Synthesis, Structure–Activity Relationships, and Pharmacological Evaluation of a Series of Fluorinated 3-Benzyl-5-indolecarboxamides: Identification of 4-[[5-[((2*R*)-2-Methyl-4,4,4-trifluorobutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide, a Potent, Orally Active Antagonist of Leukotrienes D_4 and E_4

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The continued exploration of a series of 3-(arylmethyl)-1*H*-indole-5-carboxamides by the introduction of fluorinated amide substituents has resulted in the discovery of 4-[[5-[((2*R*)-2-methyl-4,4,4-trifluorobutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (**38p**, ZENECA ZD 3523), which has been chosen for clinical evaluation. This compound exhibited a K_i of 0.42 nM for displacement of [^{3}H]LTD_4 on guinea pig lung membranes, a pK_B of 10.13 ± 0.14 versus LTE_4 on guinea pig trachea, and an oral ED_{50} of 1.14 μmol/kg opposite LTD_4-induced bronchoconstriction in guinea pigs. The *R* enantiomer was found to be modestly more potent than the *S* enantiomer **38o**. Modification of the amide substituent to afford achiral compounds was unsuccessful in achieving comparable levels of activity. Profiling of **38p** opposite a variety of functional assays has demonstrated the selectivity of this compound as a leukotriene receptor antagonist. The enantioselective synthesis of **38p**, which employed a diastereoselective alkylation of (4*R*,5*S*)-3-(1-oxo-4,4,4-trifluorobutyl)-4-methyl-5-phenyl-2-oxazolidinone (**27**) as the key step to establish the chirality of the amide substituent, provided an efficient route for generating **38p** in >99% enantiomeric purity.

Introduction

Since their discovery in 1979, the peptidoleukotrienes LTC_4 (**1**), LTD_4 (**2**), and LTE_4 (**3**) have been the subject of intense exploration. This interest lies in the fact that the leukotrienes (LTs) are potent constrictors of smooth muscle and, as such, have been implicated as important mediators in the development of asthma in humans.[1] One attractive strategy for moderating the bronchoconstrictive properties of LTs has centered on the development of LT receptor antagonsists. Early efforts to establish the effectiveness of LT antagonists for the treatment of asthma were hindered by the relatively low potency of the initial lead compounds such as FPL-55712 (**4**)[2] and LY171883 (**5**).[3] It was only with the discovery of the extremely potent LT antagonists ICI 204,219 (**6**),[4b,41] MK-679 (**7**),[5] and ONO-1078 (**8**)[6] that the true role of LTs in asthma could be elucidated. Since the initiation of clinical trials with ICI 204,219,[7] we have been interested in the further exploration of this interesting series of compounds[4] with the goal of choosing an additional clinical candidate. We report herein the continued evolution of a series of 3-benzyl-5-indolecarboxamides[23,24] (**38–42**), in which the key discovery was the observation that a trifluoromethyl group, when placed in the proper position along the amide chain, yielded compounds with high inherent affinity for the LT receptor as well as good oral activity. This observation has led to a representative of this series, **38p** (ZENECA ZD 3523), being selected for clinical evaluation.

Chemistry

In order to explore the effect of fluorination on biological activity, we required a series of fluorinated amines of the general structure **14**. For the most part, these amines were unreported in the literature, and they were usually prepared (see Scheme 1) either from the corresponding alcohol **10** via conversion to the intermediate phthalimide **11**[8] followed by hydrazinolysis to the amine (method A) or from the corresponding amide **13** by reduction with lithium aluminum hydride (method B). In turn, the alcohols **10** or amides **13** were prepared from the corresponding esters **9** by standard methodology. Due to the high volatility of many of the fluorinated compounds, most intermediates were not rigorously purified but, rather, carried through several steps in crude form. The phthalimides **11**, amides **13**, and amine hydrochlorides **14** served as convenient points for purification, as these compounds were generally crystalline solids.

The appropriate fluorinated esters were synthesized using a variety of starting materials and routes. Many were prepared starting from commercially available ethyl γ,γ,γ-trifluorobutyrate (**9a**). The details of these transformations are summarized in Scheme 2. Treatment of **9a** with lithium diisopropylamide (LDA) in tetrahydrofuran at low temperature generated the deep purple enolate **15a**, which was subsequently alkylated by either iodomethane or iodoethane to afford the α-alkylated derivatives **9b,c**, respectively. As described for method B (Scheme 1), hydrolysis of the esters to give the corresponding carboxylic acids, **12b,c**, followed by condensation with ammonia promoted by 1,1′-carbonyldiimidazole yielded the amides **13b,c**. Reduction of the amide afforded

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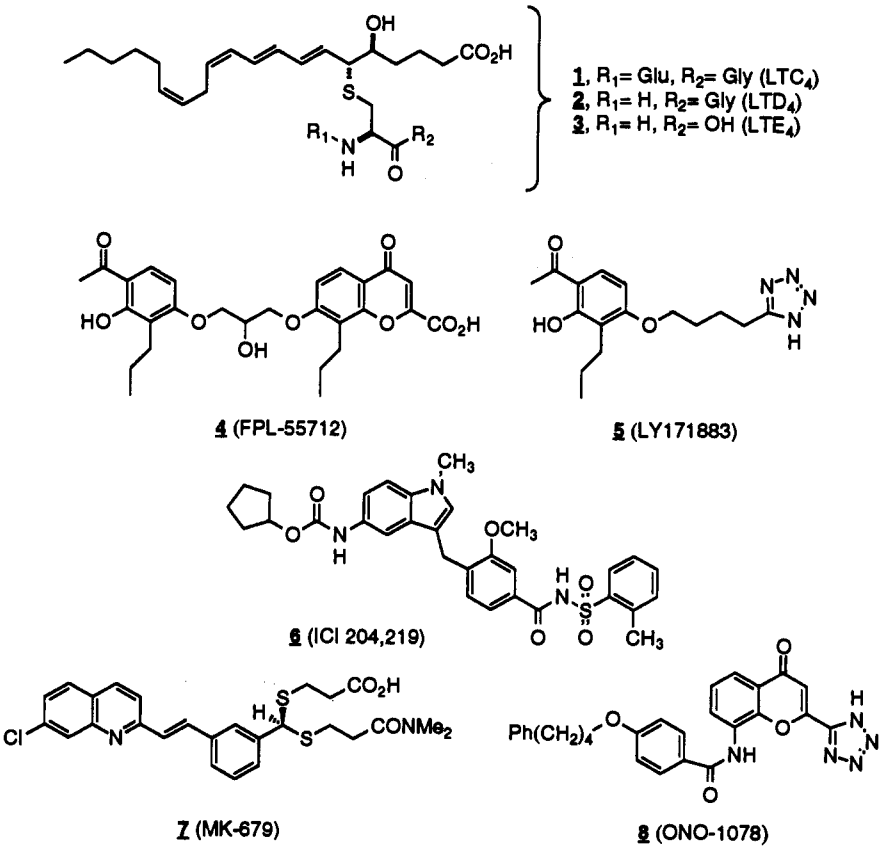
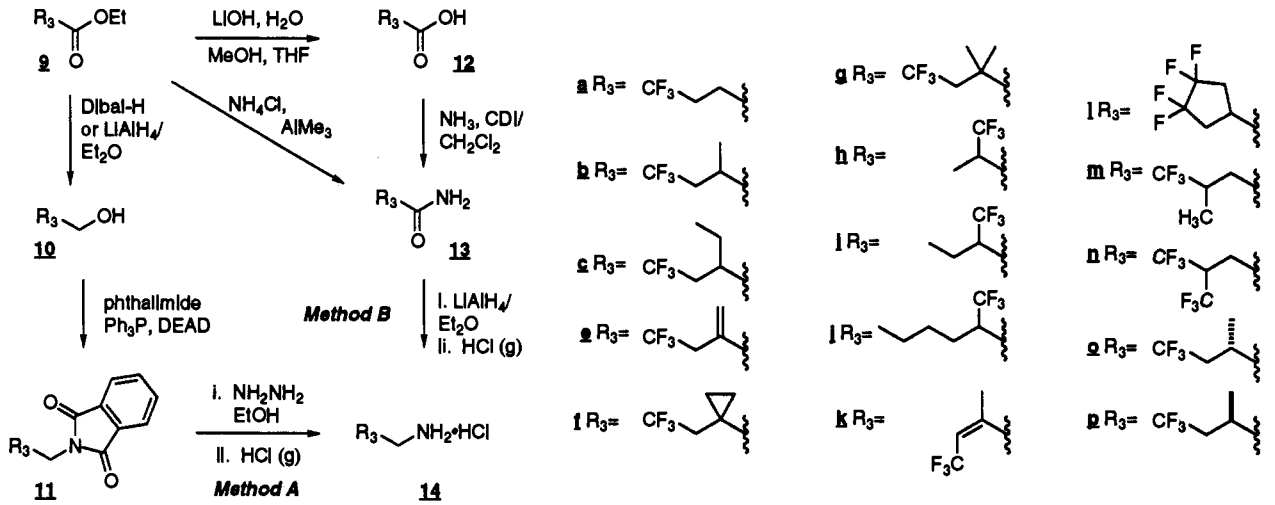


Figure 1. Leukotrienes and leukotriene antagonists.

Scheme 1. General Synthetic Routes to Fluorinated Amines



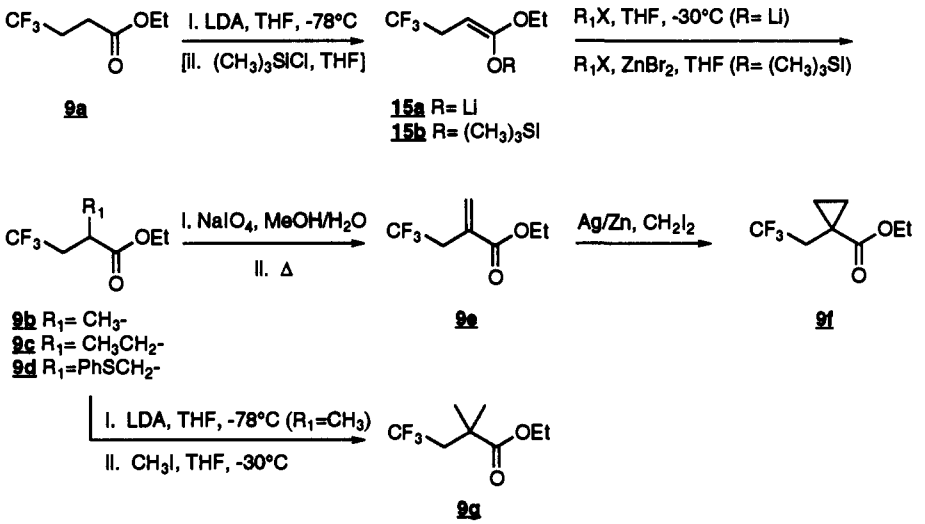
the desired primary amines **14a,b**, which were isolated and purified as the hydrochloride salts.

Preparation of the *exo*-methylene-substituted butylamine **14e** began by treatment of **9a** with LDA and chlorotrimethylsilane to afford silyl ketene acetal **15b**. Lewis-acid-catalyzed alkylation of **15b** with zinc bromide and phenyl chloromethyl thioether afforded thio ether **9d**.[9] Oxidation of **9d** to the sulfoxide by the action of sodium metaperiodate followed by thermolysis afforded the *exo*-methylene ester **9e**. This ester was treated with DIBAL-H to yield allylic alcohol **10e**, which was used in crude form in the Mitsunobu sequence described above.

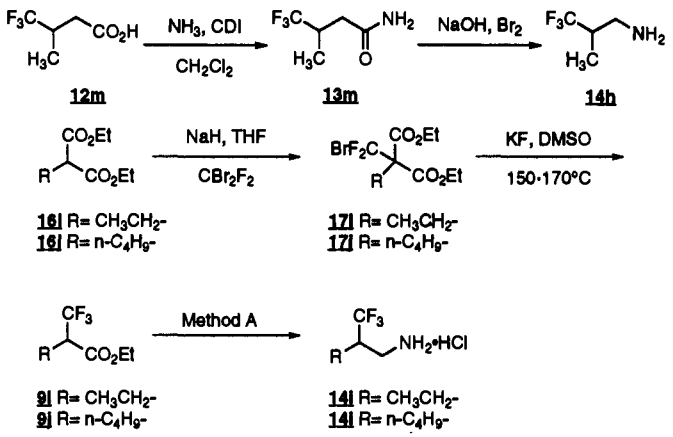
Several routes were explored for preparation of the cyclopropyl amine **14f**. We initially attempted to directly construct the cyclopropyl group by dialkylation of ethyl γ,γ,γ-trifluorobutyrate (**9a**) with a variety of ethylene derivatives,[10] a strategy which was unsuccessful. As an alternative, we explored conversion of the *exo*-methylene ester **9e** to the cyclopropyl ester **9f**. Neither treatment of **9e** with the sulfonium ylide described by Corey[11] nor treatment with diazomethane/$Pd(OAc)_2$[12] afforded any of the cyclopropanated product. However, a modified Simmons–Smith reagent which utilized Ag/Zn, diiodomethane, and sonication[13] afforded cyclopropyl ester **9f** in 25% yield from **9e**. Direct amidation of this ester using chloromethylaluminum amide[14] afforded amide **13f** in 39% yield.

Alkylation of ester **9b** utilizing lithium diisopropylamide and iodomethane afforded dimethylated ester **9g**. The latter compound was transformed to amide **14g** by aqueous hydrolysis of the ester followed by coupling with ammonia (method B, Scheme 1).

Scheme 2. Synthesis of Esters **9b–g**



Scheme 3. Synthesis of Amines **14h–j**



The synthesis of 3,3,3-trifluoro-2-methylpropylamine (**14h**) began with the commercially available 4,4,4-trifluoro-3-methylbutanoic acid (**12m**), which was converted to the corresponding primary amide **13m** (Scheme 3). Hofmann rearrangement of the amide by treatment of **13m** with aqueous sodium hydroxide and bromine afforded the desired amine **14h**, which was isolated in 22% yield as its hydrochloride salt. The syntheses of the remaining 3,3,3-trifluoropropylamines **14i,j** were accomplished by extension of the methodology reported for the preparation of α-trifluoromethyl esters from malonates.[15] In this method, summarized in Scheme 3, a diethyl alkylmalonate was alkylated by dibromodifluoromethane to afford the (bromodifluoromethyl)malonate **17**. This compound was then treated with anhydrous potassium fluoride in dimethyl sulfoxide at high temperature to give the desired esters **9**. Due to the known propensity of α-trifluoromethylated esters to undergo hydrolysis of the trifluoromethyl group to a carboxylic acid or ester,[16] method A (Scheme 1) was employed to convert these esters to the desired amines.

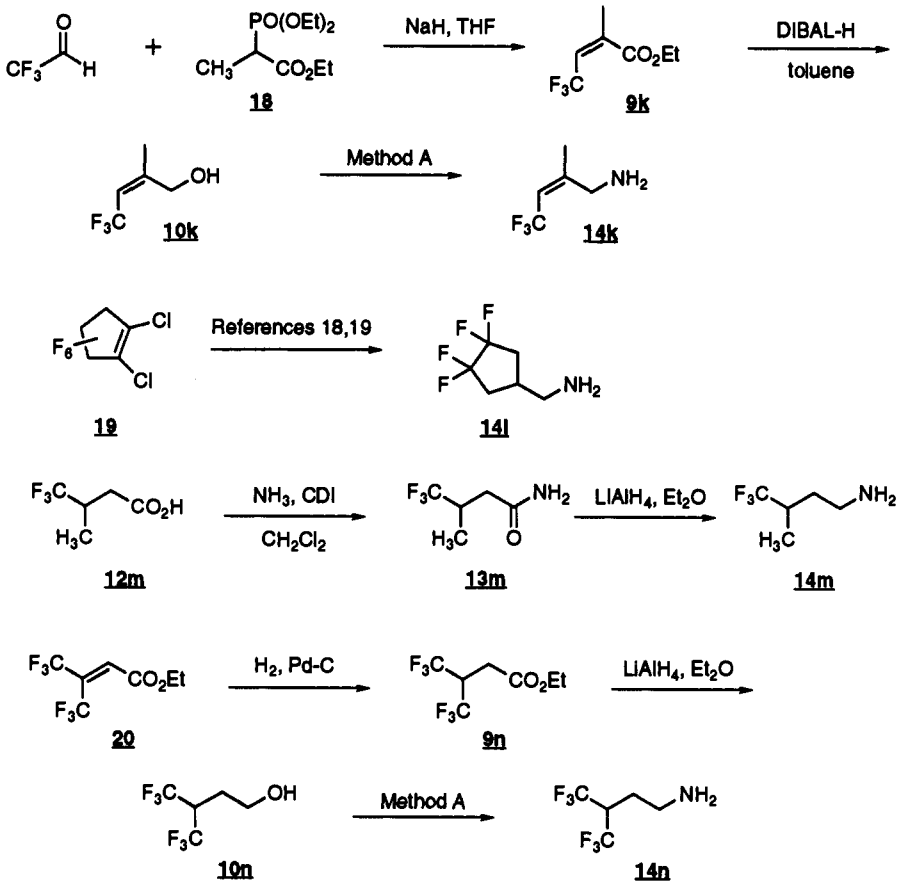
The remainder of the required fluorinated amines were prepared by the routes summarized in Scheme 4. The synthesis of 4,4,4-trifluoro-2-methyl-2-butenylamine (**14k**) began with Wittig coupling of trifluoroacetaldehyde with the Horner–Emmons reagent **18** to give the *E* olefin **9k** in low yield. Reduction with DIBAL-H afforded the allylic alcohol **10k**,[17] which was converted to amine **14k** using method A. The tetrafluorocyclopentyl amine **14l** has been previously reported and was synthesized by us from commercially available 1,2-dichlorohexafluorocyclopentene by combining the routes of Mill[18] and Park.[19] Reduction of the 4,4,4-trifluoro-3-methylbutanamide (**13m**), prepared as described earlier, with lithium aluminum hydride gave the γ-branched amine **14m**. Hydrogenation of commercially available hexafluorocrotonic acid (**20**) over Pd–C followed by reduction with lithium aluminum hydride produced alcohol **10n**.[20] This compound was converted to the hexafluoro amine **14n** using method A.

Enantioselective Synthesis of *R* and *S* Isomers of 38b. The chiral amines **14o,p** needed for the preparation of **38o,p**, the two enantiomers of compound **38b**, were each stereoselectively prepared by utilization of Evans' chiral alkylation technology.[21] The synthesis of *S* amine **14o**, summarized in Scheme 5, required the use of the L-valinol-derived oxazolidinone **21**. Acylation of **21** with γ,γ,γ-trifluorobutyryl chloride (**22**) afforded oxazolidinone **23** as an oil in 44% yield. Kinetic alkylation with LDA and iodomethane afforded a mixture of **21**, **23**, **24**, and **25** (Scheme 5) from which **24**, the major product, was isolated in 44% yield by flash chromatography.

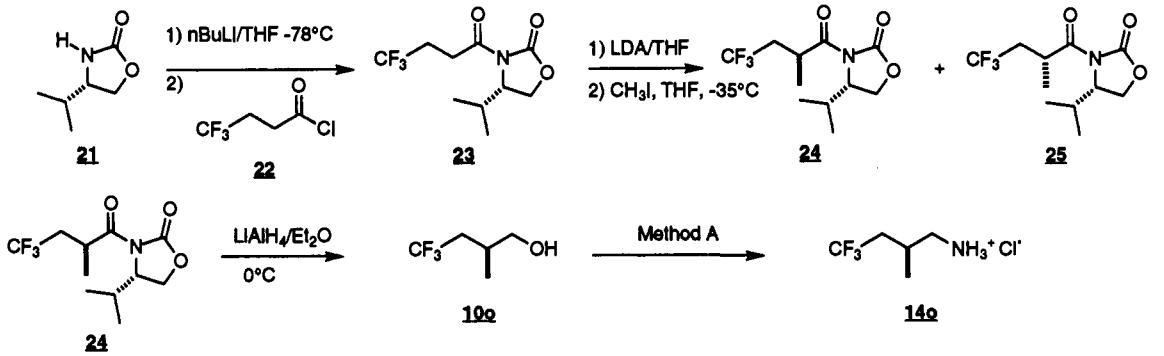
Similarily, the synthesis of *R* amine **14p**, summarized in Scheme 6, began with the ephedrine-derived oxazolidinone **26**. Acylation of **26** with γ,γ,γ-trifluorobutyryl chloride (**22**) afforded cystalline oxazolidinone **27** in 86% yield. Kinetic alkylation of **27** under conditions similar to those employed for **23**, afforded a complex mixture of **26**, **27**, **28**, and **60** from which **28**, the major product, was isolated in 36% yield by flash chromatography.

The poor yield and difficult chromatography which were required to isolate pure **28** prompted us to explore optimization of the kinetic alkylation reaction. We determined that the lithium enolate, prepared at −78 °C, was unreactive to iodomethane until ∼−35 °C, at which temperature it was also unstable. Decomposition by elimination of hydrogen fluoride with formation of a terminal olefin or by fragmentation to a ketene and unsubstituted oxazolidinone competed with the desired alkylation. Surprisingly, we found that the sodium enolate of **27**,[22] formed by treatment with sodium hexamethyldisilazide at −78 °C, was both more stable and also more reactive. The alkylation of this enolate with iodomethane could be performed at −78 °C with enhanced diastereoselectivity (>90% de), although longer reaction times were required. When the alkylation was carried out at −35 °C, an 87:13 mixture of **28**:(**60** + **27**) was obtained. Using the latter conditions, the desired diastereomer, **28**,

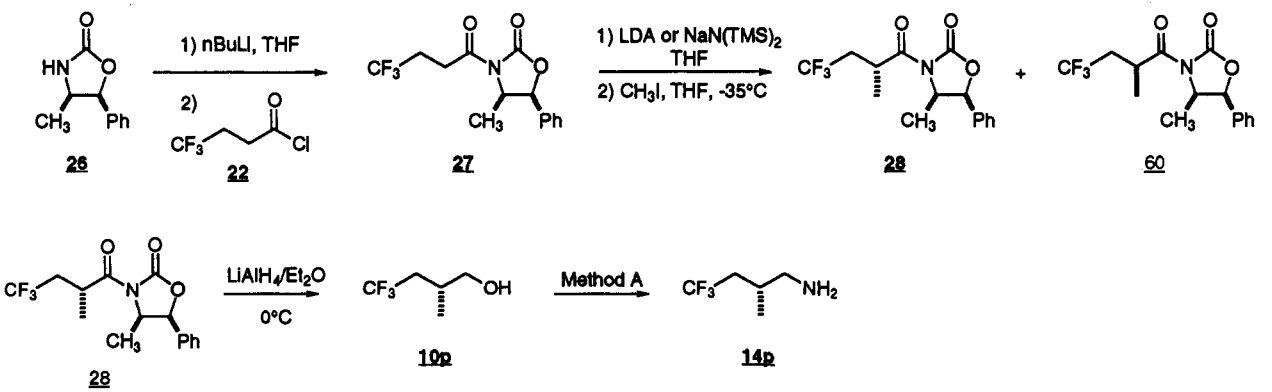
Scheme 4. Syntheses of Amines **14k–n**



Scheme 5. Synthesis of (*S*)-**14o**



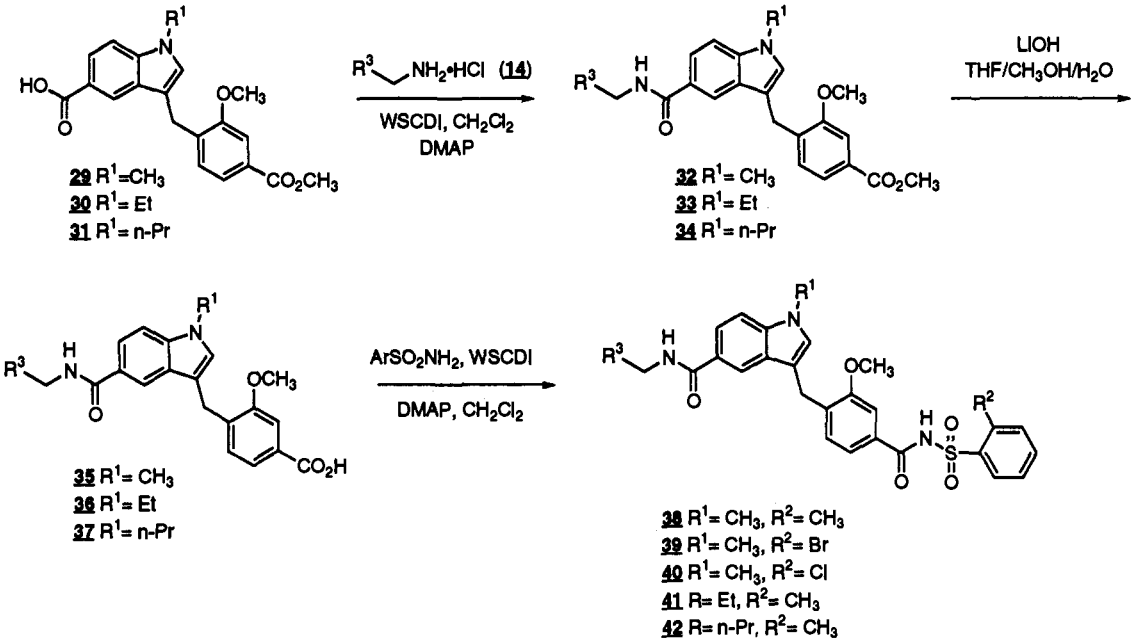
Scheme 6. Preparation of (*R*)-**14p**



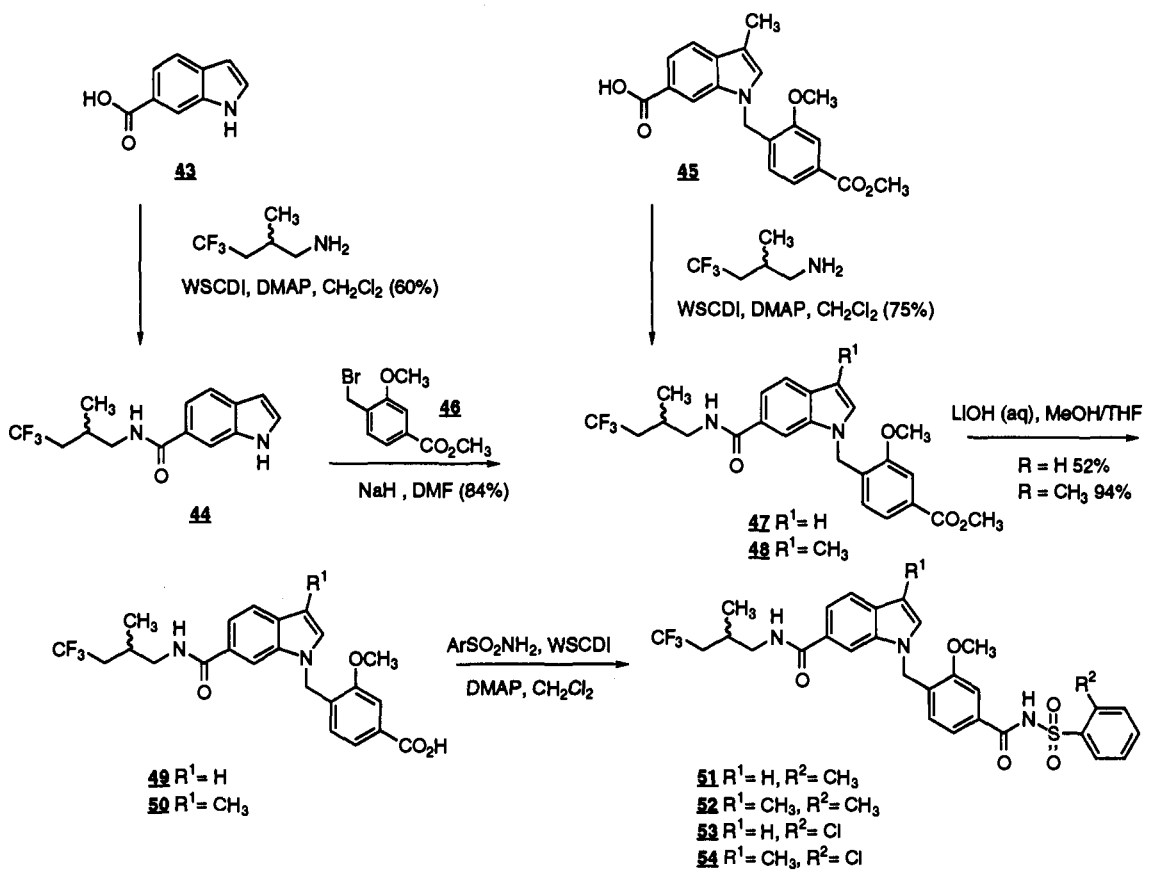
was isolated in 78% yield and >99.8% purity by two sequential crystallizations.

Reduction of oxazolidinones **24** and **28** with lithium aluminum hydride afforded alcohols **10o,p**, respectively. Conversion of alcohols **10o,p** to amines **14o,p** was effected as described earlier by formation of the phthalimide under Mitsunobu conditions followed by hydrazinolysis (method A).

Scheme 7. Synthetic Route to Indole-5-carboxamide Derivatives 38–42



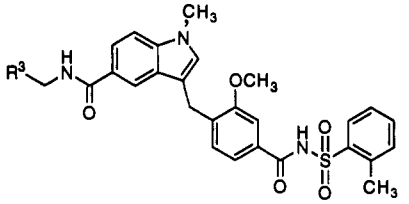
Scheme 8. Synthetic Route to Indole-6-carboxamide Derivatives 51–54



With the requisite amines 14 in hand, the completion of the synthesis of the desired drug candidates was accomplished as summarized in Scheme 7. The preparation of the key intermediate *N*-alkyl-3-benzylindole-5-carboxylic acids 29–31 as well as the details of the subsequent transformations have been described previously.[23] Condensation of acids 29–31 with the amines 14 afforded the amides 32–34 in generally high yield. Subsequent hydrolysis of the methyl ester and condensation of the resultant carboxylic acids 35–37 with an arylsulfonamide afforded the desired drug candidates 38–42.

The synthesis of the 1,6-disubstituted indole analogues 51–54 started with the previously reported acids 43 and 45 (Scheme 8).[24] Coupling of acid 43 with racemic amine 14b followed by N-alkylation of the intermediate indole 44 with sodium hydride and bromo ester 46[25] produced amide ester 47 (50% overall yield). The analogous compound 48, required for the C(3)-methyl indole series,

Table 1. Fluorinated Transposed Amides: Comparison to Non-Fluorinated Analogues



no.	R^3	K_i (nM)[a]	pK_B (n)[b]	po ED_{50}[c] (μmol/kg)	iv ED_{50}[c] (μmol/kg)	po/iv[d]	analysis
55[e]		4.7	8.0 (12)	14.73	1.09	14	$C_{32}H_{37}N_3O_5S \cdot 0.2H_2O$
38c		5.3	9.6 (12)	2.64	0.047	56	$C_{32}H_{34}F_3N_3O_5S$
56[e]		5.2	8.7 (6)	19.96	1.39	14	$C_{31}H_{35}N_3O_5S$
38b		0.57	9.93 (6)	1.44	0.036	40	$C_{31}H_{32}F_3N_3O_5S$

[a] Inhibition constant for displacement of [^{3}H]LTD_4 on guinea pig lung parenchymal membranes; K_i values are the mean of two experiments conducted in duplicate with separate batches. For detailed description of this binding assay, see ref 29. [b] K_B determined in guinea pig tracheal spirals with LTE_4 as agonist. Values are expressed as -log(K_B) "pK_B". See ref 30. n = number of concentration–response curves. [c] Determined in a conscious guinea pig "dyspnea" model; see ref 31. Percent protection from LTD_4-induced dyspnea was plotted as a function of dose. In general, the SEM for percent protection was ≤25% at each dose. ED_{50} values were obtained by regression analysis employing at least three doses from the linear portion of the dose–response curve. [d] Ratio of po ED_{50}/iv ED_{50}, which is a reflection of oral bioavailability. [e] See ref 23.

was directly prepared from acid **45** by coupling with amine **14b** (75%). Similarly to the sequence previously described for the inverted indoles (see Scheme 7) aqueous hydrolysis of esters **47** and **48** followed by coupling of resultant carboxylic acids **49** and **50** with the appropriate sulfonamide afforded the *N*-acylsulfonamides **51–54**.

Discussion

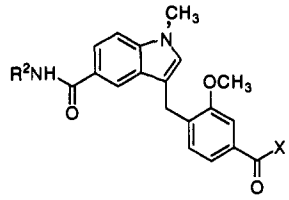
In our initial explorations of the indolecarboxamides[23,24] (a series we referred to as the "transposed amides" to distinguish them from the carbamoylindoles, e.g., **6**), we had observed that increasingly lipophilic amide substituents afforded drug candidates that were more potent following oral administration to conscious guinea pigs. This strategy was of limited value, however, as amide substituents containing more than six carbon atoms began to lose affinity for the LT receptor, as indicated by significant decreases in the ability of such molecules to displace [^{3}H]-LTD_4 from the LT receptor. Also, further attempts to exploit the apparent trend between lipophilicity and oral activity by introduction of longer aliphatic substituents onto N(1) of the indole nucleus were not clearly successful. While such modifications afforded moderate increases in oral activity, the potency of such compounds following intravenous administration to guinea pigs increased more rapidly, indicating poorer oral bioavailability of these analogues.

The replacement of hydrogen atoms by fluorine in biologically active molecules has been found to have significant, and often beneficial, effects on the activity of such molecules.[26] It has been proposed that these changes in biological profile are a result of the ability of the fluorinated group to change the lipophilicity, metabolic lability, or electronic character of the drug molecule. Given the limitations of the strategies described in our earlier exploration of the transposed amides, summarized above, we felt that incorporation of a fluorinated substituent into this series might serve to improve activity and, in particular, oral activity of these molecules. On the basis of our synthetic route to indole derivatives of this general structure (e.g., **38–42**) and the structure-activity relationships (SAR) found for this series, we felt that introduction of a fluorine-containing group in either the N(1) substituent or the amide side chain would be most attractive. Attempts to carry out the former strategy were complicated by poor reactivity of fluorinated alkyl halides such as 2,2,2-trifluoro-1-iodoethane.[27] Much greater success was encountered for introduction of fluorinated amide substituents.

In addition to the effects of fluorine on metabolic stability and lipophilicity, we were concerned about the inductive effects that a fluorinated substituent would have on both the hydrogen bonding capabilities and the pK_a of the amide group. In a study of the effects on acidity of straight-chain alcohols, Muller[28] has shown that placement of a trifluoromethyl group more than two carbons from the hydroxyl group has virtually no effect on the pK_a of the alcohol, whereas trifluoromethyl groups less than two carbons away dramatically increase the acidity of this proton. For this reason, we chose to introduce the fluorine atoms at the terminus of a 2-ethylbutyl substituent. This was also a favorable location, based on our earlier findings for the structure–activity relationships of this region.

The first group of compounds prepared to test this strategy is presented in Table 1. Initial evaluation of the first fluorinated compounds in a radioligand binding assay (K_i vs [^{3}H]LTD_4)[29,30] was quite encouraging, as **38c** was measured to have a K_i which was not significantly different from that of the non-fluorinated analogue **55**. When **38c** was evaluated for its ability to inhibit contractions of guinea pig trachea induced by LTE_4,[31] we were very pleased to find that the introduction of the fluorinated substituent resulted in more than a 10-fold increase in functional activity. Similarly, comparison of **38b** with its non-fluorinated analogue **56** confirmed the superior profile of the fluorinated amides *in vitro*, as **38b** was found to be ca.

Table 2. Octanol/Water Partition Coefficients for Selected Compounds



no.	R^2	X	c log P^b	log P^c	c log P - log P
56[d]	$CH_3CH_2CH(CH_3)CH_2$	STol[a]	6.97	5.85	1.12
38b	$CF_3CH_2CH(CH_3)CH_2$	STol	6.38	6.18	0.20
55[d]	$(CH_3CH_2)_2CHCH_2$	STol	7.50	6.29	1.21
38c	$CF_3CH_2CH(CH_3CH_2)CH_2$	STol	6.91	6.45	0.46
38m	$CF_3CH(CH_3)CH_2CH_2$	STol	6.38	6.30	0.08
38h	$CF_3CH(CH_3)CH_2$	STol	5.85	5.89	-0.04
57[d]	$CH_3CH_2CH(CH_3)CH_2$	OH	5.58	4.86	0.72
35b	$CF_3CH_2CH(CH_3)CH_2$	OH	4.99	5.12	-0.13
58[d]	$(CH_3CH_2)_2CHCH_2$	OH	6.11	5.42	0.69
35c	$CF_3CH_2CH(CH_3CH_2)CH_2$	OH	5.52	5.53	-0.01

[a] STol = o-toluenesulfonamide. [b] Calculated using CLOGP3 v3.4; see ref 32. [c] Measured by HPLC; see ref 33. [d] See ref 23.

10-fold more potent than **56** in both the binding and functional assays.

The improved potency *in vitro* cannot be explained by greater metabolic stability of the fluorinated compounds and, consequently, was attributed to physicochemical properties such as lipophilicity. We were a bit surprised to find that the calculated partition coefficient (c log P) values[32] for the fluorinated compounds were lower (i.e., indicating lower lipophilicity) than for the hydrocarbon analogues, as this is in contrast to the general belief that fluorination of a drug molecule results in increased lipophilicity.[26] When partition coefficients were measured[33] for several representatives of the two series (Table 2), it was discovered that our initial premise was correct, as in those cases examined, each fluorinated amide was slightly more lipophilic than its hydrocarbon analogue. Since the final drug candidate arylsulfonimides were very lipophilic and near the upper limit of measurability, we also compared the corresponding carboxylic acids, where a similar trend was observed.

Closer examination of both the calculated and measured data reveals that the calculated partition coefficients for the hydrocarbon amides are overestimated by approximately 1.1 log units for the arylsulfonimides and by approximately 0.7 log unit for the carboxylic acids. By comparison, the calculated partition coefficients for the fluorinated amides are very close to the measured values. Therefore, the overestimation of partition coefficients for the non-fluorinated amides was responsible for the incorrect trend observed in the c log P data.

Examination of the activity of the fluorinated analogues in conscious guinea pigs (see Table 1) demonstrated that these new derivatives were about an order of magnitude more potent than their non-fluorinated analogues. The most interesting example in this early SAR was the 2-methyl-4,4,4-trifluorobutylamide **38b**, which exhibited both high intrinsic activity and a level of oral activity competitive with some of the best compounds in earlier series.[4b,4c]

Evaluation of several analogues of **38b**, where changes were made to either the N(1) substituent or the 2-substituent on the arylsulfonimide moiety, revealed that the improved profile observed for **38b,c** was expressed in these analogues as well (see Table 3). As expected from previous SAR in our other indole/indazole series, comparable activity was observed for the (2-bromophenyl)sulfonimide **39c** and the (2-chlorophenyl)sulfonimide **40b**, which were approximately equipotent with **38c,b**. Incorporation of an ethyl substituent on N(1) of the indole ring afforded **41b**, which exhibited subnanomolar activity in isolated guinea pig trachea ($pK_B = 10.1$) but was only slightly more potent in the conscious guinea pig. The corresponding *N*-propyl derivative **42b** was approximately 3-fold less potent in the binding assay and was not examined further (extended hydrocarbon chains in this region of the molecule had also been detrimental to activity in earlier series[24]). Finally, movement of the C(2) methyl substituent to C(3) of the amide afforded **38m**, which was approximately 10-fold less potent than **38b**.

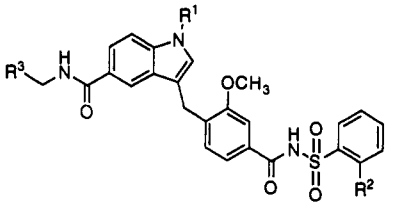
In order to further probe the effect of fluorination in the amide substituent on activity, several 3,3,3-trifluoropropyl derivatives (**38i,h**, and **41i**) were prepared. In these analogues, the trifluoromethyl group has been moved one carbon atom closer to the amide. These compounds were about 10-fold less potent than **38b** (and similar 4,4,4-trifluorobutylamides) when evaluated in both the binding assay and functional screen. Due to the lower activity of these compounds, we focused on the 4,4,4-trifluorobutylamide derivatives.

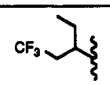
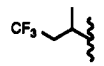
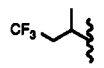
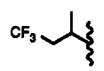
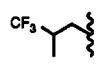
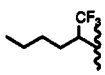
Although the bulk of our efforts focused on the indole 5-carboxamides, we felt it important to explore the effect of the best fluorinated side chain in the related indole-6-carboxamides. Incorporation of a methyl substituent at C(3) resulted in an ~20-fold increase in K_i in this series (compare **51b** with **52b**, Table 4). Thus, compound **52b** appeared very similar to **38b** in both the binding and functional assays. Surprisingly to us, the corresponding pair of compounds (**53b** and **54b**) in the (2-chlorophenyl)-sulfonamide series was approximately equipotent in terms of receptor affinity. As had been observed in the non-fluorinated series,[23] the oral activity measured for **52b** was very similar to that measured for **38b**.

While the emergence of **38b** and **52b** as leads from this early SAR exploration was very encouraging, of prime concern to us was the chiral nature of the amide substituent in these compounds, which were initially prepared as racemates. We were concerned by this feature since the clinical development of racemates poses additional complexities as compared to the development of either achiral or enantiomerically pure compounds.[34] In order to address this concern, we chose to prepare several achiral analogues as well as both enantiomers of **38b**. We chose the indole-5-carboxamide series for this expanded effort due to the superior oral activity of **38b** and its corresponding (2-chlorophenyl)sulfonamide (**40b**) over that of the analogous indole-6-carboxamides **52b** and **54b**.

Several strategies to prepare achiral analogues of **38b** were explored, and the results of this study are summarized in Table 5. The simple unbranched amide **38a** was 10-fold less potent in both the binding and *in vitro* functional assays. We noted that compounds in which the chiral sp^3 carbon was replaced by an sp^2 atom or was substituted with two identical groups were no longer chiral. Two examples of the former strategy, the *exo*-methylene analogue **38e** and the olefin **38k**, were prepared and found to be 5–10-fold less potent than **38b** in the binding assay. As an example of the latter case, we prepared the *gem*-dimethyl analogue **38g**. The K_i of this compound was

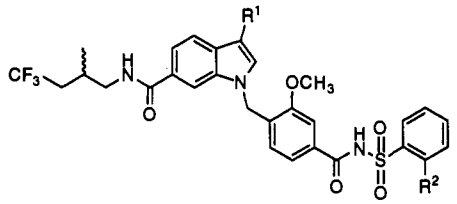
Table 3. Structure–Activity Relationships of Fluorinated Amides[a]



no.	R^3	R^1	R^2	K_i (nM)	pK_B (*n*)	po ED_{50} (μmol/kg)	iv ED_{50} (μmol/kg)	po/iv	analysis
39c		CH_3	Br	2.4	9.3 (6)	2.50	0.045	56	$C_{31}H_{31}BrF_3N_3O_5S$
40b		CH_3	Cl	0.57	9.7 (12)	2.50	0.024	110	$C_{30}H_{29}ClF_3N_3O_5S$
41b		Et	CH_3	0.38	10.1 (6)	1.42	0.011	129	$C_{32}H_{34}F_3N_3O_5S{\cdot}0.2H_2O$
42b		^{n}Pr	CH_3	1.7	NT[b]	NT	NT	ND[c]	$C_{33}H_{26}F_3N_3O_5S$
38m		CH_3	CH_3	7.3	NT	NT	NT	ND	$C_{31}H_{32}F_3N_3O_5S$
38j		CH_3	CH_3	5.0	8.8	NT	NT	ND	$C_{33}H_{36}F_3N_3O_5S{\cdot}0.2H_2O$
38h		CH_3	CH_3	12	NT	NT	NT	ND	$C_{30}H_{30}F_3N_3O_5S{\cdot}0.3H_2O$
41i		Et	CH_3	5.3	9.0	NT	NT	ND	$C_{32}H_{34}F_3N_3O_5S$

[a] For explanatory footnotes, see Table 1. [b] NT = not tested. [c] ND = not determined.

Table 4. Fluorinated Transposed Amides: Indole-6-carboxamides[a]



no.	R^1	R^2	K_i (nM)	pK_B (*n*)	po ED_{50} (μmol/kg)	po/iv	analysis
51b	H	CH_3	7.7	NT	NT	ND	$C_{30}H_{30}F_3N_3O_5S$
52b	CH_3	CH_3	0.44	9.6 (5)	2.29	ND	$C_{31}H_{32}F_3N_3O_5S$
53b	H	Cl	4.2	8.9 (5)	NT	ND	$C_{29}H_{27}ClF_3N_3O_5S$
54b	CH_3	Cl	4.9	NT	NT	ND	$C_{30}H_{29}ClF_3N_3O_5S$

[a] For explanatory footnotes, see Tables 1 and 2.

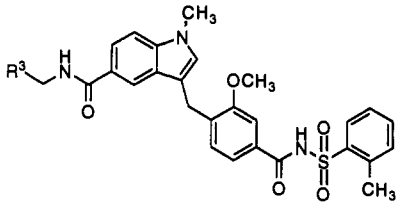
4-fold higher than that of **38b**, suggesting that the leukotriene receptor does not have sufficient space to accommodate the second methyl group without some loss of binding affinity. Although a cyclopropyl substituent is smaller than a *gem*-dimethyl group, the cyclopropyl analogue **38f** exhibited similar affinity. Since the dihedral angle between the two geminal substituents on the cyclopropyl groups is ~116° [35] as compared to 109.5° for the acyclic chain, it is possible that in the cyclopropyl analogue the trifluoromethyl group is no longer optimally placed for interaction with the receptor.

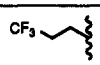
In the original 5-carbamoylindole series of LT antagonists exemplified by **6**, a cyclopentyl ring had been found to provide some of the most potent compounds.[4a] Although the cyclopentylmethyl-transposed amide was not the most potent compound prepared in the non-fluorinated series,[23] the ready availability of 1-(3,3,4,4-tetrafluorocyclopentyl)-methylamine (**14l**), an achiral compound, prompted us to explore this modification. Comparison of **38l** to its non-fluorinated analogue **55**[23,24] revealed only small improvements in both *in vitro* and *in vivo* activity as a result of fluorination. These results show **38l** to be significantly less potent than **38b**.

In our earlier non-fluorinated transposed amides, the need for substitution at the β-carbon of the amide for optimal activity was established. This trend in the SAR continued in the current fluorinated series, as the γ-branched isomer **38m** (Table 3) was found to be approximately 10-fold less potent than **38b**. Fluorination of the second methyl group in **38m** led to the achiral **38n**, which approached the *in vitro* activity of **38b** but remained significantly weaker *in vivo*.

Comparison of Enantiomers of 38b and Focus on 38p. Since racemic **38b** remained the most interesting compound from this exploration, we deemed it imperative to prepare and characterize both enantiomers. Previously, there have been several enantiomeric pairs prepared within the structurally dissimilar SmithKline,[36] ICI,[4] and Merck[5] series of LT antagonists. In the SKF series, which is structurally very similar to the natural agonists, the receptor showed significant (ca. 35-fold) enantioselectivity for the "natural" *2S,3R* stereochemistry.[37] In a previous study of 5-carbamoylindole derivatives similar to **6**, evaluation of enantiomerically pure α-branched amides revealed a small difference (ca. 4-fold) between the two enantiomers.[38] Finally, in the Merck series, a small (3-fold) difference between **7** and its enantiomer was observed.[39] In the case of **38b**, a small difference in activity was observed between the enantiomers **38o,p** (Table 6).

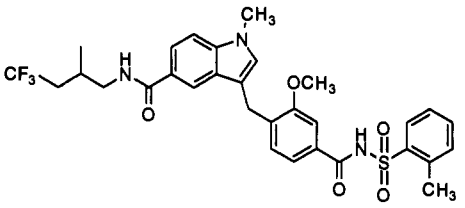
Table 5. Achiral Analogue in the Indole-5-carboxamide Series[a]



no.	R^3	K_i (nM)	pK_B (n)	po ED_{50} (μmol/kg)	iv ED_{50} (μmol/kg)	po/iv	analysis
38a		7.5	8.7 (5)	NT	NT	ND	$C_{30}H_{30}F_3N_3O_5S$
38e		3.8	NT	NT	NT	ND	$C_{31}H_{30}F_3N_3O_5S$
38k		2.1	NT	NT	NT	ND	$C_{31}H_{30}F_3N_3O_5S$
38g		2.2	8.9 (7)	NT	NT	ND	$C_{32}H_{34}F_3N_3O_5S \cdot 0.33H_2O$
38f		4.6	NT	NT	NT	ND	$C_{32}H_{32}F_3N_3O_5S \cdot 1.0H_2O$
38l		1.3	8.6 (7)	11% @ 3 μmol/kg	NT	ND	$C_{32}H_{31}F_4N_3O_5S$[c]
55[b]		3.2	8.4 (6)	19.2	0.69	28	$C_{32}H_{35}N_3O_5S \cdot 0.7H_2O$
38n		1.2	9.3 (5)	19% @ 3 μmol/kg	NT	ND	$C_{31}H_{29}F_6N_3O_5S$[d]

[a] For explanatory footnotes, see Tables 1 and 2. [b] See ref 23 and 24. [c] C: calcd, 57.43; found, 57.95. [d] C: calcd, 55.60; found, 56.01.

Table 6. Comparison of Enantiomers of 38b[a]



no.	stereochem	K_i (nM) (n)	$pK_B \pm$ SEM (n)[b]	po ED_{50} (μmol/kg)	iv ED_{50} (μmol/kg)	po/iv	analysis
38b	*R,S*	0.57 (2)	9.93 ± 0.14 (6)	1.44	0.036	40	$C_{31}H_{32}F_3N_3O_5S$
38o	*S*	1.45 ± 0.54 (5)	9.28 ± 0.19 (6)	3.73	0.047	79	$C_{31}H_{32}F_3N_3O_5S \cdot 0.5H_2O$
38p	*R*	0.42 ± 0.12 (5)	10.13 ± 0.14 (6)	1.14	0.022	52	$C_{31}H_{32}F_3N_3O_5S$
6[c]		0.34 ± 0.03 (5)	9.67 ± 0.13 (8)	0.54	ND	ND	

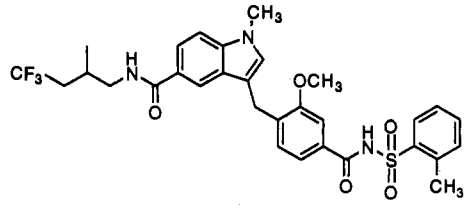
[a] For explanatory footnotes, see Table 1. [b] pK_B values determined with [LTE_4] = 1 nM. [c] Reference 4b.

The *R* enantiomer, **38p**, appeared to be slightly more potent (a consistent but not statistically significant difference) than **38b** in both the binding and isolated tissue assays. Although the *S* enantiomer, **38o**, exhibited significant biological activity (K_i= 1.45 nM, pK_B= 9.28), it was significantly weaker than either **38p** or **38b**. When evaluated in conscious guinea pigs, **38p** continued to profile as superior to **38o**, as the *R* enantiomer was approximately 3-fold more potent following oral administration and twice as potent following intravenous dosing.

The consistency in rank order of activity between the *in vitro* and *in vivo* activity of **38o,p** is in contrast to the Merck series (7), in which the less potent enantiomer *in vitro* was more potent *in vivo*.[40] This discrepancy was attributed to a more rapid rate of metabolism for the more active enantiomer, which resulted in an apparent lower bioavailability. Pharmacokinetic studies of **38o,p** reveal no such difference in these compounds, as summarized in Table 7. Measurements of clearance rates and absolute bioavailabilities of the racemate **38b** and the two enantiomers **38o,p** in rat showed no statistically significant differences between these compounds. Further evaluation of **38p** in guinea pig and dog demonstrated it to have good bioavailability in these species (14.6% and 37.5%, respectively).

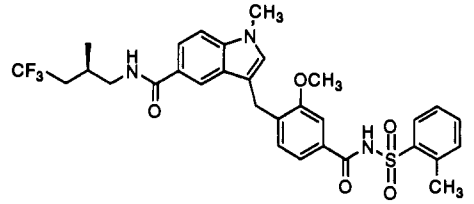
Selectivity of 38p. The *in vitro* selectivity of **38p** was evaluated at a standard concentration of 10 μM. At this concentration, no effect on agonist responses at adrenergic (α_2, β_1), histaminic (H_1), muscarinic (M_1), thromboxane (TP_1), or prostagladin (EP_2) receptors or Ca^{2+} channels was observed (Table 8). Weak antagonist activity was observed in isolated guinea pig ileum against PGE_2-induced contraction and in rabbit aorta against the thromboxane receptor (TP_2) agonist U46619. On the basis of these results, which are qualitatively similar to those

Table 7. Pharmacokinetic Characterization of 4,4,4-Trifluoro-2-methylbutylamides



no.	stereochem	species	clearance (L/h kg^{-1})	oral bioavailability (%)
38b	*R,S*	rat	0.11	33
38o	*S*	rat	0.10	23
38p	*R*	rat	0.07	33
38b	*R,S*	guinea pig	0.74	12
38p	*R*	guinea pig	0.85	15
38p	*R*	dog	0.31	38

Table 8. Selectivity Studies with ZD 3523 (**38p**)



receptor	isolated tissue	agonist	*n*	pK_B
α_2	mouse vas deferens	clonidine	3	<5
β_1	guinea pig right atrium	isoproterenol	3	<5
H_1	guinea pig ileum	histamine	3	<5
muscarinic	guinea pig ileum	acetylcholine	3	<5
TP_1	rat aorta	U46619	3	<5
TP_2	rabbit aorta	U46619	6	5.14 ± 0.27
EP_1	guinea pig ileum	PGE_2	5	5.23 ± 0.34
EP_2	guinea pig trachea	PGE_2	4	<5

observed for **6**,[41] we conclude that **38p** is highly selective for the LT receptor.

Summary

Our exploration of the effect of the introduction of fluorinated substitutents in the amide region of substituted 3-(phenylmethyl)-1*H*-indole-5-carboxamides on leukotriene antagonist activity has revealed that an appropriately positioned trifluoromethyl group dramatically improves both the *in vitro* and *in vivo* profiles of these compounds. Attempts to prepare achiral analogues of an initial lead, **38b**, a racemate, failed to provide a compound with a profile which matched or exceeded that of **38b**. Therefore, the individual enantiomers of **38b** were prepared by stereoselective synthesis. It was found that the *R* enantiomer **38p** exhibited modest, but consistently superior, activity when compared to the *S* enantiomer **38o**. As a result of these observations, **38p** has been selected for evaluation in clinical trials for the treatment of asthma.

Experimental Section

General Methods. Proton NMR (^{1}H NMR) spectra were recorded on an IBM NR-80 (80 MHz), Bruker WM 250 (250 MHz), or Bruker WM 300 (300 MHz) instrument in the solvent indicated. Chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane. Peaks are reported as: s, singlet; d, doublet; t, triplet; b, broad; or ex, exchanged by added deuteriotrifluoroacetic acid. For compounds **32–42** and **47–54**, the following system for reporting of NMR data was used. H-C(2) represents hydrogen on C(2) of the methoxy-substituted aromatic ring, H-C(2′) represents hydrogen on C(2) of the indole nucleus, and H-C(2″) represents hydrogen on C(2) of the amide substituent. Mass spectra (CIMS) were recorded on a Kratos MS-80 or Finnigan MAT-60 instrument operating in the chemical ionization mode using methane as reagent gas. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Combustion analyses for carbon, hydrogen, and nitrogen were performed on a Perkin-Elmer 241 instrument by ICI Americas Analytical Department and are within ±0.4% of theoretical values. Flash chromatography was performed using the indicated solvent ratios (v/v) on Kieselgel 60 (230–400 mesh) supplied by E. Merck. Ethyl 4,4,4-trifluorobutanoate was obtained from Fairfield Chemical Co. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl; dichloromethane, pyridine, *N,N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were distilled from calcium hydride. All other reagents were purified by standard methods (recrystallization or distillation) as needed. Many of the intermediates for the preparation of amines **14** were low-boiling liquids which were difficult to isolate free from residual solvent and were consequently used in crude form for subsequent transformations.

Ethyl 4,4,4-Trifluoro-2-methylbutanoate (9b). A solution of diisopropylamine (14.06 g, 0.14 mol) in THF (400 mL) was cooled to 0 °C and treated dropwise with butyllithium (71 mL of a 1.5 M solution in hexanes, 0.11 mol). The resulting mixture was stirred at 0 °C for 30 min and then cooled to −70 °C and treated dropwise with a solution of ethyl 4,4,4-trifluorobutanoate (**9a**) (15.75 g, 0.09 mol) in THF (50 mL). The resulting deep purple solution was stirred at −70 °C for 30 min and then treated with iodomethane (26.2 g, 0.18 mol). The resulting colorless suspension was allowed to warm to room temperature, and then the reaction was quenched with water (25 mL) and the solvent evaporated. The residue was dissolved in dichloromethane (200 mL), washed sequentially with water (100 mL), 3 N hydrochloric acid (2 × 100 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and evaporated to leave an amber oil. Distillation afforded the alkylated ester **9b** (7.77 g, 0.042 mol, 46%) as a clear liquid, bp 65 °C (65 Torr). ^{1}H NMR: 4.17 (q, J = 7.2 Hz, 2H, CH_2CH_3), 2.79–2.63 (m, 2H, H-C(3)), 2.16 (m, 1H, H-C(2)), 1.28 (d, J = 7.1 Hz, 3H, CH_3-C(2)), 1.27 (t, J = 7.2 Hz, 3H, CH_2CH_3). CIMS: m/z 185 ((M + H)$^+$, 100%).

Also prepared by this procedure was **ethyl 4,4,4-trifluro-2-ethylbutanoate (9c)**, bp 54–55 °C (15 Torr). ^{1}H NMR ($CDCl_3$): 4.17 (q, J = 7.2 Hz, 2H, CH_2CH_3), 2.64–2.55 (m, 2H, H-C(3)), 2.17 (t, J = 10.8 Hz, 1H, H-C(2)), 1.66 (m, 2H, CH_3CH_2-C(2)), 1.27 (t, J = 7.2 Hz, 3H, CH_2CH_3), 0.93 (t, J = 7.2 Hz, 3H, CH_3CH_2-C(2)).

1-Ethoxy-1-[(trimethylsilyl)oxy]-4,4,4-trifluoro-1-butene (15b). A solution of diisopropylamine (1.87 g, 18.5 mmol) in THF (25 mL) was cooled to 0 °C and treated dropwise with butyllithium (7.7 mL of a 2.4 M solution in hexanes, 18.5 mmol). The resulting pale yellow solution was stirred for 20 min at 0 °C, cooled to −78 °C, and treated with a solution of ethyl 4,4,4-trifluorobutanoate (**9a**) (3.0 g, 17.6 mmol) in THF (10 mL). The resulting deep purple solution was stirred at −78 °C for 30 min and rapidly treated with chlorotrimethylsilane (2.1 g, 19.4 mmol). The solution immediately turned yellow and was warmed to room temperature. The THF was removed by distillation at atmospheric pressure to afford a yellow residual oil. The product **15b** was isolated as a clear oil (3.7 g, 15.3 mmol) by distillation at ~100 °C and ~600 mmHg pressure. CIMS: m/z 243 ((M + H)$^+$, 100).

Ethyl 2-[(Phenylthio)methyl]-4,4,4-trifluorobutanoate (9d). To a solution of **15b** (3.7 g, 15.3 mmol) in dichloromethane (40 mL) at room temperature were added phenyl chloromethyl thioether (2.9 g, 18.4 mmol) and $ZnBr_2$ (34 mg, 0.15 mmol). After the mixture was stirred for 20 h the solvent was removed *in vacuo* and the product **9d** isolated as a pale yellow oil (1.1 g) by flash chromatography using 1:9 dichloromethane/hexane as the eluent. ^{1}H NMR ($CDCl_3$): 7.4–7.25 (m, 5H), 4.20–4.05 (m, 2H), 3.24 (q_{AB}, J = 6.6, 13.5 Hz, 1H), 3.22 (q_{AB}, J = 7.1, 13.5 Hz, 1H), 2.88–2.82 (m, 1H), 2.70–2.44 (m, 2H), 1.24 (t, J = 7 Hz, 3H).

Ethyl 2-(2,2,2-Trifluoroethyl)-2-propenoate (9e). To a solution of **9d** (5.5 g, 18.8 mmol) in methanol (65 mL) at 0 °C was added a solution of $NaIO_4$ (5.13 g, 24.4 mmol) in water (40 mL). The solution was stirred and allowed to slowly warm to room temperature overnight by which point a white precipitate had

formed. The mixture was diluted with water and washed with dichloromethane (5 ×). The dichloromethane washings were combined, dried, and concentrated by distillation to afford the crude sulfoxide which was immediately taken on via thermolysis by dissolving in hexane and heating to reflux overnight. A dark precipitate had formed which was removed by filtration. The solvent was removed from the filtrate by distillation at atmospheric pressure. The product **9e** was isolated as a pink oil (2.36 g) contaminated with hexane (29 mol % by ^{1}H NMR) by distillation at ~60 °C and 50 mbar. ^{1}H NMR ($CDCl_3$): 6.51 (s, 1H), 5.9 (s, 1H), 4.26 (q, J = 9 Hz, 2H), 3.19 (q_{AB}, J = 12.9, 25 Hz, 2H), 1.33 (t, J = 9 Hz, 3H).

Ethyl 1-(2,2,2-Trifluoroethyl)cyclopropanecarboxylate (9f). To a solution of **9e** (~0.6 g, ~3.3 mmol) in diethyl ether were added freshly prepared Zn–Ag couple (~550 mg) and diiodomethane (0.35 mL, 1.5 g, 4.3 mmol), and the reaction mixture was placed in an ultrasonic bath overnight at 40 °C. The addition of diiodomethane was repeated twice for a total reaction period of 60 h. The mixture was cooled to 0 °C and 0.43 mL pyridine added. The resultant precipitated salts were removed by filtration. Pyridine was again added until no more precipitate formed. The ether was removed by distillation and the product **9f** isolated, by bulb-to-bulb distillation at 60 °C and ~60 mbar, as a pale yellow oil (961 mg), contaminated with diiodomethane (43 mol % by ^{1}H NMR) and diethyl ether (42 mol % by ^{1}H NMR), which was directly used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$ partial): 4.15 (q, J = 7.5 Hz, OCH_2CH_3 2H), 2.5 (q, J = 10.5, H_2, CH_2CF_3, 2H), 1.36 (m, 2H), 0.93 (m, 2H).

(*Z*/*E*)-Ethyl 4,4,4-Trifluoro-2-methyl-2-butenoate (9k). A solution of triethyl 2-phosphonopropionate (10 g, 0.042 mol) in THF (50 mL) was added dropwise to a slurry of sodium hydride (1.07 g, 0.044 mol) in THF (130 mL) at 0 °C. After the mixture was stirred for 0.5 h, gaseous trifluoroacetaldehyde, generated by dropping ethyl trifluoroacetylaldehyde hemiacetal (22 g, 0.144 mol) onto hot (160 °C) polyphosphoric acid, was bubbled through the solution. After the solution was stirred for 4 h at 0 °C, the reaction was quenched with triethylamine hydrochloride and the THF removed by atmospheric distillation. The residue was partitioned between aqueous sodium dihydrogen phosphate and dichloromethane. A precipitate of polymeric trifluoroacetaldehyde was removed by filtration, and the organic layer was washed with brine, dried over sodium sulfate, and fractionally distilled to afford ~2.3 g (20% yield) of **9k** as predominantly the *Z* isomer which was used without further purification. ^{1}H NMR ($CDCl_3$, partial): 6.7 (b q, J = 1.5 Hz, 0.1H, CF_3CH (*E* isomer)), 5.7 (b q, J = 1.5 Hz, 0.9H, CF_3CH (*Z* isomer)), 4.27 (q, J = 7 Hz, 2H), 1.29 (t, J = 7 Hz, 3H).

General Procedure for Reduction of Esters 9 to Alcohols 10: (*R,S*)-2-(Trifluoromethyl)-1-butanol (10i). A solution of ethyl (2-trifluoromethyl)butanoate[15] (**9i**) (5.18 g, 28.2 mmol) in diethyl ether (40 mL) was added dropwise to a suspension of lithium aluminum hydride (1.60 g, 42.2 mmol) in diethyl ether (20 mL) at such a rate as to maintain gentle reflux. Upon complete addition, the reaction mixture was maintained at reflux temperature for 30 min and then cooled to 0 °C and the reaction quenched by addition of saturated aqueous sodium sulfate. The solids were removed by filtration, and the filter cake was washed with diethyl ether. The diethyl ether was removed from the filtrate by distillation at atmospheric pressure to afford the crude alcohol **10i** (4.00 g, 28 mmol, 99%) as a pale yellow liquid which was used immediately without further purification. ^{1}H NMR ($CDCl_3$): 3.82 (m, 2H, H-C(1)), 2.17 (m, 1H, H-C(2)), 1.64 (m, 2H, H-C(3)), 1.04 (t, J = 7.5 Hz, H-C(4)). CIMS: m/z 143 ((M + H)$^+$, 6.1), 125 ((M + H − H_2O)$^+$, 14), 123 ((M + H − HF)$^+$, 28), 105 (100).

General Procedure for Conversion of Alcohols 10 to Phthalimides 11: (*R,S*)-2-[2-(Trifluoromethyl)butyl]-1*H*-isoindole-1,3(2*H*)-dione (11i). A suspension of 2-(trifluoromethyl)-1-butanol (4.00 g, 28.2 mmol), phthalimide (4.14 g, 28.2 mmol), and triphenylphosphine (7.39 g, 28.2 mmol) in THF (50 mL) was cooled to 0 °C and treated dropwise with diethyl azodicarboxylate (4.44 mL, 4.91 g, 28.2 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The solvent was then evaporated, and the residue was slurried in diethyl ether (100 mL). The solids were removed by filtration and washed with ether, and the filtrate was evaporated. The residue was purified by flash chromatography (1:5:5 ethyl acetate/dichloromethane/hexane) to afford **11i** (5.74 g, 21.2 mmol, 75%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): 7.85 (m, 4H), 3.84 (dd, J = 7.2, 13.6 Hz, 1H, H-C(1)), 3.71 (dd, J = 6.2, 13.6 Hz, 1H, H-C(1)), 2.73 (m, 1H, H-C(2)), 1.59 (m, 2H, H-C(3)), 1.03 (t, J = 7.6 Hz, 3H, H-C(4)). CIMS: m/z 272 ((M + H)$^+$, 55%), 252 ((M + H − HF)$^+$, 28), 176 (100),

General Procedure for Hydrazinolysis of Phthalimides 11 to Amine Hydrochlorides 14: (*R,S*)-2-(Trifluoromethyl)-1-hexylamine (14j). A solution of phthlamide **11i** (5.00 g, 16.7 mmol) in ethanol (21 mL) was treated with hydrazine monohydrate (0.83 g, 16.7 mmol). The reaction mixture was heated to reflux temperature for 1 h and then cooled to room temperature and acidified to pH ~1 by addition of concentrated hydrochloric acid. The mixture was filtered, and the solids were washed with ethanol. The filtrate was concentrated, washed with ethyl acetate (3×), and then basified to pH ~10 by addition of 20% aqueous sodium hydroxide. The mixture was extracted with diethyl ether (3×). The organic extracts were washed with water and brine, combined, dried, filtered, and evaporated to afford **14j** as a white foam (1.22 g, 6.4 mmol, 39%). ^{1}H NMR (DMSO-d_6): 7.75 (b, 2H, NH_2), 3.50 (m, 1H, H-C(1)), 3.18 (m, 1H, H-C(1)), 2.67 (m, 1H, H-C(2)), 1.38 (m, 6H), 0.92 (t, J = 7.3 Hz, H-C(6)).

General Procedure for Hydrolysis of Esters 9 to Carboxylic acids 12: 4,4,4-Trifluorobutanoic Acid (12a). A solution of lithium hydroxide monohydrate (324 g, 7.72 mol) in water (1.8 L) was added to a stirred solution of ethyl 4,4,4-trifluorobutanoate (436 g, 2.56 mol) in methanol (2.0 L) and THF (2.0 L). The suspension was stirred overnight and then concentrated *in vacuo*. The residue was diluted with water and washed with ether (1 L). The aqueous layer was acidified with 6 N hydrochloric acid and extracted twice with diethyl ether (2 L, 1 L). The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated. The residue was distilled (bp 165–168 °C) to give 4,4,4-trifluorobutanoic acid (347 g, 2.44 mol 95%) as a low-melting solid, mp 27–30 °C. ^{1}H NMR ($CDCl_3$): 2.66 (t, 2H, H-C(2)), 2.33–2.57 (m, 2H, H-C(3)).

General Procedure for Conversion of Carboxylic Acids 12 to Amides 13: (*R,S*)-4,4,4-Trifluoro-2-methylbutanamide (13b). A solution of (*R,S*)-4,4,4-trifluoro-2-methylbutanoic acid (**12b**) (6.50 g, 41.8 mmol) in dichloromethane (5 mL) was added to a solution of 1,1′-carbonyldiimidazole (7.50 g, 46.0 mmol) in dichloromethane (78 mL). The resulting mixture was warmed to reflux temperature for 30 min and then cooled to room temperature, and ammonia was bubbled through the mixture for 20 min. The mixture was then stirred at room temperature for 18 h, diluted with dichloromethane (50 mL), and washed with 10% hydrochloric acid (2×), water, and brine. The aqueous washes were extracted with ethyl acetate (2×). The organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated to afford the amide **13b** (4.45 g, 28.7 mmol, 70%) as a white solid. ^{1}H NMR ($CDCl_3$): 5.56 (b, 2H, NH_2), 2.73 (m, 1H, H-C(2)), 2.65 (m, 1H, H-C(3)), 2.12 (m, 1H, H-C(3)), 1.30 (d, J = 6.8 Hz, 3H, CH_3-C(2)).

General Procedure for Reduction of Amides 13 to Amine Hydrochlorides 14: (*R,S*)-4,4,4-Trifluoro-2-methylbutanamine (14b). A solution of the amide **13b** (4.45 g, 28.7 mmol) in diethyl ether (100 mL) was added to a suspension of lithium aluminum hydride (1.6 g, 43.1 mmol) in diethyl ether (44 mL) at a rate such that gentle reflux was maintained. Following complete addition, the reaction mixture was heated at reflux temperature for 12 h and then cooled to room temperature and the reaction quenched by sequential addition of water (1.6 mL), 10% aqueous sodium hydroxide (1.6 mL), and water (4.8 mL). The white precipitate was removed by filtration and washed with diethyl ether. The diethyl ether was removed by distillation at atmospheric pressure, and the residue was distilled bulb-to-bulb (bath temperature ca. 175 °C) at atmospheric pressure to give the amine **14b** (3.55 g, 25.2 mmol, 88%) as a colorless liquid. The hydrochloride salt was prepared by bubbling hydrogen chloride (g) through a solution of the amine in diethyl ether to afford a white solid. ^{1}H NMR (DMSO-d_6): 8.30 (b, 2H, NH_2), 2.82, 2.71 (b, 2H, H-C(1)), 2.51 (m, 1H, H-C(3)), 2.25 (m, 1H, H-C(3)), 2.18 (m, 1H, H-C(2)), 1.04 (d, J = 6.1 Hz, 3H, CH_3-C(2)).

General Procedure for Preparation of Amides 32–34: Preparation of Methyl (*R,S*)-3-Methoxy-4-[[1-methyl-5-[(2-methyl-4,4,4-trifluorobutyl)carbamoyl]indol-3-yl]methyl]-benzoate (32b). A solution of 4,4,4-trifluoro-2-methylbutanamine (**14b**) (366 mg, 2.54 mmol), carboxylic acd **29**[23] (750 mg, 2.12 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (497 mg, 2.55 mmol), and 4-(dimethylamino)pyridine (260 mg, 2.12 mmol) in dichloromethane (11 mL) was stirred at room temperature for 18 h. The mixture was then diluted with dichloromethane (20 mL) and washed with 10% hydrochloric acid (25 mL), water (25 mL), and brine (25 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated to leave an amber oil. Purification by flash chromatography (1:3 ethyl acetate/hexane) yielded **32b** (640 mg, 1.34 mmol, 63%) as a white solid, mp 168–170 °C. ^{1}H NMR ($CDCl_3$): 8.02 (d, J = 1.4 Hz, 1H, H-C(4′)), 7.62 (dd, J = 1.4, 8.6 Hz, 1H, H-C(6′)), 7.54 (s, 1H, H-C(2)), 7.52 (d, J = 7.7 Hz, 1H, H-C(6)), 7.29 (d, J = 8.6 Hz, 1H, H-C(7′)), 7.14 (d, J = 7.7 Hz, 1H, H-C(5)), 6.83 (s, 1H, H-C(2′)), 6.21 (b, 1H, NH), 4.13 (s, 2H, indole-CH_2), 3.93 (s, 3H, CO_2CH_3), 3.90 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 3.52–3.34 (m, 2H, H-C(1″)), 2.40–2.07 (m, 2H, H-C(2″), H-C(3″)), 2.07–1.93 (m, 1H, H-C(3″)), 1.12 (d, J = 6.6 Hz, 3H, CH_3-C(2″)).

General Procedure for Preparation of Carboxylic Acids 35–37: Preparation of (*R,S*)-3-Methoxy-4-[[1-methyl-5-[(2-methyl-4,4,4-trifluorobutyl)carbamoyl]indol-3-yl]methyl]-benzoic Acid (35b). A solution of ester **32b** (640 mg, 1.34 mmol) in THF (3.5 mL) and methanol (3.5 mL) was treated with a solution of lithium hydroxide monohydrate (339 mg, 8.1 mmol) in water (1.3 mL). The mixture was stirred at room temperature for 18 h and then concentrated *in vacuo*. The aqueous residue was diluted with water (10 mL) and acidified to pH ~2 by addition of 3 N hydrochloric acid. The precipitate which formed was isolated by filtration, washed with water, and dried *in vacuo* (100 °C, 0.1 Torr) to give **35b** (547 mg, 1.18 mmol, 88%) as an ivory solid. ^{1}H NMR (DMSO-d_6): 8.44 (b, 1H, NH), 8.10 (d, J = 1.1 Hz, 1H, H-C(4′)), 7.69 (dd, J = 1.1, 8.6 Hz, 1H, H-C(6′)), 7.50–7.42 (m, 3H), 7.18–7.14 (m, 2H), 4.07 (s, 2H, indole-CH_2), 3.90 (s, 3H, OCH_3), 3.76 (s, 3H, NCH_3), 3.21 (m, H-C(1″)), 2.40–1.93 (m, 3H), 1.00 (d, J = 6.6 Hz, 3H, CH_3-C(2″)). CIMS: m/z 463 ((M + H)$^+$, 100), 445 (17), 443 (30), 322 (26).

General Procedure for Preparation of *N*-Acylsulfonamides 38–42: Preparation of 4-[[5-[((*R,S*)-2-Methyl-4,4,4-trifluorobutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (38b). A solution of carboxylic acid **35b** (250 mg, 0.54 mmol), 2-toluenesulfonamide (95 mg, 0.56 mmol), 1-[(3-dimethylamino)propyl]-3-ethylcarbodiimide (127 mg, 0.65 mmol), and 4-(dimethylamino)-pyridine (70 mg, 0.55 mmol) in dichloromethane (5 mL) was stirred at room temperature for 18 h. The mixture was then diluted with dichloromethane (25 mL) and washed with 3 N hydrochloric acid (3 × 25 mL) and water (3 × 25 mL). The organic extract was dried over $MgSO_4$, filtered, and diluted with hexane (50 mL). The precipitate which formed was isolated by filtration, washed with hexane, and dried *in vacuo* (50 °C, 0.5 Torr) to afford **38b** (189 mg, 0.31 mmol, 57%) as an ivory solid, mp 147–149 °C. ^{1}H NMR (DMSO-d_6): 8.41 (b, 1H, NH (amide)), 8.09 (d, J = 1.0 Hz, 1H, H-C(4′)), 8.03 (dd, J = 1.4, 7.9 Hz, 1H, H-C(6)), 7.69 (dd, J = 1.0, 8.6 Hz, 1H, H-C(6′)), 7.60–7.38 (m, 7H), 7.16 (d, J = 7.9 Hz, 1H, H-C(5)), 7.12 (s, 1H, H-C(2′)), 4.05 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 3.22 (m, 2H, H-C(1″)), 2.60 (s, 3H, $ArCH_3$), 2.36 (m, 1H), 2.11 (m, 2H), 1.00 (d, J = 6.6 Hz, 3H, CH_3-C(2″)). CIMS: m/z 616 ((M + H)$^+$, 1.4), 172 (19), 155 (5), 129 (4), 123 (9). Anal. $C_{31}H_{32}F_3N_3O_5S$: C,H,N.

Also prepared by this method were the following:

4-[[5-[(4,4,4-Trifluorobutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (38a). Mp 229–230 °C. ^{1}H NMR (DMSO-d_6): 8.39 (b, 1H, NH (amide)), 8.07 (d, J = 1.4 Hz, 1H, H-C(4′)), 8.03 (dd, J = 1.2, 7.9 Hz, 1H, H-C(6)), 7.68 (dd, J = 1.4, 8.6 Hz, 1H, H-C(6′)), 7.60–7.38 (m, 6H), 7.14 (d, J = 7.2 Hz, 1H, H-C(5)), 7.13 (s, 1H, H-C(2′)), 4.05 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 3.34 (m, 2H, H-C(1″)), 2.60 (s, 3H, $ArCH_3$), 2.38 (m, 2H, H-C(3″)), 1.75 (m, 2H, H-C(2″)). CIMS: m/z 602 ((M + H)$^+$, 7.3), 321 (22), 285 (11), 172 (18), 171 (16), 158 (12), 157 (43), 156 (29), 155 (15), 93 (100). Anal. $C_{30}H_{30}F_3N_3O_5S$: C,H,N.

4-[[5-[((*R,S*)-2-Ethyl-4,4,4-trifluorobutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)-sulfonyl]benzamide (38c). Mp 138–140 °C. ^{1}H NMR (DMSO-d_6): 8.41 (b, 1H, NH (amide)), 8.07 (s, 1H, H-C(4′)), 8.03 (d, J = 7.9 Hz, 1H, H-C(6)), 7.68 (d, J = 8.6 Hz, 1H, H-C(6′)), 7.60–7.38 (m, 7H), 7.15 (d, J = 7.9 Hz, 1H, H-C(5)), 7.13 (s, 1H, H-C(2′)), 4.05 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 3.22 (m, 2H, H-C(1″)), 2.60 (s, 3H, $ArCH_3$), 2.44–2.08 (m, 2H), 1.98 (m, 1H), 1.46 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H, CH_3CH_2). CIMS: m/z 631 ((M + H + 1)$^+$, 28), 630 ((M + H)$^+$, 79), 614 (20), 610 (12), 504 (21), 477 (47), 476 (93), 475 (40), 459 (50), 321 (37), 172 (100), 157 (65). Anal. $C_{32}H_{34}F_3N_3O_5S$: C,H,N.

4-[[5-[[2-(2,2,2-Trifluoroethyl)prop-2-enyl]carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)-sulfonyl]benzamide (38e). Mp 120–124 °C. ^{1}H NMR (DMSO-d_6): 8.60 (b t, 1H, (amide)), 8.13 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H, H-C(4′)), 7.72 (dd, J = 1.4, 8.6 Hz, 1H), 7.58–7.41 (m, 6H), 7.16 (d, J = 7.9 Hz, 1H, H-C(5)), 7.13 (s, 1H, H-C(2′)), 5.18 (s, 1H, H-C(3″)), 5.14 (s, 1H, H-C(3″)), 4.04 (s, 2H, indole-CH_2), 3.91 (b, 5H), 3.75 (s, 3H, N-CH_3), 3.16 (q, J = 10 Hz, 2H, CF_3CH_2), 2.50 (s, 3H, $ArCH_3$). CIMS: m/z 187 (100). Anal. $C_{31}H_{30}F_3N_3O_5S$: C,H,N.

4-[[5-[[[1-(2,2,2-Trifluoroethyl)cycloprop-1-yl]methyl]-carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (38f). Mp 135–138 °C. ^{1}H NMR (DMSO-d_6): 8.32 (b t, 1H, (amide)), 8.08 (s, 1H), 8.03 (d, J = 8.1 Hz, 1H, H-C(4′)), 7.69 (d, J = 8.1 Hz, 1H), 7.60–7.39 (m, 6H), 7.15 (d, J = 7.8 Hz, 1H, H-C(5)), 7.12 (s, 1H, H-C(2′)), 4.05 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.75 (s, 3H, N-CH_3), 2.60 (s, 3H, $ArCH_3$), 2.50 (m, 2H, H-C(1″)), 2.38 (q, J = 11.5 Hz, 2H, CF_3CH_2), 0.64 (m, 2H), 0.50 (m, 2H). CIMS: m/z 656 ((M + 29)$^+$, 17), 628 ((M + H)$^+$, 100). Anal. $C_{32}H_{32}F_3N_3O_5S \cdot 1.0H_2O$: C,H,N.

4-[[5-[(4,4,4-Trifluoro-2,2-dimethylbutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)-sulfonyl]benzamide (38g). Mp 133–138 °C. ^{1}H NMR (DMSO-d_6): 8.30 (b t, 1H, (amide)), 8.09 (s, 1H), 8.04 (d, J = 7.7 Hz, 1H, H-C(4′)), 7.71 (d, J = 8.5 Hz, 1H), 7.59–7.39 (m, 6H), 7.18–7.13 (m, 2H), 4.06 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.76 (s, 3H, N-CH_3), 3.23 (d, J = 5.0 Hz, 2H, H-C(1″)), 2.60 (s, 3H, $ArCH_3$), 2.57 (q, J = 12.6 Hz, 2H, H-C(3″)), 1.03 (s, 6H, CH_3-C(2″)). CIMS: m/z 658 ((M + 29)$^+$, 16), 630 ((M + H)$^+$, 100). Anal. $C_{32}H_{34}F_3N_3O_5S \cdot 0.33H_2O$: C,H,N.

4-[[5-((*R,S*)-2-Methyl-3,3,3-trifluoropropyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)-sulfonyl]benzamide (38h). Mp 139–142 °C. ^{1}H NMR (DMSO-d_6): 8.53 (b, 1H, NH (amide)), 8.08 (d, J = 1.2 Hz, 1H, H-C(4′)), 8.03 (dd, J = 1.2, 7.9 Hz, 1H), 7.70–7.38 (m, 7H), 7.14 (s, 1H, H-C(2′)), 7.14 (d, J = 7.9 Hz, 1H, H-C(5)), 4.05 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 3.53 (m, 1H, H-C(1″)), 3.31 (m, 1H, H-C(1″)), 2.70 (m, 1H, H-C(2″)), 2.59 (s, 3H, $ArCH_3$), 1.08 (d, J = 7.0 Hz, CH_3-C(2″)). CIMS: m/z 602 ((M + H)$^+$, 0.2), 172 (10), 155 (3). Anal. $C_{30}H_{30}F_3N_3O_5S \cdot 0.3H_2O$: C,H,N.

4-[[5-[[(*R,S*)-2-(Trifluoromethyl)hexyl]carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (38j). Mp 123–125 °C. ^{1}H NMR (DMSO-d_6): 8.51 (b, 1H, NH (amide)), 8.05 (d, J = 1.3 Hz, 1H, H-C(4′)), 8.02 (dd, J = 1.2, 7.9 Hz, 1H), 7.68–7.38 (m, 6H), 7.14 (s, 1H, H-C(2′)), 7.13 (d, J = 7.9 Hz, 1H, H-C(5)), 4.04 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 3.40 (m, 2H, H-C(1″)), 2.59 (s, 3H, $ArCH_3$), 1.51–1.24 (m, 6H), 0.82 (t, J = 7.2 Hz, H-C(6″)). CIMS: m/z 644 ((M + H)$^+$, 11.8), 225 (10), 172 (34), 155 (30), 151 (31), 129 (51), 123 (100), 112 (14). Anal. $C_{33}H_{36}F_3N_3O_5S \cdot 0.2H_2O$: C,H,N.

4-[[5-[(4,4,4-Trifluoro-2-methylbut-2-enyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)-sulfonyl]benzamide (38k). Mp 125–130 °C. ^{1}H NMR (DMSO-d_6): 8.60 (b t, 1H, (amide)), 8.11 (s, 1H), 8.02 (d, J = 7.2 Hz, 1H, H-C(4′)), 7.57 (d, J = 8.6 Hz, 1H), 7.51–7.38 (m, 6H), 7.15 (d, J = 8.1 Hz, 1H, H-C(5)), 7.13 (s, 1H, H-C(2′)), 5.81 (q, J = 10 Hz, 1H, H-C(3″)), 4.15 (b s, 2H, H-C(1″)), 4.04 (s, 2H, indole-CH_2), 3.90 (s, 3H, OCH_3), 3.75 (s, 3H, N-CH_3), 2.59 (s, 3H, $ArCH_3$), 1.81 (b s, 3H, CH_3-C(2)). CIMS: m/z 642 ((M + 29)$^+$, 18), 614 ((M + H)$^+$, 100). Anal. $C_{31}H_{30}F_3N_3O_5S$: C,H,N.

4-[[5-[[(3,3,4,4-Tetrafluorocyclopent-1-yl)methyl]carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (38l). Mp 157–161 °C. ^{1}H NMR (DMSO-d_6): 8.48 (b, 1H, (amide)), 8.07 (d, J = 1.3 Hz, 1H), 8.03 (dd, J = 1.2, 8.0 Hz, 1H, H-C(4′)), 7.67 (dd, J = 1.6, 8.7 Hz, 1H), 7.61–7.38 (m, 6H), 7.14 (d, J = 7.5 Hz, 1H, H-C(5)), 7.13 (s, 1H, H-C(2′)), 4.04 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.75 (s, 3H, N-CH_3), 3.40–3.26 (m, 2H), 2.60 (s, 3H, ArCH_3), 2.58–2.43 (m, 3H), 2.23–2.13 (m, 2H). CIMS: m/z 646 ((M + H)$^+$, <1), 79 (100). Anal. $C_{32}H_{31}F_4N_3O_5S$: C,H,N.

4-[[5-[[(*R,S*)-3-(Trifluoromethyl)butyl]carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (38m). Mp 203–204 °C. ^{1}H NMR (DMSO-d_6): 8.43 (b, 1H, NH (amide)), 8.07 (d, J = 1.3 Hz, 1H, H-C(4′)), 8.03 (dd, J = 1.2, 7.9 Hz, 1H), 7.69–7.38 (m, 7H), 7.14 (d, J = 6.9 Hz, 1H, H-C(5)), 7.13 (s, 1H, H-C(2′)), 4.05 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 3.35 (b s, 2H, H-C(1″)), 2.60 (s, 3H, ArCH_3), 2.46 (m, 1H, H-C(3″)), 1.93 (m, 1H, H-C(2″)), 1.50 (m, 1H, H-C(2″)), 1.12 (d, J = 6.9 Hz, 3H, H-C(4″)). CIMS: m/z 616 ((M + H)$^+$, 78), 475 (58), 445 (100), 172 (49). Anal. $C_{31}H_{32}F_3N_3O_5S$: C,H,N.

4-[[5-[[4,4,4-Trifluoro-3-(trifluoromethyl)butyl]carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (38n). Mp 159–162 °C. ^{1}H NMR (DMSO-d_6): 8.53 (b, 1H, (amide)), 8.06 (d, J = 1.4 Hz, 1H), 8.03 (dd, J = 1.3, 6.7 Hz, H-C(4′)), 7.58–7.38 (m, 6H), 7.13 (d, J = 7.80 Hz, 1H, H-C(5)), 7.13 (s, 1H, H-C(2′)), 4.07–4.00 (m, 1H), 4.04 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.75 (m, 3H, NCH_3), 3.46–3.40 (m, 2H), 2.60 (s, 3H, ArCH_3), 2.03 (m, 2H). CIMS: m/z 670 ((M + H)$^+$, < 1), 93 (100). Anal. $C_{31}H_{29}F_6N_3O_5S$: C,H,N.

4-[[5-[((*R,S*)-2-Ethyl-4,4,4-trifluorobutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-bromophenyl)-sulfonyl]benzamide (39c). Mp 134–136 °C. ^{1}H NMR (DMSO-d_6): 8.39 (b, 1H, NH (amide)), 8.20 (dd, J = 1.8, 7.8 Hz, 1H), 8.09 (d, J = 1.4 Hz, 1H, H-C(4′)), 7.83 (d, J = 7.9 Hz, 1H, H-C(6)), 7.70–7.56 (m, 6H), 7.43 (m, 2H), 7.15 (d, J = 7.9 Hz, 1H, H-C(5)), 7.13 (s, 1H, H-C(2′)), 4.05 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 3.26 (m, 2H, H-C(1″)), 2.44-2.08 (m, 2H), 1.93 (m, 1H), 1.41 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H, CH_3CH_2). CIMS: m/z 696 ((M + H)$^+$, ^{81}Br, 81), 694 ((M + H)$^+$, ^{79}Br, 81), 676 (13), 674 (13), 642 (14), 616 (16), 615 (23), 614 (66), 541 (26), 539 (23), 505 (34), 504 (17), 477 (35), 460 (28), 459 (100), 458 (32), 457 (11), 325 (11). Anal. $C_{31}H_{31}BrF_3N_3O_5S$: C,H,N.

4-[[5-[((*R,S*)-2-Methyl-4,4,4-trifluorobutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-chlorophenyl)-sulfonyl]benzamide (40b). Mp 199–200 °C. ^{1}H NMR (DMSO-d_6): 8.39 (b, 1H, NH (amide)), 8.17 (dd, J = 1.5, 7.8 Hz, 1H), 8.09 (s, 1H, H-C(4′)), 7.71–7.40 (m, 7H), 7.15 (d, J = 7.9 Hz, 1H, H-C(5)), 7.13 (s, 1H, H-C(2′)), 4.05 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 3.21 (m, 2H, H-C(1″)), 2.38 (m, 1H), 1.93 (m, 2H), 1.00 (d, J = 5,8 Hz, 3H, CH_3-C(2″)). CIMS: m/z 638 ((M + H)$^+$, ^{37}Cl, 20), 636 ((M + H)$^+$, ^{35}Cl, 57), 616 (15), 497 (11), 495 (23), 445 (42), 321 (11), 192 (13), 113 (34). Anal. $C_{30}H_{29}ClF_3N_3O_5S$: C,H,N.

4-[[5-[((*R,S*)-2-Methyl-4,4,4-trifluorobutyl)carbamoyl]-1-ethylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)-sulfonyl]benzamide (41b). Mp 138–140 °C. ^{1}H NMR (DMSO-d_6): 8.42 (b, 1H, NH (amide)), 8.08 (d, J = 1.3 Hz, 1H, H-C(4′)), 8.03 (dd, J = 1.3, 7.9 Hz, 1H), 7.69–7.38 (m, 6H), 7.21 (s, 1H, H-C(2′)), 7.14 (d, J = 7.9 Hz, 1H, H-C(5)), 4.17 (q, J = 6.9 Hz, 2H, NCH_2CH_3), 4.05 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.20 (m, 2H, H-C(1″)), 2.60 (s, 3H, ArCH_3), 2.38 (m, 1H, H-C(2″)), 2.10 (m, 2H, H-C(3″)), 1.31 (t, J = 6.9 Hz, 3H, NCH_2CH_3), 0.99 (d, J = 6.0 Hz, 3H, CH_3-C(2″)). CIMS: m/z 630 ((M + H)$^+$, 22), 212 (16), 172 (63), 157 (64), 155 (20), 139 (19), 123 (12), 72 (100). Anal. $C_{32}H_{34}F_3N_3O_5S$0.2 H_2O: C,H,N.

4-[[5-[[(*R,S*)-2-(Trifluoromethyl)butyl]carbamoyl]-1-ethylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)sulfonyl]benzamide (41i). Mp 175–178 °C. ^{1}H NMR (DMSO-d_6): 8.48 (b, 1H, NH (amide)), 8.06 (s, 1H, H-C(4′)), 8.03 (d, J = 7.9 Hz, 1H), 7.68–7.38 (m, 7H), 7.22 (s, 1H, H-C(2′)), 7.14 (d, J = 7.9 Hz, 1H, H-C(5)), 4.17 (q, J = 7.2 Hz, 2H, NCH_2CH_3), 4.05 (s, 2H, indole-CH_2), 3.91 (s, 3H, OCH_3), 3.46 (m, 2H, H-C(1″)), 2.56 (s, 3H, ArCH_3), 2.54 (m, 1H, H-C(2″)), 1.58 (m, 2H, H-C(3″)), 1.32 (t, J = 7.2 Hz, 3H, NCH_2CH_3), 0.99 (t, J = 7.4 Hz, 3H, H-C(4″)). CIMS: m/z 630 ((M + H)$^+$, 1), 198 (18), 172 (10), 72 (11). Anal. $C_{32}H_{34}F_3N_3O_5S$: C,H,N.

4-[[5-[((*R,S*)-2-Methyl-4,4,4-trifluorobutyl)carbamoyl]-1-propylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)-sulfonyl]benzamide (42b). Mp 138–140 °C. ^{1}H NMR (DMSO-d_6): 8.41 (b, 1H, NH (amide)), 8.06 (d, J = 1.3 Hz, 1H, H-C(4′)), 8.02 (d, J = 7.9 Hz, 1H), 7.68–7.37 (m, 7H), 7.19 (s, 1H, H-C(2′)), 7.12 (d, J = 7.9 Hz, 1H, H-C(5)), 4.10 (t, J = 6.8 Hz, 2H, $NCH_2CH_2CH_3$), 4.05 (s, 2H, indole-CH_2), 3.90 (s, 3H, OCH_3), 3.20 (m, 2H, H-C(1″)), 2.59 (s, 3H, ArCH_3), 2.38 (m, 1H, H-C(2″)), 2.05 (m, 2H, H-C(3″)), 1.74 (sxt, J = 6.8 Hz, 2H, $NCH_2CH_2CH_3$), 0.99 (d, J = 6.0 Hz, 3H, CH_3-C(2″)), 0.80 (t, J = 6.8 Hz, 3H, $NCH_2CH_2CH_3$). CIMS: m/z 644 ((M + H)$^+$, 55), 172 (11), 129 (10), 123 (20), 72 (100). Anal. $C_{33}H_{36}F_3N_3O_5S$: C,H,N.

4,4,4-Trifluorobutyryl Chloride (22b). *N,N*-Dimethylformamide (1.0 mL) and oxalyl chloride (347 g, 2.74 mol) were added to a 0 °C solution of 4,4,4-trifluorobutyric acid (343 g, 2.44 mol) in dichloromethane (230 mL). The solution was warmed to room temperature and stirred for 16 h. The dichloromethane was removed by distillation and the residue further distilled to yield 4,4,4-trifluorobutyryl chloride (328 g, 2.27 mol, 85%) as a clear liquid, bp 103–106 °C. ^{1}H NMR ($CDCl_3$): 3.19 (t, 2H, H-C(2)), 2.47–2.64 (m, 2H, H-C(3)).

(4*R*,5*S*)-3-(1-Oxo-4,4,4-trifluorobutyl)-4-methyl-5-phenyl-2-oxazolidinone (27). A solution of (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone (353 g, 2.00 mol) in THF (2.5 L) was cooled to −78 °C and treated with *n*-butyllithium (1.33 L of a 1.5 M solution in hexane, 2.00 mol). The solution was stirred at −70 °C for 15 min and then treated with 4,4,4-trifluorobutyryl chloride (320 g, 2.21 mol), added over 30 min. The mixture was allowed to warm to room temperature and then was stirred for 16 h. The solvent was evaporated, and the residue was partitioned between diethyl ether (2 L) and water (500 mL). The ether extract was washed with 1 N hydrochloric acid (500 mL) and brine (2 × 500 mL), dried over $MgSO_4$, filtered, and evaporated to yield crude product (604 g, >100%). Filtration through 3000 cc of silica gel using 1:1 dichloromethane/hexane as eluent afforded a white solid, which was recrystallized from dichloromethane/hexane to afford the pure acyloxazolidinone **27** (519 g, 1.72 mol, 86%) as white needles, mp 93–95 °C. ^{1}H NMR ($CDCl_3$): 7.30–7.44 (m, 5H, ArH), 5.70 (d, 1H, H-C(5)), 4.78 (p, 1H, H-C(4)), 3.18–3.40 (m, 2H, H-C(2′)), 2.45–2.65 (m, 2H, H-C(3′)), 0.91 (d, 3H, CH_3).

(4*R*,5*S*)-3-((2*R*)-2-Methyl-1-oxo-4,4,4-trifluorobutyl)-4-methyl-5-phenyl-2-oxazolidinone (28). A solution of sodium bis(trimethylsilylamide) (1.9 L of a 1 M solution in THF, 1.9 mol) in THF was cooled to −40 °C and treated with a solution of (4*R*,5*S*)-3-(1-oxo-4,4,4-trifluorobutyl)-4-methyl-5-phenyl-2-oxazolidinone (**27**) (517 g, 1.72 mol) in THF (800 mL). The mixture was maintained at −40 °C for 0.5 h and then warmed to −35 °C over an additional 0.5 h. This mixture was then treated with iodomethane (320 g, 2.26 mol) over approximately 15 min, maintaining the internal reaction temperature between −35 and −30 °C. The reaction mixture was then stirred for an additional 2 h at −30 °C, and the cold reaction mixture was then poured into chilled aqueous ammonium chloride (700 mL). The aqueous mixture was extracted with diethyl ether (1 L). The organic extract was washed with aqueous sodium bisulfate (2.0 L) and brine, and the aqueous washes were extracted with 1:1 dichloromethane/diethyl ether (2 L) and dichloromethane (1 L). The organic extracts were dried ($MgSO_4$), filtered, and evaporated to yield crude product as a reddish oil (595 g). Filtration through silica gel (3000 cc), using a gradient of 1–5% ethyl acetate in hexanes as eluent, afforded a white solid which was a mixture of the desired product **28**, its diastereomer **29**, and starting material **27**. Crystallization of this solid from diethyl ether/hexanes afforded (4*R*,5*S*)-3-((2*R*)-1-oxo-2-methyl-4,4,4-trifluorobutyl)-4-methyl-5-phenyl-2-oxazolidone (**28**) (370 g, 1.17 mol, 68%) as a white solid, mp 68–70 °C. ^{1}H NMR ($CDCl_3$): 7.26–7.44 (m, 5H, ArH), 5.71 (d, 1H, H-C(5)), 4.79 (p, 1H, H-C(4)), 4.03–4.17 (m, 1H, H-C(2′)), 2.74–2.97 (m, 1H, H-C(3′)), 2.10–2.31 (m, 1H, H-C(3′)), 1.33 (d, 3H, CH_3-C(2′)), 0.89 (d, 3H, CH_3-C(4)).

(*R*)-2-Methyl-4,4,4-trifluorobutan-1-ol (10p). Lithium aluminum hydride (10.26 g, 0.27 mol) was added to a stirred solution of (4*R*,5*S*)-3-((2*R*)-1-oxo-2-methyl-4,4,4-trifluorobutyl)-4-methyl-5-phenyl-2-oxazolidone (**28**) (28.0 g, 88.9 mmol) in dry diethyl ether (200 mL) at −20 °C. The mixture was then allowed

Also prepared by an analogous route from **45** was the following:

4-[[6-[((*R,S*)-4,4,4-Trifluoro-2-methylbutyl)carbamoyl]-3-methylindol-1-yl]methyl]-3-methoxy-*N*-[(2-chlorophenyl-)sulfonyl]benzamide (54b). Mp 120–123 °C. ^{1}H NMR (DMSO-d_6): 8.44 (b t, 1H, (amide)), 8.16 (d, 1H), 7.91 (s, 1H), 7.38 (d, 1H), 7.34 (s, 1H), 6.63 (d, 1H), 5.40 (s, 2H, indole-CH_2), 3.95 (s, 3H, OCH_3), 3.20 (b t, 2H, H-C(1″)), 2.46–2.36 (m, 1H, H-C(2″)), 2.28 (s, 3H, CH_3-C(3′)), 2.17–2.04 (m, 2H, H-C(3″)), 0.99 (d, 3H, CH_3-C(2″)). CIMS: *m/z* 664 ((M + 29)$^+$, 12), 636 (M + H)$^+$, 100). Anal. $C_{30}H_{29}ClF_3N_3O_5S$: C,H,N.

Also prepared by an analogous route from **43** were the following:

4-[[6-[((*R,S*)-4,4,4-Trifluoro-2-methylbutyl)carbamoyl]-indol-1-yl]methyl]-3-methoxy-*N*-(2-methylphenyl)sulfonyl]-benzamide (51b). Mp 150–152 °C. ^{1}H NMR (DMSO-d_6): 8.45 (b t, 1H, (amide)), 8.02 (dd, J = 1.0, 8.0 Hz, 1H), 7.95 (s, 1H), 7.64–7.55 (m, 5H), 7.46–7.34 (m, 3H), 6.64 (d, J = 7.9 Hz, 1H), 6.57 (d, J = 3.1 Hz, 1H), 5.48 (s, 2H, indole-CH_2), 3.95 (s, 3H, OCH_3), 3.20 (b s, 2H, H-C(1″)), 2.58 (s, 3H, $ArCH_3$), 2.5–2.0 (m, 3H), 0.98 (d, J = 5.8 Hz, 3H, CH_3-C(2″)). CIMS: *m/z* 602 ((M + H)$^+$, 5), 157 (100). Anal. $C_{30}H_{30}F_3N_3O_5S$ C,H,N.

4-[[6-[((*R,S*)-4,4,4-Trifluoro-2-methylbutyl)carbamoyl]-indol-1-yl]methyl]-3-methoxy-*N*-[(2-chlorophenyl)sulfonyl]-benzamide (53b). Mp 170–171 °C. ^{1}H NMR (DMSO-d_6): 8.45 (b s, 1H, (amide)), 8.16 (d, J = 7.1 Hz, 1H), 7.96 (s, 1H), 7.73–7.56 (m, 7H), 7.37 (d, J = 7.3 Hz, 1H), 6.56 (d, J = 3.1 Hz, 1H), 6.32 (d, J = 7.9 Hz, 1H), 5.47 (s, 2H, indole-CH_2), 3.95 (s, 3H, OCH_3), 3.20 (b s, 2H, H-C(1″)), 2.50–2.33 (m, 1H), 2.20–2.07 (m, 2H), 0.98 (d, J = 5.9 Hz, 3H, CH_3-C(2″)). CIMS: *m/z* 622 ((M + H)$^+$, 3), 177 (100). Anal. $C_{29}H_{27}ClF_3N_3O_5S$: C,H,N.

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(*R*)-2-(2-Methyl-4,4,4-trifluorobutyl)-1*H*-isoindole-1,3-(2*H*)-dione (11p). A suspension of alcohol **10p** (ca. 12.0 g, 85 mmol), phthalimide (13.4 g, 91.2 mmol), and triphenylphosphine (23.7 g, 90.5 mmol) in tetrahydrofuran (110 mL) was cooled to 0 °C and treated with diethyl azodicarboxylate (17.0 g, 97.8 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was then evaporated and the residue suspended in dichloromethane and filtered, and the filtrate was evaporated. The residue was purified by flash chromatograpy (1:1 dichloromethane/hexane) to afford pure **11p** (17.1 g, 63.1 mmol, 74%) as a white solid, mp 45–47 °C. ^{1}H NMR ($CDCl_3$): 3.64 (dd, 1H, CH_2N), 3.58 (dd, 1H, CH_2N), 2.36–2.50 (m, 1H, $CHCH_3$), 2.14–2.31 (m, 1H, CF_3CH_2), 1.94–2.07 (m, 1H, CF_3CH_2), 1.08 (d, 3H, CH_3).

(*R*)-2-Methyl-4,4,4-trifluorobutylamine Hydrochloride (14p). Hydrazine monohydrate (3.2 g, 63.9 mmol) was added to a stirred solution of 2-((2*R*)-2-methyl-4,4,4-trifluorobutyl)-1*H*-isoindole-1,3(2*H*)-dione (17.1 g, 63.1 mmol) in anhydrous ethanol (85 mL), and the solution was heated to reflux temperature. After 3 h at reflux, the mixture was cooled, diluted with ethanol (40 mL), acidifed to pH ~1 by addition of concentrated hydrochloric acid, and filtered. The filtrate was evaporated to afford crude **14p**, which was purified by sublimation (bath temperture 170 °C, 6.6 Pa) to yield pure (2*R*)-2-methyl-4,4,4-trifluorobutylamine hydrochloride (9.89 g, 55.7 mmol, 88%) as a white solid, mp 187–191 °C. ^{1}H NMR (DMSO-d_6/D_2O): 8.20 (b s, 2H, NH_2), 2.87 (dd, 1H, CH_2N), 2.73 (dd, 1H, CH_2N), 2.36–2.54 (m, 1H, $CHCH_3$), 2.06–2.36 (m, 2H, CF_3CH_2), 1.05 (d, 3H, CH_3).

Methyl (*R*)-3-Methoxy-4-[[1-methyl-5-[(2-methyl-4,4,4-trifluorobutyl)carbamoyl]indol-3-yl]methyl]benzoate (32p). A mixture of **14p** (9.79 g, 55.2 mmol), **29** (20.55 g, 58.2 mmol), 4-(dimethylamino)pyridine (7.45 g, 61.0 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (15.07 g, 79.2 mmol), and triethylamine (6.75 g, 66.7 mmol) in dichloromethane (240 mL) was stirred for 18 h. The mixture was then diluted with dichloromethane (200 mL) and washed with 1 N hydrochloric acid (2×). The combined aqueous washes were extracted with dichloromethane. The organic extracts were combined, washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash chromatography (97:3 dichloromethane/ethyl acetate) to give **32p** (14.48 g, 30.4 mmol, 55%) as a white solid, mp 150–151 °C. ^{1}H NMR ($CDCl_3$): 6.23 (b t, 1H, (amide)), 4.13 (s, 2H, indole-CH_2), 3.93 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.76 (s, 3H, NCH_3), 3.30–3.58 (m, 2H, CH_2N), 2.12–2.44 (m, 2H, CF_3CH_2), 1.98–2.08 (m, 1H, $CHCH_3$), 1.12 (d, 3H, CH_3).

(*R*)-3-Methoxy-4-[[1-methyl-5-[(2-methyl-4,4,4-trifluorobutyl)carbamoyl]indol-3-yl]methyl]benzoic Acid (35p). A solution of lithium hydroxide monohydrate (7.68 g, 183 mmol) in water (50 mL) was added to a stirred solution of **32p** (14.38 g, 30.2 mmol) in methanol (120 mL) and THF (120 mL). The mixture was stirred for 18 h and then concentrated and the residue dissolved in water (250 mL) and THF (23 mL). Upon acidification to pH 1 by addition of concentrated hydrochloric acid, a precipitate formed, which was isolated by filtration and washed with water to give **35p** (14.2 g, 30.2 mmol, 100%) as a white solid, mp 218–223 °C. ^{1}H NMR (DMSO-d_6): 8.43 (b t, 1H, (amide)), 4.07 (s, 2H, $ArCH_2Ar'$), 3.90 (s, 3H, OCH_3), 3.76 (s, 3H, NCH_3), 3.21 (b t, 2H, CH_2N), 2.32–2.44 (m, 1H, $CHCH_3$), 2.04–2.28 (m, 2H, CF_3CH_2), 1.00 (d, 3H, CH_3).

4-[[5-[(2*R*)-2-Methyl-4,4,4-trifluorobutyl)carbamoyl]-1-methylindol-3-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)-sulfonyl]benzamide (38p). A mixture of **35p** (14.2 g, 30.2 mmol), 4-(dimethylamino)pyridine (4.39 g, 35.9 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (8.34 g, 43.7 mmol), and 2-methylbenzenesulfonamide (5.85 g, 34.2 mmol) in dichloromethane (270 mL) was stirred for 48 h. The mixture was then diluted with dichloromethane (300 mL) and washed with 1 N hydrochloric acid (3×). The combined aqueous washes were extracted with dichloromethane. The combined organic extracts were washed with water (2×), dried over $MgSO_4$, filtered, and evaporated. The residue was purified by reversed-phase flash chromatography (Regis ODS, 450 g, 50:50 methanol/water (pH 7.1)) to give **38p** (16.7 g, 27.2 mmol, 88%) as a white solid, mp 117–120 °C. ^{1}H NMR spectrum was indistinguishable from that of the racemate **38b**. Anal. $C_{31}H_{32}N_3O_5SF_3$ C,H,N.

Methyl 4-[[6-[((*R,S*)-4,4,4-Trifluoro-2-methylbutyl)carbamoyl]-3-methylindol-1-yl]methyl]-3-methoxybenzoate (48b). A solution of (*R,S*)-4,4,4-trifluoro-2-methylbutylamine hydrochloride (**14b**) (378 mg, 2.13 mmol), methyl 3-methoxy-4-[(3-methyl-6-carboxyindol-1-yl)methyl]benzoate (**45**) (775 mg, 2.20 mmol), 4-(dimethylamino)pyridine (286 mg, 2.34 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (570 mg, 2.98 mmol), and triethylamine (254 mg, 2.51 mmol) in dichloromethane (10 mL) was stirred at room temperature for 18 h. The mixture was diluted with dichloromethane (50 mL), washed with 1 N hydrochloric acid (25 mL), dried over Na_2SO_4, filtered, and evaporated to leave an amber foam. Purification by chromatography (97:3 dichloromethane/ethyl acetate) afforded **48b** (757 mg, 1.60 mmol, 75%) as a white solid, mp 105–107 °C. ^{1}H NMR ($CDCl_3$): 7.87 (s, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.55 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.28 (d, 1H), 7.04 (s, 1H), 6.64 (d, 1H), 6.27 (b t, 1H, (amide)), 5.35 (s, 2H, indole-CH_2), 3.96 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.53–3.31 (m, 2H, H-C(1″)), 2.35 (s, 3H, CH_3-C(3′)), 2.31–1.91 (m, 3H), 1.11 (d, 3H, CH_3-C(2″)). CIMS: m/z 505 ((M + 29)$^+$, 10), 477 ((M + H)$^+$, 100).

4-[[6-[((*R,S*)-4,4,4-Trifluoro-2-methylbutyl)carbamoyl]-3-methylindol-1-yl]methyl]-3-methoxybenzoic Acid (50b). A solution of methyl 4-[[6-[(4,4,4-trifluoro-2-methylbutyl)carbamoyl]-3-methylindol-1-yl]methyl]-3-methoxybenzoate (**48b**) (300 mg, 0.65 mmol) in methanol (4.5 mL), THF (4.5 mL), and water (3.0 mL) was treated with lithium hydroxide monohydrate (386 mg, 9.19 mmol). The mixture was stirred at room temperature for 18 h and then concentrated. The aqueous residue was diluted with water (5 mL) and acidified to pH 2 by addition of 1 N hydrochloric acid. The white precipitate was isolated by filtration, washed with water, and dried *in vacuo* to give **50b** (267 mg, 0.61 mmol, 94%) as a white solid. ^{1}H NMR (DMSO-d_6): 8.46 (b t, 1H, (amide)), 7.92 (s, 1H), 7.58 (d, 2H), 7.53 (d, 1H), 7.42 (dd, 1H), 7.35 (d, 1H), 6.66 (d, 1H), 5.41 (s, 2H, indole-CH_2), 3.94 (s, 3H, OCH_3), 3.20 (b t, 2H, H-C(1″)), 2.28 (s, 3H, CH_3-C(3′)), 0.99 (d, 3H, CH_3-C(2″)).

4-[[6-[((*R,S*)-4,4,4-Trifluoro-2-methylbutyl)carbamoyl]-3-methylindol-1-yl]methyl]-3-methoxy-*N*-[(2-methylphenyl)-sulfonyl]benzamide (52b). A solution of 4-[[6-[(4,4,4-trifluoro-2-methylbutyl)carbamoyl]-3-methylindol-1-yl]methyl]-3-methoxybenzoic acid (**50b**) (300 mg, 0.65 mmol), 4-(dimethylamino)pyridine (93 mg, 0.76 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (175 mg, 0.91 mmol), and 2-methylbenzenesulfonamide (123 mg, 0.72 mmol) in dichloromethane (7 mL) was stirred at room temperature for 18 h. The mixture was then diluted with dichloromethane (50 mL) and washed with 1 N hydrochloric acid (2 × 25 mL). The aqueous washes were extracted with dichloromethane (50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and evaported to leave an off-white foam. Purification by reversed-phase flash chromatography (Regis ODS, 45:55 methanol/water) afforded **52b** (306 mg, 0.49 mmol, 76%) as a white solid, mp 112–114 °C. ^{1}H NMR (DMSO-d_6): 8.02 (d, 1H), 7.90 (s, 1H), 7.61–7.51 (m, 4H), 7.48–7.31 (m, 4H), 6.63 (d, 1H), 5.44 (b t, 1H, (amide)), 5.39 (s, 2H, indole-CH_2), 3.94 (s, 3H, OCH_3), 3.20 (b t, 2H, H-C(1″)), 2.58 (s, 3H, $ArCH_3$), 2.27 (s, 3H, CH_3-C(3′)), 2.47–2.31 (m, 1H), 2.20–2.00 (m, 2H), 0.99 (d, 3H, CH_3-C(2″)). CIMS: m/z 644 ((M + 29)$^+$, 13), 616 ((M + H)$^+$, 100). Anal. $C_{31}H_{32}F_3N_3O_5S$: C,H,N.

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(39) Compounds L-688,018 and L-688,019 were reported to have IC_{50} values of 3.1 ± 0.9 and 8.0 ± 3.1 nM as inhibitors of binding of [^{3}H]LTD_4 to guinea pig lung membranes. See ref 5.

(40) The ED_{50} values of L-668,018 and L-688,019 were reported to be 0.097 and 0.028 mg/kg, respectively. This difference was not judged to be significant. See ref 5.

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