1,3,6-Trisubstituted Indoles as Peptidoleukotriene Antagonists: Benefits of a Second, Polar, Pyrrole Substituent

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1,6-Substituted and 3,5-substituted indoles and indazoles containing acylamino and *N*-arylsulfonyl amide appendages are potent antagonists of the peptidoleukotrienes LTD_4 and LTE_4. A compound from the 3,5-substituted indole series, *N*-[4-[[5-[[(cyclopentyloxy)carbonyl]amino]-1-methylindol-3-yl]methyl]-3-methoxybenzoyl]-2-methylbenzenesulfonamide (ICI 204,219), is undergoing clinical evaluation for asthma. Two new elements of structural diversity were introduced to this series of antagonists. An investigation of pyrrole substituents in the 1,6-substituted indoles demonstrated that substitution at C-2 was detrimental to biological activity, but the incorporation of hydrophilic groups at C-3 was beneficial. The introduction of a propionamide moiety at C-3 enhanced activity by 1 order of magnitude; *N*-[4-[[6-(cyclopentylacetamido)-3-[2-(*N*-methylcarbamoyl)ethyl]indol-1-yl]methyl]-3-methoxybenzoyl]benzenesulfonamide (**15c**) has a pK_B of 10.7 at the LTD_4 receptor on guinea pig trachea. Modifications of the acylamino portion of the disubstituted antagonists demonstrated that a transposition of the amide CO and NH atoms was viable. *N*-Cyclopentylmethyl amides in both the 1,6- and 3,5-disubstituted indole series were 1 order of magnitude less potent than the corresponding cyclopentylacetamides. In both series this potency loss could be regained by the incorporation of a propionamide substituent at either C-3 or N-1, respectively. For example, *N*-[4-[[6-[*N*-(cyclopentylmethyl)carbamoyl]-3-[2-(pyrrolidin-1-ylcarbonyl)ethyl]indol-1-yl]methyl]-3-methoxybenzoyl]-2-methylbenzenesulfonamide (**39c**) has a pK_B of 9.5.

The peptidoleukotrienes (LTC_4, LTD_4, and LTE_4) have been implicated as key physiological mediators of asthma[1] because of their pronounced pharmacological effects[2] on respiratory smooth muscle. The pharmaceutical community continues to show great interest in developing leukotriene antagonists as potential therapeutic agents for combating the asthmatic condition.[3] For example, a very recent study has demonstrated beneficial effects for a LTD_4 antagonist opposite exercise-induced bronchoconstriction in asthmatics.[4]

Previous reports from this laboratory[5] have described the discovery and evolution of a broad class of leukotriene antagonists based on indole and indazole ring systems (Chart I). This class encompasses both 1,6-disubstituted[5a] indoles and indazoles **1** and the corresponding 3,5-disubstituted[5b] (or "inverted") analogs **2**. Structure–activity optimizations in the lipophilic acylamino (or "western") chain identified cyclopentyl acetamides (Y = CH_2) or urethanes (Y = O) as particularly beneficial moieties.[5a] The acidic group Z was initially a carboxylic acid, with optimal activity residing in the illustrated 3-methoxy-4-methylbenzoic acid derivatives.[5a,c] Subsequent studies revealed the *N*-phenylsulfonyl amide moiety to be a particularly advantageous bioisosteric replacement for the carboxylic acid group.[5c,d] The *o*-tolylsulfonyl amide group was especially beneficial for conveying good oral activity.[5b,c] Further investigations established that the central bicyclic ring system (or "template") functioned as a scaffold, holding the western and acidic chains in a favorable orientation.[5e] Thus, a number of other bicyclic structures could be utilized in place of the four indole and indazole nuclei **1** and **2**. An indole from series **2**, ICI 204,219,[6] is currently under clinical evaluation for the treatment of asthma.[7]

This paper introduces our efforts to obtain further structural diversity within this class of leukotriene antagonists, toward the goal of selecting an additional clinical candidate. An initial study of the effects of pyrrole substituents led to the identification of an indole appendage

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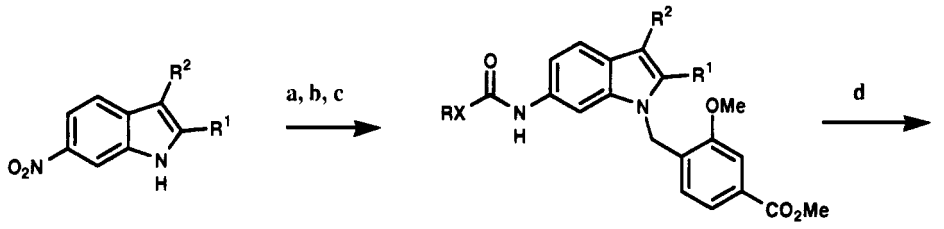
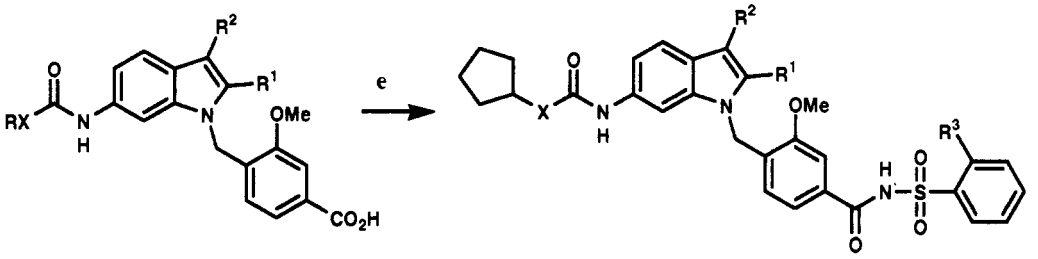
Scheme I. Pyrrole-Substituted Indoles[a]



3a $R^1, R^2 = H$
3b[b] $R^1 = Me$; $R^2 = H$
3c[c] $R^1, R^2 = Me$
3d[d] $R^1, R^2 = (CH)_4$

4a[e] $R^1, R^2 = H$; $RX = n\text{-BuO}$
4b $R^1 = Me$; $R^2 = H$; $RX = n\text{-BuO}$ (44%)[f]
4c $R^1, R^2 = Me$; $RX = n\text{-BuO}$ (71%)[f]
4d $R^1, R^2 = (CH)_4$; $RX = c\text{-}(C_5H_9)CH_2$ (78%)[f]
4e $R^1 = H$; $R^2 = Cl$; $RX = n\text{-BuO}$ (44%)
4f $R^1, R^2 = Br$; $RX = n\text{-BuO}$ (13%)
4g[e] $R^1, R^2 = H$; $RX = c\text{-}(C_5H_9)O$
4h[h] $R^1 = H$; $R^2 = Cl$; $RX = c\text{-}(C_5H_9)O$ (21%)



5a[e] $R^1, R^2 = H$; $RX = n\text{-BuO}$
5b $R^1 = Me$; $R^2 = H$; $RX = n\text{-BuO}$ (46%)
5c $R^1, R^2 = Me$; $RX = n\text{-BuO}$ (36%)
5d $R^1, R^2 = (CH)_4$; $RX = c\text{-}(C_5H_9)CH_2$ (65%)
5e $R^1 = H$; $R^2 = Cl$; $RX = n\text{-BuO}$ (61%)
5f $R^1, R^2 = Br$; $RX = n\text{-BuO}$ (53%)
5g[e] $R^1, R^2 = H$; $RX = c\text{-}(C_5H_9)O$
5h[h] $R^1 = H$; $R^2 = Cl$; $RX = c\text{-}(C_5H_9)O$ (86%)
5i[e] $R^1, R^2 = H$; $RX = c\text{-}(C_5H_9)CH_2$

6a $R^1, R^2 = (CH)_4$; $X = CH_2$; $R^3 = H$ (16%)
6b[g] $R^1, R^2 = H$; $X = O$; $R^3 = H$
6c[h] $R^1 = H$; $R^2 = Cl$; $X = O$; $R^3 = H$ (18%)
6d[g] $R^1, R^2 = H$; $X = CH_2$; $R^3 = H$
6e[g] $R^1, R^2 = H$; $X = CH_2$; $R^3 = Me$

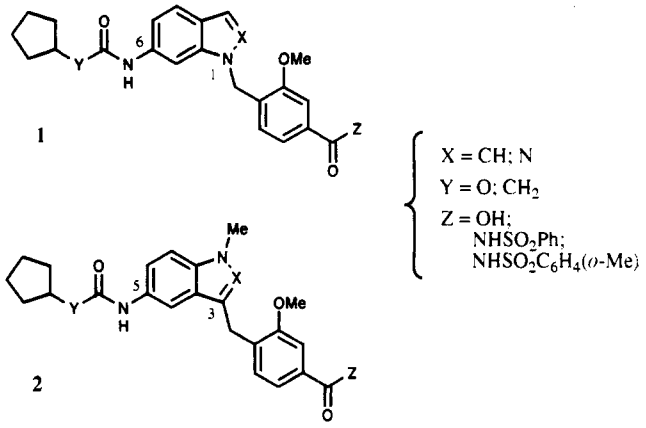
[a] (a) K_2CO_3, $BrCH_2C_6H_3(OMe)CO_2Me$, acetone; (b) 50 psi H_2, Pd/C, EtOAc; (c) ROCOCl, Et_3N, CH_2Cl_2 or RCH_2CO_2H, $Me_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$, DMAP, CH_2Cl_2; (d) $LiOH{\cdot}H_2O$, MeOH, THF, H_2O; (e) $R^3C_6H_4SO_2NH_2$, DMAP, $Me_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$, CH_2Cl_2; (f) *N*-bromosuccinimide, CCl_4; (g) *N*-chlorosuccinimide, CCl_4. [b] Reference 12. [c] Reference 8. [d] Reference 10. [e] Reference 5a. [f] Yield for the N-acylation step. [g] Reference 5c. [h] Synthetic details for this compound appear in the Experimental Section.

which took advantage of an additional binding interaction within the leukotriene receptor. This discovery enhanced the potency of the series and contributed to our understanding of how these antagonists might resemble the leukotrienes in their interaction with the receptor. The strategy was exploited further in the design of potent antagonists containing a different western appendage than has heretofore been described.

Chemistry

The general synthetic route leading to leukotriene antagonists such as benzoic acids **5** and *N*-arylsulfonyl amides **6** is summarized in Scheme I. The appropriately substituted 6-nitroindoles **3** were converted to the methyl 4-[[6-(acylamino)indol-1-yl]methyl]-3-methoxybenzoates **4** via the previously reported[5a] three-step sequence: (a) N-1 alkylation with methyl-4-(bromomethyl)-3-methoxybenzoate,[5a] (b) catalytic hydrogenation of the nitro group, and (c) acylation of the resulting amine. The esters **4** were hydrolyzed to the desired benzoic acids **5**, which could be converted to the corresponding *N*-arylsulfonyl amides **6** via a carbodiimide-mediated coupling with the requisite sulfonamide.[5c] The hydrolysis and sulfonamide coupling reactions comprise the final steps in the syntheses of all the leukotriene antagonists described herein and are exemplified in the Experimental Section by the preparation of sulfonyl amide **6c** from carboxylic acid **4h**. The introduction of specific pyrrole substituents and the preparation of alternatives to the acylamino functionality in the broad series of leukotriene antagonists **1** and **2** is the subject of this report. Synthetic details for specific compounds (as indicated by footnotes) from each of the following schemes

Chart I. Peptidoleukotriene Antagonists Derived from Indoles and Indazoles



ICI 204,219: 2, X = CH; Y = O; Z = $NHSO_2C_6H_4$(*o*-Me)

are presented in the Experimental Section to exemplify the methodology.

2,3-Dimethyl-6-nitroindole[8] (**3c**) was prepared from (*m*-nitrophenyl)hydrazine hydrochloride and methyl ethyl ketone via the Fischer indole synthesis. Cyclization of the hydrazone with boron trifluoride etherate in acetic acid at 120 °C provided a 1:1 mixture of the 4- and 6-nitroindoles, which were separated by flash chromatography. Reported attempts to increase the proportion of the 6-nitro isomer by the use of different cyclization catalysts have been notably unsuccessful.[9] 2-Nitrocarbazole[10] (**3d**) was prepared in a similar fashion utilizing the hydrazone derived from cyclohexanone. The 2- and 4-nitrotetrahydrocarbazoles[11] from Fischer indolization were separated, and the desired 2-nitro isomer was oxidized to the carbazole with chloranil.

The Fischer indole synthesis is not appropriate for the preparation of 2-methyl-6-nitroindole[12] (**3b**). The hydrazone from acetone and (*m*-nitrophenyl)hydrazine fails to cyclize even under the most stringent Fischer conditions. Thus, 2-methylindoline was quantitatively nitrated in sulfuric acid at 0 °C to give the 6-nitro derivative,[13] which was then dehydrogenated in 83% yield with chloranil.[14]

Halogen atoms could be introduced into the pyrrole ring of the indoles at the later intermediate **4a**, where the acylamino and methyl benzoate appendages are already incorporated. This strategy took advantage of the fact that nitrogen substituents stabilize 3-haloindoles,[15] and it avoided the potential problems of halogen hydrogenolysis during the reduction of the nitro group. Bromination with excess *N*-bromosuccinimide[16] gave a mixture of products from which the 2,3-dibromoindole **4f** was separated in a 13% yield. The analogous chlorination reaction was cleaner, yielding 44% of the 3-chloroindole **4e**, as indicated by the presence of a singlet at 7.52 ppm for the C-2 proton and the absence of the characteristic upfield signal for the C-3 proton at approximately 6.4 ppm in the NMR spectrum.

Indoles carrying C-3 substituents were prepared (Scheme II) via Vilsmeier acylations.[17] Under these conditions 6-nitroindole was inert, so the 6-(acylamino)-indoles **7** were utilized as the starting point. The C-3 formylated analog **8a** underwent hydrogenolysis[18] in the presence of excess lithium aluminum hydride to yield the 3-methylindole[19] **9**. This hydrogenolysis was more selective (vs amide reduction) in the case of sterically hindered amides such as 6-(2-ethylhexanamido)-3-formylindole (60% yield).[20] The 3-methylindole **9** was subsequently alkylated with sodium hydride and methyl 4-(bromomethyl)-3-methoxybenzoate in dimethylformamide. Hydrolysis of the resulting ester **10a** gave the carboxylic acid **10b**, which could then be converted to the *o*-tolylsulfonyl amide **10c**.

The strong electron withdrawing character of the C-3 carbonyl substituent[21] in the acylated indoles **8** facilitated N-alkylation, yielding compounds **11**, to the extent that the conversion could be achieved with potassium carbonate in dimethylformamide. The C-3 methyl and propyl ketones **11b** and **11c** were carried on to the desired acids **12a–c** in the manner previously discussed. As an illustration of an alternative route, sulfonyl amide **12d** was prepared, in low yield, directly from indole **8c** by alkylating with *N*-[4-(bromomethyl)-3-methoxybenzoyl]benzenesulfonamide.[5c]

The C-3 formylated *tert*-butyl ester **11a**, derived from indole **8a** by alkylation with *tert*-butyl 4-(bromomethyl)-3-methoxybenzoate,[5a] served as a key intermediate for the introduction of polar functionality. Reaction of aldehyde **11a** with methyl (triphenylphosphoranylidene)acetate in refluxing dioxane gave the methyl (*E*)-propenoate derivative **13a**. The vigorous conditions required for this Wittig reaction are another

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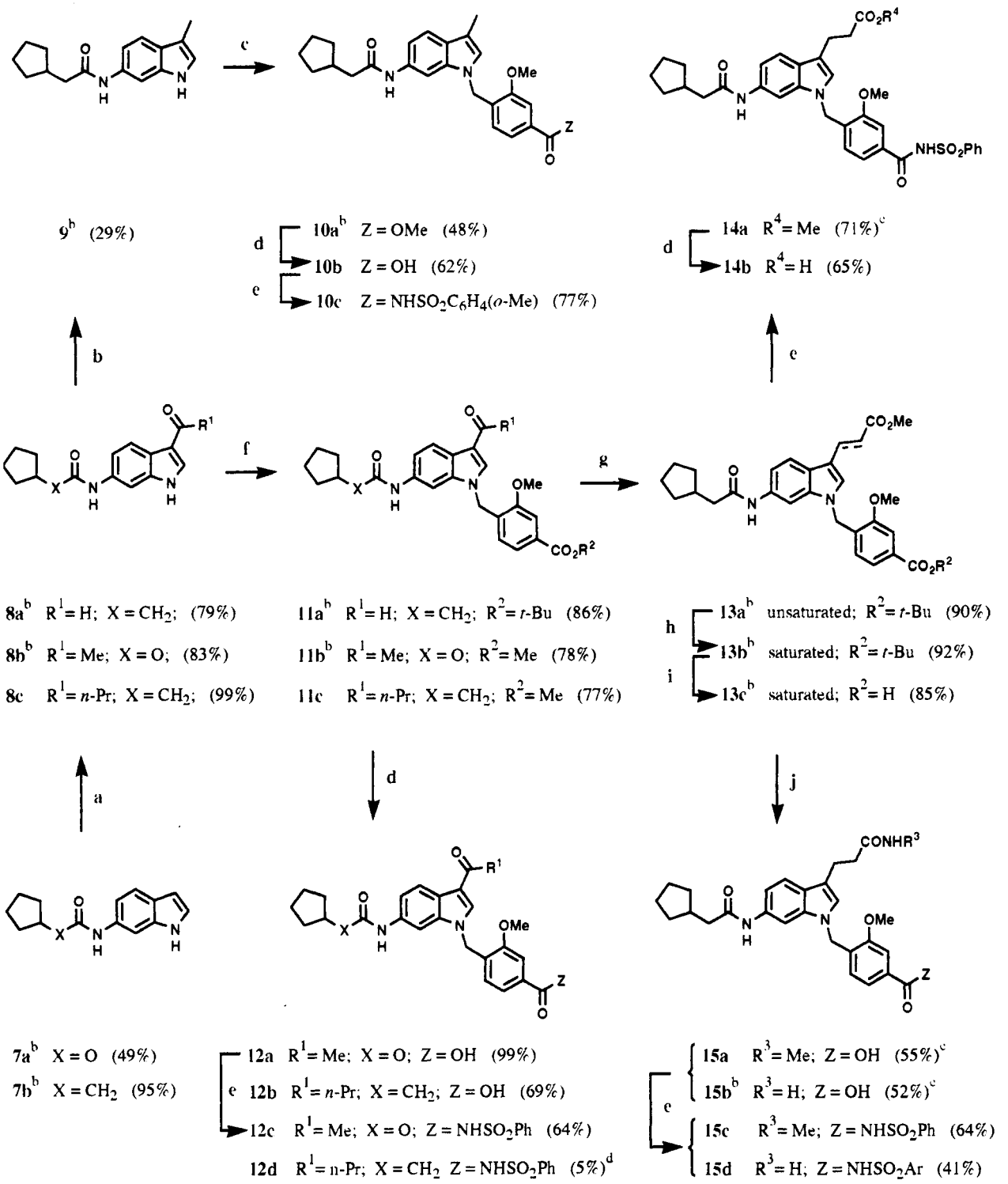
(20) Unpublished observation from this laboratory.
(21) *Chem. Heterocycl. Compd.* **1972**, *25* (1), 13.

Scheme II. C-3 Substituted Indoles[a]



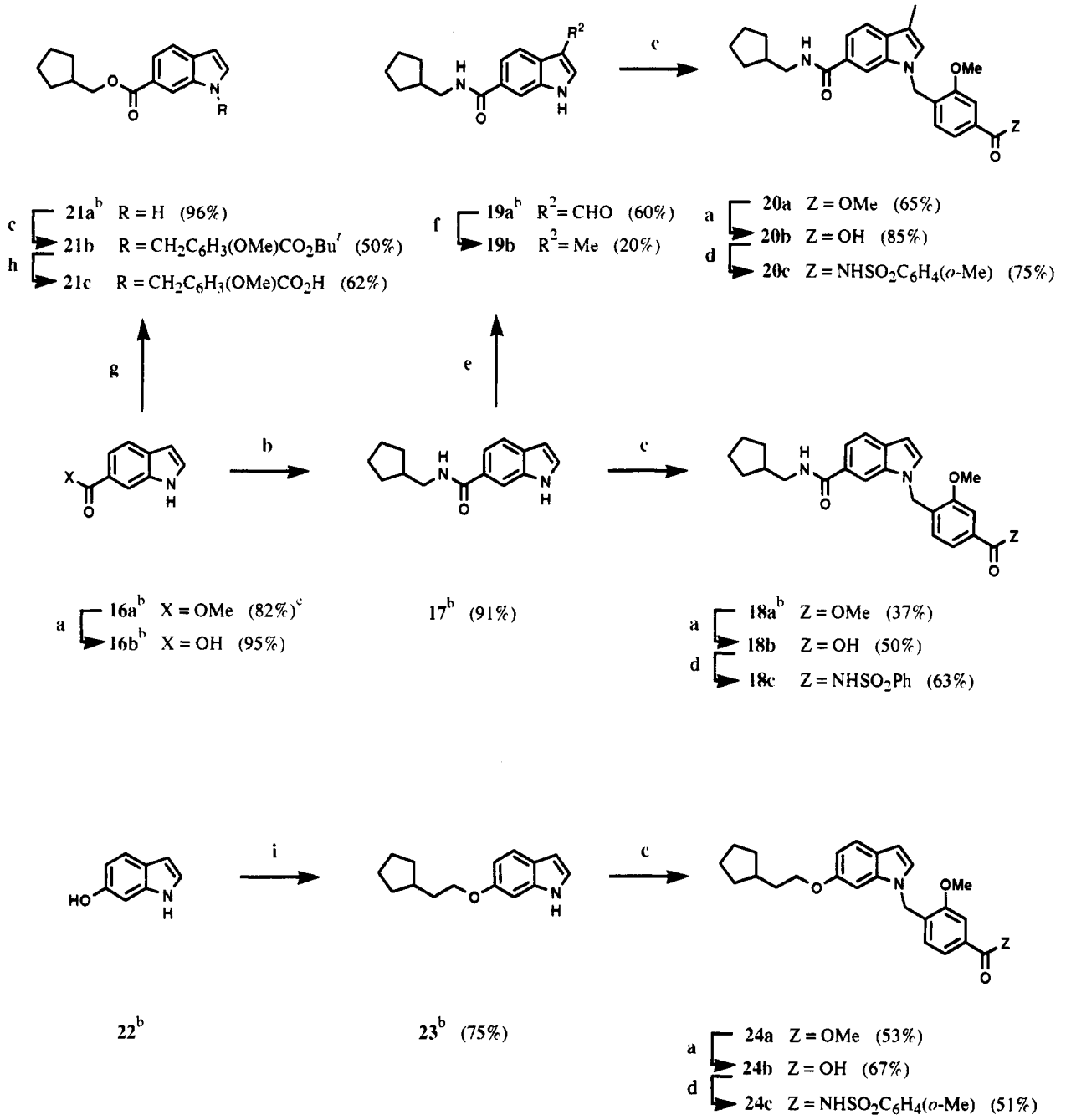
[a] (a) $POCl_3$, $R^1CON(Me)_2$ then NaOH, H_2O; (b) $LiAlH_4$, THF; (c) NaH, DMF, $BrCH_2C_6H_3(OMe)CO_2Me$; (d) $LiOH \cdot H_2O$, MeOH, THF, H_2O; (e) $ArSO_2NH_2$, DMAP, $Me_2N(CH_2)_3N{=}C{=}NEt \cdot HCl$, CH_2Cl_2; (f) K_2CO_3, $BrCH_2C_6H_3(OMe)CO_2R^2$, DMF; (g) $Ph_3P{=}CHCO_2Me$, dioxane; (h) 50 psi H_2, 10% Pd/C, MeOH, THF; (i) $CF_3SO_3Si(Me)_3$, Et_3N, dioxane; (j) R^3NH_2, DMAP. [b] Synthetic details for this compound appear in the Experimental Section. [c] Yield from **13c**. [d] Yield from **8c** by direct alkylation with *N*-[4-(bromomethyl)-3-methoxybenzoyl]-benzenesulfonamide.

reflection of the highly conjugated nature of the indole-3-carboxaldehyde system. The propenoate double bond was hydrogenated (**13b**), and the *tert*-butyl ester was selectively hydrolyzed with trimethylsilyl triflate[22] to give carboxylic acid **13c**. The acid **13c** was converted to the *N*-phenylsulfonyl amide to yield the targeted antagonist **14a**. The methyl ester functionality of **14a** was hydrolyzed to produce propionic acid **14b** as well. Alternatively, methyl propionate **13c** was reacted with amines (in a pressure vessel) to produce propionamides **15a,b**, which were carried on to the respective *N*-arylsulfonyl amides **15c,d**.

Compounds containing an alternative to the anilide link

(22) Borgulya, J.; Bernauer, K. Transformation of Carboxylic-Acid *tert*-Butyl Esters into the Corresponding Trimethylsilyl Esters or Free Acids Under Non-Acidic Conditions. *Synthesis* **1980**, 545–547.

Scheme III. Indoles Derived from the Batcho–Leimgruber Synthesis[a]



[a] (a) $LiOH·H_2O$, MeOH, THF, H_2O; (b) cyclopentylmethylamine, 1,1'-carbonyldiimidazole, CH_2Cl_2; (c) $BrCH_2C_6H_3(OMe)CO_2R$, NaH, DMF; (d) $ArSO_2NH_2$, DMAP, $Me_2N(CH_2)_3N{=}C{=}NEt·HCl$, CH_2Cl_2; (e) $POCl_3$, $HCON(Me)_2$ then NaOH, H_2O; (f) $LiAlH_4$, THF; (g) cyclopentanemethanol, 1,1'-carbonyldiimidazole, CH_2Cl_2; (h) $CF_3SO_3Si(Me)_3$, Et_3N, dioxane; (i) 2-cyclopentylethanol, Ph_3P, $EtO_2CN{=}NCO_2Et$, THF. [b] Synthetic details for this compound appear in the Experimental Section. [c] Yield from methyl 4-methyl-3-nitrobenzoate via the two-step Batcho–Leimgruber indole synthesis.

between the indole ring system and the cyclopentyl moiety were prepared via the Batcho–Leimgruber indole synthesis (Scheme III).[23] 6-Carboxyindole (**16b**) served as a starting point for a series of benzamides **18** and **20** (or "transposed" amides—to distinguish them from the previous anilides) and for a series of esters **21**. Reaction of methyl 4-methyl-3-nitrobenzoate with dimethylformamide dimethyl acetal provided a 97% yield of the corresponding dimethyl enamine, which was reductively cyclized to 6-carbomethoxyindole (**16a**) in 85% yield. The N-hydroxylated derivative of **16a** was isolated as a partial reduction byproduct.[24] Hydrolysis of ester **16a** gave the desired 6-carboxyindole (**16b**).

Carbonyldiimadazole-mediated condensation with cyclopentylmethylamine gave benzamide **17**. Alkylation of the indole nitrogen with methyl 4-(bromomethyl)-3-methoxybenzoate provided ester **18a**, which was converted to the acids **18b,c** in the usual manner. As in the anilide

(23) Batcho, A. D.; Leimgruber, W. Indoles from 2-Methylnitrobenzenes by Condensation with Formamide Acetals Followed by Reduction: 4-Benzyloxyindole. *Organic Syntheses*; Wiley: New York, 1984; Collect. Vol. VII, pp 34–41.

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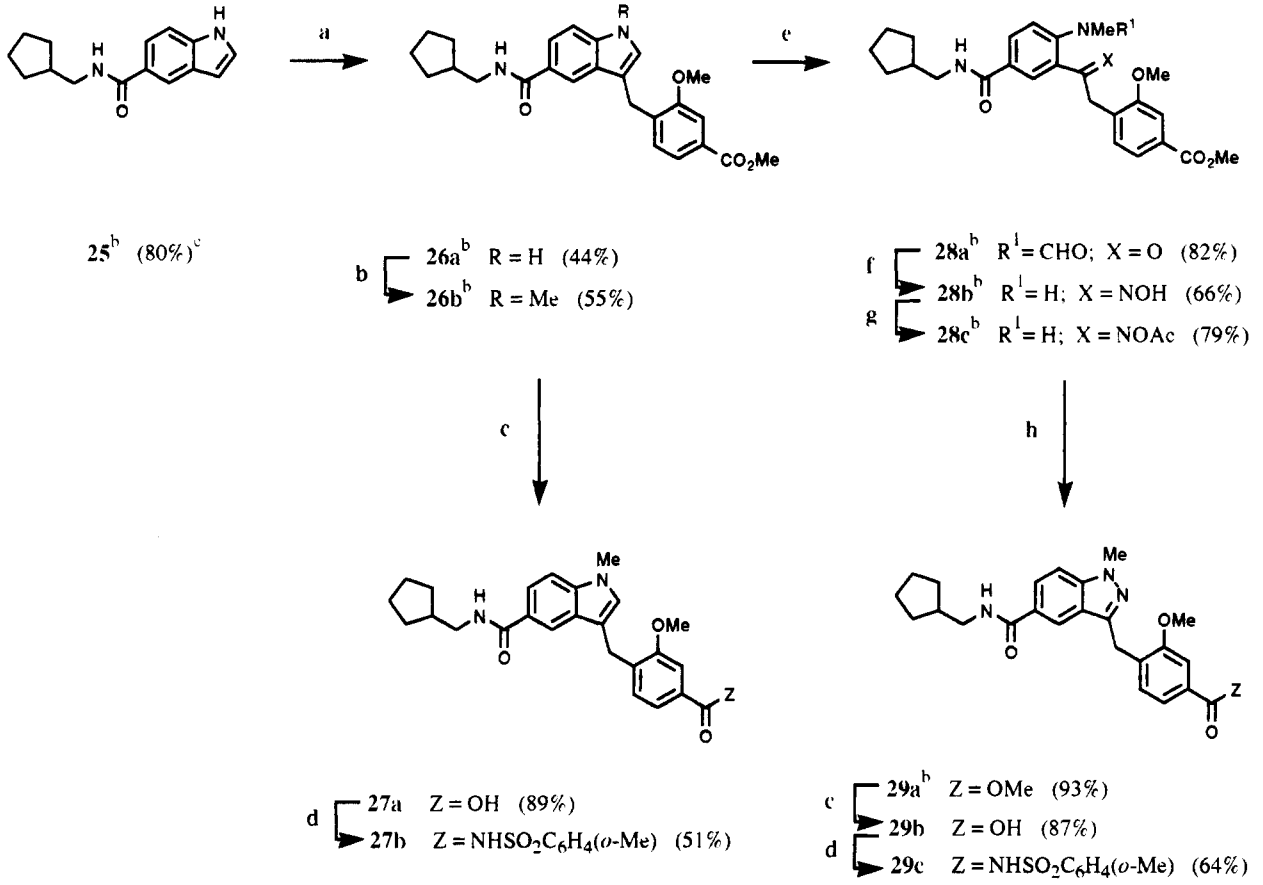
Scheme IV. 3,5-Disubstituted Indoles and Indazoles[a]



[a] (a) $BrCH_2C_6H_3(OMe)CO_2Me$, Ag_2O, dioxane; (b) MeI, NaH, DMF; (c) LiOH·H_2O, MeOH, THF, H_2O; (d) o-$MeC_6H_4SO_2NH_2$, DMAP, CH_2Cl_2, $Me_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$; (e) O_3, MeOH, CH_2Cl_2 then Me_2S; (f) $NH_2OH{\cdot}HCl$, pyridine; (g) Ac_2O, DMAP, CH_2Cl_2; (h) 210 °C, 120 mTorr. [b] Synthetic details for this compound appear in the Experimental Section. [c] Yield from 5-carboxyindole.

(or "normal amide") series (see **7–9**), a 3-methyl substituent (**19b**) could be introduced via Vilsmeier formylation of transposed amide **17** followed by reduction with lithium aluminum hydride. The N-alkylated derivatives **20** were obtained following the methodology described previously.

Alternatively, 6-carboxyindole (**16b**) could be activated with carbonyldiimidazole and condensed with cyclopentanemethanol to give ester **21a**. This compound was N-alkylated with *tert*-butyl 4-(bromomethyl)-3-methoxybenzoate to allow subsequent chemoselective hydrolysis to benzoic acid **21c**.

For a series of ether analogs **24**, the required 6-hydroxyindole (**22**) was prepared via Batcho–Leimgruber technology. The benzyl ether of 4-methyl-3-nitrophenol was converted to its dimethyl enamine derivative in 97% yield. Catalytic hydrogenation produced a 73% yield of a readily separable mixture of 6-hydroxyindole and its benzyl ether. Under Mitsunobu conditions the 6-hydroxyindole was converted to cyclopentylethyl ether **23** and then carried on to the desired acids **24b–c**.

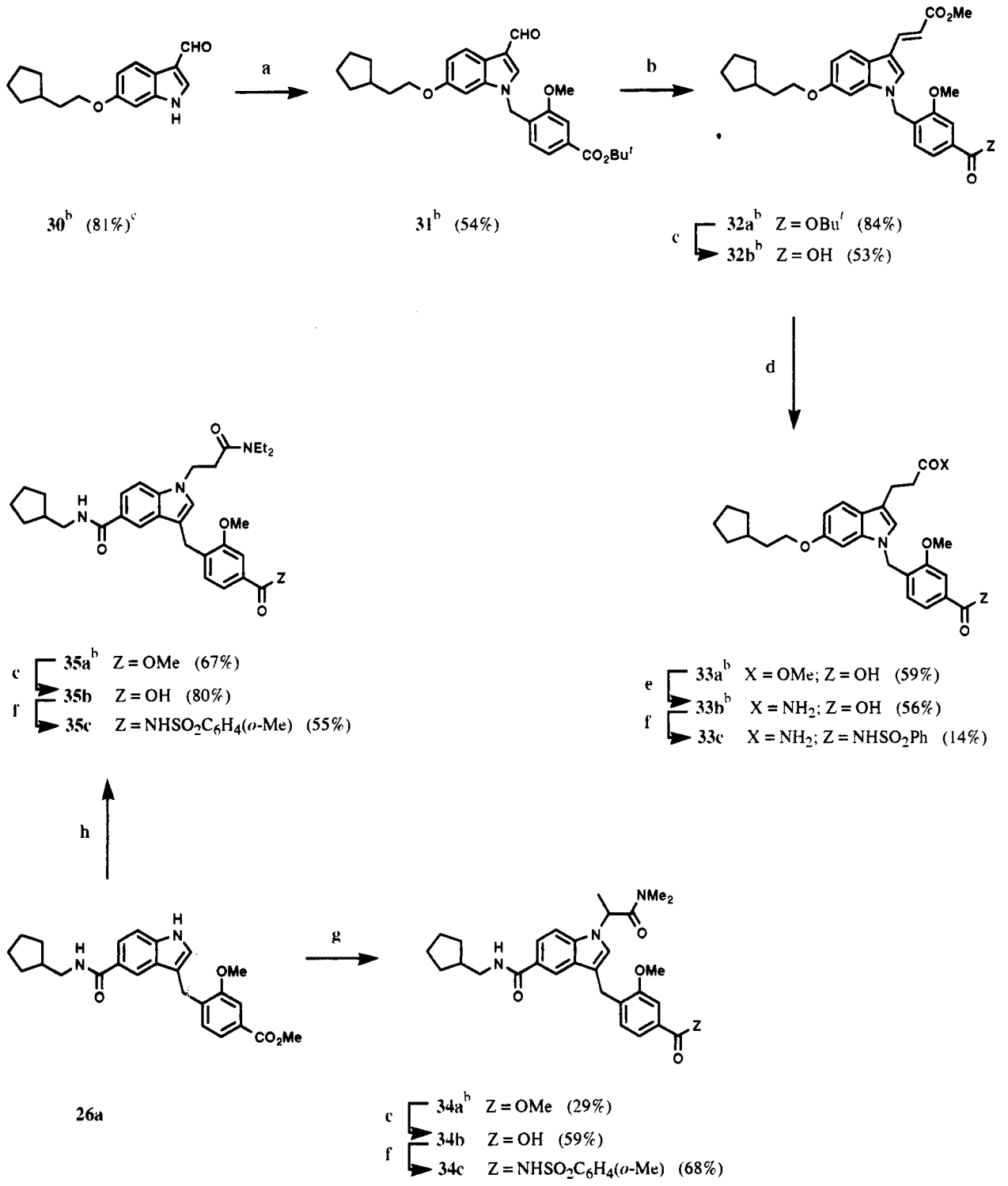
The transposed amide functionality was also incorporated into a series of 3,5-disubstituted (or inverted) indoles **27** and indazoles **29** (Scheme IV). Amidation of 5-carboxyindole with a carbodiimide and cyclopentylmethylamine provided an 80% yield of benzamide **25**. Alkylation of the indole **25** at C-3 was catalyzed by silver oxide.[5b] The yield of ester **26a** was improved by refluxing the starting indole and catalyst in dioxane prior to the addition of the bromotoluic ester. Methylation of the indole nitrogen provided ester **26b**, which was either taken on to the desired acids **27** or oxidatively cleaved with ozone[25] to ketone **28a**, a key intermediate for the preparation of the corresponding indazoles **29**. For this transposed amide, ozone proved superior to singlet oxygen[26] induced cleavage. The subsequent oxime formation with concomitant deformylation (**28b**), acetylation (**28c**), and ring closure to the indazole **29a** proceeded as expected from our previous work.[5b]

Polar "northern" appendages, such as those introduced in the normal-amide/indole antagonists (e.g. **15**), were incorporated into the ether series and the transposed-amide/inverted-indole series (Scheme V). In the case of the cyclopentylethyl ethers **33** the synthetic sequence followed that employed in Scheme II for propionamides **15**. Vilsmeier acylation of indole ether **23** gave aldehyde **30**. N-Alkylation with *tert*-butyl 4-(bromomethyl)-3-methoxybenzoate provided ester **31**, which allowed a methyl propenoate unit (**32a**) to be introduced via a Wittig reaction. Selective hydrolysis of the *tert*-butyl ester and reduction of the olefin gave methyl ester **33a**. Ammonolysis of the ester and sulfonamide coupling of the carboxylic acid produced the desired *N*-phenylsulfonyl amide **33c**. In the case of the inverted indoles, N-alkylation of indole **26a** (from Scheme IV) with either *N,N*-dimethyl-α-bromopropionamide or *N,N*-diethylacrylamide produced

(25) Sakiyama, F.; Masuda, N.; Nakazawa, T.; Katsuragi, Y. Quantitative Ozone-Oxidation of Tryptophan to N'-Formylknurenine and Kynurenine. *Chem. Lett.* **1978**, 893–896.

(26) Wassermann, H. H.; Lipshutz, B. H. Reactions of Singlet Oxygen with Heterocyclic Systems. *Organic Chemistry, A Series of Monographs*; Wassermann, H. H., Murray, R. W., Eds.; Academic: New York, 1979; pp 429–509.

Scheme V. Polar Pyrrole Appendages[a]

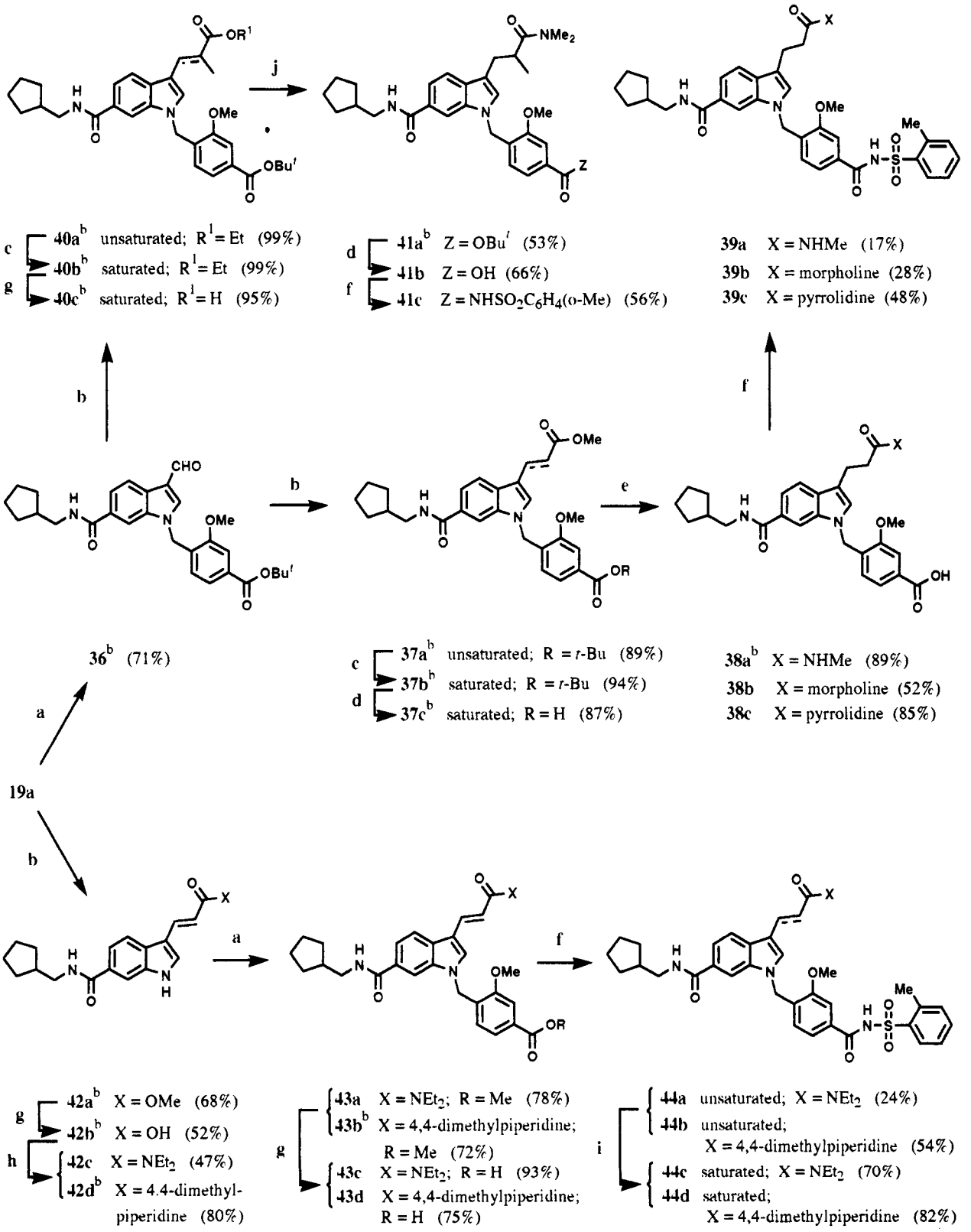


[a] (a) K_2CO_3, $BrCH_2C_6H_3(OMe)CO_2Bu^t$, DMF; (b) $Ph_3P{=}CHCO_2Me$, dioxane; (c) $LiOH{\cdot}H_2O$, MeOH, THF, H_2O; (d) 50 psi H_2, 10% Pd/C, KOH, MeOH, THF; (e) NH_3, DMAP, THF; (f) $ArSO_2NH_2$, DMAP, CH_2Cl_2, $Me_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$; (g) $BrCH(Me)CONMe_2$, NaH, DMF; (h) $CH_2{=}CHCONEt_2$, NaH, DMF. [b] Synthetic details for this compound appear in the Experimental Section. [c] Yield from Vilsmeier acylation of 6-(2-cyclopentylethoxy)indole, **23** (Scheme III).

propionamides **34a** and **35a**, respectively. These compounds were carried on to the desired sulfonyl amides **34c** and **35c**.

The various methods employed for introducing C-3 polar appendages into the transposed-amide/normal-indole series are outlined in Scheme VI. As before, the key intermediate was a C-3 formylated indole, in this case aldehyde **19a** (see Scheme III). This indole was N-alkylated with the *tert*-butyl toluic ester (**36**) in order to allow subsequent differentiation of two carboxylate functionalities during the formation of propionamides **38** and **41a**. From aldehyde **36** a Wittig reaction and subsequent hydrogenation provided methyl propionate **37b**. A number of propionamides **38** were prepared by selectively hydrolyzing the *tert*-butyl ester of diester **37b** and then directly transaminating the remaining methyl ester in the C-3 appendage. However, dimethylamine proved too weak a nucleophile for this conversion. Therefore, the methyl ester of diester **40b** was selectively hydrolyzed to yield propionic acid **40c**. Activation of this carboxylic acid with

Scheme VI. Polar C-3 Appendages in the Transposed Amide Series[a]

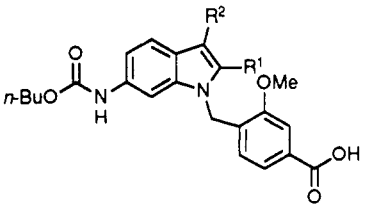


[a] (a) K_2CO_3, $BrCH_2C_6H_3(OMe)CO_2R$, DMF; (b) $Ph_3P{=}CH(R)CO_2R'$, dioxane; (c) 50 psi H_2, 10% Pd/C, MeOH; (d) $CF_3SO_3Si(Me)_3$, Et_3N, dioxane; (e) RR′NH, DMAP; (f) o-$MeC_6H_4SO_2NH_2$, DMAP, CH_2Cl_2, $Me_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$; (g) $LiOH{\cdot}H_2O$, MeOH, THF, H_2O; (h) RRNH, DMAP, CH_2Cl_2, $Me_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$; (i) 50 psi H_2, 10% Pd/C, KOH, MeOH, THF; (j) 1,1′-carbonyldiimidazole, CH_2Cl_2 then Me_2NH. [b] Synthetic details for this compound appear in the Experimental Section.

carbonyldiimidazole allowed the introduction of dimethylamine to give *N,N*-dimethylpropionamide **41a**, which was carried on to the desired acids **41b,c**.

An alternative strategy was employed for the preparation of α,β-unsaturated diethylamide **44a**. In this case the Wittig reaction was performed prior to N-alkylation to give propenoate **42a**. Ester hydrolysis and activation of the resulting carboxylic acid allowed amination with either *N,N*-diethylamine or 4,4-dimethylpiperidine to give propenamides **42c** or **42d**. Alkylation of the indole nitrogen proceeded normally to give esters **43a,b**, which were transformed to acids **43c,d** and **44a,b**. The saturated

Table I. Pyrrole-Substituted Indoles



5

compd	R^1	R^2	% inhibn/ concn, μM^a	$(K_B \pm SEM)^b \times 10^{-8}$ M; (n)
5a	H	H	25/0.33	15.5 ± 4.3 (8)
			54/0.50	
5b	Me	H	41/3.3	
5c	Me	Me	81/3.3	
			NS[c]/0.50	
5e	H	Cl	52/0.33	9.27 ± 2.4 (4)
5f	Br	Br	NS/3.3	

[a] Percent inhibition of a LTE_4 (8 nM) induced contraction of guinea pig tracheal spirals produced by the indicated concentration of the antagonist. Paired spirals receiving only vehicle served as controls; results are statistically significant ($p < 0.05$, $n \geq 4$) unless otherwise indicated. More detail is provided in the Experimental Section. [b] Dissociation constants (± standard error of the mean) on guinea pig tracheal spirals utilizing LTE_4 as agonist; (n) = the number of concentration–response curves determined. More detail is provided in the Experimental Section. [c] NS indicates the percent inhibition was low and not statistically significant ($p > 0.05$) at the indicated concentration.

analogs, propionamides **44c,d**, were readily available via catalytic hydrogenation.

Biological Evaluation

Several different assays were utilized to evaluate the in vitro potency of these leukotriene antagonists on guinea pig lung tissue. In the guinea pig trachea LTD_4 and LTE_4 share a common receptor,[27] which pharmacologically resembles the single peptidoleukotriene receptor found on human bronchus.[28] Thus, LTE_4, being metabolically more stable than LTD_4, was employed as the agonist in functional assays on guinea pig tracheal spirals.

Initially single-dose inhibitions of LTE_4-induced contractions were measured. Subsequently, the potencies of compounds of interest were further defined by the construction of cummulative concentration–response curves to determine dissociation constants (K_B) for the antagonists. Alternatively, compounds were evaluated in a ^3H-LTD_4 binding assay, using guinea pig lung parenchymal membranes, to generate inhibition constants (K_i).[29]

Selected compounds were evaluated for in vivo activity in a conscious guinea pig dyspnea model using aerosolized LTD_4 as the agonist.[30] Percent protection at a given drug dose (oral or intravenous administration) was determined by comparison of the time required for the challenged animals to exhibit labored abdominal breathing in the presence or absence of compounds.

All of these assays are described fully in the Experimental Section.

Structure–Activity Relationships

Pyrrole Substituents. Early in the evolution of the indole series we probed the steric requirements of the receptor around the pyrrole ring (Table I). At that time we were working in a series of [(*n*-butoxycarbonyl)-amino]indole methoxybenzoic acids **5**, prior to the discovery of the more potent cyclopentyl-containing western chains and the highly beneficial *N*-arylsulfonyl amide bioisostere for the carboxylic acid moiety. At that juncture the *n*-butyl carbamate **5a** was our most potent antagonist.

The introduction of a methyl group at C-2 of the pyrrole ring (**5b**) was detrimental, eliciting approximately a 6-fold decrease in activity. However, the incorporation of a second methyl substituent at C-3 (**5c**) appeared to regain some of that lost activity. The idea that a C-3 substituent by itself might prove beneficial was tested with a 3-chloro group. Chloroindole **5e** was slightly more potent than its unsubstituted progenitor **5a**, indicating that the leukotriene receptor could at least accommodate functionality at the C-3 position of the indoles. The negative effect of a C-2 substituent was again seen with the 2,3-dibromoindole **5f**.

When the more potent cyclopentyl urethane (**5g**) and cyclopentylacetamide (**5i**) "western" chains were discovered, the effects of C-3 appendages were investigated in these series (Table II). A methyl group (**10b**) and a chloro substituent (**5h**) were accommodated at C-3 in the acetamide and urethane series respectively, to generate compounds approximately equipotent to the unsubstituted analogs **5i** and **5g**. The C-3 acylated indoles **12a,b** exhibited enhanced activity, with the propyl ketone **12b** demonstrating that relatively large substituents could be successfully incorporated at C-3.

As a result of these studies the C-3 position was targeted for further synthetic work. When the corresponding *N*-arylsulfonyl amides of carboxylic acids **10b**, **5h**, and **12a,b** were prepared, the expected[5b,c] 30–100-fold increase in activity was obtained (Table II). However, those C-3 substituents which had been tolerated, or were even beneficial, in the carboxylic acid series were now detrimental to activity when incorporated into the sulfonyl amides. The 3-methylindole cyclopentylacetamide **10c** was 4-fold less potent than its unsubstituted parent **6e**, and the 3-chloroindole cyclopentylurethane **6c** was 2 times weaker than the C-3 unsubstituted analog **6b**. The one exception to this surprising trend was the methyl ketone **12c**. This compound, containing the least lipophilic of the substituents studied, was 2 times more active than its unsubstituted progenitor **6b**. Interestingly, the more lipophilic propyl ketone **12d** suffered a 4-fold drop in activity compared to methyl ketone **12c**. This decreased activity of the higher ketone homolog **12d** is probably not due to a detrimental steric interaction with the receptor since the propyl ketone moiety was accommodated readily in the carboxylic acid series (**12b**).

The conclusion from Table I that C-2 substituents imparted diminished activity was corroborated by an additional compound containing the advantageous cyclo-

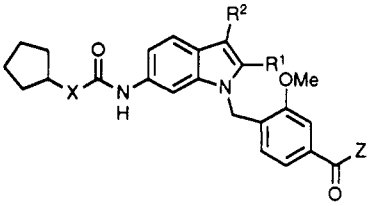
(27) Hogaboom, G. K.; Mong, S.; Wu, H.-L.; Crooke, S. T. Peptidoleukotrienes—Distinct Receptors for Leukotriene-C_4 and Leukotriene-D_4 in the Guinea-Pig Lung. *Biochem. Biophys. Res. Commun.* **1983**, *116*, 1136–1143.

(28) (a) Buckner, C. K.; Saban, R.; Castleman, W. L.; Will, J. A. Analysis of Leukotriene Receptor Antagonists on Isolated Human Intralobar Airways. *Ann. N.Y. Acad. Sci.* **1988**, *524*, 181–186. (b) Lewis, M. A.; Mong, S.; Vessella, R. L.; Hogaboom, G. K.; Wu, H.-L.; Crooke, S. T. Identification of Specific Binding-Sites for Leukotriene-C_4 in Human-Fetal Lung. *Prostaglandins* **1984**, *27*, 961–974.

(29) Aharony, D.; Falcone, R. C.; Krell, R. D. Inhibition of ^3H-Leukotriene-D_4 Binding to Guinea-Pig Lung Receptors by the Novel Leukotriene Antagonist ICI 198,615. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 921–926.

(30) Snyder, D. W.; Liberati, N. J.; McCarthy, M. M. Conscious Guinea-Pig Aerosol Model for Evaluation of Peptide Leukotriene Antagonists. *J. Pharmacol. Methods* **1988**, *19*, 219–231.

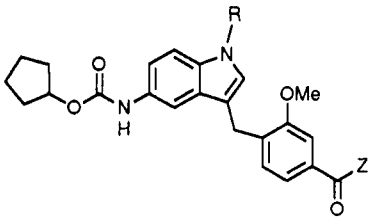
Table II. Pyrrole Substituents in Cyclopentyl Acetamides and Urethanes[a]



			Z = OH			Z = $NHSO_2C_6H_4(o\text{-}R^3)$		
R^1	R^2	X	compd	% inhibn/ concn, μM	(K_B ± SEM) × 10^{-8} M; (n)	R^3	compd	(K_B ± SEM) × 10^{-10} M; (n)
H	H	CH_2	**5i**	34/0.1	2.07 ± 0.46 (8)	Me	**6e**	1.06 ± 0.18 (6)
H	Me	CH_2	**10b**	59/0.1		Me	**10c**	4.56 ± 1.91 (16)
H	H	O	**5g**	61/0.1	1.57 ± 0.15 (8)	H	**6b**	2.90 ± 0.60 (7)
H	Cl	O	**5h**	41/0.1		H	**6c**	7.18 ± 3.15 (5)
H	COMe	O	**12a**	83/0.1		H	**12c**	1.23 ± 0.22 (4)
H	$COPr^n$	CH_2	**12b**	96/0.1		H	**12d**	4.96 ± 0.83 (5)
	$-(CH)_4-$	CH_2				H	**6a**	77.3 ± 28.2 (4)
H	H	CH_2				H	**6d**	2.43 ± 0.86 (4)

[a] See the footnotes in Table I for explanations of the data.

Table III. Lipophilic N-1 Substituents[a]



	pK_B[b]	
R	Z = OH	Z = $NHSO_2Ph$
H	7.32	9.84
Me	7.84	9.69
$n\text{-}C_3H_7$	7.72	8.44
$c\text{-}C_5H_9$	7.67	7.84

[a] These compounds and their biological activities are described in ref 5b. [b] Negative logarithm of the molar dissociation constant.

pentylacetamide and arylsulfonyl amide appendages. Carbazole **6a** was 30 times less active than the corresponding indole **6d**. As a template, the carbazole ring system is less active by at least 1 order of magnitude than any of the bicyclic nuclei previously employed as alternatives for the indole or indazole rings.[5e]

The data of Table II suggest that although C-3 substituents are accommodated by the leukotriene receptor, the overall lipophilicity of the antagonist molecules has to be appropriately balanced. Thus, while lipophilic substituents did not adversely affect the carboxylic acid series, they were detrimental in the inherently less polar *N*-arylsulfonyl amide analogs. A similar correlation[5b] has been observed in the inverted indole series (Table III), where hydrocarbon chains at N-1 enhanced in vitro activity in the carboxylic acid analogs but diminished that activity in the corresponding phenylsulfonyl amides.

The beneficial effect of the polar methyl ketone functionality in the sulfonyl amide series (**12c**) prompted us to consider employing other polar substituents at C-3, especially since the receptor did not appear to impose severe steric restraints (e.g. **12b**) on this region of the indole antagonists. The choice of polar C-3 appendages was influenced by our thoughts on the possible similarities between these molecules and the leukotrienes. One of the reasons for our initial interest in the indole-based leukotriene antagonists was the hypothesis that they could be compared with our earlier series of hydroxyacetophenone-derived antagonists.[5a] These hydroxyacetophenones, in turn, had been postulated to mimic the tetraene and peptide arms of the LTD_4 molecule.[31] Thus, we speculated that our potent acylamino, sulfonyl amide antagonists (**1** and **2**) were binding to those portions of the receptor normally accepting the lipophilic tetraene and polar peptide portions of the leukotrienes, respectively. Two recent leukotriene antagonists[32] appear to take advantage of all three of the putative leukotriene binding domains[33] in the receptor—a hydrophobic pocket for the tetraene chain, an ionic site associated with the peptide, and a hydrophilic, non-ionic region accepting the C-1 acid segment. We reasoned that perhaps the C-3 site on our indole antagonists could be used to incorporate an appendage which might bind in the polar site accommodating the C-1 carboxyl of LTD_4.

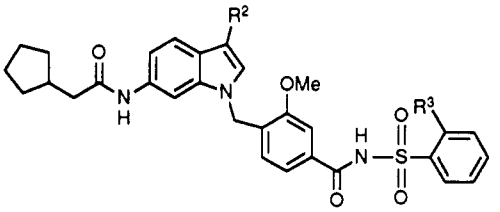
Our initial targets were a series of indoles substituted at C-3 with propionic acid derivatives (Table IV). It was felt that such appendages could place a polar functionality in the vicinity of the putative binding pocket for the leukotriene C-1 carboxyl group without introducing excessive flexibility into the molecules or exceeding the permissable steric parameter previously defined by the propyl ketone substituent.

(31) Brown, F. J.; Bernstein, P. R.; Cronk, L. A.; Dosset, D. L.; Hebbel, K. C.; Maduskuie, T. P., Jr.; Shapiro, H. S.; Vacek, E. P.; Yee, Y. K.; Willard, A. K.; Krell, R. D.; Snyder, D. W. Hydroxyacetophenone-Derived Antagonists of the Peptidoleukotrienes. *J. Med. Chem.* **1989**, *32*, 807–826.

(32) For example: (a) Gauthier, J. Y.; Jones, T.; Champion, E.; Charette, L.; DeHaven, R.; Ford-Hutchinson, A. W.; Hoogstein, K.; Lord, A.; Masson, P.; Piechuta, H.; Pong, S. S.; Springer, J. P.; Therien, M.; Zamboni, R.; Young, R. N. Stereospecific Synthesis, Assignment of Absolute Configurations, and Biological Activity of the Enantiomers of 3-[[[3-[2-(7-Chloroquinoline-2-yl)-(E)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propionic Acid, a Potent and Specific Leukotriene D_4 Receptor Antagonist. *J. Med. Chem.* **1990**, *33*, 2841–2845. (b) Gleason, J. G.; Hall, R. F.; Perchonock, C. D.; Erhard, K. F.; Frazee, J. S.; Ku, T. W.; Kondrad, K.; McCarthy, M. E.; Mong, S.; Crooke, S. T.; Chi-Rosso, G.; Wasserman, M. A.; Torphy, T. J.; Muccitelli, R. M.; Hay, D. W.; Tucker, S. S.; Vickery-Clark, L. High-Affinity Leukotriene Receptor Antagonists—Synthesis and Pharmacological Characterization of 2-Hydroxy-3-[(2-Carboxyethyl)thio]-3-[2-(8-Phenyloctyl)phenyl]propanoic Acid. *J. Med. Chem.* **1987**, *30*, 959–961.

(33) Young, R. N. Structural-Analysis of Sulfido-Peptide Leukotrienes—Application to the Design of Potent and Specific Antagonists of Leukotriene-D_4. *Adv. Prostagland. Thrombox. Leukotriene Res.* **1989**, *19*, 643–646.

Table IV. Propionic Acid Derivatives at C-3



compd	R^2	R^3	(K_B ± SEM)[a] × 10^{-11} M; (n)	% protection[b]/po dose, μmol/kg; (m/n)
6d	H	H	24.3 ± 8.6 (4)	43 ± 6/30 (0/6)
14a	$(CH_2)_2CO_2Me$	H	27.3 ± 5.0 (3)	63 ± 14/10 (3/7)
14b	$(CH_2)_2CO_2H$	H	7.31 ± 1.82 (4)	35 ± 17/10 (2/7)[c]
15c	$(CH_2)_2CONHMe$	H	1.97 ± 0.11 (10)	74 ± 10/10 (4/10)
15d	$(CH_2)_2CONH_2$	Me	9.50 ± 6.98 (7)	63 ± 3/3 (4/9)
6e	H	Me	10.6 ± 1.8 (6)	40 ± 6/1 (0/8)
10c	Me	Me	45.6 ± 19.1 (16)	54 ± 10/0.3 (8/19)

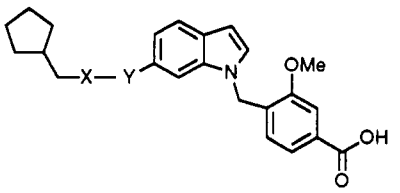
[a] See footnote *b* in Table I. [b] Percent protection of conscious guinea pig lung function against an aerosolized LTD_4 challenge was determined by the time delay to the onset of labored abdominal breathing engendered by the indicated oral dose (administered 180 min prior to the LTD_4 challenge) of the antagonist (compared to placebo, $p < 0.05$). The ratio (m/n) is the ratio of the number of animals fully protected (m) by the antagonist (no dyspnea observed during the test period) vs the total number of animals (n) receiving the antagonist. More detail is provided in the Experimental Section. [c] Not significantly different from control.

The first such compound, methyl propionate **14a**, did not provide any additional in vitro potency over that of the parent indole **6d**. However, the corresponding acid **14b** was 3 times more potent, and the related *N*-methylpropionamide **15c** gained over 1 order of magnitude in activity. In light of the latter result, it is worth noting that the C-1 carboxyl group of LTD_4 has been replaced with an amide functionality without precipitating any substantial loss of agonist activity.[34] The achievement of a 12-fold increase in potency was gratifying. *N*-Methylpropionamide **15c** represents one of the most potent leukotriene antagonists known. However, the fact that oral activity had not increased to a commensurate degree was disappointing. The transition from unsubstituted indole **6d** to propionamide **15c** had increased the oral potency by only a factor of approximately 3. Substantial improvements were going to be required to match the oral activity of ICI 204,219, which has an ED_{50} of 0.5 μmol/kg in the identical assay.[6]

The introduction of an *o*-tolylsulfonyl amide in place of a phenylsulfonyl amide had previously enhanced oral potency by a factor of 10.[5b] Thus, a propionamide appendage was introduced in the *N*-tolylsulfonyl amide series (**15d**). The in vitro activity of the primary propionamide **15d** was not any better than that of the corresponding C-3 unsubstituted indole **6e**, although it was almost 5 times greater than that of the C-3 methylated analog **10c**. As hoped, the oral activity of propionamide *tolyl*sulfonyl amide **15d** surpassed that of any of the propionic acid derivatives in the *phenyl*sulfonyl amide series (**14a,b**, **15c**). However, it remained inferior to that of the unsubstituted indole tolylsulfonyl amide **6e** and substantially worse than that of the 3-methylindole tolylsulfonyl amide **10c**.

The study outlined in Table IV demonstrated that C-3 hydrophilic substituents were capable of substantially improving the in vitro activity of some series. Given the relatively small number of polar groups that were explored, the potential for further optimization remained high. Simultaneously to this exploration of pyrrole substituents, new modifications to the western chain were under investigation. Further delineation of the structure–activity relationships of the polar group, especially with respect to oral efficacy, was undertaken in conjunction with these studies of the western chain (vide infra).

Table V. Alternatives to the Acylamino Link



compd	X–Y	% inhibn/ concn, μM[a]
21c	OC(O)	74/10 10/3.3
24b	CH_2O	75/10
18b	NHC(O)	45/3.3
5i	C(O)NH	34/0.1

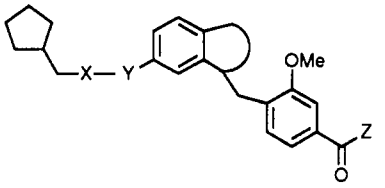
[a] See footnote *a* in Table I.

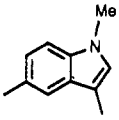
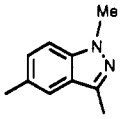
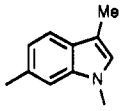
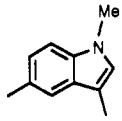
Western Chain Alternatives. As outlined in the introduction, previous papers[5] have discussed explorations of the three major structural portions of the indole/indazole-based leukotriene antagonists **1** and **2**: the western chain, the central template fragment, and the acidic moiety. Alternatives yielding high in vitro potency were discovered for each of these molecular fragments. However, these molecules always retained the anilide structure as a constant linking group to connect the western lipophilic group with the central bicyclic template.

For the sake of structural diversity in a potential clinical follow-up to ICI 204,219, a brief survey of alternatives to the acylamino linking group was undertaken (Table V). The cyclopentyl group had emerged as an optimal lipophilic moiety for the western chain in the anilide series,[5a] so it was retained. Previous work[5a] had shown that *N*-methylamide, thiourea, or sulfonamide groups were all inferior to the corresponding amide link. Therefore, three different replacements for the acylamino link were investigated: an ester, an ether, and a benzamide (or transposed amide) connection. The transposed amide derivative **18b** offered the greatest potential, although it was still significantly less potent than the corresponding

(34) Lewis, R. A.; Drazen, J. M.; Austen, K. F.; Toda, M.; Brion, F.; Marfat, A.; Corey, E. J. Contractile Activities of Structural Analogs of Leukotriene-C and Leukotriene D—Role of the Polar Substituents. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4579–4583.

Table VI. Transposed Amides



template	X–Y	Z = OH compd	Z = OH % inhibn[a]/ concn, μM	Z = OH K_i, nM[b]	Z = $NHSO_2C_6H_4$(o-Me) compd	Z = $NHSO_2C_6H_4$(o-Me) K_i, nM[b]	Z = $NHSO_2C_6H_4$(o-Me) (K_B ± SEM)[c] × 10^{-10} M; (n)
	HNCO	**27a**	33/1	422	**27b**	3.21	42.8 ± 4.9 (5)
	HNCO	**29b**	37/3.3		**29c**	1.87	
	HNCO				**20c**	9.89	
	CONH	**45**[d]	94/0.1	80	**46**[d]	0.30	2.45 ● 0.44 (4)

[a] See footnote *a* in Table I. [b] Inhibition constant for displacement of ^{3}H-LTD_4 on guinea pig lung parenchymal membranes; values are the mean of two experiments conducted in duplicate. More detail is provided in the Experimental Section. [c] See footnote *b* in Table I. [d] These compounds are described in ref 5b.

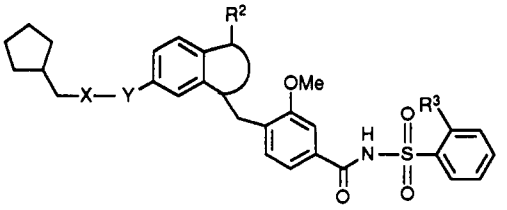
anilide **5i**. The ester **21c** and ether **24b** exhibited even weaker activity. On the basis of these results, the transposed amide was selected for futher attention. Our earlier work had demonstrated that the various anilide series exhibited an amazing interseries concordance. For example, the beneficial effect of cyclopentyl-containing western chains, originally discovered in indoles, applied equally well to indazoles; and the enhanced potency imparted to compounds of series 1 by the arylsulfonyl amide also extended to the compounds of the inverted series 2. It was gratifying to find that these fundamental structure–activity relationships could also be applied to transposed amides. It was possible to translocate the transposed amide functionality from indole **18b** (Table V) to the corresponding inverted indole (**27a**) or inverted indazole (**29b**) and obtain equivalent or more potent antagonists (Table VI). Furthermore, replacement of the carboxylic acid group with the *o*-tolylsulfonyl amide moiety (e.g. **27a** to **27b**) provided more than a 100-fold increase in potency, just as in the anilide series (e.g. **45** to **46**). However, a comparison of transposed amides **27b**, **29c**, and **20c** with representative anilide **46** illustrates that at the *o*-tolylsulfonyl amide stage the transposed amides are still about 1 order of magnitude less potent than the anilides.

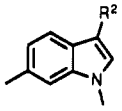
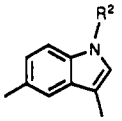
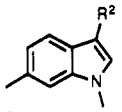
We decided to ascertain if the interseries structure–activity concordance could be pushed even further. Could the beneficial effects of the propionamide substituent in the anilide series be extended to the transposed amides? Indeed, the incorporation of the *N*-methylpropionamide group, the best polar appendage from the anilide series (Table IV), into the transposed amide series (**39a**) purchased a significant increase in activity over either the corresponding 3-methylindole **20c** or the C-3 unsubstituted indole **18c** (Table VII). It was anticipated that the propionamide moiety would also provide benefits to the inverted (3,5-disubstituted) indole series. While this concept of a N-1 (or "northern") propionamide appendage had not been explored in the anilides, it was successful with transposed amides. Replacing the *N*-methyl substituent of **27b** with a propionamide group (**35c**) gave a 7-fold increase in potency. Interestingly, a propionamide appendage linked via its α-carbon to the indole (**34c**) proved to be a detrimental substituent. The fact that the benefits of the polar group were dependent upon it being in a particular location relative to the rest of the molecule supported the view that it was binding specifically to a particular portion of the leukotriene receptor.

Having established the generality of the propionamide effect across several series, we tried applying it to the case where the acylamino group had been replaced with an ether link (see **24b**, Table V). The propionamide **33c** was more active by a factor of 10 than the C-3 unsubstituted ether **24c**. Thus, it appeared the "northern" propionamide group could be used as a rather general ploy to enhance the activity of the indole-based leukotriene antagonists. With the propionamide appendage, transposed amide indoles such as **39a** and **35c** were elevated to potencies comparable to those achieved in the anilide series (activity at sub-nanomolar concentrations).

N-Methylpropionamide **39a** was utilized as the starting point for a more comprehensive investigation of the structure–activity relationships of the propionamide appendage within the transposed amide series. In the anilide series (Table IV) the oral activity of the propionic acid derivatives had been disappointing given their excellent in vitro potency. Therefore, it was important to assess the effect of the propionamide group on both in vitro and in vivo potency in the transposed amides. Despite having a comparable dissociation constant, the *N*-methylpropionamide **39a** was approximately 100 times less active orally than the 3-methylindole **10c** (Table IV) from the anilide series. Thus, structural modifications to enhance the oral

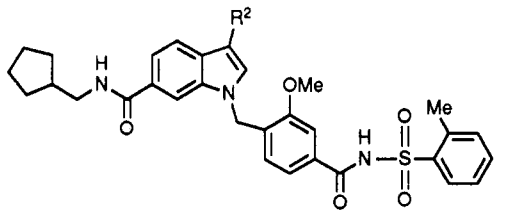
Table VII. Propionamide Substituents[a]

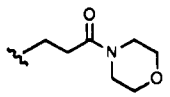
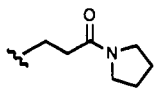
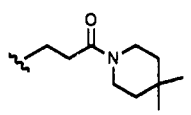


compd	template	X-Y	R^2	R^3	% inhibn/ concn, nM	K_i, nM	(K_B ± SEM) × 10^{-9} M; (*n*)
18c		NHCO	H	H	46/100	86.8	14.2 ± 0.19 (6)
39a	*b*	NHCO	$(CH_2)_2CONHMe$	Me	51/1	1.53	0.40 ± 0.08 (8)
20c	*b*	NHCO	Me	Me		9.89	
27b		NHCO	Me	Me	36/10	3.21	4.28 ± 0.49 (5)
35c	*b*	NHCO	$(CH_2)_2CONEt_2$	Me		0.43	
34c	*b*	NHCO	$CH(Me)CONMe_2$	Me			12.1 ± 3.3 (6)
24c		CH_2O	H	Me	21/100		
33c	*b*	CH_2O	$(CH_2)_2CONH_2$	H	29/10		10.3 ± 1.9 (8)

[a] See footnotes in Tables I and VI for explanations of the data. [b] Same structure as above.

Table VIII. C-3 Propionamides in Transposed Amides[a]



compd	R^2	K_i, nM	(K_B ± SEM) × 10^{-10} M; (*n*)	% protection/po dose, μmol/kg; (*m*/*n*)
39a	$CH_2CH_2CONHMe$	1.53	3.99 ± 0.85 (8)	44 ± 11/30 (1/8)
41c	$CH_2CH(Me)CONMe_2$	2.32	6.50 ± 0.15 (5)	37 ± 11/10 (0/8)
44c	$CH_2CH_2CONEt_2$	0.54		NS/1
44a	$CH{=}CHCONEt_2$	4.90		NS/10
39b			2.89 ± 0.53 (6)	53 ± 13/10 (2/8)
39c			4.68 ± 1.88 (8)	49 ± 9/3 (4/18)
44d			44.5 ± 14.1 (5)	

[a] See footnotes in Tables I, IV, and VI for explanations of the data.

activity without hurting the in vitro potency were required.

In the anilide series (compounds of type **1** and **2**), there had been a reasonable correlation (42 compounds; $r = 0.85$) between oral activity (log of the reciprocal of the oral ED_{50}) and a combination of lipophilicity plus in vitro potency (0.70 clog D + 0.54 pK_b).[20] An indication of this influence of lipophilicity on oral potency is evident in Table IV. The oral potency of the C-3 unsubstituted indole phenylsulfonyl amide **6d** increased 30-fold with the incorporation of a methyl group into the *N*-phenylsulfonyl amide moiety (**6e**). This increase is too large to be attributed solely to the 2-fold enhancement of in vitro potency. The addition of a second methyl substituent, now at C-3 of the indole (**10c**), decreased the in vitro potency by a factor of 4, but increased oral activity a further 3-fold. If the C-3 methyl of indole **10c** was then replaced with a polar propionamide substituent (**15d**), the oral activity dropped by a factor of 10 despite a 5-fold increase of in vitro potency.

In the transposed amide series we were faced with a dilemma. A polar northern appendage was required to

bring the in vitro potency up to the nanomolar level, but the decreased lipophilicity was then detrimental to oral activity. Propionamide **39a** (Table VIII) had a dissociation constant comparable to that of the better anilides, but a 100-fold increase in oral activity was required to match the oral activity of anilides such as ICI 204,219 (po ED_{50} = 0.5 μmol/kg) or the 3-methylindole **10c** (Table IV). We postulated that N,N-dialkylated amides would retain the beneficial in vitro effect of the earlier propionamides, but being more lipophilic, might achieve a better oral profile. However, a balance would have to be maintained as excessive lipophilicity would probably be detrimental to in vitro potency, as previously observed in the anilide arylsulfonyl amides (Tables II and III).

The pharmacologic profile of the *N,N*-dimethyl analog **41c** (Table VIII) was encouraging, demonstrating that a tertiary amide moiety was still tolerated by the receptor. Despite suffering a modest fall in the dissociation constant compared to that of the monomethyl analog **39a**, the two additional methyl groups of compound **41c** provided approximately a 3-fold gain in oral activity. The *N,N*-diethyl amide **44c** exhibited a significant increase in potency, which was negated by the introduction of a double bond into the linking carbon chain (**44a**). The 9-fold loss of potency suffered by this latter compound again corroborates the importance of the relative positioning of the polar function within these antagonists. Neither of these *N,N*-diethyl derivatives exhibited any oral activity at doses commensurate with their in vitro potency. The morpholine amide **39b** was 2 times more potent than the *N,N*-dimethyl analog, but only marginally more active orally. However, the pyrrolidine amide **39c** provided a further 3-fold enhancement of oral potency. Further increases in the lipophilicity of the propionamide moiety, as in the dimethylpiperidine analog **44d**, were detrimental to the in vitro potency. Thus, there was a limit to what could be achieved in the way of enhanced oral activity via increased lipophilicity within the northern amide appendage.

As an assessment of relative bioavailability, the ratio of activities following oral versus intravenous dosing (po/iv) was computed for several of these compounds. The po/iv ratio for the *N,N*-diethyl amide **44c** was greater than 220 (iv ED_{50} = 4.6 nmol/kg), and that for the pyrrolidine amide **39c** was greater than 50 (iv activity = 100% at 60 nmol/kg). A similarly large po/iv ratio (greater than 120; po activity = NS at 0.5 μmol/kg; iv ED_{50} = 4.3 nmol/kg) was measured for the *N,N*-diethylpropionamide in the inverted indole series (**35c**, Table VII). These ratios compare unfavorably with the po/iv ratio of 11 for ICI 204,219.[6] These data suggest that the propionamide appendage, while effectively enhancing in vitro activity, is deleterious to the bioavailability of these antagonists. In fact, no detectable plasma levels could be found for either **35c** or **39c** following oral dosing.[35]

Summary and Conclusions

An investigation of the biological effects of pyrrole substituents in leukotriene antagonists derived from 1,6-disubstituted indoles demonstrated that relatively large groups could be accommodated at the C-3 position, but not at C-2. Within the advantageous *N*-arylsulfonyl amide derivatives, polar groups were preferred over lipophilic substituents. A potential mode of overlapping antagonists **1** and **2** with LTD_4 suggested that the incorporation of propionic acid derivatives at C-3 might take advantage of an additional binding site within the leukotriene receptor. Indeed, a propionamide substituent was found to enhance the in vitro activity of the anilide series **1** by 1 order of magnitude.

Simultaneously, greater structural diversity was being sought with series **1** and **2** through modification of the common anilide link between the lipophilic western chains and the central bicyclic rings. The transposed amide moiety was selected as one of the more promising alternatives. The structure–activity relationships previously elucidated in the anilide series applied equally well to transposed amides. Thus, this moiety could be successfully incorporated into inverted indoles or indazoles, and the *N*-arylsulfonyl amide replacement for the carboxylic acid moiety provided the expected enhancements in potency. However, the transposed amides remained approximately 1 order of magnitude less active than their anilide counterparts.

Therefore, it was gratifying to find that the incorporation of northern propionamide appendages (either at C-3 in indoles or at N-1 in inverted indoles) could also be used to enhance the activity of series containing alternatives to the anilide-linked western chain. In particular, transposed amides could be elevated to potency levels comparable with those of the disubstituted indole anilides.

The consistency of the northern propionamide effect across several series lends credence to the suggestion that the polar group is taking advantage of a specific interaction with the leukotriene receptor. Additional corroborating evidence for this concept is provided by the fact that changes in the relative positioning of the amide function (e.g. shortening the linking carbon chain by one or introducing a double bond) are deleterious to activity. The incorporation of this third functionalized appendage into the indoles **1** and **2** allowed, for the first time, the conceptual visualization that these antagonists were mimicing all three arms (tetraene, peptide, and carboxyl regions) of the leukotrienes. It is tempting to speculate that the propionamide moiety is binding in that portion of the receptor meant to accommodate the C-1 carboxylic acid end of LTD_4. Furthermore, the ability to so successfully extrapolate the structure–activity relationships from one series to another within this broad class of indole/indazole-derived antagonists implies that they are all binding in a similar fashion to the same receptor site.

The initial propionic acid derivatives utilized in the anilide series had not provided oral activity at levels commensurate with the high in vitro potencies of the compounds. The structure–activity relationships of the propionamide appendage were explored further in the transposed amide series to address this issue. By utilizing tertiary amides of greater lipophilicity, 1 order of magnitude increase in oral potency was achieved. However, the northern propionamide appendage appeared to be a liability for the oral bioavailability of these leukotriene antagonists.

The best compound from the transposed amide series, pyrrolidine amide **39c**, was still approximately 10-fold less active orally than the better anilides without northern appendages, such as **10c** (Table IV). Given the poor apparent bioavailability of several propionamides, it was decided that the polar northern appendage approach to enhanced activity was not going to deliver a compound with a suitable in vivo profile.

Experimental Section

General Methods. Proton NMR (^{1}H NMR) spectra were recorded on a Brucker WM 250 (250 MHz) or an IBM NR-80 (80 MHz) instrument using the indicated solvents. Chemical shifts are reported in parts per million relative to tetramethylsilane as

(35) We thank Ms. Karin Kirkland of our Drug Disposition and Metabolism Department for these studies.

internal standard. Complete ^{1}H-NMR data are reported for all synthetic intermediates. The usual abbreviations are used to describe peak shape and multiplicity: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; etc. Mass spectra (MS) were recorded on a Kratos MS-80 instrument operating either in the electron impact (EI) or chemical ionization (CI) mode. Melting points were measured 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. Pyridine was distilled from calcium hydride. Aromatic sulfonamides were generally recrystallized from ethanol prior to use. Unless otherwise indicated, reaction workups culminated in drying with anhydrous $MgSO_4$ and removing the solvent by evaporation under reduced pressure.

Methyl 4-[[6-[*N*-[(Cyclopentyloxy)carbonyl]amino]-3-chloroindol-1-yl]methyl]-3-methoxybenzoate (4h). A stirred slurry of *N*-chlorosuccinimide (158 mg, 1.18 mmol) in CCl_4 (6 mL) was treated with a solution of **methyl 4-[[6-[*N*-[(cyclopentyloxy)carbonyl]amino]indol-1-yl]methyl]-3-methoxybenzoate (4g)** (500 mg, 1.18 mmol) in CCl_4 (6 mL) and heated to reflux for 15 min. The mixture was filtered. The filtrate was washed with 10% aqueous $NaHCO_3$, water, and brine and then dried ($MgSO_4$). Evaporation gave a residue which was purified by flash chromatography on silica gel, eluting with EtOAc–CH_2Cl_2 (1:49), to give chloroindole **4h** (115 mg, 21%). ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.5–2.0 (br m, 8 H, $(CH_2)_4$), 3.9 (s, 3 H, CO_2CH_3), 4.0 (s, 3 H, OCH_3), 5.3 (m, 3 H, NCH_2, NCO_2CH), 6.5 (br, 1 H, NH), 6.6 (m, 2 H, H^5-benzoate, H^5-indole), 7.0 (s, 1 H, H^2-indole), 7.5 (m, 3 H), 7.7 (d, 1 H, H^7-indole).

4-[[6-[*N*-[(Cyclopentyloxy)carbonyl]amino]-3-chloroindol-1-yl]methyl]-3-methoxybenzoic Acid (5h). A solution of ester **4h** (115 mg, 0.250 mmol) in a mixture of MeOH (1 mL) and THF (1 mL) was treated with water (0.5 mL, 20% v/v) and lithium hydroxide monohydrate (63.7 mg, 1.50 mmol) and then stirred at room temperature for 6 h. The organic solvents were removed by evaporation, and the residue was taken up in water. Acidification of the resulting aqueous solution with 10% HCl gave a precipitate which was collected by filtration and recrystallized from EtOAc–hexane to give acid **5h** as white needles (94.8 mg, 86%). Mp: 234–235 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.6 (m, 6 H, cyclopentyl), 1.8 (m, 2 H, cyclopentyl), 3.9 (s, 3 H, OCH_3), 5.1 (m, 1 H, NCO_2CH), 5.3 (s, 2 H, NCH_2), 6.7 (d, J = 7.8 Hz, 1 H, H^5-benzoate), 7.1 (d, J = 8.6 Hz, 1 H, H^5-indole), 7.40 (d, J = 8.6 Hz, 1 H, H^4-indole), 7.45 (dd, J = 1.5, 7.8 Hz, 1 H, H^6-benzoate), 7.5 (d, J = 1.5 Hz, 1 H, H^2-benzoate), 7.6 (s, 1 H, H^2-indole), 7.7 (s, 1 H, H^7-indole), 9.5 (s, 1 H, NH).

***N*-[4-[[6-[*N*-[(Cyclopentyloxy)carbonyl]amino]-3-chloroindol-1-yl]methyl]-3-methoxybenzoyl]benzenesulfonamide (6c).** A solution of carboxylic acid **5h** (81 mg, 0.19 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (38 mg, 0.20 mmol), 4-(dimethylamino)pyridine (24 mg, 0.20 mmol), and benzenesulfonamide (31 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 8 h. The solution was diluted with CH_2Cl_2, washed sequentially with 10% aqueous HCl, water, and brine, and evaporated. The residue was recrystallized first from EtOAc–hexane and subsequently from MeOH–water to give sulfonyl amide **6c** as white needles (20 mg, 18%). Mp: 199–200 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.6 (m, 6 H, cyclopentyl), 1.8 (m, 2 H, cyclopentyl), 3.9 (s, 3 H, OCH_3), 5.1 (m, 1 H, NCO_2CH), 5.3 (s, 2 H, NCH_2), 6.7 (d, J = 7.9 Hz, 1 H, H^5-benzoate), 7.1 (d, J = 8.5 Hz, 1 H, H^5-indole), 7.40 (d, J = 8.5 Hz, 2 H), 7.52 (d, J = 1.2 Hz, 1 H, H^2-benzoate), 7.53 (s, 1 H, H^2-indole), 7.6 (m, 4 H), 8.0 (dd, J = 1.6, 7.1 Hz, 2 H, *o*-benzenesulfonamide), 9.5 (s, 1 H, CONH), 12.6 (br, SO_2NH). Anal. ($C_{29}H_{28}ClN_3O_8S$) C, H, N.

6-[*N*-[(Cyclopentyloxy)carbonyl]amino]indole (7a). A stirred solution of 6-aminoindole (23.3 g, 180 mmol) and cyclopentyl chloroformate (21 mL, 160 mmol) in CH_2Cl_2 (300 mL) was cooled to 0 °C and treated dropwise with triethylamine (32 mL, 230 mmol). After stirring at 0 °C for 30 min the solution was allowed to warm to ambient temperature and stirred an additional 90 min. The solution was diluted with CH_2Cl_2 and washed with 20% aqueous NaOH. A precipitate which formed in the organic layer was separated by filtration. The filtrate was washed sequentially with 10% aqueous $NaHSO_4$, water, and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel, eluting with EtOAc–CH_2Cl_2 (3:97) to give (acylamino)indole **7a** as a white solid (19.2 g, 49%). ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.5–2.0 (br m, 8 H, $(CH_2)_4$), 5.2 (br m, 1 H, CO_2CH), 6.4 (m, 1 H, H^3-indole), 6.6 (br s, 1 H, NH), 6.8 (dd, J = 1.9, 8.4 Hz, 1 H, H^5-indole), 7.1 (dd, J = 2.4, 3.2 Hz, 1 H, H^2-indole), 7.5 (d, J = 8.4 Hz, 1 H, H^4-indole), 7.7 (br s, 1 H, H^7-indole), 8.3 (br, 1 H, NH).

6-(Cyclopentylacetamido)indole (7b). A solution of 6-aminoindole (12.2 g, 92.4 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (18.5 g, 94.7 mmol), 4-(dimethylamino)pyridine (11.7 g, 94.7 mmol), and cyclopentylacetic acid (12.3 mL, 94.7 mmol) in CH_2Cl_2 (300 mL) was stirred for 24 h, after which time a suspended precipitate was present. The mixture was diluted with CH_2Cl_2 (the precipitate remained) and washed with 10% v/v aqueous HCl and then water. The precipitate suspended in the organic layer was collected by filtration to give (acylamino)indole **7b** as a white solid (21.3 g, 95%). Mp: 195–196 °C dec. ^{1}H NMR (80 MHz, DMSO-d_6): δ 1.2–1.8 (m, 8 H, $(CH_2)_4$), 2.3 (br s, 3 H, $COCH_2CH$), 6.3 (m, 1 H, H^3-indole), 7.0 (dd, J = 1.8, 8.4 Hz, 1 H, H^5-indole), 7.2 (t, J = 2.6 Hz, 1 H, H^2-indole), 7.4 (d, J = 8.4 Hz, 1 H, H^4-indole), 7.9 (br s, 1 H, H^7-indole), 9.7 (br s, 1 H, NH), 10.9 (br, 1 H, NH).

6-(Cyclopentylacetamido)-3-formylindole (8a). Dimethylformamide (30 mL) was cooled in an ice bath and slowly treated with $POCl_3$ (9.8 mL, 105 mmol). The resulting yellow solution was stirred for 15 min and then treated slowly with a solution of indole **7b** (20.0 g, 82.6 mmol) in DMF (10 mL). This solution was warmed to 35 °C, stirred for 1 h, and then cooled in an ice bath. The mixture was treated with ice and 20% v/v aqueous NaOH, heated to reflux for 15 min, and allowed to cool. The precipitate which formed was collected by filtration to give aldehyde **8a** as a white solid (17.7 g, 79%). ^{1}H NMR (80 MHz, DMSO-d_6): δ 1.1–1.7 (m, 8 H, $(CH_2)_4$), 2.3 (br s, 3 H, $COCH_2CH$), 7.2 (dd, J = 1.9, 8.5 Hz, 1 H, H^5-indole), 7.9 (d, J = 8.5 Hz, 1 H, H^4-indole), 8.1 (d, J = 1.5 Hz, 1 H, H^7-indole), 8.2 (d, J = 3.0 Hz, 1 H, H^2-indole), 9.9 (br s, 2 H, CHO, NH), 11.9 (br, 1 H, NH).

3-Acetyl-6-[*N*-[(cyclopentyloxy)carbonyl]amino]indole (8b). Dimethylacetamide (8 mL) was cooled in an ice bath and slowly treated with $POCl_3$ (3.94 mL, 42.2 mmol). The resulting yellow solution was allowed to warm to ambient temperature with stirring and then was treated with a solution of indole **7a** (4.69 g, 19.2 mmol) in dimethylacetamide (3 mL). This solution was stirred at ambient temperature for 2 h, heated to 60 °C for 30 min, and then cooled in an ice bath. The mixture was treated with ice, brought to pH 14 with 20% aqueous NaOH, heated to reflux for 10 min, and cooled. The precipitate which formed was collected by filtration and triturated with ether to give ketone **8b** as a pale brown solid (4.58 g, 83%). ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.6–1.8 (br m, 8 H, $(CH_2)_4$), 2.5 (s, 3 H, $COCH_3$), 5.2 (br m, 1 H, CO_2CH), 6.6 (br, 1 H, NH), 6.9 (dd, J = 1.9, 8.5 Hz, 1 H, H^5-indole), 7.8 (d, J = 3.0 Hz, 1 H, H^2-indole), 7.9 (br d, J = 1.7 Hz, 1 H, H^7-indole), 8.2 (d, J = 8.5 Hz, 1 H, H^4-indole), 8.6 (br, 1 H, NH).

6-(Cyclopentylacetamido)-3-methylindole (9). A refluxing solution of aldehyde **8a** (2.7 g, 10 mmol) in THF (70 mL) was treated with a solution of lithium aluminum hydride (0.76 g, 20 mmol) in THF (30 mL) at a rate sufficient to maintain reflux. The resulting solution was heated to reflux for an additional 30 min and then cooled to 0 °C. The addition of saturated aqueous Na_2SO_4 solution gave a precipitate which was separated by filtration. Evaporation of the filtrate gave a residue which was taken up in EtOAc. This solution was sequentially washed with aqueous $NaHSO_4$, water, and brine, then dried ($MgSO_4$), and evaporated. The resulting residue was purified by flash chromatography on silica gel, eluting with EtOAc–hexane (1:3) to give **9** (0.74 g, 29%). ^{1}H NMR (80 MHz, DMSO-d_6): δ 1.1–1.8 (br m, 8 H, $(CH_2)_4$), 2.2 (d, J = 1.0 Hz, 3 H, CH_3), 2.3 (br s, 3 H, $COCH_2CH$), 7.0 (m, 2 H, H^2-, H^5-indole), 7.3 (d, J = 8.5 Hz, 1 H, H^4-indole), 7.9 (d, J = 1.4 Hz, 1 H, H^7-indole), 9.6 (br s, 1 H, NH), 10.5 (br, 1 H, NH).

Methyl 4-[[6-(Cyclopentylacetamido)-3-methylindol-1-yl]methyl]-3-methoxybenzoate (10a). A stirred suspension of

NaH (63.6 mg, 2.65 mmol) in DMF (6 mL) was cooled in an ice bath, treated with a solution of indole **9** (740 mg, 2.89 mmol) in DMF (4 mL), and stirred for 1 h at 0 °C. The mixture was allowed to warm to ambient temperature, treated with a solution of methyl 4-(bromomethyl)-3-methoxybenzoate[5a] (624 mg, 2.41 mmol) in DMF (4 mL), and then stirred for 8 h. The mixture was diluted with water, and the resulting precipitate was collected by filtration to give ester **10a** as a white solid (600 mg; 48%): ^{1}H NMR (80 MHz, DMSO-d_6): δ 1.1–1.8 (br m, 8 H, $(CH_2)_4$), 2.2 (br s, 6 H, CH_3, $COCH_2CH$), 3.8 (s, 3 H, OCH_3), 3.9 (s, 3 H, OCH_3), 5.2 (s, 2 H, NCH_2), 6.6 (d, J = 7.8 Hz, 1 H, H^5-benzoate), 7.1 (m, 2 H, H^2-, H^5-indole), 7.3–7.5 (m, 3 H), 7.7 (d, J = 1.0 Hz, 1 H, H^7-indole), 9.7 (br, 1 H, NH).

***tert*-Butyl 4-[[6-(Cyclopentylacetamido)-3-formylindol-1-yl]methyl]-3-methoxybenzoate (11a).** A mixture of indole **8a** (15 g, 56 mmol), *tert*-butyl 4-(bromomethyl)-3-methoxybenzoate[5a] (20 g, 67 mmol), and K_2CO_3 (11 g) in DMF (250 mL), was stirred for 48 h. The mixture was diluted with a small quantity of water and extracted with EtOAc–Et_2O (1:1). The organic extract was washed sequentially with 10% aqueous HCl, water, and brine, then dried ($MgSO_4$), and evaporated. The residue was taken up in CH_2Cl_2 and eluted rapidly through a column of silica gel. Evaporation of the eluent gave a gum which was triturated with water to provide ester **11a** as an amber solid (24 g, 86%). An analytical sample was obtained by flash chromatography on silica gel, eluting with EtOAc–hexane (1:3). ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.1–1.8 (br m, 17 H, $C(CH_3)_3$, $(CH_2)_4$), 2.4 (br s, 3 H, $COCH_2CH$), 3.9 (s, 3 H, OCH_3), 5.3 (s, 2 H, NCH_2), 6.9 (dd, J = 1.8, 8.4 Hz, 1 H, H^5-indole), 7.0 (d, J = 8.2 Hz, 1 H, H^5-benzoate), 7.4–7.6 (m, 3 H, ArH, NH), 7.7 (s, 1 H, H^2-benzoate), 8.2 (d, J = 8.4 Hz, H^4-indole), 8.3 (br s, 1 H, H^7-indole), 9.9 (s, 1 H, CHO).

Methyl 4-[[3-Acetyl-6-[*N*-[(cyclopentyloxy)carbonyl]amino]indol-1-yl]methyl]-3-methoxybenzoate (11b). A solution of 3-acetylindole **8b** (6.74 g, 28 mmol) and methyl 4-(bromomethyl)-3-methoxybenzoate (8.59 g, 33 mmol) in DMF (138 mL) was treated with K_2CO_3 (5.6 g, 41 mmol) and stirred at ambient temperature for 48 h. The DMF was removed by evaporation. The resulting residue was triturated with EtOAc. The organic solution was washed sequentially with 10% aqueous HCl, water, and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel, eluting with EtOAc–hexane of increasing polarity from 1:4 to 3:2, to give ester **11b** as an off-white solid (9.15 g; 78%). ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.5–1.8 (2 m, 8 H, $(CH_2)_4$), 2.4 (s, 3 H, $COCH_3$), 3.8 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.2 (m, 1 H, OCH), 5.4 (s, 2 H, NCH_2), 6.9 (d, J = 7.8 Hz, 1 H, H^5-benzoate), 7.2 (dd, J = 1.6, 8.7 Hz, 1 H, H^5-indole), 7.5 (dd, J = 1.2, 7.8 Hz, 1 H, H^6-benzoate), 7.6 (d, J = 1.1 Hz, 1 H, H^2-indole), 7.7 (br s, 1 H, H^7-indole), 8.0 (d, J = 8.7 Hz, 1 H, H^4-indole), 8.4 (s, 1 H, H^2-benzoate), 9.6 (br s, 1 H, NH). Anal. ($C_{26}H_{28}N_2O_6$) C, H, N.

***tert*-Butyl (*E*)-4-[[3-(2-Carbomethoxyvinyl)-6-(cyclopentylacetamido)indol-1-yl]methyl]-3-methoxybenzoate (13a).** A solution of aldehyde **11a** (20.2 g, 41.3 mmol) and methyl (triphenylphosphoranylidene)acetate (30.4 g, 90.8 mmol) in dioxane (200 mL) was heated to reflux for 48 h. The residue resulting from evaporation of the dioxane was taken up in ether and then precipitated by the addition of hexane to give, after filtration, a brown powder. Three quarters of this material (recrystallizations were attempted on the remainder) was purified by flash chromatography on silica gel, eluting with EtOAc–hexane (1:3), to give α,β-unsaturated ester **13a** as a white solid (15.2 g, 90%). ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.1–1.8 (br m, 17 H, $C(CH_3)_3$, $(CH_2)_4$), 2.4 (br s, 3 H, $COCH_2CH$), 3.8 (s, 3 H, CO_2CH_3), 3.9 (s, 3 H, OCH_3), 5.3 (s, 2 H, NCH_2), 6.3 (d, J = 15.9 Hz, 1 H, C=$CHCO_2$), 6.7–7.0 (m, 3 H), 7.2–7.4 (m, 3 H), 7.6 (m, 2 H, HC=$CHCO_2$, H^2-benzoate), 7.8 (d, J = 8.5 Hz, 1 H, H^4-indole), 8.1 (br s, 1 H, H^7-indole).

***tert*-Butyl 4-[[3-(2-Carbomethoxyethyl)-6-(cyclopentylacetamido)indol-1-yl]methyl]-3-methoxybenzoate (13b).** A solution of α,β-unsaturated ester **13a** (5.17 g, 9.47 mmol) in a mixture of MeOH–THF (50 mL, 2:1) was added to 10% Pd/C (1.3 g, 25% w/w) in a Parr flask. The mixture was shaken under a 50 psi atmosphere of hydrogen for 1.5 h, and then filtered through diatomaceous earth. The filtrate was dried ($MgSO_4$) and evaporated to give saturated ester **13b** as a white solid (4.77 g, 92%). ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.1–1.8 (3 m, 17 H, $C(CH_3)_3$, $(CH_2)_4$), 2.2 (m, 3 H, $COCH_2CH$), 2.7 (t, J = 7.5 Hz, 2 H, CH_2CO_2), 2.9 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CO_2$), 3.6 (s, 3 H, CO_2CH_3), 3.9 (s, 3 H, OCH_3), 5.3 (s, 2 H, NCH_2), 6.6 (d, J = 7.8 Hz, 1 H, H^5-benzoate), 7.0 (dd, J = 1.8, 8.5 Hz, 1 H, H^5-indole), 7.1 (s, 1 H, H^2-indole), 7.3 (dd, J = 1.2, 7.8 Hz, 1 H, H^6-benzoate), 7.5 (m, 2 H), 7.8 (d, J = 1.0 Hz, 1 H, H^7-indole), 9.7 (s, 1 H, NH).

4-[[3-(2-Carbomethoxyethyl)-6-(cyclopentylacetamido)-indol-1-yl]methyl]-3-methoxybenzoic Acid (13c). A solution of *tert*-butyl ester **13b** (4.77 g, 8.70 mmol) and triethylamine (2.9 mL, 20.9 mmol) in dioxane (29 mL) was treated with trimethylsilyl triflate (3.5 mL, 18.3 mmol) and stirred overnight. TLC indicated some starting material remained, so additional quantities of triethylamine (0.73 mL, 5.2 mmol) and trimethylsilyl triflate (0.84 mL, 4.3 mmol) were added, and stirring was continued for another 2 h. The mixture was diluted with water and extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated to yield acid **13c** as an amber foam (3.63 g, 85%). An analytical sample was obtained by flash chromatography on silica gel using EtOAc–toluene (1:3) containing acetic acid (0.7% v/v) as the eluent. ^{1}H NMR (80 MHz, DMSO-d_6): δ 1.1–1.8 (br m, 8 H, $(CH_2)_4$), 2.2 (br s, 3 H, $COCH_2CH$), 2.7 (m, 2 H, CH_2CO_2), 2.9 (m, 2 H, $CH_2CH_2CO_2$), 3.6 (s, 3 H, CO_2CH_3), 3.9 (s, 3 H, OCH_3), 5.3 (s, 2 H, NCH_2), 6.6 (d, J = 7.8 Hz, 1 H, H^5-benzoate), 7.1 (m, 2 H), 7.3–7.5 (m, 3 H), 7.8 (br s, 1 H, H^7-indole), 9.7 (s, 1 H, NH).

4-[[3-(2-Carbamoylethyl)-6-(cyclopentylacetamido)indol-1-yl]methyl]-3-methoxybenzoic Acid (15b). A pressure vessel was charged with ester **13c** (345 mg, 0.702 mmol), 4-(dimethylamino)pyridine (85.7 mg, 0.702 mmol), and condensed ammonia (5 mL). The vessel was sealed and heated to 90 °C (250 psi) for 8 h. After the ammonia was allowed to evaporate, the residue was taken up in water. Acidification of the aqueous solution gave a precipitate which was recrystallized from MeOH–THF–H_2O to give amide **15b** as a white solid (175 mg, 52%). Mp: 244–245 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.1–1.8 (3 m, 8 H, $(CH_2)_4$), 2.2 (m, 3 H, $COCH_2CH$), 2.4 (t, J = 7.6 Hz, 2 H, CH_2CH_2CON), 2.9 (t, J = 7.6 Hz, 2 H, CH_2CH_2CON), 3.9 (s, 3 H, OCH_3), 5.3 (s, 2 H, NCH_2), 6.6 (d, J = 7.9 Hz, 1 H, H^5-benzoate), 6.7 (br s, 1 H, NH), 7.1 (m, 2 H), 7.3 (br s, 1 H, NH), 7.4–7.5 (m, 3 H), 7.5 (m, 2 H), 7.8 (s, 1 H, H^7-indole), 9.7 (s, 1 H, ArNH). MS (CI, m/z): 478 (M + 1). Anal. ($C_{27}H_{31}N_3O_5$) C, H, N.

Methyl (*E*)-4-[2-(Dimethylamino)vinyl]-3-nitrobenzoate. A solution of methyl 4-methyl-3-nitrobenzoate (4.46 g, 22.9 mmol) in *N*,*N*-dimethylformamide (23 mL) was treated with *N*,*N*-dimethylformamide dimethyl acetal (9.12 mL, 68.6 mmol) and heated to 130 °C for 2 h. The solvent was evaporated and the residue was triturated with ether to give the title enamine as a red powder (5.58 g, 97%). ^{1}H NMR (80 MHz; $CDCl_3$): δ 2.98 (s, 6 H, $N(CH_3)_2$), 3.89 (s, 3 H, OCH_3), 5.90 (d, J = 13.3 Hz, 1 H, CHN), 7.14 (d, J = 13.3 Hz, 1 H, CH=CHN), 7.45 (d, J = 8.7 Hz, 1 H, H^5-Ar), 7.90 (dd, J = 1.8, 8.7 Hz, 1 H, H^6-Ar), 8.47 (d, J = 1.8 Hz, 1 H, H^2-Ar).

6-Carbomethoxyindole (16a). A solution of methyl (*E*)-4-[2-(dimethylamino)vinyl]-3-nitrobenzoate (5.58 g, 22.3 mmol) in tetrahydrofuran (100 mL) was hydrogenated at 50 psi in the presence of 10% palladium-on-carbon (1.1 g, 20% w/w) for 35 min. The catalyst was removed by filtration through diatomaceous earth, the filtrate was evaporated, and the residue was dissolved in ethyl acetate. This solution was washed successively with 10% aqueous hydrochloric acid, water, and brine, then dried ($MgSO_4$), and evaporated to give indole **16a** as a white solid (3.32 g, 85%). Mp: 71–72 °C. ^{1}H NMR (80 MHz; $CDCl_3$): δ 3.92 (s, 3 H, OCH_3), 6.57 (m, 1 H, H^3-indole), 7.32 (t, J = 2.8 Hz, 1 H, H^2-indole), 7.62 (d, J = 8.4 Hz, 1 H, H^4-indole), 7.82 (dd, J = 1.4, 8.4 Hz, 1 H, H^5-indole), 8.16 (br s, 1 H, H^7-indole), 8.7 (br, 1 H, NH).

6-Carboxyindole (16b). A solution of ester **16a** (11.0 g, 62.8 mmol) in a mixture of tetrahydrofuran (150 mL), methanol (150 mL), and water (63 mL) was treated with lithium hydroxide monohydrate (15.8 g, 377 mmol). The mixture was stirred at 60 °C for 6 h and then concentrated to remove the organic solvents. The resultant residue was dissolved in water, and the solution was acidified with 50% hydrochloric acid. The precipitate which formed was collected by filtration and dried to give acid **16b** as a tan powder (9.6 g, 95%). Mp: 253–254 °C. ^{1}H NMR (80 MHz;

DMSO-d_6): δ 6.50 (m, 1 H, H^3-indole), 7.55 (m, 3 H), 8.04 (m, 1 H, H^7-indole), 11.42 (br s, 1 H, NH), 12.42 (br, 1 H, OH).

6-[*N*-(Cyclopentylmethyl)carbamoyl]indole (17). A solution of 6-carboxyindole (**16b**) (9.41 g, 58.4 mmol) and 1,1'-carbonyldiimidazole (10.6 g, 61.4 mmol) in methylene chloride (290 mL) was heated at reflux, under nitrogen, for 30 min. The solution was cooled and treated with (cyclopentylmethyl)amine (8.04 mL, 70.1 mmol). This mixture was heated to reflux for 30 min. The mixture was then diluted with methylene chloride, washed successively with 10% (v/v) hydrochloric acid, 20% (w/v) aqueous sodium hydroxide, and brine, dried ($MgSO_4$), and evaporated to give amide **17** as an ivory solid (14.4 g, 91%). Mp: 148–150 °C. ^1H NMR (80 MHz, DMSO-d_6): δ 1.2–1.8 (m, 8 H, $(CH_2)_4$), 2.2 (m, 1 H, NCH_2CH), 3.1 (m, 2 H, NCH_2), 6.5 (d, J = 3.0 Hz, 1 H, H^3-indole), 7.5 (m, 3 H), 7.9 (d, J = 1.0 Hz, 1 H, H^7-indole), 8.3 (br t, 1 H, CONH), 11.3 (br s, 1 H, NH).

Methyl 4-[[6-[*N*-(cyclopentylmethyl)carbamoyl]indol-1-yl]methyl]-3-methoxybenzoate (18a). A stirred suspension of hexane-washed NaH (110 mg, 2.6 mmol) in DMF (4 mL) was cooled to 0 °C and treated slowly with a cold solution of indole **17** (604 mg, 2.5 mmol) in DMF (4 mL). This mixture was stirred for 1 h and then allowed to warm to ambient temperature. A solution of methyl 4-(bromomethyl)-3-methoxybenzoate (711 mg, 2.7 mmol) in DMF (4 mL) was added, and the resulting mixture was stirred for 24 h. The reaction was cooled in an ice bath and quenched by the addition of saturated aqueous ammonium chloride solution. The DMF was removed by evaporation, and the residue was taken up in EtOAc. The EtOAc solution was washed sequentially with 10% aqueous HCl, water, and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel, eluting with EtOAc–hexane (3:7), to give ester **18a** as an ivory solid (390 mg, 37%). ^1H NMR (80 MHz, $CDCl_3$): δ 1.2–1.8 (m, 8 H, $(CH_2)_4$), 2.2 (m, 1 H, NCH_2CH), 3.4 (dd, J = 5.8, 6.9 Hz, 2 H, $CONCH_2$), 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.4 (s, 2 H, NCH_2Ar), 6.2 (br, 1 H, NH), 6.6 (dd, J = 0.8, 3.2 Hz, 1 H, H^3-indole), 6.7 (d, J = 7.6 Hz, 1 H, H^5-benzoate), 7.2–7.7 (m, 5 H), 7.9 (br s, 1 H, H^7-indole).

6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-formylindole (19a). *N,N*-Dimethylformamide (20 mL) was cooled to 0 °C under an atmosphere of nitrogen and treated cautiously with phosphorus oxychloride (6.6 mL, 71 mmol). This solution was stirred at 0 °C for 15 min, warmed to room temperature, and treated with a solution of indole **17** (14.3 g, 59.2 mmol) in *N,N*-dimethylformamide (100 mL). The yellow mixture was stirred for 2 h and then brought to pH 14 by the addition of ice and 20% (w/v) aqueous sodium hydroxide. The mixture was heated to reflux for 5 min and allowed to cool. The precipitate which formed was collected by filtration and triturated with ether to give aldehyde **19a** as a tan powder (9.6 g, 60%). Mp: 224–225 °C. ^1H NMR (80 MHz, DMSO-d_6): δ 1.2–1.8 (m, 8 H, $(CH_2)_4$), 2.2 (m, 1 H, NCH_2CH), 3.2 (t, J = 5.8 Hz, 2 H, $CONCH_2$), 7.7 (dd, J = 1.5, 8.2 Hz, 1 H, H^5-indole), 8.0 (d, J = 0.6 Hz, 1 H, H^2-indole), 8.1 (dd, J = 0.6, 8.2 Hz, 1 H, H^4-indole), 8.4 (s, 1 H, H^7-indole), 8.5 (br t, J = 5.8 Hz, 1 H, CONH), 10.0 (s, 1 H, CHO), 12.3 (br, 1 H, NH).

Cyclopentylmethyl Indole-6-carboxylate (21a). A solution of acid **16b** (500 mg, 3.10 mmol) and 1,1'-carbonyldiimidazole (645 mg, 3.73 mmol) in CH_2Cl_2 (16 mL) was heated to reflux under a nitrogen atmosphere for 30 min. Cyclopentanemethanol (1.11 mL, 10.2 mmol) was added in three portions over a 90-min period to the refluxing solution. The reaction mixture was diluted with $CHCl_3$, washed sequentially with 20% aqueous NaOH, water, and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatogaphy on silica gel, eluting with $CHCl_3$, to give ester **21a** as an ivory powder (726 mg, 96%). ^1H NMR (80 MHz, $CDCl_3$): δ 1.2–2.0 (m, 8 H, $(CH_2)_4$), 3.5 (m, 1 H, OCH_2CH), 4.2 (d, J = 6.9 Hz, 2 H, OCH_2), 6.6 (m, 1 H, H^3-indole), 7.4 (dd, J = 2.6, 3.1 Hz, 1 H, H^2-indole), 7.6 (br d, J = 8.4 Hz, 1 H, H^4-indole), 7.8 (dd, J = 1.4, 8.4 Hz, 1 H, H^5-indole), 8.2 (m, 1 H, H^7-indole), 8.6 (br, 1 H, NH).

(*E*)-5-(Benzyloxy)-2-[2-(dimethylamino)vinyl]nitrobenzene. A solution of 4-(benzyloxy)-2-nitrotoluene (61 g, 250 mmol) in DMF (250 mL) was treated with *N,N*-dimethylformamide dimethyl acetal (100 mL, 760 mmol) and heated to 130 °C for 48 h. An additional quantity of the acetal (33 mL, 250 mmol) was added and heating was continued at 130 °C for another 32 h while MeOH was allowed to distill. Evaporation of the DMF under high vacuum gave a red oil which solidified upon trituration with hexane to yield the title enamine as a red solid (72 g, 96%). ^1H NMR (80 MHz, $CDCl_3$): δ 2.85 [s, 6 H, $N(CH_3)_2$], 5.04 (s, 2 H, OCH_2), 5.80 (d, J = 13.5 Hz, 1 H, CHN), 6.75 (d, J = 13.5 Hz, 1 H, CH=CHN), 7.04 (m, 1 H, H^4-Ar), 7.30 (m, 7 H).

6-Hydroxyindole (22). A solution of (*E*)-5-(benzyloxy)-2-[2-(dimethylamino)vinyl]nitrobenzene (20 g, 67 mmol) in tetrahydrofuran (200 mL) was hydrogenated at 50 psi in the presence of 10% palladium-on-carbon (4 g, 20% w/w) for 30 min. The reaction was highly exothermic. The catalyst was removed by filtration through diatomaceous earth, the filtrate was evaporated, and the residue was dissolved in ethyl acetate. This solution was washed successively with 10% aqueous hydrochloric acid, water, and brine, then dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel, eluting with EtOAc–hexane (1:3), to give first 6-(benzyloxy)indole (6.35 g, 34%) and subsequently 6-hydroxyindole (**22**) as a yellow solid (3.5 g, 39%). ^1H NMR (80 MHz, $CDCl_3$): δ 6.4 (m, 1 H, H^3-indole), 6.7 (dd, J = 2.2, 8.4 Hz, 1 H, H^5-indole), 6.8 (m, 1 H, H^7-indole), 7.1 (dd, J = 2.3, 3.2 Hz, 1 H, H^2-indole), 7.5 (br d, J = 8.4, 1 H, H^4-indole), 8.0 (br NH).

6-(2-Cyclopentylethoxy)indole (23). A solution of 6-hydroxyindole (**22**) (2.10 g, 15.8 mmol), 2-cyclopentylethanol (2.30 mL, 18.9 mmol), and triphenylphosphine (8.37 g, 31.6 mmol) in THF (79 mL) was cooled in an ice bath and treated with diethyl azodicarboxylate (5.20 mL, 31.6 mmol). The mixture was allowed to warm to room temperature with stirring. Evaporation gave an oil which was purified by flash chromatography on silica gel, eluting with hexane–CH_2Cl_2 (2:3), to yield ether **23** as a white solid (2.72 g, 75%). ^1H NMR (80 MHz, $CDCl_3$): δ 1.2–1.9 (m, 11 H), 4.0 (t, J = 6.3 Hz, 2 H, OCH_2), 6.5 (m, 1 H, H^3-indole), 6.8 (m, 2 H), 7.0 (dd, J = 2.3, 3.2 Hz, 1 H, H^2-indole), 7.5 (m, 1 H, H^4-indole), 8.0 (br, 1 H, NH).

5-[*N*-(Cyclopentylmethyl)carbamoyl]indole (25). A solution of (cyclopentylmethyl)amine (2.66 g, 26.9 mmol), 5-carboxyindole (4.76 g, 29.6 mmol), 4-(dimethylamino)pyridine (3.60 g, 29.6 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (5.67 g, 29.6 mmol) in CH_2Cl_2 (60 mL) was stirred for 12 h. The amber solution was diluted with CH_2Cl_2 (150 mL), washed successively with 10% aqueous Na_2CO_3, 10% aqueous HCl, water, and brine, dried ($MgSO_4$), and evaporated. The residual amber oil was purified by flash chromatography on silica gel, eluting with EtOAc–$CHCl_3$ (1:3), to yield amide **25** as a white crystalline solid (5.17 g, 80%). Mp: 110–112 °C. ^1H NMR (80 MHz, $CDCl_3$): δ 1.0–2.3 (br m, 9 H, cyclopentyl), 3.4 (dd, J = 5.7, 7.0 Hz, 2 H, CH_2N), 6.2 (br, 1 H, CONH), 6.6 (m, 1 H, H^3-indole), 7.3 (t, J = 2.2 Hz, 1 H, H^2-indole), 7.4 (br d, J = 8.5 Hz, 1 H, H^7-indole), 7.6 (dd, J = 1.7, 8.5 Hz, 1 H, H^6-indole), 8.1 (m, 1 H, H^4-indole), 8.5 (br, 1 H, NH).

Methyl 4-[[5-[*N*-(Cyclopentylmethyl)carbamoyl]indol-3-yl]methyl]-3-methoxybenzoate (26a). To a solution of indole **25** (2.0 g, 8.3 mmol) in dioxane (15 mL) was added Ag_2O (1.92 g, 8.3 mmol). The mixture was heated under reflux for 1 h. A solution of methyl 4-(bromomethyl)-3-methoxybenzoate (2.14 g, 8.26 mmol) in dioxane (6 mL) was added, and the mixture was heated under reflux for 3.5 h. The mixture was diluted with EtOAc–Et_2O (1:1), filtered through diatomaceous earth, and evaporated. The residue was purified by two sequential flash chromatographies on silica gel, using methanol–chloroform (1:49) as the eluent, to give ester **26a** as a white solid (1.53 g, 44%). ^1H NMR (80 MHz; $CDCl_3$): δ 1.1–2.3 (br m, 9 H, cyclopentyl), 3.4 (dd, J = 5.7, 7.0 Hz, 2 H, CH_2N), 3.88 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.1 (s, 2 H, CH_2Ar), 6.1 (br t, 1 H, CONH), 6.9 (br d, J = 2.3 Hz, 1 H, H^2-indole), 7.1 (d, J = 8.2 Hz, 1 H, H^5-benzoate), 7.5 (m, 4 H), 8.0 (m, 1 H, H^4-indole), 8.5 (br s, 1 H, NH).

Methyl 4-[[5-[*N*-(Cyclopentylmethyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxybenzoate (26b). A solution of indole **26a** (1.52 g, 3.6 mmol) in DMF (5 mL) was added to a slurry of hexane-washed NaH (87 mg, 3.6 mmol) in DMF (3 mL) stirred at 0 °C. The mixture was stirred at 0 °C for 20 min and at 25 °C for 15 min. The reaction was cooled to 0 °C, treated with a cold solution of MeI (570 mg, 3.98 mmol) in DMF (2 mL), and then stirred at 25 °C for 1 h. The mixture was recooled to 0 °C, quenched with saturated aqueous NH_4Cl, and evaporated. The residue was dissolved in EtOAc, washed with water and brine,

dried ($MgSO_4$), and evaporated. The amber residue was purified by flash chromatography on silica gel, eluting with EtOAc–$CHCl_3$ (1:9), to give *N*-methylindole **26b** as a white solid (860 mg, 55%). ^1H NMR (80 MHz; $CDCl_3$): δ 1.1–2.3 (br m, 9 H, cyclopentyl), 3.4 (dd, *J* = 5.7, 7.0 Hz, 2 H, CH_2N), 3.7 (s, 3 H, NCH_3), 3.89 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.1 (s, 2 H, CH_2Ar), 6.1 (br, 1 H, CONH), 6.8 (s, 1 H, H^2-indole), 7.1 (d, *J* = 8.3 Hz, 1 H, H^5-benzoate), 7.3–7.7 (m, 4 H), 8.0 (d, *J* = 1.3 Hz, 1 H, H^4-indole).

Methyl 4-[2-[5-[*N*-(Cyclopentylmethyl)carbamoyl]-2-(*N*-formyl-*N*-methylamino)phenyl]-2-oxoethyl]-3-methoxybenzoate (28a). A stirred solution of indole **26b** (1.0 g, 2.3 mmol) in a mixture of CH_2Cl_2 (10 mL) and MeOH (58 mL) was cooled to −78 °C and exposed to a stream of ozone via a gas bubbler for 15 min. The blue solution was purged with nitrogen until the color dissipated and then was treated with dimethyl sulfide (20 mL). The solution was allowed to warm to room temperature with stirring and was evaporated. The residue was purified by flash chromatography on silica gel, eluting first with EtOAc–$CHCl_3$ (1:4) and subsequently with EtOAc, to give ketone **28a** (mixture of amide *E* and *Z* isomers) as an ivory solid (880 mg, 82%). ^1H NMR (250 MHz, $CDCl_3$): δ 1.2–1.8 (3 m, 8 H, $(CH_2)_4$), 2.2 (m, 1 H, NCH_2CH), 3.2, 3.3 (2 s, 3 H, NCH_3), 3.4 (m, 2 H, NCH_2), 3.81, 3.88 (2 s, 3 H, OCH_3), 3.90 (s, 3 H, CO_2CH_3), 4.1, 4.3 (2 s, 2 H, $COCH_2Ar$), 6.3 (br, 1 H, NH), 7.2–8.1 (7 H, ArH, CHO).

Methyl 4-[2-[5-[*N*-(Cyclopentylmethyl)carbamoyl]-2-(*N*-methylamino)phenyl]-2-(hydroxyimino)ethyl]-3-methoxybenzoate (28b). A solution of ketone **28a** (980 mg, 2.10 mmol) and hydroxylamine hydrochloride (871 mg, 12.6 mmol) in freshly distilled anhydrous pyridine (25 mL) was heated to 120 °C under nitrogen for 1.5 h. The pyridine was evaporated to give a residue which was taken up in EtOAc. The EtOAc solution was washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel, eluting with EtOAc–$CHCl_3$ (3:7), to give oxime **28b** as a white solid (624 mg, 66%). ^1H NMR (250 MHz, $CDCl_3$): δ 1.2–1.7 (3 m, 8 H, $(CH_2)_4$), 2.1 (m, 1 H, NCH_2CH), 2.9 (d, *J* = 4.9 Hz, 3 H, NCH_3), 3.3 (dd, *J* = 5.7, 7.0 Hz, 2 H, NCH_2) 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 4.3 (s, 2 H, CH_2Ar), 5.8 (br t, 1 H, CONH), 6.6 (d, *J* = 8.6 Hz, 1 H, H^3-phenyl), 7.1 (d, *J* = 7.9 Hz, 1 H, H^5-benzoate), 7.5 (d, 1 H, H^6-benzoate), 7.55 (s, 1 H, H^2-benzoate), 7.6 (dd, 1 H, H^4-phenyl), 7.67 (s, 1 H, OH), 7.73 (d, *J* = 2.1 Hz, 1 H, H^6-phenyl), 8.0 (br q, 1 H, NHMe).

Methyl 4-[2-[5-[*N*-(Cyclopentylmethyl)carbamoyl]-2-(*N*-methylamino)phenyl]-2-(acetoxyimino)ethyl]-3-methoxybenzoate (28c). A solution of oxime **28b** (624 mg, 1.40 mmol) and 4-(dimethylamino)pyridine (168 mg, 1.4 mmol) in CH_2Cl_2 (30 mL) was treated with acetic anhydride (0.13 mL, 1.4 mmol) and then stirred under nitrogen for 8 h. The solution was diluted with CH_2Cl_2, washed sequentially with 10% aqueous $NaHSO_4$, water, and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography, eluting with EtOAc–$CHCl_3$ (1:46), to give oxime acetate **28c** as a white solid (550 mg; 79%). ^1H NMR (250 MHz; $CDCl_3$): δ 1.2–1.7 (3 m, 8 H, $(CH_2)_4$), 2.1 (m, 1 H, NCH_2CH), 2.2 (s, 3 H, $COCH_3$), 3.0 (d, *J* = 4.9 Hz, 3 H, NCH_3), 3.3 (dd, *J* = 5.8, 7.0 Hz, 2 H, NCH_2), 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 4.3 (s, 2 H, CH_2Ar), 5.8 (b t, 1 H, CONH), 6.7 (d, *J* = 8.8 Hz, 1 H, H^3-phenyl), 7.0 (d, *J* = 7.8 Hz, 1 H, H^5-benzoate), 7.5 (dd, *J* = 1.3, 7.8 Hz, 1 H, H^6-benzoate), 7.55 (d, *J* = 1.3 Hz, 1 H, H^2-benzoate), 7.6 (dd, *J* = 2.0, 8.8 Hz, 1 H, H^4-phenyl), 7.9 (d, *J* = 2.0 Hz, 1 H, H^6-phenyl), 8.0 (br q, *J* = 4.9 Hz, 1 H, NHMe).

Methyl 4-[[5-[*N*-(Cyclopentylmethyl)carbamoyl]-1-methylindazol-3-yl]methyl]-3-methoxybenzoate (29a). A conical flask containing oxime acetate **28c** (63.5 mg, 0.128 mmol) and a magnetic stir bar was evacuated to 120 mTorr and immersed, with stirring, for 5 min in an oil bath preheated to 200 °C. The resulting clear amber oil was purified by flash chromatography on silica gel, eluting with EtOAc–$CHCl_3$ (1:4), to give indazole **29a** as a white solid (52 mg, 93%). ^1H NMR (250 MHz; $CDCl_3$): δ 1.2–1.8 (3 m, 8 H, $(CH_2)_4$), 2.1 (sep, 1 H, NCH_2CH), 3.4 (dd, *J* = 5.9, 7.0 Hz, 2 H, NCH_2), 3.89 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.04 (s, 3 H, NCH_3), 4.4 (s, 2 H, CH_2Ar), 6.0 (br t, 1 H, CONH), 7.2 (d, *J* = 8.2 Hz, 1 H, H^5-benzoate), 7.3 (d, *J* = 8.9 Hz, 1 H, H^7-indazole), 7.5 (m, 2 H), 7.7 (dd, *J* = 1.2, 8.9 Hz, 1 H, H^6-indazole), 8.0 (br s, 1 H, H^4-indazole).

6-(2-Cyclopentylethoxy)-3-formylindole (30). *N*,*N*-Dimethylformamide (4 mL) was cooled to 0 °C under an atmosphere of nitrogen and treated cautiously with phosphorus oxychloride (1.2 mL, 13 mmol). This solution was stirred at 0 °C for 30 min, warmed to room temperature, and treated with a solution of indole **23** (2.41 g, 10.5 mmol) in *N*,*N*-dimethylformamide (50 mL). The yellow mixture was stirred for 1 h and then brought to pH 14 by the addition of ice and 20% (w/v) aqueous sodium hydroxide. The mixture was heated to reflux for 5 min and allowed to cool. The precipitate which formed was collected by filtration and washed with water to give aldehyde **30** as a white powder (2.19 g, 81%). ^1H NMR (80 MHz, DMSO-d_6): δ 1.1–1.9 (m, 11 H), 4.0 (t, *J* = 6.4 Hz, 2 H, OCH_2), 6.8 (dd, *J* = 2.0, 8.5 Hz, 1 H, H^5-indole), 7.0 (d, *J* = 2.0 Hz, 1 H, H^7-indole), 7.9 (d, *J* = 8.5 Hz, 1 H, H^4-indole), 8.1 (br s, 1 H, H^2-indole), 9.8 (s, 1 H, CHO), 11.9 (br, 1 H, NH).

***tert*-Butyl 4-[[6-(2-Cyclopentylethoxy)-3-formylindol-1-yl]methyl]-3-methoxybenzoate (31).** A mixture of indole **30** (2.19 g, 8.51 mmol), *tert*-butyl 4-(bromomethyl)-3-methoxybenzoate (3.07 g, 10.2 mmol), and K_2CO_3 (1.7 g) in DMF (42 mL) was stirred for 72 h. The mixture was diluted with water to give a thick yellow gum which was isolated and triturated with hexane. This gum was purified by flash chromatography on silica gel, eluting with EtOAc–hexane (3:7), to give ester **31** as a white solid (2.19 g, 54%). ^1H NMR (80 MHz, $CDCl_3$): δ 1.1–1.9 (br m, 20 H), 3.9 (s, 3 H, OCH_3), 4.0 (t, *J* = 6.6 Hz, 2 H, OCH_2), 5.3 (s, 2 H, NCH_2), 6.8–7.0 (m, 3 H), 7.5–7.6 (m, 3 H), 8.1 (d, *J* = 8.5 Hz, 1 H, H^4-indole), 9.9 (s, 1 H, CHO).

***tert*-Butyl (*E*)-4-[[6-(2-Cyclopentylethoxy)-3-[2-(methoxycarbonyl)ethylidenyl]indol-1-yl]methyl]-3-methoxybenzoate (32a).** A solution of aldehyde **31** (2.17 g, 4.55 mmol) and methyl (triphenylphosphoranylidene)acetate (3.35 g, 10.0 mmol) in freshly distilled, anhydrous dioxane (23 mL) was heated to reflux for 48 h. Addition of water gave a yellow precipitate which was collected by filtration. The filtrate was extracted with CH_2Cl_2. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated to give an amber oil. The yellow precipitate and amber oil were combined and purified by flash chromotography on silica gel, eluting with ethyl acetate–hexane (1:4), to give diester **32a** as an ivory solid (2.04 g, 84%). Mp: 132–133 °C. ^1H NMR (80 MHz, $CDCl_3$): δ 1.1–1.9 (br m, 20 H), 3.8 (s, 3 H, CO_2CH_3), 3.9 (s, 3 H, OCH_3), 4.0 (t, *J* = 6.6 Hz, 2 H, OCH_2), 5.3 (s, 2 H, NCH_2), 6.4 (d, *J* = 15.9 Hz, 1 H, C=$CHCO_2$), 6.7–6.9 (m, 3 H), 7.2–7.5 (m, 3 H), 7.7 (d, *J* = 8.7 Hz, 1 H, H^4-indole), 7.8 (d, *J* = 15.9 Hz, 1 H, CH=$CHCO_2$).

(*E*)-4-[[6-(2-Cyclopentylethoxy)-3-[2-(methoxycarbonyl)ethylidenyl]indol-1-yl]methyl]-3-methoxybenzoic Acid (32b). A solution of *tert*-butyl ester **32a** (2.04 g, 3.82 mmol) in dioxane (19 mL) was treated with triethylamine (1.30 mL, 9.17 mmol) and trimethylsilyl trifluoromethanesulfonate (1.60 mL, 8.02 mmol). The pale yellow solution was stirred at room temperature for 24 h, after which time it was a bright orange color. Dilution with water gave a precipitate, which was collected by filtration and washed with water. Recrystallization from MeOH–water, followed by trituration of the crystals with ether, gave acid **32b** as a white powder (971 mg; 53%). Mp: 187–188 °C. ^1H NMR (250 MHz, DMSO-d_6): δ 1.1–1.8 (3 m, 10 H), 1.9 (sex, 1 H, $O(CH_2)_2CH$), 3.7 (s, 3 H, CO_2CH_3), 3.9 (s, 3 H, OCH_3), 4.0 (t, *J* = 6.7 Hz, 2 H, OCH_2), 5.4 (s, 2 H, NCH_2), 6.3 (d, *J* = 16.0 Hz, 1 H, C=$CHCO_2$), 6.8 (dd, *J* = 2.0, 8.6 Hz, 1 H, H^5-indole), 6.9 (d, *J* = 7.9 Hz, 1 H, H^5-benzoate), 7.0 (d, *J* = 2.0 Hz, 1 H, H^7-indole), 7.4 (dd, *J* = 1.0, 7.9 Hz, 1 H, H^6-benzoate), 7.5 (d, *J* = 1.0 Hz, 1 H, H^2-benzoate), 7.6 (d, *J* = 8.6 Hz, 1 H, H^4-indole), 7.8 (d, *J* = 16.0 Hz, 1 H, CH=$CHCO_2$), 7.9 (s, 1 H, H^2-indole). Anal. ($C_{28}H_{31}NO_6$) C, H, N.

4-[[6-(2-Cyclopentylethoxy)-3-[2-(methoxycarbonyl)ethyl]indol-1-yl]methyl]-3-methoxybenzoic Acid (33a). A solution of unsaturated ester **32b** (665 mg, 1.39 mmol) in a mixture of MeOH (20 mL) and THF (2 mL) containing 1 equiv of 6 M aqueous KOH was treated with 10% Pd/C (166 mg, 25% w/w) and subjected to 50 psi of hydrogen for 3 h. The catalyst was removed by filtration through diatomaceous earth, and the filtrate was evaporated. The resulting residue was dissolved in water and precipitated by the addition of 10% HCl. The yellow precipitate was collected and purified by flash chromatography on silica gel, eluting with MeOH–$CHCl_3$ (1:9), to give saturated ester **33a** (394

mg; 59%). ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.1–1.8 (3 m, 10 H), 1.9 (sex, 1 H, $O(CH_2)_2CH$), 2.6 (t, 2 H, CH_2CO_2), 2.9 (t, 2 H, $CH_2CH_2CO_2$), 3.6 (s, 3 H, CO_2CH_3), 3.87 (s, 3 H, OCH_3), 3.93 (t, 2 H, OCH_2), 5.2 (s, 2 H, NCH_2), 6.7 (m, 2 H), 6.9 (d, J = 1.2 Hz, 1 H, H^7-indole), 7.0 (s, 1 H, H^2-benzoate), 7.4 (m, 2 H), 7.6 (s, 1 H, H^2-indole).

4-[[6-(2-Cyclopentylethoxy)-3-(2-carbamoylethyl)indol-1-yl]methyl]-3-methoxybenzoic Acid (33b). A solution of ester **33a** (317 mg, 0.662 mmol) and 4-(dimethylamino)pyridine (80.9 mg, 0.662 mmol) in THF (7 mL) was combined with condensed ammonia (10 mL) in a pressure vessel. The vessel was sealed, and the mixture was stirred at 80 °C for 24 h. The ammonia and THF were then allowed to evaporate. The remaining residue was dissolved in water and acidified with 10% (v/v) hydrochloric acid. The resultant precipitate was collected by filtration, washed with water, and purified by flash chromatography on silica gel, eluting with MeOH–$CHCl_3$ (1:9), to give amide **33b** (172 mg; 56%). ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.1–1.8 (3 m, 10 H), 1.9 (m, 1 H, $O(CH_2)_2CH$), 2.4 (t, J = 7.5 Hz, 2 H, CH_2CO_2), 2.8 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CO_2$), 3.86 (s, 3 H, OCH_3), 3.94 (t, J = 6.4 Hz, 2 H, OCH_2), 5.2 (s, 2 H, NCH_2), 6.6–6.7 (m, 3 H), 6.9 (s, 1 H, H^7-indole), 7.0 (s, 1 H, H^2-benzoate), 7.3 (s, 1 H, NH), 7.4 (m, 2 H), 7.6 (s, 1 H, H^2-indole).

Methyl 4-[[5-[*N*-(Cyclopentylmethyl)carbamoyl]-1-[1-(*N*,*N*-dimethylcarbamoyl)ethyl]indol-3-yl]methyl]-3-methoxybenzoate (34a). A stirred suspension of hexane-washed NaH (47 mg, 1.9 mmol) in DMF (2 mL) was cooled to 0 °C and treated with a solution of indole **26a** (800 mg, 1.9 mmol) in DMF (2 mL). The mixture was stirred at 0 °C for 20 min, warmed to room temperature for 15 min, and then cooled back to 0 °C. The dark red solution was treated with a solution of *N*,*N*-dimethyl-2-bromopropionamide (377 mg, 2.1 mmol) in DMF (1 mL) and stirred at room temperature for 15 min. The reaction was cooled back to 0 °C and quenched with saturated ammonium chloride solution and water. The liquids were decanted from the gum which formed and were extracted with EtOAc. The gum was taken up in EtOAc and combined with the organic extract. The combined EtOAc solution was washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel, eluting with MeOH–CH_2Cl_2 (1:99), to give amide **34a** (288 mg, 29%). ^{1}H NMR (80 MHz; $CDCl_3$): δ 1.2–2.2 (m, 12 H), 2.8 (s, 3 H, NCH_3), 2.9 (s, 3 H, NCH_3), 3.4 (m, 2 H, NCH_2), 3.88 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 4.1 (s, 2 H, CH_2Ar), 5.3 (q, J = 6.7 Hz, 1 H, COCH), 6.1 (br t, 1 H, CONH), 7.0 (s, 1 H, H^2-indole), 7.1 (d, J = 8.0 Hz, 1 H, H^5-benzoate), 7.4–7.7 (m, 4 H), 8.0 (d, J = 1.2 Hz, 1 H, H^4-indole).

Methyl 4-[[5-[*N*-(Cyclopentylmethyl)carbamoyl]-1-[2-(*N*,*N*-diethylcarbamoyl)ethyl]indol-3-yl]methyl]-3-methoxybenzoate (35a). A stirred suspension of hexane-washed NaH (20 mg, 0.7 mmol) in DMF (5 mL) was cooled to 0 °C and treated with a solution of indole **26a** (1.0 g, 2.4 mmol) in DMF (3 mL). *N*,*N*-Diethylacrylamide (0.336 mL, 2.4 mmol) was added. The reaction was allowed to warm to room temperature and then was stirred for 8 h before being quenched with saturated aqueous ammonium chloride and water. The liquids were decanted from the gum which formed and were extracted with EtOAc. The gum was taken up in EtOAc and combined with the organic extract. The combined EtOAc solution was washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel, eluting with $CHCl_3$, to give amide **35a** as an ivory solid (0.75 g, 67%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.9 (t, J = 7.1 Hz, 3 H, NCH_2CH_3), 1.0 (t, J = 7.1 Hz, 3 H, NCH_2CH_3), 1.2–1.8 (3 m, 8 H, $(CH_2)_4$), 2.2 (sep, J = 7.5 Hz, 1 H, NCH_2CH), 2.7 (t, J = 6.7 Hz, 2 H, $COCH_2$), 3.0 (q, J = 7.1 Hz, 2 H, NCH_2CH_3), 3.3 (q, J = 7.1 Hz, 2 H, NCH_2CH_3), 3.4 (dd, J = 6.0, 7.0 Hz, 2 H, $CONHCH_2$), 3.89 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.1 (s, 2 H, CH_2Ar), 4.5 (t, J = 6.7 Hz, 2 H, NCH_2CH_2), 6.0 (br t, 1 H, CONH), 7.0 (s, 1 H, H^2-indole), 7.1 (d, J = 7.7 Hz, 1 H, H^5-benzoate), 7.3 (d, J = 8.6 Hz, 1 H, H^7-indole), 7.5 (m, 2 H), 7.6 (dd, J = 1.4, 8.6 Hz, 1 H, H^6-indole), 8.0 (d, J = 1.4 Hz, 1 H, H^4-indole).

***tert*-Butyl 4-[[6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-formylindol-1-yl]methyl]-3-methoxybenzoate (36).** A mixture of aldehyde **19a** (0.92 g, 3.4 mmol), *tert*-butyl 4-(bromomethyl)-3-methoxybenzoate (1.2 g, 4.1 mmol), and potassium carbonate (0.7 g, 5.1 mmol) in *N*,*N*-dimethylformamide (17 mL) was stirred for 48 h under a nitrogen atmosphere. Water was added to give a precipitate, which was collected by filtration and dried to yield ester **36** as an ivory powder (1.2 g, 71%). Mp: 134–135 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.3 (m, 2 H, cyclopentyl), 1.6 (m, 13 H, cyclopentyl, *tert*-butyl), 1.8 (m, 2 H, cyclopentyl), 2.2 (sep, J = 7.5 Hz, 1 H, $CONCH_2CH$), 3.4 (t, J = 6.5 Hz, 2 H, $CONCH_2$), 3.9 (s, 3 H, OCH_3), 5.4 (s, 2 H, NCH_2Ar), 6.4 (br t, 1 H, NH), 7.0 (d, J = 7.7 Hz, 1 H, H^5-benzoate), 7.5 (m, 3 H), 7.8 (s, 1 H, H^2-benzoate), 8.1 (s, 1 H, H^7-indole), 8.3 (d, J = 8.3 Hz, 1 H, H^4-indole), 10.0 (s, 1 H, CHO).

***tert*-Butyl (*E*)-4-[[6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-[2-(methoxycarbonyl)ethylidenyl]indol-1-yl]methyl]-3-methoxybenzoate (37a).** A solution of aldehyde **36** (5.00 g, 10.2 mmol) and methyl (triphenylphosphoranylidene)-acetate (7.51 g, 22.4 mmol) in freshly distilled, anhydrous dioxane (51 mL) was heated to reflux for 48 h. The solvent was evaporated. The resultant residue was purified by flash chromatography on silica gel, eluting with ethyl acetate–hexane (1:1), to give diester **37a** as a pale yellow solid (4.93 g, 89%). Mp: 163–164 °C. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.2–2.2 (br m, 18 H, cyclopentyl, *tert*-butyl), 3.4 (dd, J = 5.7, 7.0 Hz, 2 H, $CONCH_2$), 3.8 (s, 3 H, CO_2CH_3), 3.9 (s, 3 H, $ArOCH_3$), 5.4 (s, 2 H, NCH_2Ar), 6.2 (br t, 1 H, NH), 6.4 (d, J = 16.0 Hz, 1 H, $C{=}CHCO_2$), 6.7 (d, J = 7.8 Hz, 1 H, H^5-benzoate), 7.4–7.5 (m, 4 H), 7.8–8.0 (m, 3 H).

***tert*-Butyl 4-[[6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-[2-(methoxycarbonyl)ethyl]indol-1-yl]methyl]-3-methoxybenzoate (37b).** A solution of α,β-unsaturated ester **37a** (1.11 g, 2.03 mmol) in methanol (10 mL) was treated with 10% palladium on carbon (0.28 g, 25% w/w) and shaken under 50 psi of hydrogen for 24 h. The catalyst was removed by filtration through diatomaceous earth, and the filtrate was evaporated to give ester **37b** as a gray foam (1.04 g, 94%). Mp: 58–60 °C. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.2–2.0 (br m, 17 H, cyclopentyl, *tert*-butyl), 2.2 (m, 1 H, $CONCH_2CH$), 2.7 (m, 2 H, CH_2CO_2), 3.1 (m, 2 H, $CH_2CH_2CO_2$), 3.4 (dd, J = 5.7, 7.0 Hz, 2 H, $CONCH_2$), 3.6 (s, 3 H, CO_2CH_3), 3.9 (s, 3 H, $ArOCH_3$), 5.3 (s, 2 H, NCH_2Ar), 6.2 (br t, 1 H, NH), 6.6 (d, J = 7.8 Hz, 1 H, H^5-benzoate), 7.0 (s, 1 H, H^2-indole), 7.3–7.5 (m, 3 H), 7.6 (d, J = 8.2, 1 H, H^4-indole), 7.9 (br s, 1 H, H^7-indole).

4-[[6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-[2-(methoxycarbonyl)ethyl]indol-1-yl]methyl]-3-methoxybenzoic Acid (37c). A solution of *tert*-butyl ester **37b** (2.38 g, 4.35 mmol) in freshly distilled dioxane (15 mL) was treated with freshly distilled triethylamine (1.45 mL, 10.4 mmol) and trimethylsilyl trifluoromethanesulfonate (1.77 mL, 9.13 mmol). The solution was heated to reflux for 30 min and then diluted with water to give a precipitate. The precipitate was collected by filtration, washed with water, and dried to give acid **37c** as a pale brown powder (1.86 g, 87%). An analytical sample was obtained by recrystallization from ethyl acetate–hexane. Mp: 181–2 °C. ^{1}H NMR (80 MHz, DMSO-d_6): δ 1.2–2.2 (br m, 8 H, cyclopentyl), 2.2 (m, 1 H, $CONCH_2CH$), 2.7 (m, 2 H, CH_2CO_2), 3.0 (m, 2 H, $CH_2CH_2CO_2$), 3.2 (m, 2 H, $CONCH_2$), 3.6 (s, 3 H, CO_2CH_3), 3.9 (s, 3 H, $ArOCH_3$), 5.4 (s, 2 H, NCH_2Ar), 6.6 (d, J = 7.8 Hz, 1 H, H^5-benzoate), 7.3–7.6 (m, 5 H), 7.9 (br s, 1 H, H^7-indole), 8.3 (br t, 1 H, NH).

4-[[6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-[2-(*N*-methylcarbamoyl)ethyl]indol-1-yl]methyl]-3-methoxybenzoic Acid (38a). A mixture of acid **37c** (295 mg, 0.600 mmol) and 4-(dimethylamino)pyridine (73.4 mg, 0.600 mmol) was combined with condensed monomethylamine (75 mL) in a pressure vessel. The mixture was stirred for 24 h. The amine was then allowed to evaporate. The remaining residue was dissolved in water and acidified with 10% (v/v) hydrochloric acid. The resultant precipitate was collected by filtration and washed with water to give amide **38a** as a white powder (260 mg, 89%). Mp: 274–275 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.2 (m, 2 H, cyclopentyl), 1.4–1.7 (br m, 6 H, cyclopentyl), 2.1 (sep, J = 7.2 Hz, 1 H, $CONCH_2CH$), 2.4 (t, J = 7.5 Hz, 2 H, CH_2CO_2), 2.5 (d, J = 4.6 Hz, 3 H, NCH_3), 2.9 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CO_2$), 3.2 (t, J = 6.4 Hz, 2 H, $CONCH_2$), 3.9 (s, 3 H, $ArOCH_3$), 5.4 (s, 2 H, NCH_2Ar), 6.6 (d, J = 7.8 Hz, 1 H, H^5-benzoate), 7.3 (s, 1 H, H^2-indole), 7.4 (d, J = 7.8 Hz, 1 H, H^6-benzoate), 7.6 (m, 3 H), 7.7 (q, J = 4.6, 1 H, CONHMe), 7.9 (s, 1 H, H^7-indole), 8.3 (br t, 1 H, NH). MS (CI, m/z); 492 (M + 1). Anal. ($C_{28}H_{33}N_3O_5 \cdot 0.1H_2O$) C, H, N.

tert-Butyl (*E*)-4-[[6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-[2-(ethoxycarbonyl)-1-propenyl]indol-1-yl]methyl]-3-methoxybenzoate (40a). A solution of aldehyde **36** (2.84 g, 5.79 mmol) and (carbethoxyethylidene)triphenylphosphorane (4.56 g, 12.6 mmol) in freshly distilled, anhydrous dioxane (29 mL) was heated to reflux for 18 h. The solvent was evaporated. The resulting residue was purified by flash chromatography on silica gel, eluting with EtOAc–hexane (1:4) to give α,β-unsaturated ester **40a** as a pale yellow solid (3.31 g, 99%). Mp: 118–120 °C. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.2–1.9 (br m, 20 H), 2.1 (d, J = 1.1 Hz, 3 H, C=CCH_3), 2.2 (m, 1 H, NCH_2CH), 3.4 (dd, J = 5.7, 6.9 Hz, 2 H, NCH_2), 3.9 (s, 3 H, OCH_3), 4.2 (q, J = 7.0 Hz, 2 H, OCH_2), 5.4 (s, 2 H, NCH_2Ar), 6.2 (br t, 1 H, NH), 6.8 (d, J = 7.7 Hz, 1 H, H^5-benzoate), 7.4–7.6 (m, 4 H), 7.8 (d, J = 8.4 Hz, 1 H, H^4-indole), 8.0 (m, 2 H, H^7-indole, C=CH).

tert-Butyl 4-[[6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-[2-(ethoxycarbonyl)propyl]indol-1-yl]methyl]-3-methoxybenzoate (40b). A solution of α,β-unsaturated ester **40a** (3.31 g, 5.77 mmol) in methanol (30 mL) was treated with 10% Pd/C (0.83 g, 25% w/w) and shaken under 50 psi of hydrogen for 18 h. The catalyst was removed by filtration through diatomaceous earth, and the filtrate was evaporated to give diester **40b** as a colorless oil (3.30 g, 99%). ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.2–2.2 (br m, 24 H), 2.9 (m, 3 H, COCH(Me)CH_2), 3.4 (m, 2 H, $CONCH_2$), 3.9 (s, 3 H, OCH_3), 4.1 (q, J = 6.9 Hz, 2 H, OCH_2), 5.3 (s, 2 H, NCH_2Ar), 6.1 (br t, 1 H, NH), 6.6 (d, J = 7.8 Hz, 1 H, H^5-benzoate), 7.0 (s, 1 H, H^2-indole), 7.3–7.5 (m, 3 H), 7.6 (d, J = 8.3 Hz, 1 H, H^4-indole), 7.8 (s, 1 H, H^7-indole).

tert-Butyl 4-[[6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-(2-carboxypropyl)indol-1-yl]methyl]-3-methoxybenzoate (40c). A solution of ethyl ester **40b** (750 mg, 1.3 mmol) in a mixture of tetrahydrofuran (3.5 mL), methanol (3.5 mL), and water (1.3 mL) was treated with lithium hydroxide monohydrate (330 mg, 7.8 mmol) and stirred at 30 °C for 6 h. The organic solvents were removed by evaporation and water was added to give a solution. Acidification of this solution with 10% aqueous HCl gave a precipitate which was collected by filtration to yield acid **40c** as a white solid (680 mg, 95%). Mp: 195–197 °C. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.2–2.2 (br m, 21 H), 2.9 (m, 3 H, COCH(Me)CH_2), 3.4 (m, 2 H, $CONCH_2$), 3.9 (s, 3 H, OCH_3), 5.2 (s, 2 H, NCH_2Ar), 6.2 (br t, 1 H, NH), 6.6 (d, J = 7.7 Hz, 1 H, H^5-benzoate), 7.0 (s, 1 H, H^2-indole), 7.3–7.5 (m, 3 H), 7.6 (d, J = 8.3 Hz, 1 H, H^4-indole), 7.8 (s, 1 H, H^7-indole).

tert-Butyl 4-[[6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-[2-(*N*,*N*-dimethylcarbamoyl)propyl]indol-1-yl]methyl]-3-methoxybenzoate (41a). A solution of acid **40c** (960 mg, 1.75 mmol) and 1,1′-carbonyldiimidazole (420 mg, 2.59 mmol) in CH_2Cl_2 (9 mL) was heated to reflux under nitrogen for 1 h. This solution was transferred under nitrogen to a pressure vessel containing condensed dimethylamine (60 mL). The vessel was sealed and heated at 60 °C for 90 h. The amine was allowed to evaporate. The resulting residue was partitioned between CH_2Cl_2 and dilute acid. The organic extract was washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel, eluting with MeOH–$CHCl_3$ (1:49) to give amide **41a** as a white solid (530 mg, 53%). Mp: 73–75 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.2 (d, J = 6.3 Hz, 3 H, $CHCH_3$), 1.3–1.8 (3 m, 21 H), 2.2 (sep, 1 H, $CONCH_2CH$), 2.7 (s, 3 H, NCH_3), 2.8 (s, 3 H, NCH_3), 3.1 (m, 2 H, COCH(Me)CH_2), 3.4 (dd, J = 5.8, 7.1 Hz, 2 H, $CONHCH_2$), 3.9 (s, 3 H, OCH_3), 5.3 (s, 2 H, NCH_2Ar), 6.2 (br t, 1 H, NH), 6.6 (d, J = 7.7 Hz, 1 H, H^5-benzoate), 7.1 (s, 1 H, H^2-indole), 7.4 (m, 2 H), 7.5 (d, J = 1.4 Hz, 1 H, H^2-benzoate), 7.6 (d, J = 8.3 Hz, 1 H, H^4-indole), 7.9 (br s, 1 H, H^7-indole).

(*E*)-6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-[2-(methoxycarbonyl)ethylidenyl]indole (42a). A solution of aldehyde **19a** (6.60 g, 24.4 mmol) and methyl (triphenylphosphoranylidene)acetate (17.98 g, 53.8 mmol) in freshly distilled, anhydrous dioxane (122 mL) was heated to reflux under nitrogen for 24 h. The solvent was evaporated. The resultant residue was purified by flash chromatography on silica gel, eluting with MeOH–$CHCl_3$ (5:95), to give ester **42a** as a white solid (5.42 g, 68%). ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.3 (m, 2 H, cyclopentyl), 1.6 (br m, 6 H, cyclopentyl), 2.2 (sep, 1 H, NCH_2CH), 3.2 (dd, J = 6.1, 6.8 Hz, 2 H, NCH_2), 3.7 (s, 3 H, OCH_3), 6.4 (d, J = 16.0 Hz, 1 H, C=CHCO_2), 7.5 (m, 0.5 H, NH), 7.7 (dd, J = 1.2, 8.4 Hz, 1 H, H^5-indole), 7.8 (d, J = 16.0 Hz, 1 H, CH=CHCO_2), 7.9 (d, J = 8.4 Hz, 1 H, H^4-indole), 8.0 (s, 1 H, H^2-indole), 8.1 (d, J = 2.8 Hz, 1 H, H^7-indole), 8.5 (br t, 1 H, CONH), 12.0 (d, J = 2.0 Hz, 0.5 H, NH).

(*E*)-6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-(2-carboxyethylidenyl)indole (42b). A solution of ester **42a** (5.38 g, 16.5 mmol) in a mixture of tetrahydrofuran (41 mL), methanol (41 mL), and water (16 mL) was treated with lithium hydroxide monohydrate (4.16 g, 99 mmol) and stirred at 40 °C for 18 h. The organic solvents were removed by evaporation, and water was added to give a solution. Acidification of this solution with 50% aqueous HCl gave a precipitate, which was collected by filtration and washed with water to yield acid **42b** as a pale brown solid (2.69 g, 52%).

(*E*)-6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-[2-[(4,4-dimethylpiperidin-1-yl)carbonyl]ethylidenyl]indole (42d). A mixture of acid **42b** (1.70 g, 5.44 mmol), 4-(dimethylamino)pyridine (1.36 g, 11.2 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.28 g, 6.53 mmol), and 4,4-dimethylpiperidine hydrochloride (0.892 g, 5.99 mmol) in CH_2Cl_2 (27 mL) was stirred for 36 h. The mixture was diluted with CH_2Cl_2 to give a solution from which a precipitate formed upon treatment with 10% aqueous HCl. The precipitate was collected by filtration and washed with CH_2Cl_2 to give amide **42d** as an ivory solid (1.77 g, 80%). ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.0 (s, 6 H, 2 CH_3), 1.3 (m, 6 H, cyclopentyl, piperidinyl), 1.6 (br m, 6 H, cyclopentyl), 2.2 (sep, J = 7.1 Hz, 1 H, NCH_2CH), 3.2 (m, 2 H, $CONHCH_2$), 3.6 (br s, 4 H, piperidinyl), 7.0 (d, J = 15.3 Hz, 1 H, C=CHCO), 7.6 (dd, J = 1.0, 8.4 Hz, 1 H, H^5-indole), 7.7 (d, J = 15.3 Hz, 1 H, CH=CHCO), 7.9 (m, 2 H), 8.0 (d, J = 2.7 Hz, 1 H, H^7-indole), 8.5 (br t, 1 H, CONH), 11.9 (d, J = 2.0 Hz, 1 H, NH). MS (CI, m/z): 408 (M + 1).

Methyl (*E*)-4-[[6-[*N*-(Cyclopentylmethyl)carbamoyl]-3-[2-[(4,4-dimethylpiperidin-1-yl)carbonyl]ethylidenyl]indol-1-yl]methyl]-3-methoxybenzoate (43b). A stirred suspension of hexane-washed NaH (98.8 mg, 3.99 mmol) in DMF (10 mL) was cooled to 0 °C and treated with a solution of indole **42d** (1.77 g, 4.36 mmol) in DMF (6 mL). The mixture was stirred at room temperature for 60 min and then treated with a solution of methyl 4-(bromomethyl)-3-methoxybenzoate (940 mg, 3.63 mmol) in DMF (6 mL). The reaction mixture was stirred for 8 h, cooled to 0 °C, quenched by the addition of saturated aqueous ammonium chloride solution, and diluted with water. The precipitate which formed was collected by filtration and purified by flash chromatography on silica gel, eluting with MeOH–$CHCl_3$ (5:95) to give ester **43b** as a white solid (1.54 g, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.0 (s, 6 H, 2 CH_3), 1.3 (m, 2 H, piperidinyl), 1.4 (m, 4 H, cyclopentyl, piperidinyl), 1.6 (m, 4 H, cyclopentyl), 1.8 (m, 2 H, cyclopentyl), 2.2 (sep, 1 H, NCH_2CH), 3.2 (dd, 2 H, $CONHCH_2$), 3.6 (br, 4 H, piperidinyl), 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.4 (s, 2 H, NCH_2Ar), 6.3 (br t, 1 H, CONH), 6.8 (d, J = 7.9 Hz, 1 H, H^5-benzoate), 7.0 (d, J = 15.4 Hz, 1 H, C=CHCO), 7.5 (m, 4 H), 7.9 (m, 2 H), 8.0 (d, J = 1.1 Hz, 1 H, H^7-indole).

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

The ability of test compounds to inhibit the LTE_4 (8 nM) contractile response was assessed as follows: After a 60-min equilibration period, the tissues were challenged with 8 nM LTE_4 for 10 min and the responses recorded. Following washout and reequilibration (25 min), the tissues were again exposed to 10 nM LTE_4, and the response was recorded. After obtaining reproducible control responses to 10 nM LTE_4, the test compound was

added to the bath at selected concentrations for 10 min. Any significant change in resting tension after the 10-min incubation period was noted. In the presence of test compounds, the tissues were challenged with 10 nM LTE_4, and the contractile response was recorded. The paired sections of trachea received vehicle to serve as control. Percent inhibition was determined by the following equation:

$$\% \text{ inhibition} = [(\text{2nd LTE4} - \text{3rd LTE4})/\text{2nd LTE4}] \times 100$$

An adjusted percent inhibition was determined by subtracting the percent inhibition obtained with the vehicle treated tissues from that obtained with the drug treated tissues. Significant differences ($P < 0.05$) between the contractile response of the second and third LTE_4 challenges were determined using Student's paired t test.[36]

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

LTE_4 concentration–response curves were obtained by addition of the agonist to the tissue bath to establish log increments of bath agonist concentration over a particular range according to the method of van Rossum.[37] Each successive concentration was added only after the plateau of the contraction due to the preceding agonist concentration was reached. Contractile responses were expressed as a percentage of the response obtainable to a maximally effective concentration of carbachol (30 μM), which was added to the bath after the 60-min stabilization period. Following the carbachol challenge, the tissues were washed and allowed 60 min to restabilize to base-line tension before the LTE_4 concentration–response curves were begun. EC_{50} values, the molar concentration of agonist required to produce a contraction equal to 50% of the maximal response, were derived by linear regression. The test compound was incubated for 30 min prior to starting the curves. Paired control tissues received vehicle. EC_{50} values were determined in the absence and presence of test compounds and significance ($p < 0.05$) was established with Student's paired t test. Dissociation constants for the receptor-antagonist complex were calculated by the method of Furchgott[38] using the equation K_B = [antagonist]/(dose ratio − 1). The dose ratio (DR) represents the EC_{50} value in the presence of antagonist divided by the EC_{50} value in the absence of antagonist. Only one concentration–response curve was obtained from each tissue.

Radioligand Binding Assay. Male albino, Hartley-strain guinea pigs (300–400 g) were decapitated, and the lungs were perfused in situ with modified Tyrode's buffer and then excised. Large blood vessels and all visible necrotic tissue were resected, and the remainder frozen at −70 °C. Pooled frozen lungs (50 g) were thawed, chopped with a McIlwain tissue chopper into small segments, and washed several times with ice-cold phosphate-buffered saline (0.1 M, pH 7.5). The lung tissue was suspended in Tris-HCl/sucrose buffer (10 mM, pH 7.5/0.25 M) containing several protease inhibitors, homogenized with a Brinkman PT-20 Polytron, and subjected to a differential centrifugation. The 32000g pellet was suspended carefully in buffer with a Teflon homogenizer and recentrifuged. The final pellet was resuspended in Tris-HCl/piperazine-N,N'-bis(2-ethanesulfonic acid) (PIPES) buffer (10 mM/10 mM, pH 7.5) to a final concentration of 1.61 ± 0.17 mg of protein/mL (mean ± SEM, $n = 6$) and stored at −70 °C until used. (No deterioration of receptor binding was observed after storage for up to 18 months.)

Incubations were carried out in 10 mM PIPES buffer (pH 7.5) containing 10 mM $CaCl_2$, 10 mM $MgCl_2$, 2 mM cysteine, and 2 mM glycine. In drug competition assays, incubation mixtures (0.31 mL) containing 1 nM ^{3}H-LTD_4, receptor protein (170 ± 30 μg/mL), and competing agents were incubated at 22 °C for 30 min with or without 2 μM LTD_4. Separation of receptor-bound from free ^{3}H-LTD_4 was achieved by dilution into ice-cold buffer (5 mL of 10 mM Tris-HCl/100 mM NaCl), immediate filtration under vacuum (Whatman GF/C filters), and thorough washing (20 mL of the dilution buffer at 0 °C). The radioactivity retained on rinsed filters was determined by a liquid scintillation counter (Beckman Spectrometer LS7500). Specific binding was defined as the difference in total ^{3}H-LTD_4 binding minus nonspecific binding determined in the presence of 2 μM LTD_4. Data from binding assays were plotted as log concentration versus percent inhibition, and the half-maximal inhibition (IC_{50}) determined by computerized nonlinear least-squares analysis. The binding constant (K_i) was then calculated from the Cheng–Prusoff equation: $K_i = IC_{50}/(1 + [L]/[KD])$, where [L] is ^{3}H-$LTD_4$ concentration, and KD is the affinity constant of LTD_4, determined separately for each batch. K_i values are the mean of two experiments conducted in duplicate with separate batches.

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

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

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

Maximum aerosol time was 300 s. Mean control time was the time to dyspnea for all vehicle-treated animals run concomitantly with a given compound. The animals in each run were pretreated with compound or vehicle at the indicated times prior to LTD_4 challenge. At least two vehicle-treated animals were contained in each test run, and the experimenter was blind as to treatment groups. Differences in means between the drug group and vehicle group were compared using the Student's unpaired t test with $p < 0.05$ considered significant. Failure to reach the end point by 300 s was considered 100% protection.

The determination of oral ED_{50} values was carried out as follows: test compounds, dissolved in PEG400 (<10% v/v) phosphate-buffered saline, were administered orally 180 min before LTD_4 challenge. ED_{50} values were calculated by linear regression analysis of the linear portion of a semilogarithmic plot of percent inhibition vs dose of compound in micromoles/kilogram.

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