Substituted 3-(Phenylmethyl)-1*H*-indole-5-carboxamides and 1-(Phenylmethyl)indole-6-carboxamides as Potent, Selective, Orally Active Antagonists of the Peptidoleukotrienes

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Substituted indole-5-carboxamides and indole-6-carboxamides have been found to be potent and selective antagonists of the peptidoleukotrienes. Initial derivatives of these series (4-[[5-[(cyclopentylmethyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (**5a**) and 4-[[6-[(cyclopentylmethyl)carbamoyl]-3-methylindol-1-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (**6a**), respectively), when compared to the corresponding indole amides (e.g. **28** and **29**), were found to be approximately 10-fold less potent in vitro and substantially less active when administered orally to guinea pigs. Efforts to improve the potency of the title series by variation of the amide, indole, or sulfonamide substituents led to compounds of comparable in vitro potency to ICI 204,219, but of somewhat lower oral activity. A trend which suggested that more lipophilic transposed amides were needed to increase oral activity was exploited with some success and has led to the discovery of **5q** (4-[[5-[(2-ethylbutyl)-carbamoyl]-1-ethylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide), a transposed amide with subnanomolar affinity for the leukotriene receptor and an oral ED_{50} of 5 mg/kg in a model of asthma in guinea pigs. In this model, ICI 204,219 was active at 0.4 mg/kg. The absolute bioavailability of **5q** has been found to be 28% in the rat, as compared to 68% for ICI 204,219, with significant levels of **5q** observed in the blood of rats up to 24 h postdose.

Introduction

Since their discovery and characterization in the late 1970's, the peptidoleukotrienes LTD_4 (**1**) and LTE_4 (**2**) (Figure 1) have been known to be potent constrictors of smooth muscle tissue, and as such, have been implicated as important mediators in asthma.[1] The discovery and evaluation of molecules that block the effects of the peptidoleukotrienes, therefore, might provide useful therapies for the control of asthma. One such group of molecules which has been the subject of extensive exploration has been antagonists of the LTD_4/LTE_4 receptor.[2]

Previous reports from these laboratories[3] have described the discovery and development of specific antagonists of the leukotrienes, both from a series of hydroxyacetophenone derivatives,[3a] and more recently, compounds based on indazoles (e.g. **3**) or indoles (e.g. **4**).[3b-f] From this latter series, ICI 204,219 (**4**) was chosen for clinical trials in asthmatic patients.[4] As part of our continued efforts to further explore the structural features important to binding to the leukotriene receptor(s), we initiated a study where the carbamoyl moiety at C(5) of the indole nucleus was varied. Early results in this area demonstrated that this functionality could be replaced with a carboxamide group (a "transposed amide") without series loss of in vitro activity.[5] It was viewed as necessary, however, to introduce a polar side chain at the N(1) position of the indole nucleus in order to improve the in vitro activity to a level competitive with the earlier urethane series, a strategy which was found to decrease the oral bioavailability of the transposed amides. Although these studies suggested that

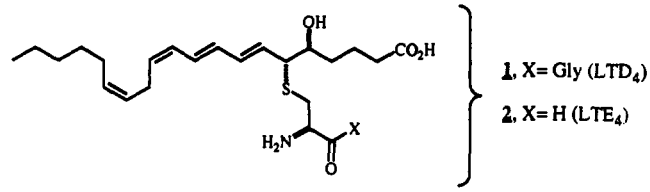

Figure 1.

the gross structure–activity relationships developed in the urethane and amide series held in this new series, it was deemed important to further explore the effects of variations in the amide, nucleus, and sulfonamide regions of the transposed amides. We now report the results of investigations in the 3-benzylindole-5-carboxamides **5** and the 1-benzylindole-6-carboxamides **6** (Figure 2).

Chemistry

Our initial synthesis of transposed amides in the 1,3,5-trisubstituted indole (**5**) series began with the commercially available 5-carboxyindole (**7**), which was condensed with cyclopentylmethylamine[6] to give the amide **8a**. Alkylation of **8a** with methyl 4-(bromomethyl)-3-methoxybenzoate (**9**)[7] using silver oxide catalysis gave a mixture of the desired C(3)-benzylated product **10a**, the C(2)-benzylated isomer, and the product of 2,3-dibenzylation. Flash chromatography afforded clean **10a** in moderate (30–40%) yield. Alkylation of the indole nitrogen using sodium hydride/iodomethane in anhydrous *N*,*N*-dimethylformamide proceeded in moderate yield to furnish the key intermediate amide ester **11a** (Scheme I). Reversing the order of the two alkylation steps, i.e. alkylation on N(1) using sodium hydride/iodomethane followed by silver-catalyzed C(3) benzylation was found to give comparable yields of the desired intermediate **11a**, with no significant advantage

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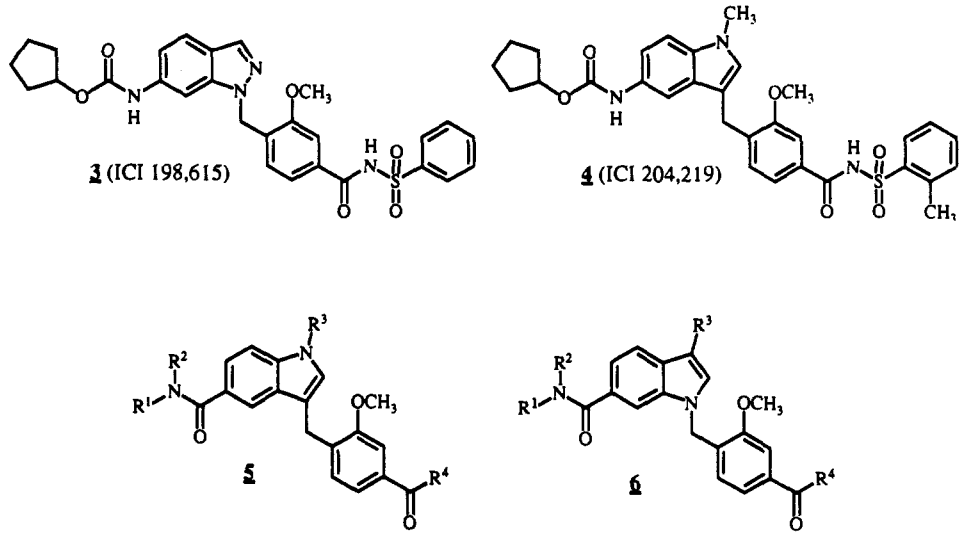
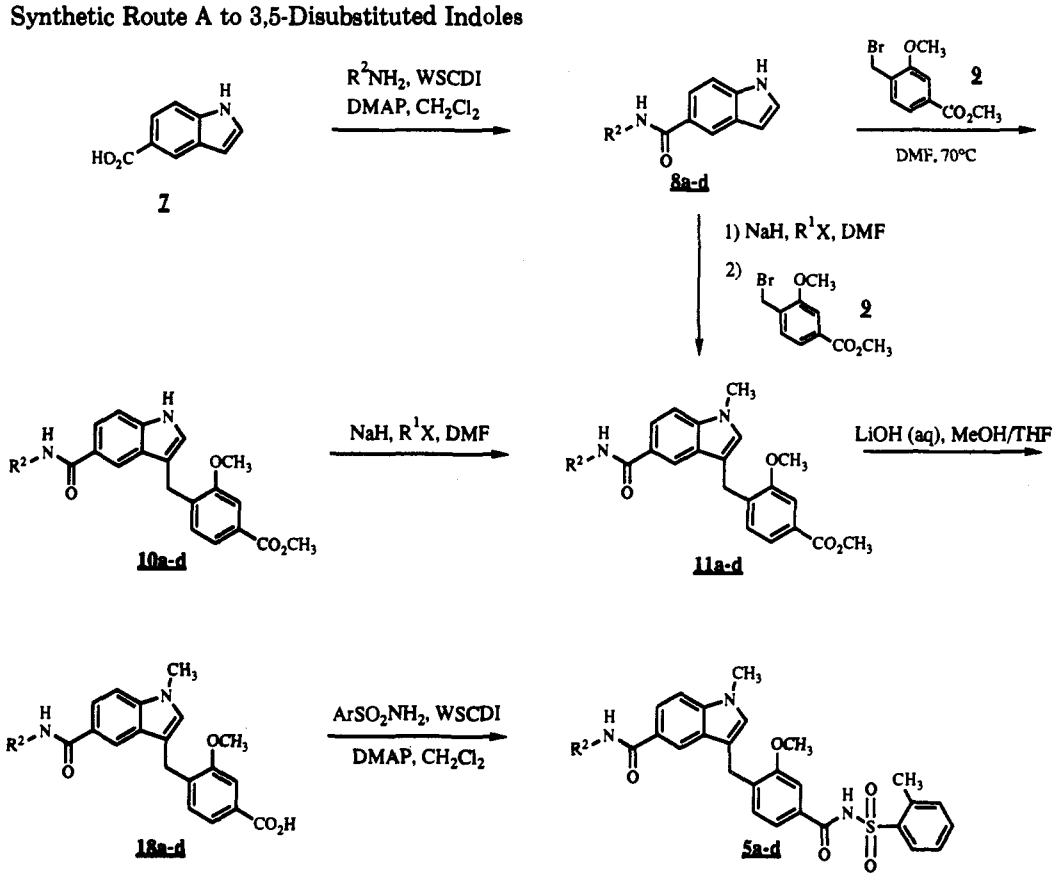


Figure 2.

Scheme I. [a] Synthetic Route A to 3,5-Disubstituted Indoles

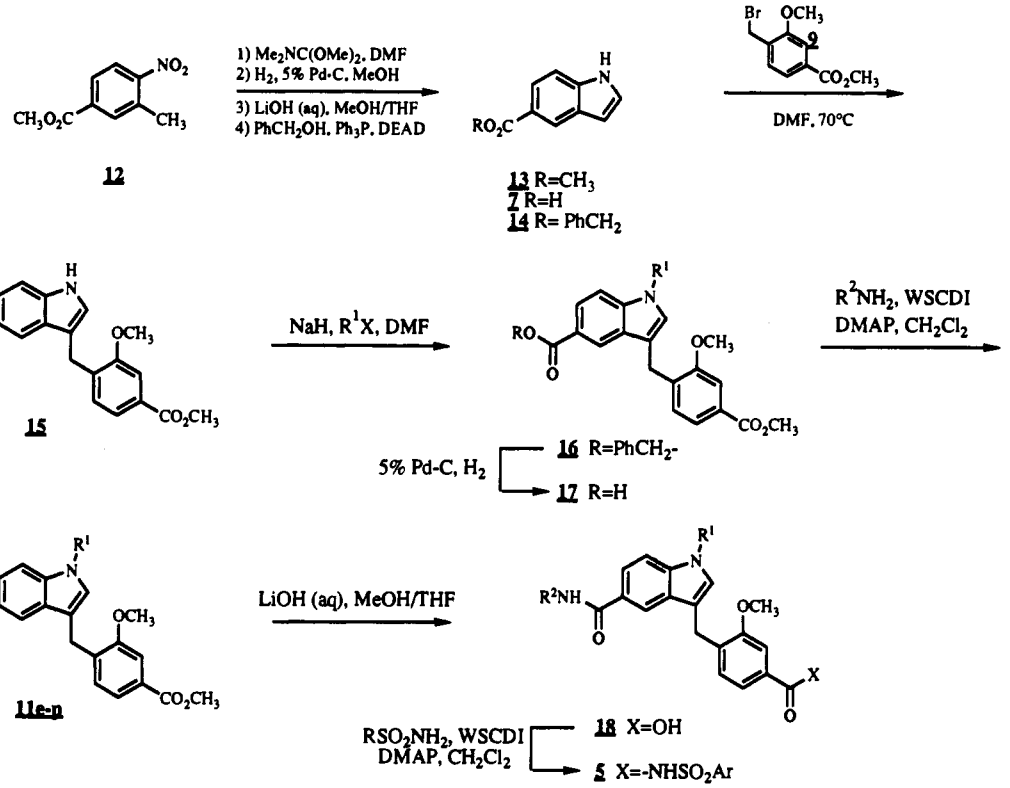


[a] **a**, R^2 = c-$C_5H_9CH_2$; **b**, R^2 = $CH_3(CH_2)_3(CH_3CH_2)CH$; **c**, R^2 = c-C_6H_{13}; **d**, R^2 = $(CH_3)_2CH(CH_2)_2$.

in separability from the C(2)-benzylated and dialkylated products. The ester moiety of **11a** could be converted to the desired drug candidates **5a** in two steps (vide infra). Also prepared by this general strategy were the amides **5b–d**.

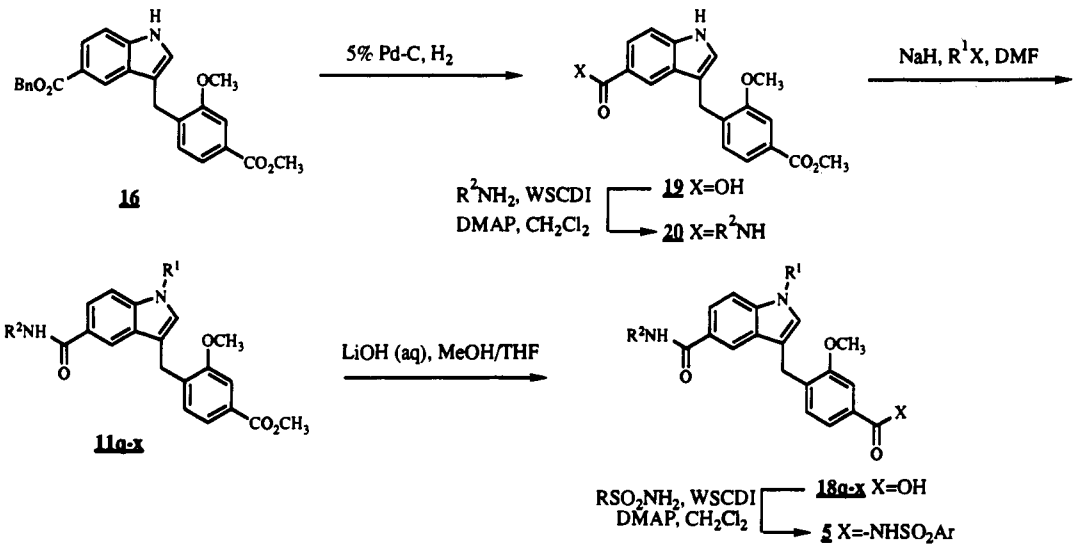
With increased interest in the transposed amide series due to the interesting pharmacologic profile exhibited by the first member of the series, we were faced with the lengthy sequence of amide formation, C(3) alkylation and N(1) alkylation for each amide substituent if the above procedure was employed. Therefore, we examined the feasibility of performing the C(3) benzylation on a suitable ester of 5-carboxyindole, as outlined in Scheme II. Furthermore, it was found to be more economical to prepare the desired benzyl ester **14** via a Batcho–Leimgruber cyclization approach[8] from methyl 3-methyl-4-nitrobenzoate (**12**) followed by saponification of the methyl ester **13** to acid **7** and condensation with benzyl alcohol under neutral conditions.[9] The silver-catalyzed reaction of **14** with **9** was found to give low (and variable) yields of the desired product **15**. Fortunately, reaction of **14** with **9** in warm *N,N*-dimethylformamide in the absence of catalyst afforded the desired differentiated diester **15** in moderate (45%, based on recovered **14**), yet reliable yield. Treatment of **15** with sodium hydride to generate the indole anion followed by alkylation with either iodomethane or allyl bromide gave the *N*-alkylindoles **16** in good yield. Hydrogenolysis of the benzyl ester (accompanied by

Scheme II. [a] Synthetic Route B to 3,5-Disubstituted Indoles



[a] For $R^1 = CH_3$: e $R^2 = CH_3(CH_2)_3CH(CH_3CH_2)CH_2$; f $R^2 = (CH_3CH_2)_2CHCH_2$; g, $R^2 = (CH_3)_2CHCH_2$; h, $R^2 = CH_3CH_2(CH_3)_2CHCH_2$; i $R^2 = CH_3(CH_2)_2(CH_3)CHCH_2$; j, $R^2 = CH_3(CH_2)_4(CH_3)CHCH_2$; k, $R^2 = CH_3(CH_2)_5(CH_3)CHCH_2$; l, $R^2 = Ph(CH_2)_2$; m, R = 4-ethylpiperidyl; n, $R^2 = (C_4H_9)_2$; o, $R^2 = (CH_3)_2CHCH_2$ [N-CH_3]; p, $R^2 = (CH_3)_3CCH_2$; for R^1 = Pr: r, $R^2 = (CH_3CH_2)_2CHCH_2$; x, $R^2 = (CH_3)_2CHCH_2$.

Scheme III. [a] Synthetic Route C to 3,5-Disubstituted Indoles



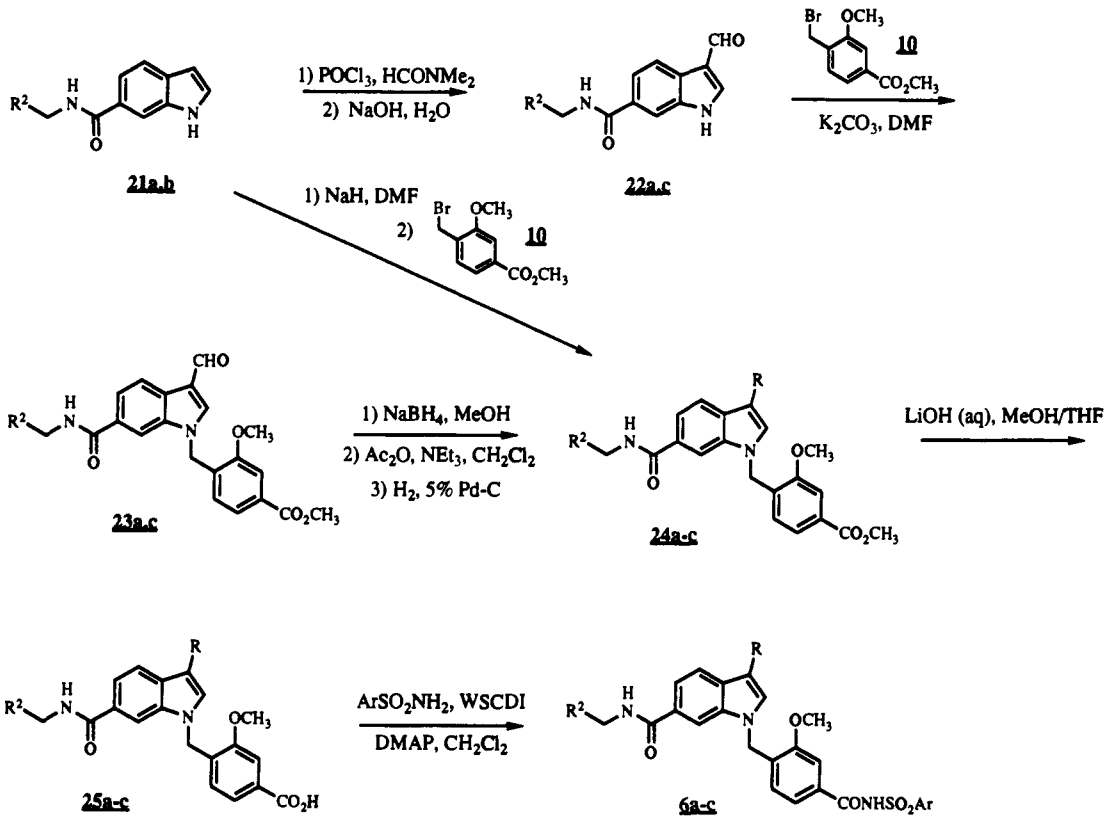
[a] For $R^2 = (CH_3CH_2)_2CHCH_2$; q, $R^1 = CH_3CH_2$; s, $R^1 = (CH_3)_2CH$; t, R^1 = c-C_5H_9; u, $R^1 = PhCH_2$; for $R^2 = C_5H_9CH_2$: v, $R^1 = CH_2{=}CHCH_2$; w, $R^1 = CH_3CH_2CH_2$.

hydrogenation of the allyl substituent to *N*-propyl in the case of **16b**) followed by condensation of the acid **17** with an amine gave the amide esters **11**. Saponification of the benzoate, followed by condensation with an arylsulfonamide gave the final drug candidates of generalized structure **5**.

For examination of the structure–activity relationships in the indole N(1) substituent, a minor modification of the above sequence was used (Scheme III). Hydrogenation of **16** to the monosubstituted indole acid **19**, followed by amide formation and N-alkylation gave the intermediate amide esters **11**, which were converted to drug candidates **5** as described above. This route provided easy access to a wide variety of N(1) substituents, including the benzyl and allyl groups, which were inaccessible via the previous route due to incompatibility of these substituents with the hydrogenolysis conditions.

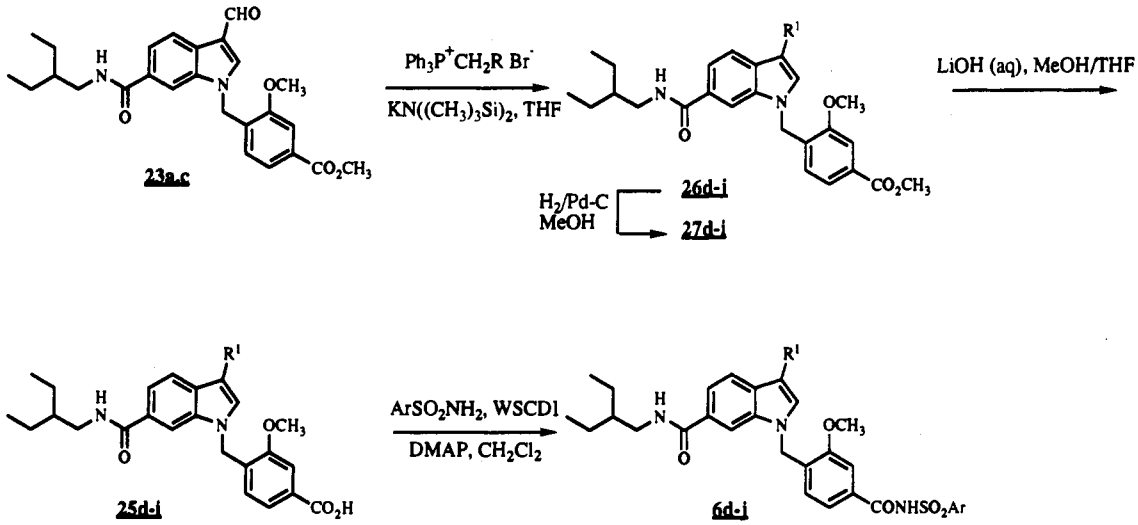
Our approach to the 1,3,6-trisubstituted indolecarboxamides **6** began with the known[5] indole-6-carboxamides **21** (Scheme IV). Deprotonation of the indole nitrogen atom using sodium hydride, followed by alkylation with the bromo toluic ester **10** in *N,N*-dimethylformamide provided the C(3)-unsubstituted derivative **24b** in good yield. Conversion to the corresponding carboxylic acid

Scheme IV. [a] Synthetic Route to 3-Unsubstituted and 3-Methylindoles 6



[a] **a**, R = CH_3, R^2 = c-C_5H_9; **b**, R = H, R^2 = $(CH_3CH_2)_2CH$; **c**, R = CH_3, R^2 = $(CH_3CH_2)_2CH$.

Scheme V. [a] Synthetic Route to 3-Alkenyl- and 3-Alkylindoles 6



[a] For **26**: **d**, R^1 = CH_2=CH; **e**, R^1 = CH_3CH=CH; **f**, R^1 = $(CH_3)_2CH$=CH; **g**, R^1 = C_6H_{10}=CH; **h**, R^1 = C_5H_8=CH; **i**, R^1 = PhCH=CH; **j**, R^1 = CH_3CH=CH; for **27** and **25**: **d**, R^1 = CH_3CH_2; **e**, R^1 = $CH_3CH_2CH_2$; **f**, R^1 = $(CH_3)_2CH_2CH_2$; **g**, R^1 = $C_6H_{11}CH_2$; **h**, R^1 = $C_5H_9CH_2$; **i**, R^1 = $PhCH_2CH_2$; **j**, R^1 = CH_3CH=CH.

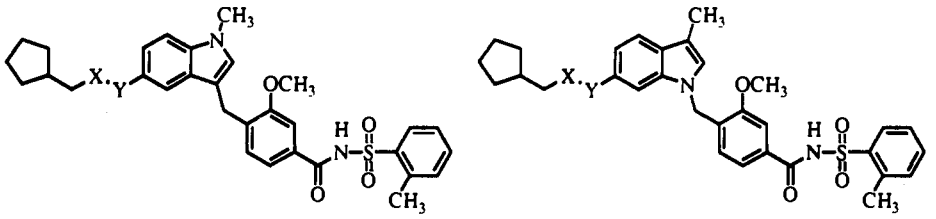
25b and sulfonimide **6b** was completed as described previously. For analogs substituted at C(3), the key intermediates, 3-formylindoles **22**, were prepared under standard Vilsmeier formylation conditions.[5] Reduction of the aldehyde moiety to the primary alcohol, followed by acetate formation and hydrogenolysis of the benzylic acetate afforded the C(3)-methyl derivatives **24a** and **24c**, which were similarly transformed into sulfonimides **6a** and **6c**, respectively.

The remaining C(3)-substituted indole-6-carboxamides were prepared as described in Scheme V. A Wittig reaction was performed on the 3-formylindole derivative **23** to afford the olefin **26**. The unsaturated derivatives could be transformed directly to the corresponding sulfonimides **6** via the carboxylic acid **25** or could first be hydrogenated to the saturated C(3) substituent **27**, which was subsequently converted to **6**.

Structure–Activity Relationships (SAR)

Introduction. Evaluation of the first members of the indole-5 and -6-carboxamide series (**5a** and **6a**, respectively) showed them to have affinity for the LTD_4 receptor at nanomolar concentrations, using a radioligand binding assay,[10,11] and they were active at similar concentrations in an in vitro functional assay.[12] Comparison to the corresponding indole amides **28**[3c] and **29**[5] (for structures,

Table I. Initial Comparison of Transposed Amides with 5- or 6-Carbamoylindoles



X–Y	no.	pK_i vs [^{3}H]LTD$_4$, guinea pig lung[a]	pK_B vs LTE$_4$, guinea pig trachea (n)[b]	ED_{50} in guinea pig[c] (μmol/kg) po	iv	ED_{50} ratio: po/iv	no.	pK_i vs [^{3}H]LTD$_4$, guinea pig lung[a]	pK_B vs LTE$_4$, guinea pig trachea (n)[b]	ED_{50} in guinea pig[c] (μmol/kg) po	iv	ED_{50} ratio: po/iv
	**28**	9.3	9.7 (6)	0.41	0.02	22	**29**	–	9.3 (6)	0.3	–	–
	**5a**	8.5	8.4 (6)	19.2	0.69	28	**6a**	8.0	8.9 (6)	~30	1.62	~20

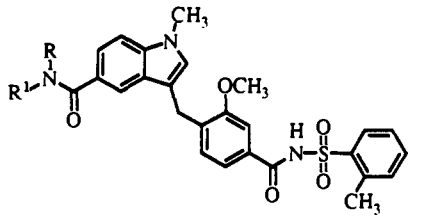
[a] Inhibition constant for displacement of [^{3}H]LTD$_4$ on guinea pig lung parenchymal membranes; K_i values are the mean of two experiments conducted in duplicate with separate batches. For detailed description of this binding assay, see ref 10. For ease of comparison between the wide potency range of compounds reported, the -log (K_i) "pK_i" values are tabulated. [b] K_B determined in guinea pig tracheal spirals with LTE$_4$ as agonist. See ref 11. n = number of concentration–response curves. [c] Determined in a conscious guinea pig "dyspnea" model, see ref 13. Percent protection from LTD$_4$-induced dyspnea was plotted as a function of dose. In general, the SEM for percent protection was ≤25% at each dose. ED_{50} values were obtained by regression analysis employing at least three doses from the linear portion of the dose–response curve.

see Table I) suggested that the transposed amides were approximately 10-fold less potent in terms of binding to the leukotriene receptor and antagonism of the effects of LTE$_4$ on isolated guinea pig trachea. When evaluated against the effects of LTD$_4$ in conscious guinea pigs,[13] however, a much larger difference in potency was noted between the two series. Following oral administration of the test compounds, the transposed amides were 40–100 times less active than their amide counterparts (Table I). Comparison of the oral and intravenous ED_{50}'s *within* series, however, suggested that the oral bioavailability of the transposed amides was similar to that observed in the amide series. The results of this comparison suggested that while the transposed amides were intrinsically less potent than the indole amides, the transposition of the amide moiety was tolerated by the receptor. Furthermore, the low po/iv ratios were interpreted as suggesting a grossly similar metabolism/distribution profile for the new series. Finally, the higher potency of the 3,5-disubstituted indole representative prompted us to explore this group of compound more extensively than the 3,6-disubstituted indole analogs. Encouraged by this comparison, our efforts were directed at the improvement of the inherent affinity of the transposed amides for the LT receptors, while maintaining their (presumably) good bioavailability. Examination of the generalized transposed amide structures suggested several regions of the molecules be systematically varied for this purpose. We will specifically discuss variations of the amide region, the 1-(or 3-)substituent of the indole nucleus, and the acylsulfonamide substituent.

Variations of the Amide Substituent in the Indole-5-carboxamide Series. The first region of the transposed amide series which was modified in an attempt to improve potency without affecting bioavailability was the amide substituent. In the 5-carbamoylindole series, it had been discovered that β-branched amides or α-branched urethane derivatives were clearly superior to other branched or unbranched derivatives.[3b] Similar evaluation of the transposed amide series suggested that the same general SAR held in this series as well. The results of this phase of the work are presented in Table II. It is apparent from the data presented in Table II that β-branched secondary amides **5a,e–k** were found to be approximately 10-fold more potent in binding to the LTD$_4$ receptor than α-branched (**5b,c**), phenethyl (**5l**), and cyclic or acyclic tertiary amides (**5m–o**). The β,β-disubstituted (**5p**) or γ-branched amides (**5d**) were the next most favorable substitution patterns, but were still 3 times less potent than the isomeric β-branched amide **5h**. The more potent compounds were examined in a functional in vitro assay where the ability of the test compound to inhibit the contractile response of guinea pig trachea to LTE$_4$ was evaluated. Work in previous series had generally shown good correlation between the binding assay and this functional paradigm. We were encouraged to find that this approximate correlation existed in the transposed amide series as well. Finally, evaluation of the best compounds in vivo versus LTD$_4$-induced bronchoconstriction in guinea pigs demonstrated low to moderate levels of oral activity. The effect of lipophilicity of the amide substituent on oral activity was clear from this data. Comparison of **5e** with **5g**, for example, shows the more lipophilic 2-ethylhexyl amide **5e**, 3-fold less potent in the pK_B assay, to be 3 times more potent orally than the 2-methylpropyl amide **5g** when administered to conscious guinea pigs. It was also clear, however, that the large increases in oral activity required for the transposed amides to be nearly as potent as the earlier urethane series were not going to be found simply by increasing the lipophilicity of the amide substituent further, as the more lipophilic members of the series (e.g. **5k**) exhibited loss of binding and functional in vitro activity.

Modifications of the Indole Nitrogen Substituent. Indole-5-carboxamides. We hypothesized that it was possible that the decreases in in vitro activity observed for the more lipophilic amide substituents could have been at least partially due to unfavorable steric effects in that region of the molecule. It was decided, therefore, to concurrently examine various substitutions at the N-1 position of the indole nucleus, with an emphasis on simple aliphatic groups. Incorporation of these substituents on the indole nitrogen atom of the inverted indole series was

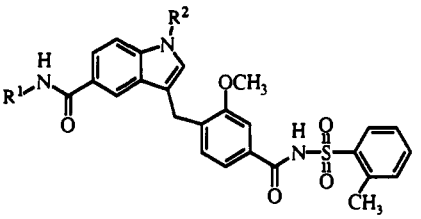
Table II. Structure–Activity Relationships in the Amide Substituent



no.	route	R¹RN	pK_i vs [³H]LTD₄, guinea pig lung[a]	pK_B vs LTE₄, guinea pig trachea (n)[b]	ED₅₀ in guinea pig (μmol/kg)[c] po	ED₅₀ in guinea pig (μmol/kg)[c] iv	ED₅₀ ratio: po/iv	analysis (C, H, N)
5a	A	$C_5H_9CH_2NH$	8.3	8.4 (6)	19.2	0.69	28	$C_{32}H_{35}N_3O_5S\cdot0.7H_2O$
5e	B	$C_4H_9(C_2H_5)CHCH_2NH$	8.2	8.1 (6)	8.06	0.28	29	$C_{34}H_{41}N_3O_5S$
5f	B	$(C_2H_5)_2CHCH_2NH$	8.7	8.0 (12)	14.73	1.09	14	$C_{32}H_{37}N_3O_5S\cdot0.2H_2O$
5g	B	$(CH_3)_2CHCH_2NH$	8.2	8.6 (6)	>30	–	–	$C_{30}H_{33}N_3O_5S\cdot0.5H_2O$
5h	B	$CH_3CH_2(CH_3)CHCH_2NH$	8.3	8.7 (5)	20.0	1.39	14	$C_{31}H_{35}N_3O_5S$
5i	B	$CH_3(CH_2)_2(CH_3)CHCH_2NH$	8.2	8.5 (6)	–	–	–	$C_{32}H_{37}N_3O_5S$
5j	B	$CH_3(CH_2)_4(CH_3)CHCH_2NH$	8.0	–	–	–	–	$C_{34}H_{41}N_3O_5S\cdot0.2H_2O$
5k	B	$CH_3(CH_2)_5(CH_3)CHCH_2NH$	8.1	7.5 (4)	–	–	–	$C_{35}H_{43}N_3O_5S$
5l	B	$Ph(CH_2)_2NH$	7.1	–	–	–	–	$C_{34}H_{33}N_3O_5S$
5b	A	$C_4H_9CH(C_2H_5)NH$	6.9	–	–	–	–	$C_{33}H_{39}N_3O_5S\cdot1.3H_2O$
5c	A	$C_6H_{11}NH$	7.0	–	–	–	–	$C_{32}H_{35}N_3O_5S\cdot0.1H_2O$
5d	A	$(CH_3)_2CH(CH_2)_2NH$	7.8	–	–	–	–	$C_{31}H_{35}N_3O_5S\cdot0.2H_2O$
5m	B	4-C_3H_7(cyc-C_5H_9N)	7.0	–	–	–	–	$C_{34}H_{39}N_3O_5S\cdot0.2H_2O$
5n	B	$(C_4H_9)_2N$	7.1	–	–	–	–	$C_{34}H_{41}N_3O_5S$
5o	B	$(CH_3)_2CHCH_2N(CH_3)$	7.2	–	–	–	–	$C_{31}H_{35}N_3O_5S$
5p	B	$(CH_3)_3CCH_2NH$	7.8	7.5 (4)	–	–	–	$C_{31}H_{35}N_3O_5S\cdot1.0H_2O$

[a] See Table I, footnote *a*. [b] See Table I, footnote *b*. [c] See Table I, footnote *c*.

Table III. Variation of the Indole Nitrogen Substituent

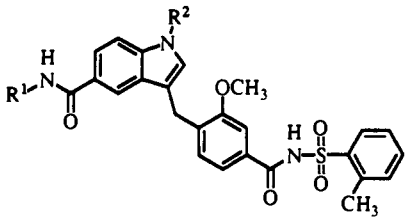


no.	route	R¹	R²	pK_i vs [³H]LTD₄, guinea pig lung[a]	pK_B vs LTE₄, guinea pig trachea (n)[b]	ED₅₀ in guinea pig (μmol/kg)[c] po	ED₅₀ in guinea pig (μmol/kg)[c] iv	ED₅₀ ratio: po/iv	analysis (C, H, N)
5f	B	2-EtBu[d]	CH_3	8.4	8.1 (6)	14.7	1.09	14	$C_{32}H_{37}N_3O_5S\cdot0.2H_2O$
5q	C,B	2-EtBu	Et	9.0	9.5 (5)	5.3	0.07	81	$C_{33}H_{39}N_3O_5S$
5r	B	2-EtBu	n-Pr	9.1	8.9 (12)	5.6	0.04	137	$C_{34}H_{41}N_3O_5S\cdot0.4H_2O$
5s	C	2-EtBu	i-Pr	9.3	8.8 (5)	4.7	0.02	300	$C_{34}H_{41}N_3O_5S$
5t	C	2-EtBu	c-C_5H_9	8.6	–	–	–	–	$C_{36}H_{43}N_3O_5S$
5u	C	2-EtBu	$PhCH_2$	8.9	8.3 (5)[g]	–	–	–	$C_{38}H_{41}N_3O_5S$
5a	B	cpCH_2[e]	CH_3	8.5	8.4 (6)	19.2	0.69	28	$C_{32}H_{35}N_3O_5S\cdot0.7H_2O$
5v	C	cpCH_2	allyl	9.4	8.3 (5)	9.9	0.03	355	$C_{34}H_{37}N_3O_5S$
5w	C	cpCH_2	n-Pr	9.5	8.7 (6)	4.8	0.03	179	$C_{34}H_{39}N_3O_5S\cdot0.5H_2O$
5g	B	2-MePr[f]	CH_3	8.2	8.6 (6)	>30	–	–	$C_{30}H_{33}N_3O_5S\cdot0.5H_2O$
5x	B	2-MePr	n-Pr	8.7	9.1 (6)	31.0	0.07	456	$C_{32}H_{37}N_3O_5S\cdot0.2H_2O$

[a] See Table I, footnote *a*. [b] See Table I, footnote *b*. As an example of K_B variability, the K_B of **5q** is $3.62 \pm 0.32 \times 10^{-10}$ M; the pK_B is 9.45 ± 0.04. [c] See Table I, footnote *c*. [d] 2-Ethylbutyl. [e] Cyclopentylmethyl. [f] 2-Methylpropyl. [g] An 11% suppression of the maximum contractile response of the tracheal tissue was observed.

easily accomplished via our synthetic route to these compounds. Since it had previously been observed that this region of the LT receptor could accommodate sterically demanding groups such as tertiary propionamides,[5] we felt confident that substantial changes in this region would not impair binding to the leukotriene receptor. In addition, concurrent results observed in a series of indole 5-propionamides,[14] where two methylene units were inserted between the indole nucleus and the carboxamide at C(5), suggested that a longer substituent (n-propyl) was beneficial to both in vitro and in vivo potency. The results of modification of the N(1) substituent are summarized in Table III. When more lipophilic substituents were placed on the indole nitrogen of 2-ethylbutyl amides, increases in receptor binding affinity were observed. This trend was followed by other amide substituents such as the cyclopentylmethyl or 2-methylpropyl derivatives. In all cases, the n-propyl chain was found to increase binding by 3–10-fold over the methyl-substituted indole. The ethyl (**5q**), n-propyl (**5r**), and isopropyl (**5s**) derivatives were of similar binding affinity, with the ethyl derivative in the 2-ethylbutyl amide series optimal when evaluated in the in vitro functional assay (pK_B = 9.5). The observation that a further increase in functional activity was not observed for either **5r** or **5s** suggests that an upper limit of lipophilicity has been surpassed in these derivatives.[3f]

Table IV. Pharmcokinetic Studies on Selected Transposed Amides



no.	R^1	R^2	po/iv	dose (mg/kg)	species (n)[a]	C_{max}[b] (ng/mL)	AUC[c] (ng/h per mL)	bioavailability (%)
5f	2-EtBu[d]	CH_3	14	1.0	rat(2)	410	5741	-
5q	2-EtBu	Et	81	2.5	rat(4)	1349 ± 390 (540)[f]	10185 ± 741 (4073)[f]	28.1 ± 2.0
5q	2-EtBu	Et		5.0	GP (2)	92	207	5.1
5w	$cpCH_2$[e]	Pr	179	1.0	rat (2)	106	1611	-

[a] n = number of animals. [b] Maximum concentration of unchanged drug in whole blood recorded in the period 0–24 h postdose. [c] Integrated area under the blood concentration vs time curve for the period 0–24 h postdose. [d] 2-Ethylbutyl. [e] Cyclopentylmethyl. [f] Numbers in parentheses are "normalized" to a 1.0 mg/kg dose for purposes of comparison.

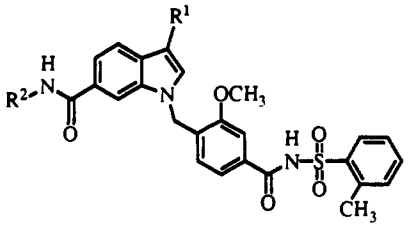
Attempts to decrease the overall lipophilicity of the molecule, and thus maintain good in vitro functional activity, by use of a less lipophilic amide substituent[15] in combination with an n-propyl substituent on N(1) afforded compounds **5w** and **5x**. While **5w** was found to be 6 times less active in the functional screen compared to its receptor binding affinity, similar to the direction of the potency difference observed for **5r**, compound **5x** exhibited the reverse trend, being twice as active in the functional screen than suggested by its binding affinity. Subsequent evaluation of these N-alkylated indoles in the conscious guinea pig model revealed a serious limitation of this strategy. While large increases in inherent in vivo potency (iv administration) were observed with longer N(1) substituents (e.g., compare **5f** with **5q**, Table III), the oral potencies of the ethyl (**5q**), n-propyl (**5r**), and isopropyl (**5s**) derivatives in the 2-ethylbutyl amide series were found to be marginally improved over that observed for **5f**, resulting in apparently low relative bioavailability of **5q**, **5r**, and **5s**. Since we had earlier observed that a po/iv ratio of <100 was the limit of "acceptable bioavailability" predicted by this model, we deemed the n-propyl and isopropyl compounds unacceptable; the ethyl derivative was judged acceptable. A similar trend in in vivo data was observed for the cyclopentylmethyl amides (**5a**, **5w**), while the 2-methylpropyl amides **5g** and **5x** were found to be insufficiently active following oral administration for further consideration. We feel that the lower bioavailability observed in the longer chain length substituents is a consequence of increased propensity to oxidative metabolism.[17] Incorporation of a benzyl group (**5u**) or an unsaturated substituent (**5v**) was also tried, but these compounds were not superior to the simple aliphatic analogs. The N-benzyl derivative **5u** was found to suppress the maximum contractile response of isolated trachea in the functional assay, suggestive of noncompetitive antagonism.[12]

In order to confirm that the po/iv ratio measured for the transposed amides was predictive of bioavailability in this series, blood levels were determined following oral administration of several transposed amides (**5f,q,w**) in both rat and guinea pig. In addition, the oral bioavailability of **5q** was measured in each species. The results of these studies are summarized in Table IV. The two compounds with acceptable po/iv ratios, N-methylindole **5f** and N-ethylindole **5q**, were found to produce blood levels following oral dosing in rats 2.5–3.5× those found for the N-propyl derivative **5w**, but were not significantly different from one another in this parameter. This observation suggested that our cutoff point for po/iv ratio in the conscious guinea pig model of 100 was reasonable for compounds of similar bioavailability. In addition, the maximum blood concentrations (C_{max}) and integrated area under the blood level versus time curve (AUC) for **5f** and **5q** compared well with the corresponding values previously observed for ICI 204,219. The bioavailability of **5q** in rat (28.1%) was approximately one-half that reported for ICI 204,219 (68%),[3c,18] but was still considered acceptable. The bioavailability measured for **5q** in guinea pig was significantly lower (5.1%) than that recorded in the rat. This difference could be understood on the basis of a more rapid clearance of **5q** by the guinea pig, as the time of maximum blood concentration (T_{max}) was found to be significantly shorter in the guinea pig (T_{max}(rat) = 4.0 h, T_{max}(gp) = 0.5 h). A similar species difference had also been observed in the 5-carbamoylindole series. As a consequence of this pharmacokinetic profile, the lower oral activity (in guinea pig) observed for transposed amides such as **5q**, in comparison to 5-carbamoylindoles such as ICI 204,219, could be ascribed to a combination of effects: lower inherent potency at the receptor and poorer bioavailability.

Variation of the Indole 3-Substituent in Indole-6-carboxamides. Concurrent with our efforts in the indole-5-carboxamide series, we explored the effect of variation of the 3-substituent of the 1-benzylindole-6-carboxamide series. The results of these variations are summarized in Table V. Given the absence of any clear superiority of the 3-substituted 1-benzylindole-6-carboxamide derivatives to the previous "inverted" indole series at the in vitro level, coupled with the earlier observation (Table I) that the "inverted" indole nucleus provided approximately 1.5 times the oral activity of the indole nucleus (i.e. **5a** vs **6a**), further evaluation of these compounds was not pursued.

Variation of the Acidic Functionality. In the original development of the substituted indole series of leukotriene antagonists, it was discovered that the acidic moiety could be varied with significant effects on both the in vitro and in vivo activity. Specifically, replacement of the carboxylic acid with an aryl-substituted sulfonimide was found to improve oral activity by a factor of 100.[3c,3d] Further exploration of sulfonimides revealed that o-substituted arylsulfonimides were especially beneficial.[3d] Consequently, we prepared phenyl, 2-tolyl, 2-chlorophenyl, and 2-bromophenyl sulfonimides in the current study. Selected examples are summarized in Table VI. It was quickly apparent that the arylsulfonimides were superior in vitro when compared to the corresponding carboxylic

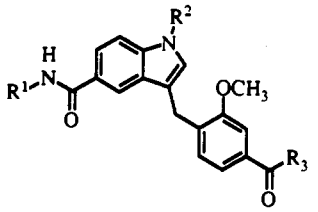
Table V. Variation of the 3-Substituent in Indole-6-carboxamides



no.	R^1	R^2	pK_i vs [^{3}H]LTD$_4$, guinea pig lung[a]	pK_B vs LTE$_4$, guinea pig trachea (n)[b]	analysis (C, H, N)
6a	CH_3	cpCH_2[c]	8.0	8.9 (6)	$C_{32}H_{35}N_3O_5S$
6b	H	2-EtBu[d]	7.9	-	$C_{31}H_{35}N_3O_5S$
6c	CH_3	2-EtBu	8.6	8.4 (6)	$C_{32}H_{37}N_3O_5S$
6d	Et	2-EtBu	8.5	8.2 (5)	$C_{33}H_{39}N_3O_5S$
6e	n-Pr	2-EtBu	8.9	8.8 (5)[e]	$C_{34}H_{41}N_3O_5S\cdot0.5H_2O$
6f	i-PrCH_2	2-EtBu	8.2	8.2 (5)	$C_{35}H_{43}N_3O_5S$
6g	$C_6H_{11}CH_2$	2-EtBu	8.6	-	$C_{38}H_{47}N_3O_5S$
6h	$cC_5H_9CH_2$	2-EtBu	9.0	-	$C_{37}H_{45}N_3O_5S\cdot0.5H_2O$
6i	$PhCH_2CH_2$	2-EtBu	7.6	-	$C_{39}H_{43}N_3O_5S$
6j	(*Z*)-CH_3CH=CH	2-EtBu	7.3	-	$C_{34}H_{39}N_3O_5S\cdot0.3H_2O$

[a] See Table I, foonote *a*. [b] See Table I, footnote *b*. [c] Cyclopentylmethyl. [d] 2-Ethylbutyl. [e] An 11% suppression of the maximum contractile response of the tracheal tissue was observed.

Table VI. Variation of Acidic Region



no.	route	R^1	R^2	R^3	pK_i vs [^{3}H]LTD$_4$, guinea pig lung[a]	pK_B vs LTE$_4$, guinea pig trachea (n)[b]	ED$_{50}$ in guinea pig[c] (μmol/kg) po	ED$_{50}$ in guinea pig[c] (μmol/kg) iv	ED$_{50}$ ratio: po/iv	analysis (C,H,N)
18x	B	2-MePr[d]	nPr	OH	5.6	-	-	-	-	$C_{25}H_{30}N_2O_4$
5x	B	2-MePr	nPr	$NHSO_2$(2-$CH_3C_6H_4$)	8.7	9.1 (6)	31	0.07	456	$C_{32}H_{37}N_3O_5S\cdot0.2H_2O$
5y	B	2-MePr	nPr	$NHSO_2C_6H_5$	8.1	7.6 (6)	-	-	-	$C_{31}H_{35}N_3O_5S$
18r	B	2-EtBu[e]	nPr	OH	6.2	-	-	-	-	$C_{27}H_{34}N_2O_4\cdot0.2H_2O$
5r	B	2-EtBu	nPr	$NHSO_2$(2-$CH_3C_6H_4$)	9.1	8.9 (12)	5.6	0.04	137	$C_{34}H_{41}N_3O_5S\cdot0.4H_2O$
5z	C	2-EtBu	nPr	$NHSO_2C_6H_5$	8.4	7.7 (5)	-	-	-	$C_{33}H_{39}N_3O_5S$
18f	B	2-EtBu	CH_3	OH	6.0	-	-	-	-	$C_{25}H_{30}N_2O_4\cdot0.2H_2O$
5f	B,C	2-EtBu	CH_3	$NHSO_2$(2-$CH_3C_6H_4$)	9.0	8.1 (6)	14.7	1.09	14	$C_{32}H_{37}N_3O_5S\cdot0.2H_2O$
5aa	C	2-EtBu	CH_3	$NHSO_2$(2-ClC_6H_4)	8.2	-	-	-	-	$C_{31}H_{34}ClN_3O_5S$
5bb	C	2-EtBu	CH_3	$NHSO_2$(2-BrC_6H_4)	8.4	9.1 (6)	21.4	0.84	25	$C_{31}H_{34}BrN_3O_5S\cdot0.2H_2O$

[a] See Table I, footnote *a*. [b] See Table I, footnote, *b*. [c] See Table I, footnote *c*. [d] 2-Methylpropyl. [e] 2-Ethylbutyl.

acids in the transposed amide series, exhibiting a 100-fold increase in affinity for the LT receptor. As expected, the *o*-substituted derivatives provided further increases in in vitro activity and possessed good in vivo activity. No substantial differences were observed between the 2-tolyl (e.g., **5f**) and 2-bromophenyl (e.g. **5bb**) sulfonimides, and the 2-chlorophenyl (e.g. **5aa**) derivatives were marginally less potent, which paralleled observations made in the 5-carbamoylindole series. Consequently, no extensive exploration of further modifications of this region was pursued.

Summary and Conclusion

The current study has extended the structural scope of leukotriene antagonists based on the indole nucleus by transposition of the amide functionality found in earlier series. Examples of the transposed amide series have been shown to be potent in vitro antagonists of the LTD$_4$ receptor and have exhibited moderate levels of protection in an in vivo model of labored breathing induced by LTD$_4$. Structure–activity studies in three regions of the transposed amide molecule have afforded increased in vitro potency to levels comparable to the 5-carbamoylindole series, while oral activity of similar magnitude to ICI 204,-219 has remained elusive. A trend which suggested that more lipophilic transposed amides were needed to increase oral activity was exploited with some success and has led to the discovery of **5q**, a transposed amide with subnanomolar affinity for the leukotriene receptor and an oral ED$_{50}$ of 5 mg/kg in a model of asthma in guinea pigs. In this model, ICI 204,219 was active at 0.4 mg/kg. The absolute bioavailability of **5q** has been found to be 28% in the rat, as compared to 68% for ICI 204,219, with significant levels of **5q** observed in the blood of rats up to 24 h postdose. By comparison, the bioavailability of **5q** was somewhat lower in guinea pig (5.1%), a trend which had been observed for ICI 204,219. These results suggest that the transposed amide series, exemplified by **5q**, offer an opportunity to duplicate the in vitro and in vivo profile of leukotriene antagonist properties of ICI 204,219 with

only minor additional modification of the amide, indole, or sulfonamide substituents.

Experimental Section

General Methods. Proton NMR (^{1}H NMR) spectra were recorded on either an IBM NR-80 (80 MHz), Bruker WM 250 (250 MHz) or Bruker WM 300 (300 MHz) instrument in the solvent indicated. Chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane. Peaks are reported as the following: s, singlet; d, doublet; t, triplet; b, broad; ex, exchanged by added deuterotrifluoroacetic acid. Mass spectra (CIMS) were recorded on a Kratos MS-80 instrument or Finnigan MAT-60 operating in the chemical ionization mode using methane as reagent gas. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Combustion analyses for carbon, hydrogen, and nitrogen were performed on a Perkin-Elmer 241 instrument by ICI Americas Analytical Department, and are within ±0.4% of theoretical values. Flash chromatography was performed using the indicated solvent ratios (v/v) on Kieselgel 60 (230–400 mesh) supplied by E. Merck. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl; dichloromethane, pyridine, *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were distilled from calcium hydride. All other reagents were purified by standard methods (recrystallization or distillation) as needed.

General Procedure for Hydrolysis of Benzoate Esters 11. 4-[[5-[(Cyclopentylmethyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxybenzoic Acid (18a). A solution of **11a** (350 mg, 0.81 mmol) in tetrahydrofuran (2 mL) and methanol (2 mL) was treated with a solution of lithium hydroxide monohydrate (203 mg, 4.84 mmol) in water (0.8 mL). The resulting solution was stirred at room temperature for 18 h. The organic solvents were then removed in vacuo, and the aqueous residue was diluted to ca. 5 mL with water and washed with ethyl acetate (5 mL). The aqueous layer was separated and then acidified to pH = 1.5. The white precipitate which formed was isolated by filtration, washed with a few drops of water, and dried in vacuo (100 °C, 0.05 Torr) to afford **18a** (295 mg, 0.70 mmol, 87%) as a white powder: mp 237–239 °C; ^{1}H NMR (d_6-DMSO) δ 8.31 (m, 1 H, NHCO), 8.08 (s, 1 H, H-C(4')), 7.65 (d, J = 8.8 Hz, 1 H, H-C(6')), 7.49–7.40 (m, 3 H), 7.15 (d, J = 7.8 Hz, 1 H, H-C(5)), 7.13 (s, 1 H, H-C(2')), 4.06 (s, 2 H, indole-CH_2), 3.91 (s, 3 H, OCH_3), 3.75 (s, 3 H, NCH_3), 3.18 (t, J = 6.4 Hz, 2 H, $(C_5H_9)CH_2$), 2.16 (m, 1 H), 1.65–1.20 (m, 8 H).

General Procedure for Preparation of *N*-Acylsulfonamides 5. 4-[[5-[(2-Ethylbutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5f). A solution of carboxylic acid **18f** (482 mg, 1.14 mmol), 2-toluenesulfonamide (201 mg, 1.18 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (268 mg, 1.37 mmol) and 4-(dimethylamino)pyridine (147 mg, 1.17 mmol) in dichloromethane (6 mL) was stirred at room temperature for 36 h. The reaction mixture was diluted with dichloromethane (25 mL), washed sequentially with 10% hydrochloric acid (3 × 25 mL), water (25 mL), and brine (25 mL), dried over $MgSO_4$, and filtered and the solvent evaporated to leave a white foam. Trituration with hexane and filtration afforded **5f** (560 mg, 0.97 mmol, 85%) as a white solid: mp 134–136 °C; ^{1}H NMR (d_6-DMSO) δ 12.58 (brs, 1 H, SO_2NH), 8.06 (t, 1 H, NH(amide), 8.21 (s, 1 H), 8.06 (d, J = 3.7 Hz, 1 H), 7.70–7.38 (m, 7 H), 7.17–7.12 (m, 2 H), 4.05 (s, 1 H, indole-CH_2), 3.91 (s, 3 H, OCH_3), 3.75 (s, 3 H, NCH_3), 3.18 (t, J = 6.1 Hz, 2 H, $(CH_3CH_2)_2CHCH_2N$), 2.60 (s, 3 H, $ArCH_3$), 1.51 (m, 1 H, $(CH_3CH_2)_2CHCH_2N$), 1.30 (m, 4 H, $(CH_3CH_2)_2CHCH_2N$), 0.86 (t, 6 H, $(CH_3CH_2)_2CHCH_2N$); CIMS m/z 578 ($(M + H + 2)^+$, 11%), 577 ($(M + H + 1)^+$, 37), 576 ($(M + H)^+$, 100), 405 (17), 172 (98), 155 (12). Anal. ($C_{32}H_{37}N_3O_5S \cdot 0.2H_2O$) C, H, N.

5-[(Cyclopentylmethyl)carbamoyl]indole (8a). A suspension of indole-5-carboxylic acid (**7**) (15.0 g, 93.17 mmol), cyclopentylmethylamine (8.39 g, 84.60 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (17.89 g, 94.07 mmol), and 4-(dimethylamino)pyridine (11.37 g, 93.07 mmol) in dichloromethane (233 mL) was stirred at room temperature for 48 h. The homogeneous mixture was washed with 10% hydrochloric acid (3 × 100 mL), water (100 mL), 10% aqueous sodium carbonate (3 × 100 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and evaporated to leave a white powder. Purification by flash chromatography (1:4 EA/$CHCl_3$) gave amide **8a** (15.53 g, 68.11 mmol, 73%) as a white powder: ^{1}H NMR (80 MHz, d_6-DMSO) δ 8.25 (m, 1 H, NHCO), 8.09 (m, 1 H, H-C(4)), 7.66–7.33 (m, 3 H), 6.50 (m, 1 H, H-C(3)), 3.18 (m, 2 H, CH_2N), 2.49–1.12 (m, 9 H, C_5H_9).

Also prepared in this manner were the following: **(*R*,*S*)-5-[(1-Ethylbutyl)carbamoyl]indole (8b)**: yield 36%; ^{1}H NMR (80 MHz, d_6-DMSO) δ 9.06 (m, 1 H, indole-NH), 8.07 (d, J = 1.1 Hz, 1 H, H-C(4)), 7.70–7.23 (m, 3 H), 6.59 (d, J = 3.2 Hz, 1 H, H-C(3)), 5.91 (brd, J = 9.1 Hz, 1 H, NHCO), 4.15 (m, 1 H, CHN), 1.81–1.20 (m, 8 H), 1.06–0.80 (m, 6 H, 2 × CH_3).

5-(Cyclohexylcarbamoyl)indole (8c): yield 52%; ^{1}H NMR (80 MHz, d_6-DMSO) δ 11.24 (m, 1 H, indole-NH), 8.09 (m, 1 H, H-C(4)), 7.95 (d, J = 8.0 Hz, 1 H, CONH), 7.68–7.31 (m, 3 H), 6.49 (m, 1 H, H-C(3)), 3.73 (m, 1 H, CHN), 1.81–1.21 (m, 10 H).

5-[(3-Methylbutyl)carbamoyl]indole (8d): yield 82%; ^{1}H NMR (80 MHz, $CDCl_3$) δ 8.53 (br, 1 H, indole-NH), 8.08 (s, 1 H, H-C(4)), 7.70–7.22 (m, 3 H), 6.64 (m, 1 H, H-C(3)), 6.09 (br, 1 H, CONH), 3.53 (m, 2 H, CH_2NHCO), 1.55 (m, 3 H), 0.95 (d, J = 5.9 Hz, 6 H, $(CH_3)_2CH$).

Methyl 4-[[5-[(Cyclopentylmethyl)carbamoyl]indol-3-yl]methyl]-3-methoxybenzoate (10a). A mixture of indole amide **8a** (3.97 g, 16.40 mmol) and silver oxide (3.84 g, 16.55 mmol) in dioxane (35 mL) was heated to reflux for 2 h and then was treated with a solution of methyl 4-(bromomethyl)-3-methoxybenzoate (**9**) (4.25 g, 16.41 mmol) in dioxane (5 mL). The mixture was heated at reflux for an additional 4 h and cooled to room temperature, and the inorganic salts were removed by filtration through diatomaceous earth. The filtrate was concentrated to leave an amber foam. Purification by flash chromatography (99:1 $CHCl_3$/MeOH) afforded the desired C(3)-alkylated indole **10a** (2.10 g, 5.00 mmol, 30%) as an ivory solid: ^{1}H NMR (80 MHz, $CDCl_3$) δ 8.22 (br, 1 H, indole-NH), 7.99 (brs, 1 H, H-C(4')), 7.65–6.95 (m, 6 H), 6.11 (brm, 1 H, NHCO), 4.14 (s, 2 H, indole-CH_2), 3.91 (s, 3 H, OCH_3), 3.83 (s, 3 H, CO_2CH_3), 3.40 (dd, J = 6.9, 5.8 Hz, 2 H, CH_2NCO), 1.91–1.17 (m, 9 H, C_5H_9).

Methyl 4-[[5-[(Cyclopentylmethyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxybenzoate (11a). A solution of methyl 4-[[5-[(cyclopentylmethyl)carbamoyl]-indol-3-yl]methyl]-3-methoxybenzoate (**10a**) (1.52 g, 3.62 mmol) in DMF (5 mL) was added to a 0 °C suspension of sodium hydride (87 mg, 3.63 mmol) in DMF (3 mL). The mixture was stirred at 0 °C for 0.5 h and then was treated with iodomethane (570 mg, 3.98 mmol). The reaction was allowed to warm to room temperature, stirred for 2 h, and then quenched by careful addition of 10% aqueous ammonium chloride (5 mL). The excess DMF was removed in vacuo and the residue partitioned between water (25 mL) and ethyl acetate (25 mL). The organic extract was washed with water (2 × 25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and evaporated to leave an amber oil. Purification by flash chromatography (1:10 EA/$CHCl_3$) afforded **11a** (860 mg, 1.98 mmol, 55%): ^{1}H NMR (80 MHz, $CDCl_3$) δ 7.99 (d, J = 1.3 Hz, 1 H, H-C(4')), 7.68–7.09 (m, 5 H), 6.79 (s, 1 H, H-C(2')), 6.11 (brm, 1 H, NHCO), 4.12 (s, 2 H, indole-CH_2), 3.92 (s, 3 H, OCH_3), 3.89 (s, 3 H, CO_2CH_3), 3.73 (s, 3 H, N-CH_3), 3.40 (dd, J = 6.9, 5.7 Hz, 2 H, CH_2NCO), 2.18–1.16 (m, 9 H, C_5H_9).

(*R*,*S*)-Methyl 4-[[5-[(1-Ethylpentyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxybenzoate (11b). A solution of 5-[(1-ethylpentyl)carbamoyl]indole (**8b**) (1.23 g, 4.54 mmol) in DMF (10 mL) was added to a 0 °C suspension of sodium hydride (135 mg, 5.63 mmol) in DMF (5 mL). The resulting solution was stirred at 0 °C for 0.5 h, then was treated with iodomethane (651 mg, 4.58 mmol), and allowed to warm to room temperature. After 1 h at room temperature, the reaction was quenched by careful addition of 10% aqueous ammonium chloride (1 mL) and then was poured into water (25 mL). The precipitate which formed was removed by filtration, washed with water (10 mL), and dried in vacuo to afford a peach-colored solid (1.13 g, 3.96 mmol, 87%). A mixture of this product and silver oxide (964 mg, 4.16 mmol) in dioxane (10 mL) was heated to reflux for 4 h and then was treated with methyl 4-(bromomethyl)-3-methoxybenzoate (1.08 g, 4.15 mmol) at reflux. After 18 h at reflux, an additional portion of the ester (355 mg, 1.37 mmol) was added and heating was continued for 7 h. The mixture was cooled, the silver salts were

removed by filtration through diatomaceous earth, and the filtrate was evaporated to yield an amber syrup. Purification by flash chromatography (3×, Et_2O; 1:1 EA/H; 3:10 EA/$CHCl_3$) afforded, after combination of clean fractions, **11b** (600 mg, 1.33 mmol, 34%): ^1H NMR (80 MHz, d_6-DMSO) δ 8.01 (brs, 1 H, H-C(4′)), 7.69–7.11 (m, 5 H), 6.80 (s, 1 H, H-C(2′)), 5.75 (brm, 1 H, NHCO), 4.14 (s, 3 H, indole-CH_2, C*H*NHCO), 3.93 (s, 3 H, OCH_3), 3.84 (s, 3 H, CO_2CH_3), 3.75 (s, 3 H, NCH_3), 1.65–1.26 (m, 8 H), 1.05–0.89 (m, 6 H, 2 × CH_3).

Prepared by the above sequence (method A) from indoleamides **8a–d** were the following: **4-[[5-[(2-Cyclopentylmethyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5a)**: mp 152–154 °C; ^1H NMR (d_6-DMSO) δ 12.60 (br s, 1 H, SO_2NH), 8.30 (m, 1 H, NH(amide)), 8.06 (s, 1 H), 8.03 (d, J = 7.5 Hz, 1 H), 7.66 (dd, J = 10, 1.53 Hz, 1 H, H-C(6′)), 7.58–7.38 (m, 7 H), 7.13 (d, J = 8.4 Hz, 1 H, H-C(5)), 7.12 (s, 1 H, H-C(2′)), 4.04 (s, 2 H, indole-CH_2), 3.90 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3), 3.18 (t, J = 6.05 Hz, 2 H, $CHCH_2NH$), 2.59 (s, 3 H, $ArCH_3$), 2.2–2.1 (m, 1 H), 1.64–1.15 (m, 8 H); CIMS m/z 576 ((M + H + 2)$^+$, 10%), 545 ((M + H + 1)$^+$, 31), 544 ((M + H)$^+$, 100), 225 (11), 172 (13). Anal. ($C_{32}H_{35}N_3O_5S·0.7H_2O$) C, H, N.

(*R,S*)-4-[[5-[(1-Ethylpentyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5b): mp 207–209 °C; ^1H NMR (d_6-DMSO) 8.12 (s, 1 H, H-C(4″)), 7.86 (m, 2 H), 7.67 (d, J = 8.4 Hz, 1 H), 7.49 (s, 1 H), 7.41–7.07 (m, 5 H), 7.05–7.01 (d, 2 H), 4.01 (s, 2 H, indole-CH_2), 3.78 (m, 1 H, CH_3CH), 3.82 (s, 3 H, OCH_3), 3.73 (s, 3 H, NCH_3), 3.31 (s, 3 H, $ArCH_3$), 1.57–1.39 (m, 4 H), 1.56–1.17 (m, 4 H, $CH_3(CH_2)_2$), 0.96–0.78 (m, 6 H). Anal. ($C_{33}H_{39}N_3O_5S·1.0H_2O$) C, H, N.

4-[[5-(Cyclohexylcarbamoyl)-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5c): mp 159–161 °C; ^1H NMR (d_6-DMSO) δ 12.59 (br s, 1 H, SO_2NH), 8.14–7.93 (m, 3 H), 7.75–7.35 (m, 7 H), 7.21–7.11 (m, 2 H), 4.04 (s, 2 H, indole-CH_2), 3.91 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3), 2.60 (s, 3 H, $ArCH_3$), 1.89–1.0 (m, 10 H); CIMS m/z 574 ((M + H)$^+$, 2.3%), 172 (29), 147 (83), 106 (15), 97 (17), 79 (34), 74 (100). Anal. ($C_{32}H_{35}N_3O_5S·0.1H_2O$) C, H, N.

4-[[5-[(3-Methylbutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5d): mp 134–135 °C; ^1H NMR (d_6-DMSO) δ 8.24 (t, 1 H, SO_2NH), 8.06–8.01 (m, 2 H), 7.67–7.37 (m, 7 H), 7.14–7.12 (m, 2 H), 4.04 (s, 2 H, indole-CH_2), 3.91 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3), 3.33–3.26 (m, 2 H, CH_2N), 2.59 (s, 3 H, $ArCH_3$), 1.67–1.51 (m, 1 H, $(CH_3)_2CH$), 1.46–1.40 (m, 2 H, $(CH_3)_2CHCH_2$), 0.90 (d, J = 6.7 Hz, 6 H, $(CH_3)_2CH$); CIMS m/z 564 ((M + H + 2)$^+$, 12%), 563 ((M + H + 1)$^+$, 35), 562 ((M + H)$^+$, 100), 475 (11), 437 (15), 409 (27), 408 (22). Anal. ($C_{31}H_{35}N_3O_5S·0.2H_2O$) C, H, N.

Benzyl Indole-5-carboxylate (14). A solution of indole-5-carboxylic acid (7) (20.0 g, 0.12 mol), benzyl alcohol (64.9 g, 0.60 mol), and triphenylphosphine (157.0 g, 0.59 mol) in dry THF (1.2 L) was cooled to 5 °C and treated dropwise with diethyl azodicarboxylate (90.0 g, 0.51 mol). Upon complete addition, the mixture was allowed to warm to room temperature. The reaction was stirred for 24 h and then concentrated to remove the solvent. The residue was suspended in ether (1 L) and filtered and the filtrate evaporated to yield a yellow syrup. Purification by flash chromatography on silica gel (3.8 kg), eluting with 2:1 hexane/dichloromethane (4 L), 1:1 hexane/dichloromethane (4 L), and 1:2 hexane/dichloromethane (4 L) gave a yellow-white solid, which upon trituration with 1:1 hexane/dichloromethane afforded the product (74.2 g, 0.30 mol, 70%) as a white solid: mp 127–129 °C; ^1H NMR (80 MHz, $CDCl_3$) δ 8.43 (d, J = 1.6 Hz, 1 H, H-C(4)), 8.42 (br, 1 H, NH), 7.92 (dd, J = 1.6, 8.6 Hz, 1 H, H-C(6)), 7.48–7.18 (m, 7 H), 6.61 (m, 1 H, H-C(3)), 5.37 (s, 2 H, CH_2O).

Methyl 4-[[5-(Benzyloxycarbonyl)indol-3-yl]methyl]-3-methoxybenzoate (15). A solution of benzyl indole-5-carboxylate (14) (1.0 g, 3.98 mmol) and methyl 4-(bromomethyl)-3-methoxybenzoate (9) (2.06 g, 7.97 mmol) in dry DMF (10 mL) was heated at 80 °C for 24 h. The reaction was cooled, poured into water (100 mL), and extracted with ethyl acetate (3 × 75 mL). The organic extracts were washed with water (50 mL) and brine (50 mL), combined, dried over $MgSO_4$, and evaporated to give an amber oil. Purification by flash chromatography (1:4 EA/H) yielded recovered **9** (1.11 g, 4.28 mmol), recovered **14** (300 mg, 1.20 mmol), and **15** (540 mg, 1.26 mmol, 32%, 45% based on recovered 14): ^1H NMR (80 MHz, $CDCl_3$) δ 8.38 (d, J = 1.6 Hz, 1 H, H-C(4′)), 8.18 (br, 1 H, indole-NH), 7.92 (dd, J = 1.6, 8.6 Hz, 1 H, H-C(6′)), 7.58–7.09 (m, 9 H), 6.97 (d, J = 2.2 Hz, 1 H, H-C(2′)), 5.37 (s, 2 H, $PhCH_2O$), 4.13 (s, 2 H, indole-CH_2), 3.90 (s, 3 H, OCH_3), 3.86 (s, 3 H, CO_2CH_3).

Methyl 4-[[5-(Benzyloxycarbonyl)-1-methylindol-3-yl]methyl]-3-methoxybenzoate (16a). A solution of methyl 4-[5-(benzyloxycarbonyl)indol-3-yl]methyl-3-methoxybenzoate (**15**) (2.0 g, 4.7 mmol) in dry DMF (10 mL) was added to a slurry of sodium hydride (127 mg, 5.1 mmol) in dry DMF (25 mL) at 0 °C. The mixture was stirred for 1 h, then was treated with iodomethane (668 mg, 4.7 mmol), and allowed to warm to room temperature over 1 h. The mixture was cooled to 0 °C, quenched by careful addition of 10% aqueous NH_4Cl (5 mL), and poured into water (50 mL). The solution was decanted from the semisolid product, which was then dissolved in ethyl acetate (100 mL). The organic solution was washed with water (50 mL) and brine (50 mL). Each aqueous wash was extracted with ethyl acetate (100 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated to leave an amber gum. Purification by flash chromatography (1:4 EA/H) afforded **16a** as a clear syrup (1.06 g, 2.40 mmol, 51%): ^1H NMR (80 MHz, $CDCl_3$) δ 8.38 (d, J = 1.6 Hz, 1 H, H-C(4′)), 7.92 (dd, J = 1.6, 8.6 Hz, 1 H, H-C(6′)), 7.58–7.09 (m, 9 H), 6.97 (d, J = 2.2 Hz, 1 H, H-C(2′)), 5.37 (s, 2 H, $PhCH_2O$), 4.13 (s, 2 H, indole-CH_2), 3.90 (s, 3 H, OCH_3), 3.86 (s, 3 H, CO_2CH_3), 3.75 (s, 3 H, NCH_3).

Methyl 4-[[5-Carboxy-1-methylindol-3-yl]methyl]-3-methoxybenzoate (17a). A solution of methyl 4-[[5-(benzyloxycarbonyl)-1-methylindol-3-yl]methyl]-3-methoxybenzoate (**16a**) (3.29 g, 7.42 mmol) in THF/methanol (1:1, 100 mL) was added to a suspension of 10% palladium on carbon (410 mg) in methanol (10 mL). The heterogeneous mixture was placed under an atmosphere of hydrogen (50 psi) and shaken for 1.5 h. Some of the product precipitated during the reaction. The catalyst was removed by filtration through diatomaceous earth and the filter cake rinsed with THF (3 × 250 mL). Evaporation of the filtrate gave **17a** (2.30 g, 6.51 mmol, 88%): ^1H NMR (80 MHz, d_6-DMSO) δ 8.14 (d, J = 1.0 Hz, 1 H, H-C(4′)), 7.75 (m, 1 H, H-C(6′)), 7.50–7.15 (m, 4 H), 7.19 (s, 1 H, H-C(2′)), 4.07 (s, 2 H, indole-CH_2), 3.91 (s, 3 H, OCH_3), 3.82 (s, 3 H, CO_2CH_3), 3.76 (s, NCH_3).

Methyl 4-[[5-[(2-Ethylbutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxybenzoate (11f). A solution of methyl 4-[[5-carboxy-1-methylindol-3-yl]methyl]-3-methoxybenzoate (**17a**) (750 mg, 2.12 mmol), 2-ethylbutylamine (241 mg, 2.34 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (497 mg, 2.55 mmol), and 4-(dimethylamino)pyridine (268 mg, 2.12 mmol) in dichloromethane (11 mL) was stirred at room temperature for 36 h. The mixture was diluted with dichloromethane (50 mL), washed with 10% hydrochloric acid (2 × 25 mL), water (25 mL), and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated to give a yellow foam. Purification by flash chromatography (1:4 EA/H) afforded **11f** (610 mg, 1.40 mmol, 66%) as a white foam: ^1H NMR (d_6-DMSO) δ 8.01 (d, J = 1.6 Hz, 1 H, H-C(4′)), 7.60 (dd, J = 1.6, 8.6 Hz, 1 H, H-C(6′)), 7.54 (d, J = 2.6 Hz, 1 H, H-C(2)), 7.52 (d, J = 8.6 Hz, 1 H, H-C(7′)), 7.28 (dd, J = 2.6, 7.7 Hz, 1 H, H-C(6)), 7.15 (d, J = 7.7 Hz, 1 H, H-C(5)), 6.25 (m, 1 H, NHCO), 4.13 (s, 2 H, indole-CH_2), 3.93 (s, 3 H, OCH_3), 3.90 (s, 3 H, CO_2CH_3), 3.75 (s, 3 H, NCH_3), 3.43 (t, J = 6.0 Hz, 2 H, $(CH_3CH_2)_2CHCH_2$), 1.55 (m, 1 H, $(CH_3CH_2)_2CHCH_2$), 1.39 (m, 4 H, $(CH_3CH_2)_2CHCH_2$), 0.94 (t, J = 7.3 Hz, 6 H, $(CH_3CH_2)_2CHCH_2$).

4-[[5-[(2-Ethylbutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxybenzoic Acid (18f). A solution of **11f** (610 mg, 1.40 mmol) in THF (3.5 mL) and methanol (3.5 mL) was treated with a solution of lithium hydroxide monohydrate (350 mg, 8.33 mmol) in water (1.4 mL). The mixture was stirred at room temperature for 18 h, then was acidified to pH ~ 2 by addition of 10% hydrochloric acid. The precipitate which formed was collected and washed with water to afford the carboxylic acid **18f** (540 mg, 1.28 mmol, 91%) as a white solid: mp 222–224 °C; ^1H NMR (d_6-DMSO) δ 12.84 (brs, 1 H, CO_2H), 8.20 (t, 1 H, NH(amide), 8.06 (s, 1 H, H-C(4′)), 7.67 (d, J = 8.5 Hz, 1 H, H-C(6′)), 7.48–7.39 (m, 3 H), 7.15 (d, J = 7.7 Hz, 1 H, H-C(5)), 7.12 (s, 1 H, H-C(2′)), 4.05 (s, 1 H, indole-CH_2), 3.89 (s, 3 H,

OCH_3), 3.74 (s, 3 H, NCH_3), 3.18 (t, J = 6.1 Hz, 2 H, $(CH_3CH_2)_2CHCH_2N$), 1.51 (m, 1 H, $(CH_3CH_2)_2CHCH_2N$), 1.30 (m, 4 H, $(CH_3CH_2)_2CHCH_2N$), 0.86 (t, 6 H, $(CH_3CH_2)_2CHCH_2N$); CIMS m/z 424 ((M + H + 1)$^+$, 28%), 423 ((M + H)$^+$, 100), 405 (12), 322 (13). Anal. ($C_{25}H_{30}N_2O_4 \cdot 0.2H_2O$) C, H, N.

Prepared by the above sequence (method B) from benzyl indole-5-carboxylate (14) were the following: **(*R,S*)-4-[[5-[(2-Ethylhexyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5e)**: mp 118–120 °C; ^{1}H NMR (d_6-DMSO) δ 8.21 (m, 1 H, SO_2NH), 8.07–8.00 (m, 2 H), 7.75–7.29 (m, 7 H), 7.18–7.07 (m, 2 H), 4.04 (s, 2 H, indole-CH_2), 3.90 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3), 3.17 (m, 2 H, NCH_2), 2.59 (s, 3 H, $ArCH_3$), 1.67–1.50 (m, 1 H, $(CH_2)_2CH$), 1.36–1.16 (m, 8 H), 0.96–0.76 (m, 6 H, 2 × CH_3); CIMS m/z 604 ((M + H)$^+$, 4.4%), 450 (15), 321 (12), 287 (25), 157 (100). Anal. ($C_{34}H_{41}N_3O_5S$) C, H, N.

4-[[5-(2-Methylpropyl)-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5g): mp 217–218 °C. ^{1}H NMR (d_6-DMSO) δ 12.59 (s, 1 H, $NHSO_2$), 8.30 (m, 1 H, NHCO), 8.07 (s, 1 H, H-C(4′)), 8.03 (d, J = 7.9 Hz, 1 H, H-C(6″)), 7.70–7.38 (m, 7 H), 7.15 (d, J = 7.9 Hz, 1 H, H-C(5)), 7.12 (s, 1 H, H-C(2′)), 4.04 (s, 2 H, indole-CH_2), 3.91 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3), 3.08 (t, J = 6.3 Hz, 2 H, $(CH_3)_2CHCH_2$), 2.50 (s, 3 H, $ArCH_3$), 1.85 (spt, J = 6.3 Hz, 1 H, $(CH_3)_2CHCH_2$), 0.88 (d, J = 6.3 Hz, 6 H, $(CH_3)_2CHCH_2$), CIMS m/z 548 ((M + H)$^+$, 22%), 547 (M$^+$, 20), 476 (12), 475 (43), 378 (11), 377 (44). Anal. ($C_{30}H_{33}N_3O_5S \cdot 0.5H_2O$) C, H, N.

(*R,S*)-4-[[5-[(2-Methylbutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5h): mp 135–137 °C; ^{1}H NMR (d_6-DMSO) δ 12.59 (s, 1 H, $HNSO_2$), 8.30 (m, 1 H, NHCO), 8.07 (s, 1 H, H-C(4′)), 8.05 (d, J = 5.7 Hz, 1 H, H-C(6″)), 7.70–7.40 (m, 7 H), 7.15 (d, J = 7.9 Hz, 1 H, H-C(5)), 7.13 (s, 1 H, H-C(2′)), 4.04 (s, 2 H, indole-CH_2), 3.91 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3), 3.08 (m, 2 H, $CH_3CH_2(CH_3)CHCH_2$), 2.50 (s, 3 H, $ArCH_3$), 1.65 (m, 1 H, $CH_3CH_2(CH_3)CHCH_2$), 1.45, 1.10 (2 m, 2 H, $CH_3CH_2(CH_3)CHCH_2$), 0.90–0.84 (m, 6 H, $CH_3CH_2(CH_3)CHCH_2$; CIMS m/z 563 ((M + H + 1)$^+$, 33%), 562 ((M + H)$^+$, 100), 561 (M$^+$, 11), 475 (20), 451 (15), 437 (17), 424 (24), 423 (87), 422 (12), 391 (39), 390 (36). Anal. ($C_{31}H_{35}N_3O_5S$) C, H, N.

(*R,S*)-4-[[5-[(2-Methylpentyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5i): mp 136–138 °C; ^{1}H NMR (d_6-DMSO) δ 12.59 (s, 1 H, $NHSO_2$), 8.27 (m, 1 H, NHCO), 8.06 (s, 1 H, H-C(4′)), 8.02 (d, J = 7.9 Hz, 1 H, H-C(6″), 7.70–7.37 (m, 7 H), 7.13 (d, J = 7.9 Hz, 1 H, H-C(5)), 7.11 (s, 1 H, H-C(2′)), 4.04 (s, 2 H, indole-CH_2), 3.90 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3), 3.08 (m, 2 H, $CH_3CH_2CH_2(CH_3)CHCH_2$), 2.50 (s, 3 H, $ArCH_3$), 1.65 (m, 1 H, $CH_3CH_2CH_2(CH_3)CHCH_2$), 1.42–1.00 (m, 4 H, $CH_3CH_2CH_2(CH_3)CHCH_2$), 0.87–0.82 (m, 6 H, $CH_3CH_2CH_2(CH_3)CHCH_2$); CIMS m/z 577 ((M + H + 1)$^+$, 34%), 576 ((M + H)$^+$, 100), 475 (12). Anal. ($C_{32}H_{37}N_3O_5S$) C, H, N.

(*R,S*)-4-[[5-[(2-Methylheptyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5j): mp 113–115 °C; ^{1}H NMR (d_6-DMSO) δ 8.27 (m, 1 H, NHCO), 8.06 (s, 1 H, H-C(4′)), 8.03 (d, J = 7.9 Hz, 1 H, H-C(6″)), 7.70–7.38 (m, 7 H), 7.14 (d, J = 7.9 Hz, 1 H, H-C(5)), 7.12 (s, 1 H, H-C(2′)), 4.04 (s, 2 H, indole-CH_2), 3.91 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3), 3.08 (m, 2 H, $CH_3(CH_2)_4(CH_3)CHCH_2$), 2.50 (s, 3 H, $ArCH_3$), 1.65 (m, 1 H, $CH_3(CH_2)_4(CH_3)CHCH_2$), 1.42–1.00 (m, 8 H, $CH_3(CH_2)_4(CH_3)CHCH_2$), 0.87–0.82 (m, 6 H, $CH_3(CH_2)_4(CH_3)CHCH_2$); CIMS m/z 604 ((M + H)$^+$, 3.4%), 225 (23), 198 (13), 172 (100), 155 (47). Anal. ($C_{34}H_{41}N_3O_5S \cdot 0.2H_2O$) C, H, N.

(*R,S*)-4-[[5-[(2-Methyloctyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5k): mp 112–114 °C; ^{1}H NMR (d_6-DMSO) δ 8.27 (m, 1 H, NHCO), 8.06 (s, 1 H, H-C(4′)), 8.03 (d, J = 7.8 Hz, 1 H, H-C(6″)), 7.69–7.38 (m, 7 H), 7.14 (d, J = 7.9 Hz, 1 H, H-C(5)), 7.12 (s, 1 H, H-C(2′)), 4.04 (s, 2 H, indole-CH_2), 3.91 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3), 3.08 (m, 2 H, $CH_3(CH_2)_5(CH_3)CHCH_2$), 2.51 (s, 3 H, $ArCH_3$), 1.65 (m, 1 H, $CH_3(CH_2)_5(CH_3)CHCH_2$), 1.42–1.24 (m, 10 H, $CH_3(CH_2)_5(CH_3)CHCH_2$), 0.87–0.82 (m, 6 H, $CH_3(CH_2)_5(CH_3)CHCH_2$); CIMS m/z 618 ((M + H)$^+$, 11%), 172 (100), 157 (71), 156 (16), 155 (44). Anal. ($C_{35}H_{43}N_3O_5S$) C, H, N.

4-[[5-[(2-Phenylethyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5l): mp 166–169 °C; ^{1}H NMR (d_6-DMSO) δ 12.58 (brs, 1 H, SO_2NH), 8.39 (t, 1 H, NH (amide), 8.04 (s, 1 H), 8.02 (s, 1 H), 7.68–7.11 (m, 14 H), 4.04 (s, 2 H, indole-CH_2), 3.91 (s, 3 H, OCH_3), 3.75 (s, 3 H, NCH_3), 3.47 (m, 2 H, NCH_2), 2.84 (t, J = 8.1 Hz, 2 H, $PhCH_2$), 2.59 (s, 3 H, $ArCH_3$); CIMS m/z 598 ((M + H + 2)$^+$, 14%), 597 ((M + H + 1)$^+$, 38), 596 ((M + H)$^+$, 100), 546 (18), 475 (31), 425 (32), 424 (13), 172 (61), 155 (14). Anal. ($C_{34}H_{33}N_3O_5S$) C, H, N.

4-[[5-[(4-Propyl-1-piperidyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5m): mp 135–137 °C; ^{1}H NMR (d_6-DMSO) δ 8.03 (d, J = 7.75 Hz, 1 H), 7.57–7.12 (m, 10 H), 4.01 (s, 2 H, indole-CH_2), 3.69 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3), 2.96–2.71 (m, 2 H), 2.59 (s, 3 H, $ArCH_3$), 1.71–0.96 (m, 1 H), 0.85 (t, J = 6.75 Hz, 3 H, $CH_3(CH_2)_2$); CIMS m/z 604 ((M + H + 2)$^+$, 10%), 603 ((M + H + 1)$^+$, 29), 602 ((M + H)$^+$, 100), 533 (13), 476 (12), 448 (15), 430 (29), 225 (17). Anal. ($C_{34}H_{39}N_3O_5S \cdot 0.2H_2O$) C, H, N.

4-[[5-(*N,N*-Dibutylcarbamoyl)-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5n): mp 135–137 °C; ^{1}H NMR (d_6-DMSO) δ 12.58 (br s, 1 H, SO_2NH), 8.02 (d, J = 10 Hz, 1 H), 7.57–7.38 (m, 7 H), 7.17–7.06 (m, 3 H), 4.00 (s, 2 H, indole-CH_2), 3.89 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3), 3.24 (br, $(CH_2)_2N$), 2.59 (s, 3 H, $ArCH_3$), 1.57–0.5 (m, 14 H); CIMS m/z 605 ((M + H + 1)$^+$, 22%), 604 ((M + H)$^+$, 60), 479 (17), 478 (20), 451 (18), 450 (53), 449 (12), 432 (14), 287 (13), 172 (100), 157 (31). Anal. ($C_{34}H_{41}N_3O_5S$) C, H, N.

4-[[5-(*N*-(2-Methylpropyl)-*N*-methylcarbamoyl)-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5o): mp 130–135 °C; ^{1}H NMR (d_6-DMSO) δ 8.02 (dd, J = 1.2, 7.9 Hz, 1 H, H-C(6′)), 7.57–7.38 (m, 8 H), 7.19–7.08 (m, 3 H), 4.02 (s, 2 H, indole-CH_2), 3.89 (s, 3 H, OCH_3), 3.74 (s, 3 H, indole-NCH_3), ca. 3.2 (very broad, 2 H, $(CH_3)_2CHCH_2$), 2.87 (s, 3 H, amide-NCH_3), 2.59 (s, 3 H, $ArCH_3$), ca. 1.9 (very broad, 1 H, $(CH_3)_2CHCH_2$), ca. 0.9, 0.7 (2 very broad, 6 H, $(CH_3)_2CHCH_2$); CIMS m/z 590 ((M + H)$^+$, 2.4%), 562 (14), 408 (24), 321 (11), 192 (22), 172 (100), 157 (94), 155 (25), 139 (28). Anal. ($C_{31}H_{35}N_3O_5S$) C, H, N.

4-[[5-[(2,2-Dimethylpropyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5p): mp 147–149 °C, ^{1}H NMR (d_6-DMSO) δ 8.16 (m, 1 H, NHCO), 8.07 (s, 1 H, H-C(4′)), 8.03 (d, J = 7.7 Hz, 1 H, H-C(6″)), 7.70–7.38 (m, 7 H), 7.16 (d, J = 7.9 Hz, 1 H, H-C(5)), 7.11 (s, 1 H, H-C(2′)), 4.05 (s, 2 H, indole-CH_2), 3.90 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3), 3.11 (d, J = 6.1 Hz, 2 H, $((CH_3)_3CCH_2)$), 2.60 (s, 3 H, $ArCH_3$), 0.89 (s, 9 H, $((CH_3)_3CCH_2)$; CIMS m/z 562 ((M + H)$^+$, 5%), 302 (12), 245 (14), 172 (16), 157 (52), 155 (13). Anal. ($C_{31}H_{35}N_3O_5S \cdot 1.0H_2O$) C, H, N.

4-[[5-[(2-Ethylbutyl)carbamoyl]-1-propylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5r): mp 124–126 °C. ^{1}H NMR (d_6-DMSO) δ 8.18 (m, 1 H, NHCO), 8.05 (s, 1 H, H-C(4′)), 8.03 (d, J = 7.7 Hz, 1 H, H-C(6″)), 7.67–7.38 (m, 7 H), 7.19 (d, J = 7.9 Hz, 1 H, H-C(5)), 7.13 (s, 1 H, H-C(2′)), 4.09 (t, J = 6.9 Hz, 2 H, $NCH_2CH_2CH_3$), 4.05 (s, 2 H, indole-CH_2), 3.90 (s, 3 H, OCH_3), 3.19 (t, J = 6.0 Hz, 2 H, $(C_2H_5)_2CHCH_2$), 2.60 (s, 3 H, $ArCH_3$), 1.71 (m, 2 H, $NCH_2CH_2CH_3$), 1.50 (m, 1 H, $(C_2H_5)_2CHCH_2$), 1.26 (m, 4 H, $(CH_3CH_2)_2CHCH_2$), 0.89–0.77 (m, 9 H); CIMS m/z 604 ((M + H)$^+$, 6%), 478 (18), 451 (3), 450 (78), 433 (20), 432 (47), 350 (17), 349 (51). Anal. ($C_{34}H_{41}N_3O_5S \cdot 0.4H_2O$) C, H, N.

4-[[5-[(2-Methylpropyl)carbamoyl]-1-propylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5x): mp 186–187 °C; ^{1}H NMR (d_6-DMSO) δ 8.27 (m, 1 H, NHCO), 8.04 (s, 1 H, H-C(4′)), 8.02 (d, J = 7.7 Hz, 1 H, H-C(6″)), 7.67–7.38 (m, 7 H), 7.19 (s, 1 H, H-C(2′)), 7.12 (d, J = 7.9 Hz, 1 H, H-C(5)), 4.09 (t, J = 6.9 Hz, 2 H, $NCH_2CH_2CH_3$), 4.06 (s, 2 H, indole-CH_2), 3.90 (s, 3 H, OCH_3), 3.06 (t, J = 6.0 Hz, 2 H, $(CH_3)_2CHCH_2$), 2.59 (s, 3 H, $ArCH_3$), 1.80 (m, 1 H, $(CH_3)_2CHCH_2$), 1.74 (m, 2 H, $NCH_2CH_2CH_3$), 0.87 (d, J = 7.8 Hz, 6 H, $(CH_3)_2CHCH_2$), 0.79 (t, J = 8.9 Hz, 3 H, $NCH_2CH_2CH_3$); CIMS m/z 577 ((M + H + 1)$^+$, 35%), 576 ((M + H)$^+$, 100), 503 (18), 422 (38), 405 (35), 404 (30), 157 (34). Anal. ($C_{32}H_{37}N_3O_5S \cdot 0.2H_2O$) C, H, N.

4-[[5-[(2-Methylpropyl)carbamoyl]-1-propylindol-3-yl]methyl]-3-methoxy-*N*-(phenylsulfonyl)benzamide (5y): mp 193–194 °C; ^{1}H NMR (d_6-DMSO) δ 8.27 (m, 1 H, NHCO), 8.02 (d, J = 7.7 Hz, 2 H, H-C(2″)), 7.97 (s, 1 H, H-C(4′)), 7.71–7.38 (m, 7 H), 7.18 (s, 1 H, H-C(2′)), 7.12 (d, J = 7.9 Hz, 1 H, H-C(5)), 4.09 (t, J = 6.9 Hz, 2 H, $NCH_2CH_2CH_3$), 4.04 (s, 2 H, indole-CH_2), 3.90 (s, 3 H, OCH_3), 3.07 (t, J = 6.0 Hz, 2 H, $(CH_3)_2CHCH_2$), 1.80 (m, 1 H, $(CH_3)_2CHCH_2$), 1.74 (m, 2 H, $NCH_2CH_2CH_3$), 0.87 (d, J = 7.8 Hz, 6 H, $(CH_3)_2CHCH_2$), 0.80 (t, J = 8.9 Hz, 3 H, $NCH_2CH_2CH_3$); CIMS m/z 563 ((M + H + 1)$^+$, 32%), 562 ((M + H)$^+$, 100%), 489 (13), 422 (26), 405 (19), 349 (19) 142 (27). Anal. ($C_{31}H_{35}N_3O_5S$) C, H, N.

Methyl 4-[(5-Carboxyindol-3-yl)methyl]-3-methoxybenzoate (19a). A solution of methyl 4-[[5-(benzyloxycarbonyl)-indol-3-yl]methyl]-3-methoxybenzoate (15) (10.0 g, 23.3 mmol) in THF/methanol (1:1, 175 mL) was added to a suspension of 10% palladium on carbon (1.0 g) in methanol (25 mL). The heterogeneous mixture was placed under an atmosphere of hydrogen (50 psi) and shaken for 3 h. The catalyst was removed by filtration through diatomaceous earth and the filter cake rinsed with THF (2 × 50 mL). The filtrate was evaporated to afford **19a** (7.9 g, 23.3 mmol, 100%) as an ivory solid: ^{1}H NMR (80 MHz, d_6-DMSO) δ 12.63 (brs, 1 H, CO_2H), 8.38 (s, 1 H, H-C(4′)), 8.18 (brs, 1 H, indole-NH), 7.92 (d, J = 8.6 Hz, 1 H, H-C(6′)), 7.58–7.09 (m, 4 H), 6.97 (d, J = 2.2 Hz, 1 H, H-C(2′)), 4.05 (s, 2 H, indole-CH_2), 3.90 (s, 3 H, OCH_3), 3.86 (s, 3 H, CO_2CH_3).

Methyl 4-[[5-[(2-Ethylbutyl)carbamoyl]indol-3-yl]methyl]-3-methoxybenzoate (20a). A solution of methyl 4-[(5-carboxyindol-3-yl)methyl]-3-methoxybenzoate (19a) (7.9 g, 23.3 mmol), 2-ethylbutylamine (2.65 g, 25.6 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (5.45 g, 28.0 mmol), and 4-(dimethylamino)pyridine (2.94 g, 23.3 mmol) in dichloromethane (115 mL) was stirred at room temperature for 48 h. The solution was diluted with dichloromethane (100 mL), washed with 10% aqueous hydrochloric acid (2 × 100 mL), water (100 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash chromatography (2.5:1 H/EA) to give **20a** (9.7 g, 23.0 mmol, 99%): ^{1}H NMR (d_6-DMSO) δ 11.10 (s, 1 H, indole-NH), 8.18 (m, 1 H, CONH), 8.05 (s, 1 H, H-C(4′)), 7.64–7.35 (m, 4 H), 7.18 (s, 1 H, H-C(2′)), 7.16 (m, 1 H), 4.09 (s, 2 H, indole-CH_2), 3.92 (s, 3 H, OCH_3), 3.83 (s, 3 H, CO_2CH_3), 3.19 (m, 2 H, $(CH_3CH_2)_2CHCH_2$), 1.54 (m, 1 H, $(CH_3CH_2)_2CHCH_2$), 1.29 (m, 4 H, $(CH_3CH_2)_2CHCH_2$), 0.87 (t, J = 7.6 Hz, 6 H, $(CH_3CH_2)_2CHCH_2$); CIMS m/z 424 ((M + H + 1)$^+$, 29%), 423 ((M + H)$^+$, 100), 322 (10).

Also prepared by this method was **methyl 4-[[5-[(cyclopentylmethyl)carbamoyl]indol-3-yl]methyl]-3-methoxybenzoate (20b)**: yield 93%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.30 (brs, 1 H, indole-NH), 8.02 (s, 1 H, H-C(4′)), 7.61–7.50 (m, 3 H), 7.35 (d, J = 8.5 Hz, 1 H, H-C(7′)), 7.13 (d, J = 7.6 Hz, 1 H, H-C(5)), 6.99 (d, J = 2.3 Hz, 1 H, H-C(2′)), 8.13 (m, 1 H, NHCO), 4.15 (s, 2 H, indole-CH_2), 3.92 (s, 3 H, OCH_3), 3.89 (s, 3 H, CO_2CH_3), 3.41 (q_{ABX}, J_{AX} = 5.7 Hz, J_{BX} = 6.0 Hz, J_{AB} = 9.7 Hz, 2 H, CH_2N), 2.17 (m, 1 H), 1.81–1.26 (m, 8 H).

Methyl 4-[[5-[(2-Ethylbutyl)carbamoyl]-1-ethylindol-3-yl]methyl]-3-methoxybenzoate (11q). A solution of methyl 4-[[5-[(2-ethylbutyl)carbamoyl]indol-3-yl]methyl]-3-methoxybenzoate (19a) (1.0 g, 2.37 mmol) in DMF (10 mL) was added to a 0 °C suspension of sodium hydride (64.5 mg, 2.69 mmol) in DMF (2 mL). The solution was stirred at 0 °C for 45 min, treated with bromoethane (290 mg, 2.66 mmol), and allowed to warm to room temperature. After 16 h at room temperature, the reaction was quenched by careful addition of saturated aqueous ammonium chloride (2 mL) and poured into water (100 mL). The solid precipitate was removed by filtration, rinsed with water (10 mL), and dried. Purification of this solid by flash chromatography (1:4 EA/H) yielded **11q** (190 mg, 0.42 mmol, 18%) accompanied by a mixture of **11q** and the corresponding ethyl ester (ca. 75:25, 370 mg, 0.8 mmol, 36%) (**11q**): ^{1}H NMR (d_6-DMSO) δ 8.01 (s, 1 H, H-C(4′)), 7.63–7.14 (m, 5 H), 6.69 (s, 1 H, H-C(2′)), 6.06 (m, 1 H, CONH), 4.13 (s, 2 H, indole-CH_2), 4.12 (q, J = 7.4 Hz, NCH_2CH_3), 3.93 (s, OCH_3), 3.90 (s, 3 H, CO_2CH_3), 3.42 (t, J = 6.0 Hz, 2 H, $(CH_3CH_2)_2CHCH_2$), 1.54–1.34 (m, 8 H), 0.94 (t, J = 7.4 Hz, 6 H, $(CH_3CH_2)_2CHCH_2$).

Methyl 4-[[5-[(Cyclopentylmethyl)carbamoyl]-1-(2-propenyl)indol-3-yl]methyl]-3-methoxybenzoate (11v). A solution of methyl 4-[[5-[(cyclopentylmethyl)carbamoyl]indol-3-yl]methyl]-3-methoxybenzoate (**20b**) (900 mg, 2.14 mmol) in DMF (10 mL) was added to a 0 °C suspension of sodium hydride (60 mg, 2.50 mmol) in DMF (1 mL). After 0.5 h at 0 °C, the solution was treated with allyl chloride (180 mg, 2.36 mmol), warmed to room temperature, and stirred for 18 h. The mixture was then carefully quenched by addition of 10% aqueous ammonium chloride, diluted with water (25 mL), and extracted with ethyl acetate (3 × 25 mL). The organic extracts were washed with water (25 mL) and brine (25 mL), combined, dried over $MgSO_4$, filtered, and concentrated to afford an amber oil. Purification by flash chromatography (1:4 EA/H) yielded **11v** (500 mg, 1.09 mmol, 51%) as a white powder: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.00 (d, J = 1.4 Hz, 1 H, H-C(4′)), 7.61–7.51 (m, 3 H), 7.28 (d, J = 9.6 Hz, 1 H, H-C(7′)), 7.14 (d, J = 7.7 Hz, 1 H, H-C(5)), 6.67 (s, 1 H, H-C(2′)), 6.11 (m, 1 H, NHCO), 5.92 (m, 1 H, $CH=CH_2$), 5.21–5.01 (m, 2 H, $CH=CH_2$), 4.68 (m, 2 H, NCH_2), 4.14 (s, 2 H, indole-CH_2), 3.93 (s, 3 H, OCH_3), 3.90 (s, 3 H, CO_2CH_3), 3.40 (q_{ABX}, J_{AX} = 7.2 Hz, J_{BX} = 7.2 Hz, J_{AB} = 7.3 Hz, 2 H, CH_2N), 2.16 (m, 1 H, CH_2NCO), 1.81–1.20 (m, 8 H).

4-[[5-[(Cyclopentylmethyl)carbamoyl]-1-(2-propenyl)indol-3-yl]methyl]-3-methoxybenzoic acid (18v): ^{1}H NMR (d_6-DMSO) δ 8.31 (t, J = 5.6 Hz, 1 H, CONH), 8.07 (d, J = 1.0 Hz, 1 H, H-C(4′)), 7.64 (dd, J = 1.0, 8.7 Hz, 1 H, H-C(6′)), 7.49–7.40 (m, 3 H), 7.15 (s, 1 H, H-C(2′)), 7.14 (d, J = 7.7 Hz, 1 H, H-C(5)), 5.99 (m, 1 H, $NCH_2CH=CH_2$), 5.12, 4.97 (2 m, 2 H, $NCH_2CH=CH_2$), 4.79 (m, 2 H, $NCH_2CH=CH_2$), 4.07 (s, 2 H, indole-CH_2), 3.90 (s, 3 H, OCH_3), 3.18 (t, J = 6.4 Hz, 2 H, $cpCH_2N$), 2.15 (m, 1 H), 1.69–1.49 (m, 6 H), 1.26 (m, 2 H).

4-[[5-[(Cyclopentylmethyl)carbamoyl]-1-(2-propenyl)indol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5v): mp 135–137 °C; ^{1}H NMR (d_6-DMSO) δ 8.31 (m, 1 H, NHCO), 8.08 (s, 1 H, H-C(4′)), 8.06 (m, 1 H), 7.67–7.38 (m, 7 H), 7.15 (s, 1 H, H-C(2′)), 7.11 (d, J = 7.4 Hz, H-C(5)), 5.99 (m, 1 H, $NCH_2CH=CH_2$), 5.12, 4.96 (2 m, 2 H, $NCH_2CH=CH_2$), 4.80 (m, 2 H, $NCH_2CH=CH_2$), 4.06 (s, 2 H, indole-CH_2), 3.91 (s, 3 H, OCH_3), 3.18 (t, J = 6.3 Hz, 2 H, $cpCH_2N$), 2.60 (s, 3 H, $ArCH_3$), 2.15 (m, 1 H), 1.69–1.48 (m, 6 H), 1.28 (m, 2 H); CIMS m/z 601 (M + H + 1)$^+$, 2.4%), 600 ((M + H)$^+$, 6), 447 (4), 446 (8), 157 (100), 139 (37). Anal. ($C_{34}H_{37}N_3O_5S$) C, H, N.

Also prepared by this sequence (method C) from methyl 4-[(5-carboxyindol-3-yl)methyl]-3-methoxybenzoate (**19a**) were the following: **4-[[5-[(2-Ethylbutyl)carbamoyl]-1-ethylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5q)**: mp 182–183 °C; ^{1}H NMR (d_6-DMSO) δ 8.19 (m, 1 H, NHCO), 8.04 (d, J = 1.2 Hz, 1 H, H-C(4′)), 8.02 (dd, J = 1.2, 8.0 Hz, 1 H, H-C(5″)), 7.68–7.38 (m, 7 H), 7.20 (s, 1 H, H-C(2′)), 7.14 (d, J = 7.9 Hz, 1 H, H-C(5)), 4.16 (q, J = 7.1 Hz, 2 H, NCH_2CH_3), 4.05 (s, 2 H, indole-CH_2), 3.91 (s, 3 H, OCH_3), 3.18 (t, J = 6.1 Hz, 2 H, $(CH_3CH_2)_2CHCH_2$), 2.59 (s, 3 H, $ArCH_3$), 1.48 (m, 1 H, $(CH_3CH_2)_2CHCH_2$), 1.32 (m, 7 H, $(CH_3CH_2)CHCH_2$; NCH_2CH_3), 0.86 (t, J = 7.3 Hz, 6 H, $(CH_3CH_2)_2CHCH_2$); CIMS m/z 592 ((M + H + 2)$^+$, 13%), 591 ((M + H + 1)$^+$, 38), 590 ((M + H)$^+$, 100), 589 (13), 521 (14), 520 (25), 489 (17), 419 (21). Anal. ($C_{33}H_{39}N_3O_5S$) C, H, N.

4-[[5-[(2-Ethylbutyl)carbamoyl]-1-(1-methylethyl)indol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5s): mp 134–136 °C; ^{1}H NMR (d_6-DMSO) δ 8.18 (m, 1 H, NHCO), 8.04 (s, 1 H, H-C(4′)), 8.03 (m, 1 H), 7.67–7.35 (m, 8 H), 7.12 (d, J = 7.9 Hz, 1 H, H-C(5)), 4.74 (m, 1 H, $NCH(CH_3)_2$), 4.05 (s, 2 H, indole-CH_2), 3.92 (s, 3 H, OCH_3), 3.18 (t, J = 5.8 Hz, 2 H, $(CH_3CH_2)_2CHCH_2$), 2.59 (s, 3 H, $ArCH_3$), 1.47 (m, 1 H, $(CH_3CH_2)_2CHCH_2$), 1.42 (d, J = 6.5 Hz, 6 H, $NCH(CH_3)_2$), 1.28 (m, 4 H, $(CH_3CH_2)_2CHCH_2$), 0.86 (t, J = 7.3 Hz, 6 H, $(CH_3CH_2)_2CHCH_2$); CIMS m/z 606 ((M + H + 2)$^+$, 12%), 605 ((M + H + 1)$^+$, 37), 604 ((M + H)$^+$, 100), 603 (12), 503 (12), 433 (13). Anal. ($C_{34}H_{41}N_3O_5S$) C, H, N.

4-[[5-[(2-Ethylbutyl)carbamoyl]-1-cyclopentylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5t): mp 197–198 °C; ^{1}H NMR (d_6-DMSO) δ 8.18 (m, 1 H, NHCO), 8.03 (s, 1 H, H-C(4′)), 8.03 (m, 1 H), 7.67–7.32 (m, 9 H), 7.12 (d, J = 9.5 Hz, 1 H, H-C(5)), 4.85 (m, 1 H, $NCH(CH_2)_4$), 4.05 (s, 2 H, indole-CH_2), 3.92 (s, 3 H, OCH_3), 3.17 (t, J = 5.8 Hz, 2 H, $(CH_3CH_2)_2CHCH_2$), 2.59 (s, 3 H, $ArCH_3$), 2.11–1.69 (m, 8 H, $NCH(CH_2)_4$), 1.47 (m, 1 H, $(CH_3CH_2)_2CHCH_2$), 1.29 (m, 4 H, $(CH_3CH_2)_2CHCH_2$), 0.85 (t, J = 7.3 Hz, 6 H $(CH_3CH_2)_2CHCH_2$);

CIMS m/z 632 ((M + H + 2)$^+$, 14%), 631 ((M + H + 1)$^+$, 40), 630 ((M + H)$^+$, 100), 629 (15), 588 (12), 561 (25), 560 (63), 559 (11), 529 (16), 478 (12), 477 (34). Anal. ($C_{36}H_{43}N_3O_5S$) C, H, N.

4-[[5-[(2-Ethylbutyl)carbamoyl]-1-benzylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5u): mp 203–204 °C; ^{1}H NMR (d_6-DMSO) δ 8.18 (m, 1 H, NH (amide), 8.02 (m, 2 H), 7.60–7.14 (m, 15 H), 5.39 (s, 2 H, NCH_2-Ph), 4.06 (m, 2 H, CH_2CH$_2$CH$_3$), 3.89 (s, 3 H, OCH$_3$), 3.17 (m, 2 H, CH$_2$NCO), 2.51 (s, 3 H, CH$_3$Ar), 1.49 (m, 1 H, (C$_2$H$_5$)$_2$CHCH$_2$), 1.29 (m, 4 H, CH(CH_2CH$_3$)$_2$), 0.86 (t, J = 7.4 Hz, 6 H, CH(CH$_2$CH_3)$_2$); CIMS m/z 653 ((M + H + 1)$^+$, 42%), 652 ((M + H)$^+$, 100), 651 (13), 583 (15), 582 (31), 551 (13), 513 (25), 498 (11), 481 (24). Anal. ($C_{38}H_{41}N_3O_5S$) C, H, N.

4-[[5-[(2-Ethylbutyl)carbamoyl]-1-propylindol-3-yl]methyl]-3-methoxy-*N*-(phenylsulfonyl)benzamide (5z): mp 189–190 °C; ^{1}H NMR (d_6-DMSO) δ 8.21 (m, 1 H, NH (amide), 8.01 (m, 2 H), 7.97 (d, J = 1.5 Hz, 1 H, H-C(4′)), 7.72–7.61 (m, 4 H), 7.47–7.35 (m, 3 H), 7.18 (s, 1 H, H-C(2′)), 7.12 (d, J = 7.9 Hz, 1 H, H-C(5)), 4.06 (m, 2 H, CH_2CH$_2$CH$_3$), 4.04 (s, 2 H, indole-CH$_2$), 3.90 (s, 3 H, OCH$_3$), 3.17 (m, 2 H, CH$_2$NCO), 1.72 (m, 2 H, CH$_2$CH_2CH$_3$), 1.49 (m, 1 H, CH(C$_2$H$_5$)$_2$), 1.29 (m, 4 H, CH(CH_2-CH$_3$)$_2$), 0.86 (t, J = 7.4 Hz, 6 H, CH(CH$_2$CH_3)$_2$), 0.79 (t, J = 7.4 Hz, 3 H, CH$_2$CH$_2$CH_3); CIMS m/z 591 ((M + H + 1)$^+$, 38%), 590 ((M + H)$^+$, 100), 489 (17), 468 (15), 450 (40), 433 (32), 432 (31), 349 (28), 287 (24), 157 (45), 143 (63), 125 (22). Anal. ($C_{33}H_{39}N_3O_5S$) C, H, N.

4-[[5-[(2-Ethylbutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-(2-chlorophenyl)sulfonyl]benzamide (5aa): mp 184–185 °C; ^{1}H NMR (d_6-DMSO) δ 8.20 (m, 1 H, NH (amide)), 8.17 (dd, J = 1.5, 7.8 Hz, 1 H), 8.07 (s, 1 H, H-C(4′)), 7.70–7.54 (m, 6 H), 7.42 (d, J = 8.6 Hz, 1 H, H-C(7′)), 7.15 (d, J = 8.0 Hz, 1 H, H-C(5)), 7.13 (s, 1 H, H-C(2′)), 4.05 (s, 2 H, indole-CH$_2$), 3.91 (s, 3 H, OCH$_3$), 3.75 (s, 3 H, NCH$_3$), 3.19 (m, 2 H, CH$_2$NCO), 1.49 (m, 1 H, CH(C$_2$H$_5$)$_2$), 1.29 (m, 4 H, CH(CH_2-CH$_3$)$_2$), 0.86 (t, J = 7.4 Hz, 6 H, CH(CH$_2$CH_3)$_2$); CIMS m/z 599 ((M + H + 1)$^+$, ^{37}Cl, 14%), 598 ((M + H)$^+$, ^{37}Cl, 41), 597 ((M + H + 1)$^+$, ^{35}Cl, 37), 596 ((M + H)$^+$, ^{35}Cl, 100), 422 (44), 406 (10), 405 (33), 404 (28). Anal. ($C_{31}H_{34}ClN_3O_5S$) C, H, N.

4-[[5-[(2-Ethylbutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-bromophenyl)sulfonyl]benzamide (5bb): mp 150–152 °C; ^{1}H NMR (d_6-DMSO) δ 8.20 (d, J = 7.0 Hz, 1 H), 8.08 (s, 1 H, H-C(4′)), 7.84 (d, J = 7.5 Hz, 1 H), 7.70–7.40 (m, 6 H), 7.15 (d, J = 7.5 Hz, 1 H, H-C(5)), 7.13 (s, 1 H, H-C(2′)), 4.05 (s, 2 H, indole-CH$_2$), 3.92 (s, 3 H, OCH$_3$), 3.75 (s, 3 H, NCH$_3$), 3.20 (m, 2 H, CH$_2$NCO), 1.49 (m, 1 H, CH(C$_2$H$_5$)$_2$), 1.29 (m, 4 H, CH(CH_2CH$_3$)$_2$), 0.87 (t, J = 7.4 Hz, 6 H, CH(CH$_2$CH_3)$_2$); CIMS m/z 642 ((M + H)$^+$, ^{81}Br, 1.3%), 640 ((M + H)$^+$, ^{79}Br, 1.4%), 506 (34), 404 (13), 238 (100), 236 (100), 221 (19), 219 (18). Anal. ($C_{31}H_{34}BrN_3O_5S$·0.2H$_2$O) C, H, N.

4-[[5-[(Cyclopentylmethyl)carbamoyl]-1-propylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (5w). A solution of sulfonamide **5v** (263 mg, 0.44 mmol) in ethanol (5 mL) and 1 N aqueous sodium hydroxide (0.44 mL) was hydrogenated over 10% palladium on carbon (66 mg) at a hydrogen pressure of 50 psi for 3 h. The catalyst was removed by filtration through Celite, the solids were washed with ethanol (2 mL), and the filtrate was concentrated to ca. 1 mL. The aqueous solution was acidified to pH ~ 2 by addition of 10% hydrochloric acid and diluted with water (5 mL) and the precipitate collected by filtration, washed with water (2 mL), and dried to afford the title compound as a white solid (239 mg, 0.40 mmol, 90%): mp 129–131 °C; ^{1}H NMR (d_6-DMSO) δ 8.29 (m, 1 H, CONH), 8.04 (s, 1 H, H-C(4′)), 8.02 (m, 1 H), 7.65–7.38 (m, 7 H), 7.19 (s, 1 H, H-C(2′)), 7.12 (d, J = 7.8 Hz, 1 H, H-C(5)), 4.10 (t, J = 6.8 Hz, 2 H, NCH_2CH$_2$CH$_3$), 4.05 (s, 2 H, indole-CH$_2$), 3.91 (s, 3 H, OCH$_3$), 3.18 (t, J = 6.4 Hz, 2 H, cpCH_2N), 2.59 (s, 3 H, ArCH$_3$), 2.08 (m, 1 H), 1.76–1.22 (m, 10 H), 0.80 (t, J = 7.4 Hz, 3 H, NCH$_2$CH$_2$CH_3); CIMS m/z 603 ((M + H + 1)$^+$, 9%), 602 ((M + H)$^+$, 26), 79 (100). Anal. ($C_{34}H_{39}N_3O_5S$·0.5H$_2$O) C, H, N.

Methyl 4-[[6-[(2-Ethylbutyl)carbamoyl]indol-1-yl]methyl]-3-methoxybenzoate (24b). A solution of 6-[(2-ethylbutyl)-carbamoyl]indole (**21b**) (416 mg, 1.71 mmol) in DMF (4 mL) was added to a 0 °C suspension of sodium hydride (42 mg, 1.71 mmol) in DMF (2 mL). The mixture was stirred at 0 °C for 1 h and then was treated with **10** (464 mg, 1.79 mmol). The reaction was allowed to warm to room temperature, stirred for 18 h, and then quenched by careful addition of 10% aqueous ammonium chloride (2 mL). The aqueous mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 25 mL). The organic extracts were washed with water (10 mL) and brine (10 mL), combined, dried over MgSO$_4$, filtered, and evaporated. The residue was purified by flash chromatography (1:4 EA/H) to afford **24b** (600 mg, 1.42 mmol, 83%) as a white foam: ^{1}H NMR (CDCl$_3$) δ 7.94 (s, 1 H, H-C(7′)), 7.65 (d, J = 8.2 Hz, 1 H, H-C(5′)), 7.56 (s, 1 H, H-C(2)), 7.46 (d, J = 7.7 Hz, 1 H, H-C(6)), 7.37 (d, J = 8.2 Hz, 1 H, H-C(4′)), 7.27 (d, J = 2.9 Hz, 1 H, H-C(2′)), 6.67 (d, J = 7.8 Hz, 1 H, H-C(5)), 6.59 (d, J = 2.9 Hz, 1 H, H-C(3′)), 5.41 (s, 2 H, indole-CH$_2$), 3.42 (t, J = 5.9 Hz, 2 H, CH$_2$NCO), 1.49 (m, 1 H, CH(C$_2$H$_5$)$_2$), 1.36 (m, 4 H, CH(CH_2CH$_3$)$_2$), 0.93 (t, J = 7.4 Hz, 6 H, CH(CH$_2$CH_3)$_2$).

General Procedure for Hydrolysis of Benzoate Esters 24. 4-[[6-[(2-Ethylbutyl)carbamoyl]indol-1-yl]methyl]-3-methoxybenzoic Acid (25b). A solution of the ester **24b** (600 mg, 1.42 mmol) in tetrahydrofuan (3.5 mL) and methanol (3.5 mL) was treated with a solution of lithium hydroxide monohydrate (358 mg, 8.53 mmol) in water (1.4 mL). The mixture was stirred at room temperature for 18 h, concentrated to remove the organic solvents, diluted with water (10 mL), and acidified to pH ~ 2 by addition of 10% hydrochloric acid. The precipitate was collected, washed with water, recrystallized from methanol/water, and dried (100 °C, 0.15 Torr) to afford **25b** (400 mg, 0.98 mmol, 69%) as a white powder: mp 225–226 °C; ^{1}H NMR (d_6-DMSO) δ 8.23 (m, 1 H, NH (amide)), 7.95 (s, 1 H, H-C(7′)), 7.62–7.53 (m, 4 H), 7.41 (dd, J = 1.1, 7.7 Hz, 1 H, H-C(5′)), 6.65 (d, J = 7.9 Hz, 1 H, H-C(5)), 6.56 (d, J = 2.9 Hz, 1 H, H-C(3′)), 5.48 (s, 2 H, indole-CH$_2$), 3.95 (s, 3 H, OCH$_3$), 3.18 (t, J = 6.1 Hz, 2 H, CH$_2$-NCO), 1.49 (m, 1 H, CH(C$_2$H$_5$)$_2$), 1.28 (m, 4 H, CH(CH_2CH$_3$)$_2$), 0.85 (t, J = 7.4 Hz, 6 H, CH(CH$_2$CH_3)$_2$); CIMS m/z 410 ((M + H + 1)$^+$, 26%), 409 ((M + H)$^+$, 100). Anal. ($C_{24}H_{28}N_2O_4$) C, H, N.

General Procedure for Preparation of *N*-Acylsulfonamides 6. 4-[[6-[(2-Ethylbutyl)carbamoyl]indol-1-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (6b). A solution of carboxylic acid **25b** (358 mg, 0.88 mmol), 2-toluenesulfonamide (155 mg, 0.90 mmol), 4-(dimethylamino)pyridine (113 mg, 0.90 mmol), and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide (206 mg, 1.05 mmol) in dichloromethane (5 mL) was stirred at room temperature for 18 h. The mixture was then diluted with dichloromethane (25 mL) and washed sequentially with 10% hydrochloric acid (3 × 25 mL) and water (3 × 25 mL). The organic phase was filtered and evaporated to leave a white foam. Recrystallization from methanol/water and drying (100 °C, 0.15 Torr) afforded **6b** (362 mg, 0.64 mmol, 73%) as a white powder: mp 151–153 °C; ^{1}H NMR (d_6-DMSO) δ 8.23 (m, 1 H, NH (amide)), 8.02 (dd, J = 1.3, 7.9 Hz, 1 H), 7.94 (s, 1 H, H-C(7′)), 7.59–7.34 (m, 9 H), 6.63 (d, J = 8.0 Hz, 1 H, H-C(5)), 6.56 (d, J = 3.0 Hz, 1 H, H-C(3′)), 5.47 (s, 2 H, indole-CH$_2$), 3.18 (t, J = 6.1 Hz, 2 H, CH$_2$NCO), 2.59 (s, 3 H, ArCH$_3$), 1.49 (m, 1 H, CH-(C$_2$H$_5$)$_2$), 1.28 (m, 4 H, CH(CH_2CH$_3$)$_2$), 0.86 (t, J = 7.4 Hz, 6 H, CH(CH$_2$CH_3)$_2$); CIMS m/z 564 ((M + H + 2)$^+$, 13%), 563 ((M + H + 1)$^+$, 35), 562 ((M + H)$^+$, 100), 461 (13). Anal. ($C_{31}H_{35}N_3O_5S$) C, H, N.

6-[(Cyclopentylmethyl)carbamoyl]-3-formylindole (22a). Phosphorus oxychloride (10.86 g, 70.8 mmol) was slowly added to DMF (150 mL) at 0 °C. The mixture was stirred for 15 min and then was treated with a solution of 6-[(cyclopentylmethyl)-carbamoyl]indole (**21a**)[5] (14.34 g, 59.3 mmol) in DMF (50 mL). The reaction mixture was allowed to warm to room temperature and stirred or 2 h. After cooling to 0 °C, 20% aqueous sodium hydroxide was added until the mixture was basic to litmus and then the aqueous solution was heated to reflux for 5 min. Upon cooling to room temperature, a precipitate formed which was removed by filtration and washed extensively with water followed by diethyl ether (2 × 100 mL) to afford **22a** (9.62 g, 35.6 mmol, 60%) as a tan solid: mp 224–225 °C; ^{1}H NMR (80 MHz, d_6-DMSO) δ 9.97 (s, 1 H, CHO), 8.53–7.68 (m, 5 H), 3.22 (m, 2 H, CH$_2$NCO), 2.29–1.17 (m, 9 H, C$_5$H$_9$).

Also prepared by this route was **6-[(2-ethylbutyl)carbamoyl]-3-formylindole (22c)**: ^{1}H NMR (d_6-DMSO) δ 12.3 (s, 1 H, NH (indole)), 9.97 (s, 1 H, CHO), 8.43 (m, 2 H, H-C(7), NH (amide)), 8.11 (d, J = 8.3 Hz, 1 H, H-C(4)), 8.02 (s, 1 H, H-C(2)),

7.74 (d, J = 8.3, H-C(5)), 3.22 (t, J = 6.2 Hz, 2 H, CH_2NCO), 1.53 (m, 1 H, H-C(2')), 1.31 (m, 4 H, H-C(3')), 0.88 (t, J = 7.4 Hz, 6 H, H-C(4')).

Methyl 4-[[6-[(2-Ethylbutyl)carbamoyl]-3-formylindol-1-yl]methyl]-3-methoxybenzoate (23c). A mixture of **22c** (10.0 g, 36.8 mmol), potassium carbonate (7.44 g, 55.1 mmol), and methyl 4-(bromomethyl)-3-methoxybenzoate (**10**) (11.43 g, 44.1 mmol) in DMF (180 mL) was stirred at room temperature for 18 h. After this time, an additional quantity of **10** (1.0 g, 3.86 mmol) was added, and the mixture was stirred for 18 h. The resulting homogeneous solution was poured into water (1 L), resulting in formation of a white solid. The precipitate was removed by filtration and was washed with water (2 × 100 mL). The crude product was triturated with diethyl ether, filtered, and dried in vacuo (90 °C, 0.5 Torr) to afford **23c** (13.29 g, 29.53 mmol, 80%) as a ivory solid: ^{1}H NMR (d_6-DMSO) δ 9.95 (s, 1 H, CHO), 8.48 (d, J = 1.5 Hz, 1 H, H-C(7')), 8.36 (m, 1 H, NH (amide)), 8.14 (d, J = 8.3 Hz, 1 H, H-C(4')), 8.07 (s, 1 H, H-C(2)), 7.78 (d, J = 8.3 Hz, 1 H, H-C(5')), 7.55 (s, 1 H, H-C(2')), 7.50 (d, J = 7.8 Hz, 1 H, H-C(6)), 7.02 (d, J = 7.8 Hz, 1 H, H-C(5)), 5.59 (s, 2 H, indole-CH_2), 3.94 (s, 3 H, OCH_3), 3.83 (s, 3 H, CO_2CH_3), 3.19 (t, J = 6.1 Hz, 2 H, CH_2NCO), 1.49 (m, 1 H, $CH(C_2H_5)_2$), 1.28 (m, 4 H, $CH(CH_2CH_3)_2$, 0.86 (t, 6 H, $CH(CH_2CH_3)_2$).

Ethyl 4-[[6-[(2-Ethylbutyl)carbamoyl]-3-methylindol-1-yl]methyl]-3-methoxybenzoate (24c). A solution of **23c** (500 mg, 1.11 mmol) in ethanol (1.5 mL) was added to a solution of sodium borohydride (86 mg, 2.22 mmol) in ethanol (2 mL) at reflux. Upon complete addition, the mixture was stirred for 1 min at reflux and then cooled and the solvent evaporated. The residue was partitioned between ether (25 mL) and 1% aqueous sodium hydroxide (10 mL). The organic extract was washed with water (10 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and evaporated to leave a white foam (444 mg). This solid was dissolved in dichloromethane (5 mL) and treated with acetic anhydride (150 mg, 1.47 mmol) and triethylamine (156 mg, 1.54 mmol). The mixture was stirred at room temperature for 18 h, then diluted with dichloromethane (20 mL), washed with 10% hydrochloric acid (10 mL), water (10 mL), and brine (10 mL), dried ($MgSO_4$), filtered, and evaporated to leave a clear oil (400 mg). This oil was dissolved in ethyl acetate (10 mL), 5% palladium on carbon (100 mg) was added, and the suspension was shaken under an atmosphere of hydrogen (50 psi) for 18 h. The catalyst was removed by filtration through diatomaceous earth, the solids were washed with ethyl acetate (2 × 10 mL), and the filtrate was evaporated to leave an amber oil. Purification by flash chromatography (1:4.5:4.5 ethyl acetate/dichloromethane/hexane) afforded **24c** (210 mg, 0.48 mmol, 43% overall) as a white foam: ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1 H, H-C(7')), 7.56 (m, 3 H), 7.47 (dd, J = 1.5, 7.8 Hz, 1 H, H-C(6)), 7.36 (dd, J = 1.5, 8.3 Hz, 1 H, H-C(5')), 7.02 (d, J = 1.0 Hz, 1 H, H-C(2')), 6.66 (d, J = 7.8 Hz, H-C(5)), 6.12 (br, 1 H, NH), 5.34 (s, 2 H, indole-CH_2), 4.35 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.95 (s, 3 H, OCH_3), 3.42 (t, J = 6.0 Hz, 2 H, CH_2-NCO), 2.34 (s, 3 H, indole-CH_3), 1.50 (m, 1 H, $CH(C_2H_5)_2$), 1.38 (m, 4 H, $CH(CH_2CH_3)_2$), 0.93 (t, 6 H, $CH(CH_2CH_3)_2$); CIMS m/z 452 ((M + H + 1)$^+$, 30%), 451 ((M + H)$^+$, 100), 450 (21).

4-[[6-[(2-Ethylbutyl)carbamoyl]-3-methylindol-1-yl]methyl]-3-methoxybenzoic acid (25c): ^{1}H NMR (d_6-DMSO) δ 12.9 (br, 1 H, CO_2H), 8.23 (br, 1 H, NH), 7.91 (s, 1 H, H-C(7')), 7.56 (m, 3 H), 7.41 (dd, J = 1.1, 7.7 Hz, 1 H, H-C(5')), 7.34 (s, 1 H, H-C(2')), 6.64 (d, J = 7.8 Hz, 1 H, H-C(5)), 5.41 (s, 2 H, indole-CH_2), 3.94 (s, 3 H, OCH_3), 3.18 (m, 2 H, CH_2NCO), 2.28 (s, 3 H, indole-CH_3), 1.47 (m, $CH(C_2H_5)_2$), 1.29 (m, 4 H, $CH(CH_2CH_3)_2$), 0.86 (t, 6 H, $CH(CH_2CH_3)_2$).

4-[[6-[(2-Ethylbutyl)carbamoyl]-3-methylindol-1-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (6c): mp 168–170 °C; ^{1}H NMR (d_6-DMSO) δ 8.22 (m, 1 H, NH (amide)), 8.02 (d, J = 7.9 Hz, 1 H), 7.89 (s, 1 H, H-C(7')), 7.57–7.32 (m, 8 H), 6.62 (d, J = 7.9 Hz, 1 H, H-C(5)), 5.39 (s, 2 H, indole-CH_2), 3.94 (s, 3 H, OCH_3), 3.18 (t, J = 5.9 Hz, 2 H, CH_2-NCO), 2.58 (s, 3 H, $ArCH_3$), 2.27 (s, 3 H, indole-CH_3), 1.48 (m, 1 H, $CH(C_2H_5)_2$), 1.30 (m, 4 H, $CH(CH_2CH_3)_2$), 0.86 (t, J = 7.3 Hz, 6 H, $CH(CH_2CH_3)_2$); CIMS m/z 578 ((M + H + 2)$^+$, 11%), 577 ((M + H + 1)$^+$, 30), 576 ((M + H)$^+$, 100), 422 (16). Anal. ($C_{32}H_{37}N_3O_5S$) C, H, N.

Also prepared by this sequence from **22a** was the following: **4-[[6-[(Cyclopentylmethyl)carbamoyl]-3-methylindol-1-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (6a):** ^{1}H NMR (d_6-DMSO) δ 8.32 (m, 1 H, NHCO), 8.02 (d, J = 7.3 Hz, 1 H, H-C(5)), 7.88 (s, 1 H, H-C(7')), 7.59–7.33 (m, 8 H), 6.61 (d, J = 8.0 Hz, 1 H, H-C(5)), 5.39 (s, 2 H, indole-CH_2), 3.95 (s, 3 H, OCH_3), 3.17 (t, J = 5.8 Hz, 2 H, $(CH_2)_4CHCH_2$), 2.58 (s, 3 H, $ArCH_3$), 2.27 (s, 3 H, indole-CH_3), 2.14 (m, 1 H, $(CH_2)_4CHCH_2$), 1.66–1.50 (m, 8 H, $(CH_2)_4CHCH_2$); CIMS m/z 574 ((M + H)$^+$, 24%), 257 (48), 172 (95), 157 (100). Anal. ($C_{32}H_{35}N_3O_5S$) C, H, N.

Methyl 4-[[6-[(2-Ethylbutyl)carbamoyl]-3-[(*Z*,*E*)-1-propenyl]indol-1-yl]methyl]-3-methoxybenzoate (26j). A suspension of ethyltriphenylphosphonium bromide (1.75 g, 4.67 mmol) in tetrahydrofuran (10 mL) was cooled to 0 °C and was treated with a solution of potassium bis(trimethylsilyl)amide (8.9 mL of a 0.5 M solution in toluene, 4.44 mmol). A portion (9.5 mL, 2.23 mmol) of the resulting bright orange solution was added to a solution of methyl 4-[[6-[(2-ethylbutyl)carbamoyl]-3-formylindol-1-yl]methyl]-3-methoxybenzoate (**23c**) (1.00 g, 2.22 mmol) in tetrahydrofuran (10 mL). The mixture was stirred for 16 h at room temperature, then diluted with hexane (30 mL), and filtered through a pad of silica gel (50 × 50 mm). The solids were washed with 1:1 tetrahydrofuran/hexane (50 mL) and the combined filtrate was evaporated. The semisolid residue was purified by flash chromatography (chloroform) to afford the olefin **26j** (980 mg, 2.12 mmol, 96%) as an amber syrup: ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 1.0 Hz, 0.8 H, H-C(7')), 7.91 (s, 0.2 H, H-C(7')), 7.69–7.34 (m, 5 H), 6.70 (d, J = 7.8 Hz, 1 H, H-C(5)), 6.64 (d, J = 13.2 Hz, 0.8 H, (*Z*)-C*H*=CHCH$_3$), 6.55 (d, J = 16.2 Hz, 0.2 H, (*E*)-C*H*=CHCH$_3$), 5.79 (m, 1 H, (*Z*,*E*)-CH=C*H*CH$_3$), 5.41, 5.35 (2 s, 2 H, indole-CH_2), 3.96 (s, 3 H, OCH_3), 3.89 (s, 3 H, CO_2CH_3), 3.42 (t, J = 6.0 Hz, 2 H, CH_2NCO), 1.92 (brd, J = 7.1 Hz, 3 H, (*Z*,*E*)-CH=CHC*H*$_3$), 1.48 (m, 1 H, $CH(C_2H_5)_2$), 1.35 (m, 4 H, $CH(CH_2CH_3)_2$), 0.93 (t, J = 7.3 Hz, 6 H, $CH(CH_2CH_3)_2$).

Methyl 4-[[6-[(2-Ethylbutyl)carbamoyl]-3-propylindol-1-yl]methyl]-3-methoxybenzoate (26e). A solution of **26j** (940 mg, 2.03 mmol) in methanol (50 mL) was hydrogenated over 10% palladium on carbon (240 mg) at a hydrogen pressure of 50 psi for 3 h. The catalyst was removed by filtration through diatomaceous earth, the solids were washed with methanol (2 × 10 mL), and the filtrate was evaporated to give **26e** (910 mg, 1.96 mmol, 97%) as a colorless gum: ^{1}H NMR (d_6-DMSO) δ 7.88 (d, J = 1.1 Hz, 1 H, H-C(7')), 7.60 (d, J = 8.4 Hz, 1 H, H-C(4')), 7.54 (d, J = 1.4 Hz, 1 H, H-C(2)), 7.46 (dd, J = 1.4, 7.9 Hz, 1 H, H-C(6)), 7.36 (dd, J = 1.4 Hz, 8.4 Hz, 1 H, H-C(5')), 7.03 (s, 1 H, H-C(2')), 6.62 (d, J = 7.9 Hz, 1 H, H-C(5)), 5.35 (s, 2 H, indole-CH_2), 3.95 (s, 3 H, OCH_3), 3.89 (s, 3 H, CO_2CH_3), 3.41 (t, J = 6.0 Hz, 2 H, CH_2NCO), 2.74 (t, J = 7.6 Hz, 2 H, $CH_2CH_2CH_3$), 1.72 (m, 2 H, $CH_2CH_2CH_3$), 1.48 (m, 1 H, $CH(C_2H_5)_2$), 1.33 (m, 4 H, $CH(CH_2CH_3)_2$), 0.96 (t, J = 7.3 Hz, $CH_2CH_2CH_3$), 0.92 (m, 6 H, $CH(CH_2CH_3)_2$).

4-[[6-[(2-Ethylbutyl)carbamoyl]-3-propylindol-1-yl]methyl]-3-methoxybenzoic Acid (25e). Prepared by the general hydrolysis procedure described above from benzoate ester **24e**: ^{1}H NMR (d_6-DMSO) δ 12.97 (s, 1 H, CO_2H), 8.23 (t, J = 5.5 Hz, 1 H, NH), 7.91 (s, 1 H, H-C(7')), 7.55 (m, 3 H), 7.42 (d, J = 7.8 Hz, 1 H, H-C(5')), 7.36 (s, 1 H, H-C(2')), 6.63 (d, J = 7.8 Hz, 1 H, H-C(5)), 5.42 (s, indole-CH_2), 3.95 (s, 3 H, OCH_3), 3.19 (t, J = 6.1 Hz, 2 H, CH_2NCO), 2.69 (t, J = 7.3 Hz, 2 H, $CH_2CH_2CH_3$), 1.66 (m, 2 H, $CH_2CH_2CH_3$), 1.48 (m, $CH(C_2H_5)$), 1.30 (m, 4 H, $CH(CH_2CH_3)_2$), 0.94 (t, J = 7.3 Hz, $CH_2CH_2CH_3$), 0.86 (m, 6 H, $CH(CH_2CH_3)_2$).

4-[[6-[(2-Ethylbutyl)carbamoyl]-3-propylindol-1-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (6e): mp 138–141 °C; ^{1}H NMR (d_6-DMSO) δ 8.21 (m, 1 H, NH (amide)), 8.02 (dd, J = 1.2, 8.0 Hz, 1 H), 7.85 (s, 1 H, H-C(7')), 7.58–7.33 (m, 8 H), 6.59 (d, J = 7.9 Hz, 1 H, H-C(5)), 5.40 (s, 2 H, indole-CH_2), 3.94 (s, 3 H, OCH_3), 3.17 (t, J = 5.3 Hz, 2 H, CH_2NCO), 2.68 (t, J = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 2.58 (s, 3 H, $ArCH_3$), 1.66 (m, 2 H, $CH_2CH_2CH_3$), 1.48 (m, 1 H, $CH(C_2H_5)_2$), 1.28 (m, 4 H, $CH(CH_2CH_3)_2$), 0.93 (t, J = 7.3 Hz, 3 H, CH_2-CH_2CH_3), 0.85 (t, J = 7.4 Hz, 6 H, $CH(CH_2CH_3)_2$); CIMS m/z 606 ((M + H + 2)$^+$, 14%), 605 ((M + H + 1)$^+$, 38), 604 ((M + H)$^+$, 100). Anal. ($C_{34}H_{41}N_3O_5S \cdot 0.5H_2O$) C, H, N.

Also prepared by this sequence from **23c** were the following: **4-[[6-[(2-Ethylbutyl)carbamoyl]-3-ethylindol-1-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (6d)**: mp 168.5–169.5 °C. ^{1}H NMR (d_6-DMSO) δ 8.23 (m, 1 H, CONH), 8.03 (d, J = 8.2 Hz, 1 H), 7.89 (s, 1 H, H-C(7′)), 7.59–7.34 (m, 8 H), 6.62 (d, J = 7.8 Hz, 1 H, H-C(5)), 5.41 (s, 2 H, indole-CH_2), 3.96 (s, 3 H, OCH_3), 3.18 (m, 2 H, CH_2NCO), 2.73 (q, J = 7.4 Hz, 2 H, $CH_3CH_2C(3)$), 2.59 (s, 3 H, $ArCH_3$), 1.48 (m, 1 H, $CH(C_2H_5)_2$), 1.32–1.24 (m, 7 H, $CH(CH_2CH_3)_2$, $CH_3CH_2C(3)$), 0.86 (t, J = 7.4 Hz, 6 H, $CH(CH_2CH_3)_2$); CIMS m/z 592 ((M + H + 2)$^+$, 14%), 591 ((M + H + 1)$^+$, 38), 590 ((M + H)$^+$, 100), 589 (14), 436 (15). Anal. ($C_{33}H_{39}N_3O_5S$), C, H, N.

4-[[6-[(2-Ethylbutyl)carbamoyl]-3-(3-methylbutyl)indol-1-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (6f): mp 180–183 °C. ^{1}H NMR (d_6-DMSO) δ 8.20 (m, 1 H, NH (amide)), 8.03 (d, J = 8.0 Hz, 1 H), 7.88 (s, 1 H, H-C(7′)), 7.58–7.34 (m, 8 H), 6.57 (d, J = 7.9 Hz, 1 H, H-C(5)), 5.41 (s, 2 H, indole-CH_2), 3.94 (s, OCH_3), 3.18 (t, J = 6.1 Hz, 2 H, CH_2-NCO), 2.59 (s, 3 H, $ArCH_3$), 1.95 (m, 1 H, $(CH_3)_2CH$)), 1.48 (m, 1 H, $CH(C_2H_5)_2$), 1.35 (m, 4 H, $CH(CH_2CH_3)_2$), 0.90 (d, J = 6.6 Hz, 6 H, $(CH_3)_2CH$), 0.86 (t, J = 7.4 Hz, 6 H, $CH(CH_2CH_3)_2$); CIMS m/z 620 ((M + H + 2)$^+$, 14%), 619 ((M + H + 1)$^+$, 33), 618 ((M + H)$^+$, 100). Anal. ($C_{35}H_{43}N_3O_5S$) C, H, N.

4-[[6-[(2-Ethylbutyl)carbamoyl]-3-(cyclohexylmethyl)indol-1-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (6g): mp 212–214 °C; ^{1}H NMR (d_6-DMSO) δ 8.19 (m, 1 H, NH (amide)), 8.02 (d, J = 8.1 Hz, 1 H), 7.86 (s, 1 H, H-C(7′)), 7.57–7.32 (m, 8 H), 6.59 (d, J = 8.0 Hz, 1 H, H-C(5)), 5.40 (s, 2 H, indole-CH_2), 3.94 (s, 3 H, OCH_3), 3.16 (d, J = 6.0 Hz, 2 H, CH_2NCO), 1.69–0.82 (m, 22 H); CIMS m/z 660 ((M + H + 2)$^+$, 16%), 659 ((M + H + 1)$^+$, 42), 658 ((M + H)$^+$, 100). Anal. ($C_{38}H_{47}N_3O_5S$) C, H, N.

4-[[6-[(2-Ethylbutyl)carbamoyl]-3-(cyclopentylmethyl)-indol-1-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (6h): mp 185–186 °C; ^{1}H NMR (d_6-DMSO) δ 8.25 (m, 1 H, NH (amide)), 8.01 (dd, J = 0.9, 8.4 Hz, 1 H), 7.86 (s, 1 H, H-C(7′)), 7.57–7.33 (m, 8 H), 6.56 (d, J = 8.0 Hz, 1 H, H-C(5)), 5.40 (s, 2 H, indole-CH_2), 3.94 (s, 3 H, OCH_3), 3.17 (t, J = 6.0 Hz, 2 H, CH_2NCO), 2.69 (d, J = 7.2 Hz, $CH_2(C_2H_5)_2$), 2.57 (s, 3 H, $ArCH_3$), 2.19 (m, 1 H), 1.70–1.18 (m, 13 H), 0.84 (t, J = 7.4 Hz, $CH(CH_2CH_3)_2$); CIMS m/z 646 ((M + H + 2)$^+$, 16%), 645 ((M + H + 1)$^+$, 42), 644 ((M + H)$^+$, 100), 490 (23). Anal. ($C_{37}H_{45}N_3O_5S\cdot0.5H_2O$) C, H, N.

4-[[6-[(2-Ethylbutyl)carbamoyl]-3-phenethylindol-1-yl]-methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (6i): mp 200–201 °C. ^{1}H NMR (d_6-DMSO) δ 8.22 (m, 1 H, NH (amide)), 8.03 (dd, J = 1.0, 7.7 Hz, 1 H), 7.86 (s, 1 H, H-C(7′)), 7.63–7.14 (m, 13 H), 6.50 (d, J = 7.9 Hz, 1 H, H-C(5)), 5.37 (s, 2 H, indole-CH_2), 3.93 (s, 3 H, OCH_3), 3.17 (t, J = 6.1 Hz, 2 H, CH_2NCO), 2.98 (m, 4 H), 2.59 (s, 3 H, $ArCH_3$), 1.50 (m, 1 H, $CH(C_2H_5)_2$), 1.27 (m, 4 H, $CH(CH_2CH_3)_2$), 0.85 (m, 6 H, $CH(CH_2CH_3)_2$); CIMS m/z 668 ((M + H + 2)$^+$, 18%), 667 ((M + H + 1)$^+$, 45), 666 ((M + H)$^+$, 100). Anal. ($C_{39}H_{43}N_3O_5S$) C, H, N.

4-[[6-[(2-Ethylbutyl)carbamoyl]-3-[(*Z*,*E*)-1-propenyl]indol-1-yl]methyl]-3-methoxybenzoic acid (25j) was prepared by the general hydrolysis procedure described above from benzoate ester **24j**: mp 165–166 °C; ^{1}H NMR (d_6-DMSO) δ 8.27 (m, 1 H, NH (amide)), 7.95 (s, 1 H, H-C(7′)), 7.74–7.41 (m, 4 H), 6.69 (d, J = 7.9 Hz, 1 H, H-C(5)), 6.66 (m, 0.8 H, indole-(*Z*)-CH=$CH(CH_3)$), 6.51 (m, 0.2 H, indole-(E)-CH=$CH(CH_3)$), 5.71 (m, 1 H, indole-(*E*,*Z*)-CH=$CH(CH_3)$), 5.52 (s, 1.6 H, indole-CH_2 (*Z*)), 5.45 (s, 0.4 H, indole-CH_2 (*E*)), 3.95 (s, 3 H, OCH_3), 3.18 (m, 2 H, CH_2NCO), 1.87 (m, 3 H, indole-CH=$CH(CH_3)$), 1.49 (m, 1 H, $(CH_3CH_2)_2CHCH_2$), 1.29 (m, 4 H, $(CH_3CH_2)_2CHCH_2$), 0.86 (m, 6 H, $(CH_3CH_2)_2CHCH_2$); CIMS m/z 450 ((M + H + 1)$^+$, 30), 449 ((M + H)$^+$, 100), 448 (21), 348 (8). Anal. ($C_{27}H_{32}N_2O_4\cdot0.25H_2O$) C, H, N.

4-[[6-[(2-Ethylbutyl)carbamoyl]-3-[(*Z*,*E*)-1-propenyl]indol-1-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (6j): mp 138–141 °C; ^{1}H NMR (d_6-DMSO) δ 8.26 (m, 1 H, NH (amide)), 8.03–7.35 (m, 11 H), 6.69 (d, J = 8.1 Hz, 1 H, H-C(5)), 6.65 (m, 0.8 H, indole-(*Z*)-CH=$CH(CH_3)$), 6.51 (m, 0.2 H, indole-(*E*)-CH=$CH(CH_3)$), 5.71 (m, 1 H, indole-(*E*,*Z*)-CH=$CH(CH_3)$), 5.50 (s, 1.6 H, indole-CH_2 (*Z*)), 5.45 (s, 0.4 H, indole-CH_2 (*E*)), 3.95 (s, 3 H, OCH_3), 3.18 (m, 2 H, CH_2NCO), 2.51 (s, 3 H, $ArCH_3$), 1.87 (m, 3 H, indole-CH=$CH(CH_3)$), 1.49 (m, 1 H, $CH(C_2H_5)_2$), 1.29 (m, 4 H, $CH(CH_2CH_3)_2$), 0.86 (m, 6 H, $CH(CH_2CH_3)_2$); CIMS m/z 604 ((M + H + 2)$^+$, 18%), 603 ((M + H + 1)$^+$, 39), 602 ((M + H)$^+$, 100), 533 (12), 476 (12), 448 (14), 430 (17), 225 (21), 172 (16), 129 (14), 72 (65). Anal. ($C_{34}H_{39}N_3O_5S\cdot0.3H_2O$) C, H, N.

Pharmacokinetics Measurements. Sprague-Dawley rats were dosed orally with **5w** (1 mg/kg), **5f** (1 mg/kg), or **5q** (2.5 mg/kg) or intravenously with **5q** (2.5 mg/kg). Guinea pigs were dosed orally and intravenously with **5q** (5 mg/kg). All doses were administered as polyethylene glycol/phosphate buffered saline solution formulations. At least 20 h prior to dosing, the animals were surgically prepared under aseptic conditions by inserting a cannula into the carotid artery and/or the jugular vein. The animals were fasted overnight prior to dosing. The intravenous dose was administered via the indwelling jugular vein cannula. Blood samples were removed at various times over a 0–24-h period and analyzed for unchanged compound by HPLC. Area under the blood concentration versus time curve (AUC) was calculated using the trapezoidal rule. Absolute bioavailability was calculated using the following equation:

$$\text{AUC (oral)/AUC (iv)} \times 100$$

Reversed-phase HPLC was performed using a Zorbax/Rx C8 (25 × 0.46 cm) column from Mac-Mod Analytical (Chadds Ford, PA). The HPLC system consisted of two pumps (Model 400, ABI Analytical, Ramsey, NJ), a Model 7125 loop injector (Rheodyne, Cotati, CA), and a variable-wavelength UV detector (ABI, Model 783G). The chromatographic data was acquired and analyzed using the Multichrom data system (Version 1.8, VG Laboratory Systems, Manchester, U.K.). The detector output was also monitored using a strip-chart recorder (Model BD-41, Kipp and Zonen, Delft, the Netherlands).

A 0.2-mL aliquot of blood from each time point was extracted under acidic (pH 2, **5w** and **5f**) or basic (pH 9, **5q**) conditions with 1 mL of ethyl acetate. Following mixing and centrifugation to separate the phases, the organic portion was taken to dryness under nitrogen. The residue was reconstituted in 100 μL of HPLC mobile phase (65:35 (v/v) acetonitrile:0.1% aqueous trifluoroacetic acid (TFA) adjusted to pH 3 with triethylamine (TEA)). A standard curve over the 0–2.5 μg/mL concentration range was prepared in control blood and processed in parallel with the animal samples. All reagents were HPLC grade.

Chromatographic resolution of unchanged drug from coextracted endogenous blood components was achieved using mobile phases containing acetonitrile and 0.1% aqueous TFA/TEA (pH 3) in the proportion of 65/35 (v/v) at 1.5 mL/min. The compounds were detected by the UV absorbance at 226 nm (**5q**) or 247 nm (**5f** and **5w**). Under these conditions retention times observed were generally in the range of 7–8 min. Limits of detection for all three drugs were 22–25 ng/mL.

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