-[(6-nitroindazol-2-yl)methyl]benzoate (119**; 1.04 g; 17%). Mp: 163–163.5 °C. Partial ^{13}C NMR: 124.09 (C-3). ^1H NMR (80 MHz, $CDCl_3$): 3.9 (s, 3 H, OMe), 5.7 (s, 2 H, NCH_2), 7.4 (d, J = 9 Hz, 1 H, ArH), 7.6–8.1 (m, 3 H), 8.1 (d, J = 9 Hz, 1 H, ArH), 8.7 (m, 1 H, H^7-indazole). IR (Nujol): 1705. MS (EI, m/z): 311.

Methyl 3-Methoxy-4-[(6-nitroindazol-1-yl)methyl]benzoate (120). Alkylation of sodium 6-nitroindazolide with **117** under the conditions described for the preparation of **118** gave **120** as a fluffy white solid (28%) after crystallization from Et_2O–petroleum ether. Mp: 137.0–137.5 °C. ^1H NMR (80 MHz, $CDCl_3$): 3.9 (s, 3 H, OMe), 4.0 (s, 3 H, OMe), 5.7 (s, 2 H, NCH_2), 7.1 (d, J = 9 Hz, 1 H, ArH), 7.6 (m, 2 H, ArH), 7.9 (m, 2 H, ArH), 8.1 (d, J = 0.5 Hz, 1 H, ArH), 8.5 (br s, 1 H, H^7-indazole). IR (Nujol): 1710. MS (EI, m/z): 341. **Methyl 3-methoxy-4-[(6-nitroindazol-2-yl)methyl]benzoate (121)** was obtained as a pale yellow powder (11%) after crystallization from EtOAc–petroleum ether. Mp: 162–165 °C. ^1H NMR (80 MHz, $CDCl_3$): 3.9 (s, 3 H, OMe), 4.0 (s, 3 H, OMe), 5.7 (s, 2 H, NCH_2), 7.2 (d, J = 9 Hz, 1 H, ArH),

(22) See the following paper in this issue of *J. Med. Chem.*

7.5–7.9 (m, 4 H, ArH), 8.0 (s, 1 H, ArH), 8.7 (br s, 1 H, H^7-indazole). IR (Nujol): 1710.

Methyl 3-Methoxy-4-[(6-nitroindol-1-yl)methyl]benzoate (122). A solution of 6-nitroindole (4.0 g; 24.7 mmol) and methyl 4-(bromomethyl)-3-methoxybenzoate (6.71 g; 25.9 mmol) in dry acetone (125 mL) was treated with anhydrous K_2CO_3 (4.0 g; 29.6 mmol). The mixture was heated under reflux for 48 h. The cloudy mixture was evaporated. The residue was suspended in EtOAc, and solids were removed by filtration. The filtrate was evaporated and the residual oil was purified by flash chromatography on silica gel (850 mL) using CH_2Cl_2–hexane (1:1) as the eluent to give **122** as a bright yellow powder (8.0 g; 95%). ^1H NMR (80 MHz, $CDCl_3$): 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.4 (s, 2 H, NCH_2), 6.7 (dd, 1 H, H^3-indole), 6.8 (d, 1 H, ArH), 7.4 (d, 1 H, H^2-indole), 7.5–7.7 (m, 3 H), 8.0 (dd, 1 H, H^5-indole), 8.3 (br s, 1 H, H^7-indole).

***tert*-Butyl 3-Methoxy-4-[(6-nitroindol-1-yl)methyl]benzoate (123).** *tert*-Butyl 3-methoxy-4-(bromomethyl)benzoate was reacted with 6-nitroindole by using the procedure described for **122** to give **123** as a yellow solid (98%). ^1H NMR (80 MHz, $CDCl_3$): 0.6 [s, 9 H, $C(CH_3)_3$], 4.9 (s, 3 H, OCH_3), 5.4 (s, 2 H, NCH_2) 6.6 (dd, 1 H, H^3-indole), 6.8 (d, 1 H, ArH), 6.8–8.0 (m, 5 H, Ar), 8.4 (d, 1 H, H^7-indole).

Methyl 4-[(6-Aminoindol-1-yl)methyl]-3-methoxybenzoate (124). A solution of **122** (1.38 g; 4.05 mmol) in EtOAc (15 mL) was treated with acetic acid–EtOAc (1:4; 2 drops) and then added to a suspension of prereduced 10% Pd/C (0.34 g; 10% w/w) in EtOAc (5 mL). The mixture was shaken under 50 psi of hydrogen for 24 h and then filtered through diatomaceous earth. The residue was washed with hot $CHCl_3$, and the combined filtrate and washings were evaporated to give **124** as a tan powder (1.19 g; 95%). Mp: 121–122 °C. ^1H NMR (80 MHz, $CDCl_3$): 3.6 (br, 2 H, NH_2), 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.3 (s, 2 H, NCH_2), 6.4 (d, 1 H, H^3-indole), 6.5 (s, 1 H, H^7-indole), 6.6 (m, 2 H), 6.9 (d, 2 H, H^2-indole), 7.5 (m, 3 H).

Similar hydrogenation conditions were employed to obtain several other amines (**10**) from the corresponding nitro compounds.

Methyl 4-[(6-aminoindazol-1-yl)methyl]benzoate (125) was obtained as a colorless solid (97%). Mp: 154–155 °C dec. ^1H NMR (250 MHz, $CDCl_3$): 3.8 (br s, 2 H, NCH_2), 3.9 (s, 3 H, OMe), 5.5 (s, 2 H), 6.4 (m, 1 H), 6.6 (dd, J = 8.5 and 2.5 Hz, 1 H), 7.2 (d, J = 9 Hz, 2 H), 7.5 (dd, J = 8.5 and 0.5 Hz, 1 H), 7.9 (d, J = 0.5 Hz, 1 H), 8.0 (d, J = 9 Hz, 2 H). IR (Nujol): 3450, 3370, 1710, 1630. MS (EI, m/z): 281.

Methyl 4-[(6-aminoindazol-1-yl)methyl]-3-methoxybenzoate (126) was obtained as a solid (92%). Mp: 131.5–132 °C. ^1H NMR (250 MHz, $CDCl_3$): 3.8 (br s, 2 H, NCH_2), 3.9 (s, 3 H, OMe), 4.0 (s, 3 H, OMe), 5.4 (s, 2 H), 6.4–6.7 (m, 3 H), 7.4 (s, 1 H), 7.5 (s, 2 H), 7.9 (s, 1 H). IR (Nujol): 3400, 3300, 3175, 1705, 1610. MS (EI, m/z): 311.

***tert*-Butyl 4-[(6-aminoindol-1-yl)methyl]-3-methoxybenzoate (127)** was obtained as a pale brown solid (100%). Partial ^1H NMR: 1.6 (s, 9 H, Me_3C), 4.1 (br d, 2 H, NH_2), 5.2 (s, 2 H, NCH_2).

Methyl 3-Methoxy-4-[[6-(*N*-methylamino)indol-1-yl]methyl]benzoate (128). A solution of amine **124** (0.88 g; 2.8 mmol) and iodomethane (0.40 g; 2.8 mmol) in acetone (14 mL) was stirred with K_2CO_3 (0.45 g) for 18 h. The solvent was evaporated, and the residue was taken up in $CHCl_3$. The mixture was filtered to remove K_2CO_3. Evaporation of the filtrate gave a residue from which **128** was separated from the *N,N*-dimethyl isomer by flash chromatography on silica gel (223 mL). Elution with EtOAc–hexane (1:3) gave **128** as an ivory solid (126 mg; 14%). ^1H NMR (80 MHz; $CDCl_3$): 2.9 (s, 3 H, NCH_3), 3.5 (br, 1 H, NH), 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.2 (s, 2 H, NCH_2), 6.3–8.6 (br, m, 8 H).

Method 1. Acylation with Acid Chlorides. Methyl 4-[(6-Hexanamidoindol-1-yl)methyl]-3-methoxybenzoate (129). A stirred solution of amine **124** (0.45 g; 1.45 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C and treated with triethylamine (0.30 mL; 2.18 mmol) followed by hexanoyl chloride (0.22 mL; 1.60 mmol). The resulting solution was stirred at 0 °C for 15 min and then at room temperature for 30 min. The mixture was diluted with EtOAc and poured into cold water. The organic layer was washed sequentially with 10% v/v aqueous HCl, H_2O, and brine; dried ($MgSO_4$); and evaporated. The residue was purified by flash chromatography on silica gel (226 mL) using EtOAc–hexane (1:1.9) as the eluent to give **129** as a white solid (0.36 g; 61%). ^1H NMR (80 MHz, $CDCl_3$): 0.9 (t, 3 H, CH_3CH_2), 1.4 (m, 4 H, $CH_3CH_2CH_2$), 1.7 (m, 2 H, $COCH_2CH_2$), 2.3 (t, 2 H, $COCH_2$), 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.3 (s, 2 H, NCH_2), 6.5 (d, 1 H, H^3-indole), 6.6 (d, 1 H, ArH), 6.9 (d, 1 H, H^5-indole), 7.1 (d, 1 H, H^2-indole), 7.2 (br s, 1 H, NH), 7.5 (d, 1 H, ArH), 7.6 (m, 2 H), 8.0 (br s, 1 H, H^7-indole).

Method 2. Acylation with Carboxylic Acids Activated by Carbonyldiimidazole. Methyl 3-Methoxy-4-[[6-(2-phenylbutanamido)indol-1-yl]methyl]benzoate (130). A solution of 2-phenylbutyric acid (0.318 g; 1.93 mmol) and 1,1′-carbonyldiimidazole (0.335 g; 1.93 mmol) in CH_2Cl_2 (2 mL) was heated under reflux for 30 min and then treated with a solution of amine **124** (0.5 g; 1.61 mmol) in CH_2Cl_2 (2 mL). The mixture was heated under reflux for 30 min, stirred at room temperature for 24 h, and then diluted with EtOAc. This solution was washed sequentially with 10% v/v aqueous HCl, H_2O, and brine; dried ($MgSO_4$); and evaporated. The residue was purified by flash chromatography on silica gel (226 mL) using EtOAc–hexane (3:2) as the eluent to give **130** as a white solid (0.493 g; 74%). ^1H NMR (80 MHz, $CDCl_3$): 0.9 (t, 3 H, CH_2CH_3), 2.0 (m, 2 H, CH_3CH_2), 3.4 (m, 1 H, PhCH), 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.3 (s, 2 H, NCH_2), 6.5 (d, 1 H, H^3-indole), 6.7 (m, 2 H), 7.1 (d, 1 H, H^2-indole), 7.2 br, 1 H, NH), 7.4 (m, 8 H, ArH), 7.9 (br s, 1 H, H^7-indole).

Method 3. Acylation with Isocyanates. Methyl 4-[[6-(*N*-Butylureido)indol-1-yl]methyl]-3-methoxybenzoate (131). A solution of amine **124** (2.50 g; 8.06 mmol) in CH_2Cl_2 (20 mL) was treated with *n*-butyl isocyanate (0.92 mL; 8.14 mmol) and then sitrred for 72 h. Evaporation gave an oil, which solidified upon trituration with EtOAc to yield **131** (3.3 g; 100%). ^1H NMR (80 MHz, $CDCl_3$): 0.9 (m, 3 H, CH_2CH_3), 1.3 (m, 4 H, $CH_3CH_2CH_2$), 3.2 (br q, 2 H $NHCH_2$), 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 4.9 (br t, 1 H, CH_2NH), 5.3 (s, 2 H, NCH_2), 6.4 (br s, 1 H, ArNH), 6.5 (d, 1 H, H^3-indole), 6.7 (d, 1 H, ArH), 6.8 (dd, 1 H, H^5-indole), 7.1 (d, 1 H, H^2-indole), 7.5 (m, 4 H).

Method 4. Acylation with Chloroformates. Methyl 4-[[6-[*N*-(butoxycarbonyl)amino]indol-1-yl]methyl]-3-methoxybenzoate (132). A solution of amine **124** (3.0 g; 9.68 mmol) in CH_2Cl_2 (48 mL) was cooled to 0 °C and treated with triethylamine (2.02 mL; 14.52 mmol) followed by *n*-butyl chloroformate (1.35 mL; 10.65 mmol). The resultant solution was stirred at 0 °C for 15 min and then at room temperature for 24 h. A precipitate was removed by filtration. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel (707 mL) using EtOAc–hexane (1:1.9) as the eluent to give **132** as an ivory solid (1.96 g; 45%). ^1H NMR (80 MHz, $CDCl_3$): 0.9 (t, 3 H, CH_2CH_3), 1.5 (m, 4 H, $CH_3CH_2CH_2$), 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 4.2 (t, 2 H, OCH_2), 6.5 (dd, 1 H, H^3-indole), 6.7 (m, 2 H), 6.9 (dd, 1 H, H^5-indole), 7.1 (d, 1 H, H^2-indole), 7.5 (m, 4 H).

Method 5. Formation of an Indole Isocyanate and Reaction with Amines or Alcohols. Methyl 4-[[6-[[(Cyclopentyloxy)carbonyl]amino]indol-1-yl]methyl]-3-methoxybenzoate (138). A solution of amine **124** (0.80 g; 2.58 mmol) in anhydrous dioxane (13 mL) was treated with a solution of trichloromethyl chloroformate (0.31 mL; 2.58 mmol) in dioxane (13 mL) and stirred at room temperature. The reaction vessel was continuously purged with N_2, and the effluent was bubbled through aqueous KOH to destroy any liberated phosgene. The formation of isocyanate was monitored by TLC. After 30 min cyclopentanol (0.75 mL; 8.26 mmol) and a catalytic amount of triethylamine were added. The solution was then heated to 80 °C for 2.5 h and subsequently evaporated. The resultant residue was purified by flash chromatography on silica gel (707 mL) using EtOAc–toluene (1:13) as the eluent to give **138** as a white solid (0.92 g; 84%). ^1H NMR (250 MHz, $CDCl_3$): 1.7 (m, 8 H, $(CH_2)_4$), 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.2 (br, 1 H, CHO), 5.3 (s, 2 H, NCH_2), 6.5 (dd, 1 H, H^3-indole), 6.6 (br d, 2 H, ArH and NH), 6.8 (dd, 1 H, H^5-indole), 7.1 (d, 1 H, H^2-indole), 7.2 (d, 1 H, ArH), 7.4–7.5 (m, 3 H, ArH), 7.6 (br s, 1 H, H^7-indole).

Method 6. Acylation with Carboxylic Acids Activated by Carbodiimide. Methyl 4-[[6-(2-Cyclopentyl-2-phenylacetamido)indol-1-yl]methyl]-3-methoxybenzoate (139). A mixture of amine **124** (0.91 g; 2.9 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.57 g; 3.0 mmol),

4-(dimethylamino)pyridine (0.37 g; 3.0 mmol), and 2-cyclopentyl-2-phenylacetic acid (0.61 g; 3.0 mmol) in CH_2Cl_2 (15 mL) was stirred for 24 h. The reaction solution was diluted with CH_2Cl_2 and washed successively with 10% v/v aqueous HCl, H_2O, 20% w/v aqueous NaOH, H_2O, and brine; dried ($MgSO_4$); and evaporated to give **139** as a pale brown solid (0.96 g; 66%). ^1H NMR (80 MHz, $CDCl_3$): 0.9–1.8 (br m, 8 H, $(CH_2)_4$), 2.6 (m, 1 H, C*H*CHCO), 3.2 (d, 1 H, CHCO) 3.87 (s, 3 H, OCH_3), 3.9 (s, 3 H, OCH_3), 5.2 (s, 2 H, NCH_2), 6.5 (d, 1 H, H^3-indole), 6.6 (d, 1 H, ArH), 6.8 (dd, 1 H, H^5-indole), 7.1 (d, 1 H, H^2-indole), 8.0 (br s, 1 H, H^7-indole).

Method 7. Alkylation. Methyl 4-[[6-(*N*-Hexylamino)indol-1-yl]methyl]-3-methoxybenzoate (140). A solution of amine **124** (0.56 g; 1.8 mmol) in DMF (9 mL) was stirred with K_2CO_3 (0.28 g). This mixture was treated with 1-bromohexane (0.25 mL; 1.8 mmol) and stirred at 25 °C for 9 days. The mixture was poured into H_2O and extracted with Et_2O. The organic layer was washed sequentially with H_2O and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (112 mL) using EtOAc–hexane (1:3) as the eluent to give **140** as a colorless oil (0.24 g; 36%). ^1H NMR (80 MHz, $CDCl_3$): 0.9 (t, 3 H, C*H*$_3$CH$_2$), 1.2–1.8 [br m, 8 H, $(CH_2)_4$], 2.1 (t, 2 H, C*H*$_2$NH), 3.4 (br, 1 H, NH), 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.2 (s, 2 H, NCH_2), 6.4 (m, 2 H, H^3,H^7-indole), 6.5–6.6 (m, 2 H), 6.8 (d, 1 H, H^2-indole), 7.2–7.5 (m, 3 H).

Method 8. Sulfonylation. Methyl 4-[[6-[(Benzylsulfonyl)amino]indol-1-yl]methyl]-3-methoxybenzoate (141). A solution of amine **124** (0.46 g, 1.5 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C and treated with triethylamine (0.31 mL; 2.2 mmol) and benzylsulfonyl chloride (0.31 mL; 1.6 mmol). The resulting solution was stirred at 0 °C for 15 min and then at room temperature for 18 h. The mixture was diluted with CH_2Cl_2 and poured into cold water. The organic layer was separated and washed sequentially with 10% v/v aqueous HCl, H_2O, and brine; dried ($MgSO_4$); and evaporated. The resultant residue was purified by flash chromatography on silica gel (200 mL). Elution with EtOAc–hexane (1:3) gave **141** as an ivory solid (0.38 g; 55%). ^1H NMR (80 MHz, DMSO): 3.8 (s, 2 H, SO_2CH_2), 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.3 (s, 2 H, NCH_2), 6.5 (dd, 1 H, H^3-indole), 7.8 (d, 1 H), 7.0 (dd, 1 H, H^5-indole), 7.1–8.8 (br m, 5 H), 10 (br, 1 H, NH).

Ester Hydrolyses. 4-[[6-(Heptafluorobutanamido)indol-1-yl]methyl]-3-methoxybenzoic Acid (58). A solution of *tert*-butyl 4-[[6-(heptafluorobutanamido)indol-1-yl]methyl]-3-methoxybenzoate (0.25 g; 0.46 mmol) and triethylamine (152 μL; 1.09 mmol) in dioxane (1.0 mL) was treated with trimethylsilyl triflate (185 μL; 0.96 mmol) and then stirred for 48 h. Addition of H_2O gave a precipitate, which was collected by filtration and crystallized from EtOAc–hexane to give **58** as a pale brown powder (22 mg; 10%). Mp: 213–215 °C. ^1H NMR (250 MHz, DMSO-d_6): 3.9 (s, 3 H, OCH_3), 5.6 (s, 2 H, CH_2), 6.5 (d, 1 H, H^3-indole), 6.7 (d, 1 H), 7.3 (d, 1 H, H^5-indole), 7.4 (d, 1 H), 7.6 (d, 1 H, H^4-indole), 7.8 (s, 1 H, H^7-indole), 11.2 (s, 1 H, NH).

4-[(6-Hexanamidoindazol-1-yl)methyl]benzoic Acid (5). A solution of methyl 4-[(6-hexanamidoindazol-1-yl)methyl]-benzoate (475 mg; 1.25 mmol) in a mixture of THF (11 mL) and MeOH (16 mL) was added to a solution of $LiOH·H_2O$ (250 mg; 6.00 mmol) in H_2O (5.5 mL). The resulting solution was stirred for 30 h, diluted with H_2O (10 mL), and extracted with Et_2O. The aqueous solution was acidified with 1 N HCl (10 mL) and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and reduced to a volume of several milliliters by evaporation. Addition of Et_2O provided **5** as a colorless precipitate (371 mg; 81%). Mp: 215–215.5 °C. ^1H NMR (250 MHz, acetone-d_6): 0.9 (t, J = 7.5 Hz, 3 H, Me), 1.2 (m, 6 H), 1.6 (m, 2 H), 2.4 (t, J = 7.5 Hz, 2 H, $COCH_2$), 5.7 (s, 2 H, NCH_2), 7.2 (d, J = 9 Hz, 1 H), 7.3 (d, J = 8 Hz, 2 H), 7.7 (d, J = 9 Hz, 1 H), 7.97 (s, 1 H), 7.98 (d, J = 8 Hz, 2 H), 8.2 (s, 1 H), 9.3 (br s, 1 H). IR (Nujol): 1682, 1655; MS (CI, m/z): 366 (M + 1).

Biological Evaluation Procedures. In vitro activity was assessed on guinea pig tracheal strips. Guinea pigs were killed, 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 minutes.

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 10 nM LTE_4, and the response was recorded. After obtaining reproducible control responses to 10 nM LTE_4, 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 10 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:

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

An adjusted percent inhibition was determined by subtracting the percent 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 Student's paired t test.[23]

In vitro potencies of the more active compounds were evaluated further in isolated guinea pig tracheal strips 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.[24] 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 base-line 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.[23] 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 Student's paired t test. Dissociation constants for the receptor–antagonist complex were calculated by the method of Furchgott[25] 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.[21] Six guinea pigs were secured in a circular, plexiglass chamber via neck yokes. The head of each guinea pig was enclosed in a separate exposure chamber 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,

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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:

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

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 by using Student's unpaired t test with $p < 0.05$ considered significant.

Evolution of a Series of Peptidoleukotriene Antagonists: Synthesis and Structure/Activity Relationships of 1,3,5-Substituted Indoles and Indazoles

Victor G. Matassa,* Thomas P. Maduskuie, Jr., Howard S. Shapiro, Barrie Hesp, David W. Snyder,† David Aharony, Robert D. Krell, and Richard A. Keith

Departments of Medicinal Chemistry and Pharmacology, ICI Pharmaceuticals Group, A Business Unit of ICI Americas, Wilmington, Delaware 19897. *Received October 16, 1989*

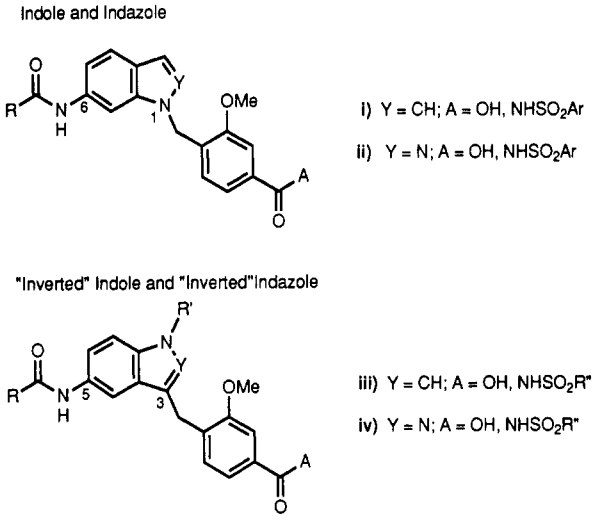
1,3,5-Substituted indoles and indazoles have been studied as receptor antagonists of the peptidoleukotrienes. The best of these compounds generally had a methyl group at the N1 position, a [(cyclopentyloxy)carbonyl]amino or 2-cyclopentylacetamido or *N'*-cyclopentylureido group at the C-5 position, and an arylsulfonyl amide group as part of the acidic chain at the C-3 position of the ring. Such compounds had in vitro dissociation constants (K_B) in the range 10^{-9}–10^{-11} M on guinea pig trachea against LTE_4 as agonist and inhibition constants (K_i) $\leq 10^{-9}$ M on guinea pig parenchymal membranes against [^{3}H]LTD_4. A number of compounds were orally effective at doses $\leq$1 mg/kg in blocking LTD_4-induced "dyspnea" in guinea pigs. Compound **45** [N-[4-[[5-[[(cyclopentyloxy)carbonyl]-amino]-1-methylindol-3-yl]methyl]-3-methoxybenzoyl]-2-methylbenzenesulfonamide, ICI 204,219; $pK_B = 9.67 \pm 0.13$, $K_i = 0.3 \pm 0.03$ nM, po ED_{50} = 0.3 mg/kg] is currently under clinical investigation for asthma. In the indole series, certain *alkyl*sulfonyl amides possessing a 3-cyanobenzyl substituent at the N-1 position (**60**, **61**) were produced that had $K_B \leq 10^{-9}$ M on guinea pig trachea.

The discovery of potent and selective peptidoleukotriene (LTC_4, LTD_4, and LTE_4) antagonists for the treatment of asthma, and other allergic conditions, remains a major focus for pharmaceutical research. The likelihood of success in this endeavor for asthma has been strengthened by the recent suggestion that, unlike on guinea pig trachea where there are distinct receptors for LTC_4 and LTD_4/LTE_4,[1a] human intralobar airways have a single receptor for the peptidoleukotrienes.[1b-e] The Fisons' hydroxyacetophenone FPL 55712 and the structures of the peptidoleukotrienes have been widely used as points of departure in the search for such antagonists. Over the past few years, these efforts have produced pharmacologically interesting molecules, some of which have been important enough to warrant clinical evaluation. Thus, the Lilly (LY 171,883)[2] and Merck (L-648,051[3] and L-649,923[4]) hydroxyacetophenones and the SK&F leukotriene-derived hydroxy acid (SKF 104,353)[5] have shown varying degrees of efficacy as LTD_4 antagonists in man, the last of these being especially interesting, although not orally active.

Recently, other classes of LTD_4 antagonists have been reported.[6-8] These new molecules bear little structural resemblance to hydroxyacetophenones or leukotrienes, and some[6,7] are significantly more potent than the earlier compounds. An accompanying report from these laboratories[9a] and previous work[6a,b,9b] have described the evolution of a new family of indole (i) and indazole (ii) benzoic acids and their *N*-arylsulfonyl amide derivatives (Chart I) which were potent and selective LTD_4 antagonists.

The goal of the present study was a better understanding of the geometric and electronic requirements of the central bicyclic ring system for receptor binding of this class of compounds. This paper describes the ("inverted") indole

Chart I. Peptidoleukotriene Antagonists: Indoles and Indazoles



† Present address: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285.

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