3-(2-(3-Pyridinyl)thiazolidin-4-oyl)indoles, a Novel Series of Platelet Activating Factor Antagonists[1]

George S. Sheppard,* Daisy Pireh, George M. Carrera, Jr., Mark G. Bures,† H. Robin Heyman, Douglas H. Steinman, Steven K. Davidsen, James G. Phillips, Denise E. Guinn, Paul D. May, Richard G. Conway, David A. Rhein, William C. Calhoun, Daniel H. Albert, Terrance J. Magoc, George W. Carter, and James B. Summers

Immunosciences Research Area, Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, Illinois 60064

Received March 8, 1994®

(2*RS*,4*R*)-3-(2-(3-Pyridinyl)thiazolidin-4-oyl)indoles represent a new class of potent, orally active antagonists of platelet activating factor (PAF). The compounds were prepared by acylation of the magnesium or zinc salts of substituted indoles with (2*RS*,4*R*)-2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl chloride. The 3-acylindole moiety functions as a hydrolytically stabilized and conformationally restricted anilide replacement, which imparts a considerable boost in potency to the series. Structure–activity relationships observed for substitution on the indole ring system are discussed. Members of the series compare favorably with other reported PAF antagonists.

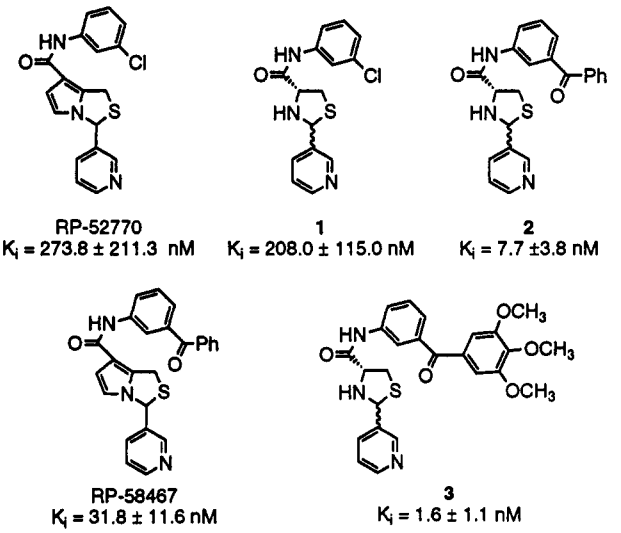
Introduction

Platelet activating factor ((2*R*)-1-*O*-octadecyl(or hexadecyl)-2-acetylglycero-3-phosphocholine), hereafter referred to as PAF, is an endogenous phospholipid inflammatory mediator.[2] In rabbit and human neutrophils and platelets, the C_{16}-PAF predominates. Inflammatory cells such as alveolar macrophages, eosinophils, platelets, and neutrophils generate PAF in response to inflammatory and immune stimuli.[3]

PAF exerts its influence by acting on specific receptors found in a variety of cell types. The measurement of direct [^{3}H]PAF binding has now been carried out on many tissues/cell types from a range of species, and the guinea pig lung and human leukocyte receptors have recently been cloned.[4,5] Most studies have observed a single class of high-affinity binding sites, and southern blotting studies have revealed only a single gene copy.[6] In addition, the reported relative binding potencies for PAF analogs and antagonists across various tissue preparations have been fairly consistent; however, there have been some suggestions in the literature of multiple conformational states in PAF receptors,[7] as well as indications of multiple PAF receptors.[8-11] At this time it is unclear if these postulates have any clinical importance.

PAF possesses many potent proinflammatory activities and consequently may be an important mediator in a wide range of pathological conditions that have inflammatory components.[12] Among the biological responses linked to PAF are increased vascular permeability, hemoconcentration, hypotension, ulcerogenesis, bronchoconstriction, the triggering of airway hyperresponsiveness, and platelet degranulation. Potential indications for PAF antagonists therefore include septic shock,[13] asthma,[14] ischemia/reperfusion injury,[15] and various inflammatory diseases. In view of the potent pathophysiologic effects of PAF and the broad scope of diseases in which it may play a role, there appears to be therapeutic potential for agents that will prevent the actions of PAF. As a result, many research groups have identified PAF antagonists representing a wide variety of structural classes.[16]

Chart 1



Initial Studies

In an effort to identify novel and potent PAF antagonists, we initiated a research program involving both a screening effort and evaluation of previously identified classes of PAF antagonists.[17] It was found that the thiazolidine compound 1, an analog of the known PAF antagonist RP-52770[18] lacking the fused pyrrole ring, displayed high affinity for the PAF receptor (Chart 1). Likewise, compounds 2 and 3 proved to be more potent than the structurally related RP-58467.[18] A number of similar compounds were prepared and evaluated.[19] A related series of pyridylthiazolidines was independently reported by workers at Yamanouchi Pharmaceutical Company, Ltd.[20]

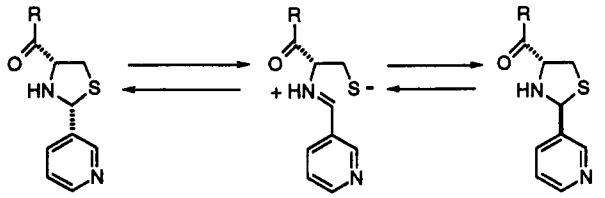
While the change from pyridylpyrrolothiazoles to pyridylthiazolidines provided a novel series with improved PAF binding affinity, it introduced new challenges as well. Removal of the fused pyrrole ring from the pyrrolothiazole introduces a second stereogenic atom to the structure, as well as the possibility of thioaminal fragmentation. It was quickly established that the preferred configuration at C-4 was *R*, as the 4*S* enantiomer of 1 was essentially inactive in our receptor binding assay.[21] All further work

† Computer-Assisted Molecular Design, D-47E, Abbott Laboratories, Abbott Park, IL 60064.

® Abstract published in *Advance ACS Abstracts*, May 15, 1994.

0022-2623/94/1837-2011$04.50/0

Scheme 1



was therefore carried out using material derived from (*R*)-cysteine (*vide infra*).

In 2,4-disubstituted thiazolidines, the *cis* and *trans* diastereomers freely interconvert in solution.[22] The ratio of diastereomers observed for compounds in the present study was typically 3:2–1:1 with the *trans* (4*R*,2*S*) diastereomer predominating, based on ^{1}H NMR spectroscopy.[23] Diastereomerization occurs at the C-2 center via an iminium intermediate (Scheme 1). This property prevents the independent examination of the biological properties of the two diastereomers; hence, the structures will be drawn and discussed throughout this paper as a diastereomeric mixture. In addition, hydrolysis of the iminium intermediate can occur, although reportedly at a rate slower than diastereomerization in the pH range of 1–12.[24] Such ring hydrolysis could reduce the duration of action of compounds with this structural feature; however, thiazolidine-4-carboxylic acids have been reported to be stable under physiological conditions.[25] Studies to address these features of the thiazolidine ring system have been reported separately.[26]

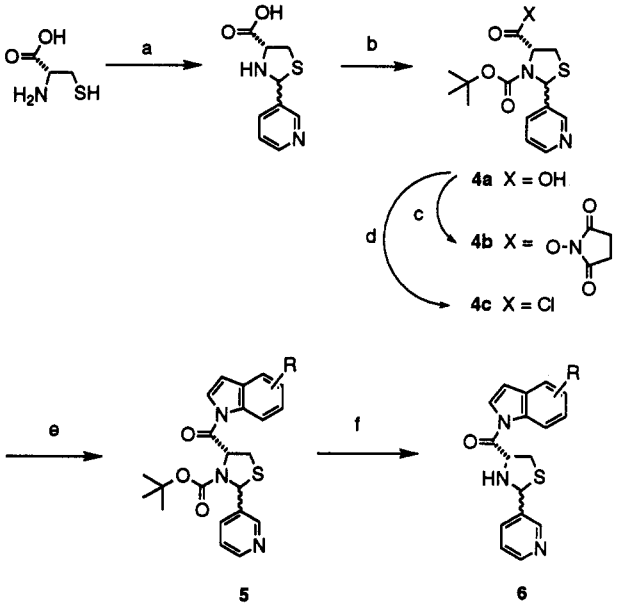
The current work discusses our efforts to find an amide bond surrogate which would improve on the activities obtained with thiazolidines **1**–**3**. While the initial results obtained with these anilids were promising, it was felt that further improvements in the *in vivo* activity were needed. Toward this end, studies were undertaken to examine replacement of the amide moiety of the lead compounds with an acylindole group connected through the indole 1- or 3-position. It was hoped that this change would provide an amide replacement which would be free of hydrolysis problems and would be conformationally restricted with respect to the *N*-aryl bond of the anilide.[27] The synthesis and the evaluation of the PAF-antagonist activity of these compounds are described below.

Chemistry

Preparation of the 1-acylated indoles **6** was achieved in a straightforward manner as outlined in Scheme 2. The thiazolidine ring system was prepared by condensation of (*R*)-cysteine and pyridine-3-carboxaldehyde. Following protection of the thiazolidine nitrogen as its *tert*-butyl carbamate, the carboxylic acid **4a** was activated and treated with the sodium salts of various indoles obtained commercially or prepared as described in the Experimental Section. Following deprotection, the desired compounds **6** were obtained.

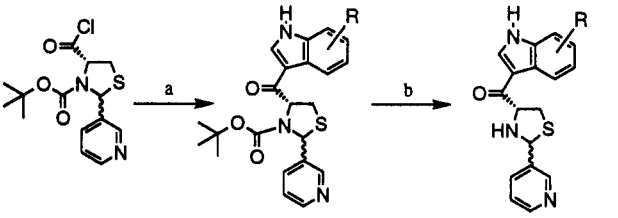
By exploiting the ambident nucleophilicity of the indole anion, we were able to obtain the isomeric 3-acylindoles from the same intermediates. Thus, reaction of the chloromagnesium salt of indole[28] with the acid chloride **4c** in benzene/methylene chloride (method A, see the Experimental Section for details) gave predominantly **7a**, along with **6a**, which was separable by chromatography. A number of substituted indoles were used in this protocol, giving variable but generally poor yields of **7** after

Scheme 2[a]



[a] Reagents: (a) pyridine-3-carboxaldehyde, EtOH/H_2O; (b) $(t\text{-}BuOCO)_2O$, NaOH, dioxane/H_2O; (c) *N*-hydroxysuccinimide, DCC, DMAP, DMF; (d) NaH, CH_2Cl_2; ClCOCOCl; (e) method A (see the Experimental Section); (f) method D or E (see Table 1 and the Experimental Section).

Scheme 3[a]



[a] Reagents: (a) method B or C (see Table 2 and the Experimental Section); (b) method D or E (see Table 2 and the Experimental Section).

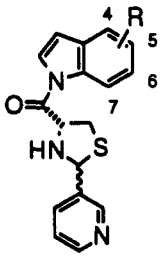
separation of **6**. A modified procedure (method B, see the Experimental Section for details) involving *in situ* generation of the zinc salt of indole in ether[29] followed by transfer to a methylene chloride solution of **4c** allowed complete control of regioselectivity, providing only 3-acylated products **7**. This procedure provided a higher yield for the synthesis of **7a**; however, the yields obtained varied considerably with the indole used (Scheme 3, Table 2). We did not routinely examine our acylation products to determine the enantiomeric purity of the C-4 center.[30] However, as the ratio of diastereomers did not change noticeably during the transformation from **4a** to **7**, we feel that only minor epimerization of the C-4 center occurred during these transformations. Removal of the BOC protecting group provided compounds **8**.

The indole nitrogen of the intermediates **7** provided the opportunity for further elaboration. As indicated in Scheme 4, deprotonation of the indole followed by reaction with a variety of electrophiles gave compounds **9** after deprotection.

The thiazolidine-protected ester-containing compounds **10** also provided an entry to carboxylic acid derivatives, as well as to urea **12** (Scheme 5).

Compound **15**, an intermediate in the synthesis of **9ff**,

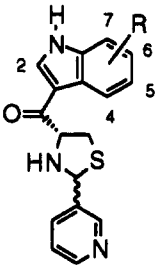
Table 1. Structure and Synthesis of 1-Acylindoles 6



compd	R	acylation yield (%)	deprot method	deprot yield (%)	salt	solvate	anal.[a]
6a	H	*b*	D	16[b]	2HCl	$0.25H_2O$	C, H; N[c]
6b	4-Cl	33	D	91	2HCl	H_2O	C, H; N[d]
6c	6-Cl	28	D	61	2HCl	$0.25CH_2Cl_2$	C, H, N
6d	$6\text{-}COC_6H_5$	*b*	D	6[b]			HRMS
6e	$5\text{-}OCH_2C_6H_5$	70	D	86	2HCl	$0.5H_2O$	C, H, N
6f	$6\text{-}OCH_2C_6H_5$	50	D	78			HRMS
6g	$7\text{-}OCH_2C_6H_5$	1[e]	E	76	oxalate	$1.5H_2O$	C, H; N[f]

[a] Unless otherwise indicated, compounds gave elemental analyses within 0.4% of theoretical values. HRMS indicates high-resolution mass spectra were obtained with observed mass within 3 millimass units of theoretical, with purity confirmed by thin-layer chromatography. [b] In these cases, the intermediate 5 was not purified and was carried forward for deprotection; one yield for the two steps is given. [c] N: calcd, 10.86; found, 10.15. [d] N: calcd, 9.66; found, 8.61. [e] This compound was isolated as a byproduct from the synthesis of 7e (*vide infra*) by Method B. [f] N: calcd, 7.89; found, 6.16.

Table 2. Structure and Synthesis of 3-Acylindoles 7 and 8



compd	R	acylation method	acylation yield (%)	deprot method	deprot yield (%)	salt	solvate	anal.[a]
8a	H	C	48	E	96	oxalate	$1.25CH_2Cl_2$	C, H, N
8b	$4\text{-}OCH_2C_6H_5$	B	5	D	74			HRMS
8c	$5\text{-}OCH_2C_6H_5$	B	7	D	92		$0.5H_2O$	C, H, N
8d	$6\text{-}OCH_2C_6H_5$	B	16	E	68			C, H, N
8e	$7\text{-}OCH_2C_6H_5$	B	9	E	96	CF_3CO_2H		C, H, N
8f	$2\text{-}CH_3$	B	23	D	100			HRMS
8g	$6\text{-}CH_3$	B	11	E	96		$0.5H_2O$	C, H; N[b]
8h	$7\text{-}CH_3$	B	9	D	60			HRMS
8i	$6\text{-}OCH_3$	B	25	E	80			HRMS
8j	$6\text{-}C_6H_5$	B	16	E	81		$0.75CH_2Cl_2$	C, H; N[c]
8k	$6(4)\text{-}OCH_2C_6H_4F$	B	20	E	58		$0.5H_2O$	C, H, N
8l	$6(3)\text{-}OCH_2C_5H_4N$	C	10	E	15		$0.25H_2O$	C, H; N[d]
8m	$6(4)\text{-}OC_6H_4F$	B	19	E	66		$0.25H_2O$	C, H, N
8n	$6\text{-}CCC_6H_5$	B	15	E	47		$0.75H_2O$	C, H, N
8o	6-F	B	32	E	98			C, N; H[e]
8p	6-Br	C	39	E	96			C, H, N
8q	$2,5\text{-}CH_3$	B	32	E	90	2oxalate		C, H, N
8r	$2\text{-}CH_3\text{-}6\text{-}OCH_2C_6H_5$	B	14	E	88		$1,5H_2O$	C, H, N
8s	$5,6\text{-}OCH_3$	C	10	E	25			C, H, N
8t	6-OH	B	5	E, TBAF[f]	56			HRMS
7u	6-Cl	B	32	*g*				
7v	$6(3)\text{-}C_5H_4N$	B	49	*g*				
7w	$6\text{-}OCH_2CH_2OCH_3$	B	12	*g*				

[a] Unless otherwise indicated, compounds gave elemental analyses within 0.4% of theoretical values. HRMS indicates high-resolution mass spectra were obtained with observed mass within 3 millimass units of theoretical, with purity confirmed by thin layer chromatography. [b] N: calcd, 12.64; found, 11.44. [c] N: calcd, 9.35; found, 8.90. [d] N: calcd, 13.30; found, 12.60. [e] N: calcd, 4.10; found, 4.51. [f] A TBS protecting group was removed with TBAF; see the Experimental Section. [g] The protected compounds 7u–w were used as intermediates (*vide infra*), but the corresponding compounds 8 were not prepared.

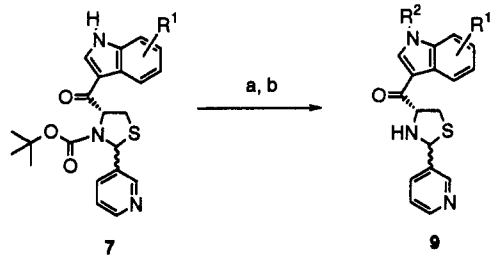
also provided an opportunity for further elaboration through Pd-catalyzed coupling reactions, as shown in Scheme 6.

It also proved possible to selectively functionalize the indole nitrogen of compounds 8 in the presence of the unprotected thiazolidine secondary amine with dialkyl dicarbonates and catalytic DMAP in CH_3CN (Scheme 7), giving compounds **19**.[31]

Taking advantage of our ability to differentiate the two nitrogens, **19a** was then used as an intermediate to prepare *N*-substituted thiazolidines **20** (Scheme 8). Separation of the pure *cis* and *trans* diastereomers from a 3.5:1 mixture by column chromatography was achieved for the trifluoroacetylated compounds **20c** and **20d**.

Finally, compound **21**, a desoxo analog of **8a**, was prepared from a protected derivative of (*R*)-tryptophan

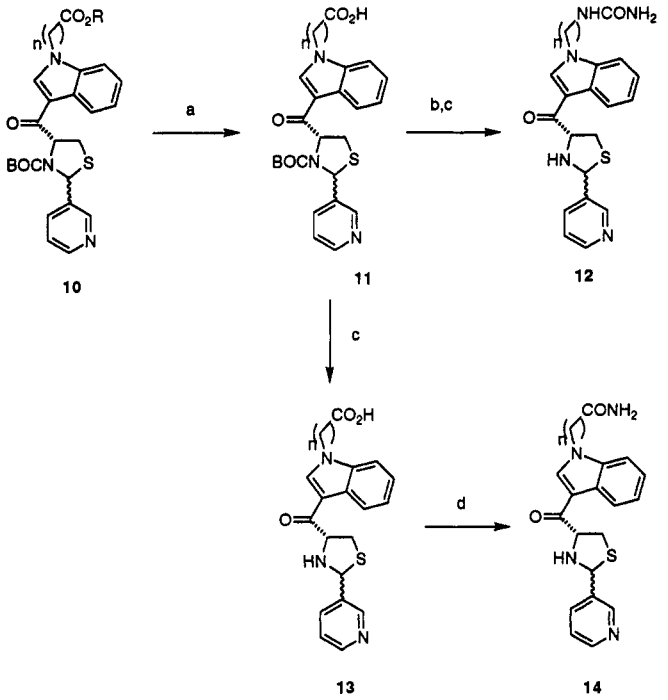
Scheme 4[a]



7 9

[a] Reagents: (a) method F, G, H, I, or J (see Table 3 and the Experimental Section); (b) method D or E (see Table 3 and the Experimental Section).

Scheme 5[a]



10 11 12 13 14

[a] Reagents: (a) method K (see Table 4 and the Experimental Section); (b) DPPA, NMM, THF, Δ; NH_3, THF; (c) method D (see Table 4 and the Experimental Section); (d) method L (see Table 4 and the Experimental Section).

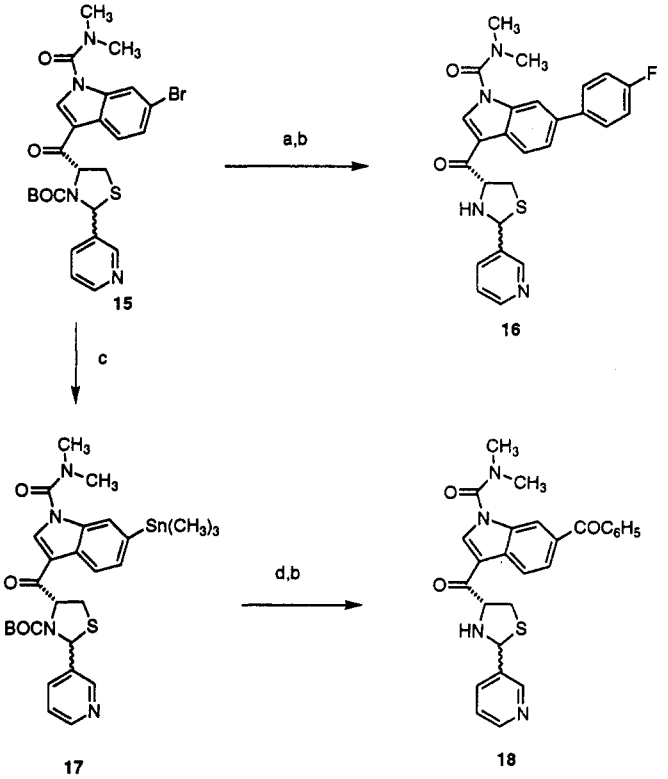
as outlined in Scheme 9. The carboxylate was reduced to the corresponding alcohol, followed by conversion to a protected thiol *via* a Mitsunobu reaction. Deprotection of the amine and thiol groups, followed by condensation with nicotinaldehyde, provided **21** in a 3% unoptimized yield for the five-step sequence (see the Experimental Section for details).

1- and 3-(2-(3-Pyridinyl)thiazolidin-4-oyl)indoles as PAF Antagonists: Results and Discussion

The primary method for evaluation of PAF antagonist activity in these studies was a radioligand binding assay employing rabbit platelet membranes, with [^{3}H]C_{18}PAF used as the radioligand (see the Experimental Section for details). The results are reported as inhibition constants (K_i).

At the outset of the current study, a series of 1-acylated indoles **6** were prepared and evaluated (Table 7). The initial compounds prepared, **6a–c**, displayed significantly greater binding affinity for the PAF receptor than the lead structure **1** (K_i = 208 nM) from which they were derived, suggesting that introduction of a conformational constraint to the anilide moiety was beneficial. Notably,

Scheme 6[a]



15 16 17 18

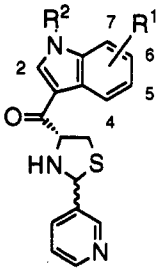
[a] Reagents: (a) pFPhB(OH)$_2$, Pd(PPh$_3$)$_4$, DME, Δ; 93%; (b) method E (see the Experimental Section); (c) $Me_3SnSnMe_3$, Pd(PPh$_3$)$_4$, DME, Δ; 85%; (d) PhCOCl, [(C_3H_5)PdCl]$_2$, proton sponge, THF Δ; 67%.

the inhibition constants were comparable to that observed for RP-58467 (K_i = 31.8 nM), despite the lack of an additional hydrophobic group corresponding to its *m*-benzoyl substituent. Compounds **6d–g** were then examined to determine the proper orientation for a hydrophobic group in this series. The 5-benzyloxy substituent of **6e** provided a modest boost in potency; however, the increase was not as dramatic as that seen in the anilide series. As these initial results were encouraging, we next undertook the study of the "inverted" 3-acylindole analogs which were anticipated to be approximately isosteric[32] and would lack the potentially labile 1-acylindole functionality.

Figure 1 shows the structures of **6e** and RP-59277 overlaid, illustrating the 3D similarity of the structures. Since RP-59277 is reportedly more active than its enantiomer,[18] we presume that the 2*R*,4*R* diastereomer of the thiazolidine compounds possesses the bulk of the observed PAF-antagonist activity. The diastereomer of **6e** possessing identical stereochemistry at the pyridyl-bearing carbon is shown. The compounds were overlaid by superimposing the pyridyl nitrogen, the carbonyl oxygen, and the nitrogen of the thiazolidine ring (to provide a third point for superposition). Each compound was subjected to conformational analysis[33] and energy minimization[34] to ensure that the chosen conformation was energetically accessible. The superposition of **8a** and **6a** (Figure 2) illustrates that the position of the indole acyl linkage (3 *vs* 1) does not change the region of space occupied by the aromatic ring system as a whole. A 3D-QSAR analysis and pharmacaphore model providing a more detailed picture of the requirements for binding activity will be reported elsewhere.

Gratifyingly, compound **8a** displayed an even greater binding affinity for the PAF receptor than **6a**. The series

Table 3. Structure and Synthesis of 3-Acylindoles 9



compd	R¹	R²	acylation method	acylation yield (%)	deprot method	deprot yield (%)	salt	solvate	anal.[a]
9a	H	C_2H_5	F	59	D	71			HRMS
9b	H	$SO_2C_2H_5$	G	78	E	100			C, H, N
9c	H	$SO_2CH(CH_3)_2$	G	30	E	87			HRMS
9d	H	$CON(CH_3)_2$	G	70	E	90		$0.25H_2O$	C, H, N
9e	H	$CON(CH_3)C_6H_5$	H	60	E	42		$0.25H_2O$	C, H, N
9f	H	$CON(C_2H_5)_2$	H	65	E	62			HRMS
9g	H	$CON(CH_2CH_2)_2O$	F	28	E	96			HRMS
9h	H	$CONHCH_3$	I	40	E	42	2oxalate		H, N; C[b]
9i	H	$CONHC(CH_3)_3$	I	53	E	81		$0.25H_2O$	C, H, N
9j	H	CO-(4)-C_6H_4Cl	G	87	E	66	$0.25CF_3CO_2H$		C, H, N
9k	H	$COC(CH_3)_3$	F	77	E	82			C; H, N[c]
9l	H	$CH_2C_6H_5$	F	60	E	42			HRMS
9m	H	$CH_2CO_2C_2H_5$	J	78	D	91			C, H; N[d]
9n	H	$CH_2CH_2CO_2CH_3$	J	43	D	79		$0.25H_2O$	C, H, N
9o	H	$CH_2CON(CH_3)_2$	J	60	D	58		$0.5H_2O$	C, H, N
9p	H	$CH_2CONHCH_3$	J	38	D	50		$0.25H_2O$	C, H; N[e]
9q	H	CH_2CF_3	*f*	28	E	53		$1.5H_2O$	C, H; N[g]
9r	6-$OCH_2C_6H_5$	$CON(CH_3)_2$	G	97	E	95	oxalate		H, N; C[h]
9r	7-$OCH_2C_6H_5$	$CON(CH_3)_2$	G	19	E	68			HRMS
9t	6-C_6H_5	$CON(CH_3)_2$	G	47	E	99		$1.5H_2O$	C, H; N[i]
9u	6-$OCH_2C_6H_5$	$CON(CH_2CH_2)_2O$	G	77	E	68			HRMS
9v	6-$OCH_2C_6H_5$	$SO_2C_2H_5$	F	50	E	100			C, H; N[j]
9w	6(4)-$OCH_2C_6H_4F$	$CON(CH_3)_2$	G	87	E	73			C, H, N
9x	2-CH_3	$CON(CH_2CH_2)_2O$	F	42	E	52		$0.75H_2O$	C, N; H[k]
9y	6(4)-OC_6H_4F	$CON(CH_3)_2$	G	65	E	70		$0.5H_2O$	C, H, N
9z	2,5-CH_3	$CON(CH_3)_2$	G	30	E	42	2oxalate	$0.75H_2O$	C, H; N[l]
9aa	2,5-CH_3	$CON(CH_2CH_2)_2O$	F	40	E	85			HRMS
9bb	6-Cl	$CON(CH_3)_2$	G	10	E	62			C, H, N
9cc	6-CCC_6H_5	$CON(CH_3)_2$	G	80	E	73		$0.5H_2O$, $0.1CHCl_3$	C, H, N
9dd	6(3)-C_5H_4N	$CON(CH_3)_2$	G	44	E	55		$0.2H_2O$, $0.2CH_2Cl_2$	C, H, N
9ee	6-$OCH_2CH_2OCH_3$	$CON(CH_3)_2$	G	26	E	48		$0.5H_2O$	C, H; N[m]
9ff	6-Br	$CON(CH_3)_2$	G	87	E	76	citrate	H_2O	C, H, N
9gg	5,6-OCH_3	$CON(CH_3)_2$	G	32	E	32			C, H, N
9hh	6-F	$CON(CH_3)_2$	G	68	E	75			C, H; N[n]

[a] Unless otherwise indicated, compounds gave elemental analyses within 0.4% of theoretical values. HRMS indicates high-resolution mass spectra were obtained with observed mass within 3 millimass units of theoretical, with purity confirmed by thin layer chromatography. [b] C: calcd, 50.55; found, 51.09. H: calcd, 6.23; found, 6.67; N: calcd, 9.99; found, 10.69. [d] N: calcd, 10.63; found, 10.04. [e] N: calcd, 14.55; found, 14.08. [f] See the Experimental Section. [g] N: calcd, 10.04; found, 9.48. [h] C: calcd, 55.85; found, 55.26. [i] N: calcd, 11.58; found, 10.53. [j] N: calcd, 5.71; found, 5.14. [k] N: calcd, 5.71; found, 5.14. [l] N: calcd, 9.30; found, 8.46. [m] N: calcd, 12.09; found, 11.51. [n] N: calcd, 14.06; found, 13.03.

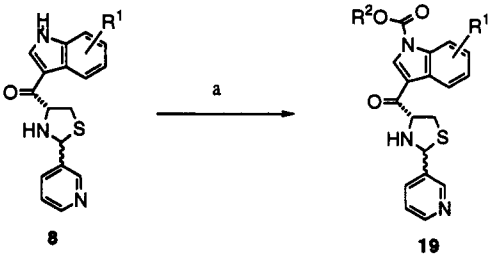
Table 4. Structure and Synthesis of 3-Acylindoles 10–14

compd	R	*n*	method	yield (%)	salt	solvate	anal.[a]
10a	CH_2CH_3	1	J	78			
10b	CH_3	2	J	43			
11a		1	K	57			
11b		2	K	92			
12		2	*b*	72		$0.5H_2O$	C, H, N
13a		1	D	82	2HCl	$0.5H_2O$	C, H; N[c]
13b		2	D	34		$0.15CHCl_3$	C, H; N[d]
14a		1	L	50		H_2O	C, H; N[e]
14b		2	L	50		$0.5CH_2Cl_2$	C, H; N[f]

[a] Unless otherwise indicated, compounds gave elemental analyses within 0.4% of theoretical values. HRMS indicates high-resolution mass spectra were obtained with observed mass within 3 millimass units of theoretical, with purity confirmed by thin-layer chromatography. [b] See the Experimental Section. [c] N: calcd, 9.35; found, 8.92. [d] N: calcd, 10.52; found, 9.89. [e] N: calcd, 14.57; found, 13.78. [f] N: calcd, 13.24; found, 12.74.

of compounds **8b–t** were then examined to explore the effects of substitution around the indole group (Table 8). It appears that hydrophobic substituents at the 6- or

Scheme 7[a]

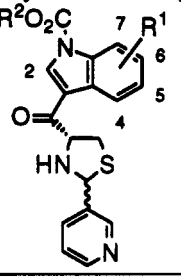


8 **19**

[a] Reagents: (a) method M (see Table 5 and the Experimental Section).

7-position afford a modest increase in binding affinity, while polar groups at the 6-position reduce activity. Substitution at positions 2, 4, or 5 appears to be deleterious to PAF receptor binding. Also included in Table 8 is a series of compounds **9a–q** and **19a–d** bearing substituents at the indole nitrogen. The structure–activity relationships at this position seem to indicate that there is little room in the receptor for large substituents in the immediate

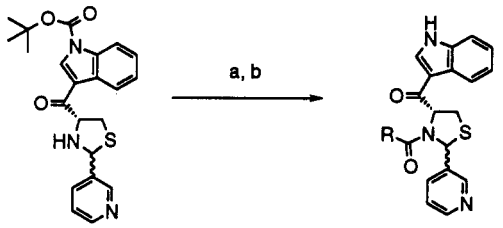
Table 5. Structure and Synthesis of 3-Acylindoles **19**



compd	R^1	R^2	yield (%)	salt	solvate	anal.[a]
19a	H	$C(CH_3)_3$	85			HRMS
19b	H	CH_3	32			HRMS
19c	H	C_2H_5	76			HRMS
19d	H	$CH_2C_6H_5$	47	oxalate		C, H, N
19e	6-$OCH_2C_6H_5$	$C(CH_3)_3$	83			HRMS
19f	2-CH_3	$C(CH_3)_3$	84	oxalate	$0.5Et_2O$	C, H, N
19g	6-CH_3	$C(CH_3)_3$	56			HRMS
19h	6-OCH_3	$C(CH_3)_3$	90	oxalate		C, N; H[b]
19i	2,5-CH_3	$C(CH_3)_3$	99	oxalate		N, H; C[c]

[a] Unless otherwise indicated, compounds gave elemental analyses within 0.4% of theoretical values. HRMS indicates high-resolution mass spectra were obtained with observed mass within 3 millimass units of theoretical, with purity confirmed by thin-layer chromatography. [b] H: calcd, 5.14; found, 5.83. [c] C: calcd, 59.19; found, 59.83.

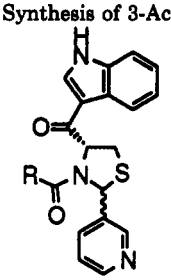
Scheme 8[a]



19a **20**

[a] Reagents: (a) general method N (see Table 6 and the Experimental Section); (b) general method D (see Table 6 and the Experimental Section).

Table 6. Structure and Synthesis of 3-Acylindoles **20**



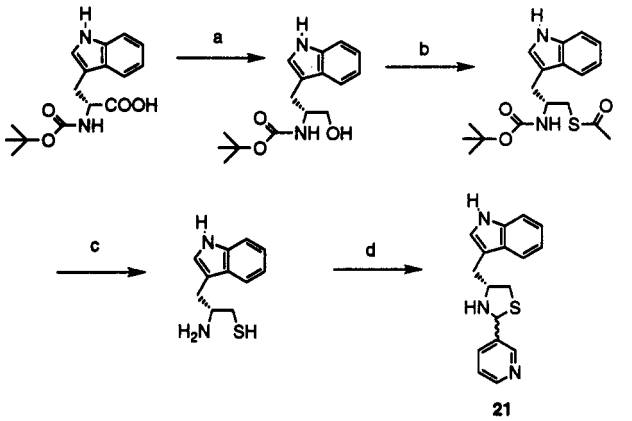
20

compd	R	yield (%)[a]	solvate	anal.[b]
20a	H	31		HRMS
20b	CH_3	65	$0.25H_2O$	C, H, N
20c (*cis* isomer)	CF_3	34[c]		C, H, N
20d (*trans* isomer)	CF_3	10[c]		C, H, N

[a] Overall yield for acylation and deprotection (see the Experimental Section). [b] Unless otherwise indicated, compounds gave elemental analyses within 0.4% of theoretical values. HRMS indicates high-resolution mass spectra were obtained with observed mass within 3 millimass units of theoretical, with purity confirmed by thin-layer chromatography. [c] Isolated yield of pure diastereomer after chromatographic separation.

vicinity of the indole nitrogen, but there is space somewhat further away. The overall picture which emerges suggests that a fairly large hydrophobic cleft exists in the PAF receptor positioned adjacent to carbons 6, 7, and 7a of the

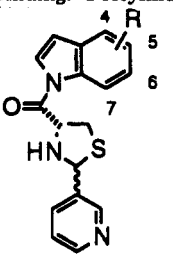
Scheme 9[a]



21

[a] Reagents: (a) BH_3-THF, THF; 54%; (b) PPh_3, DPAD, CH_3COSH; 84%; (c) MeOH, Δ; HCl, HOAc; (d) pyridine-3-carboxaldehyde, EtOH; 6%.

Table 7. PAF Receptor Binding: 1-Acylindoles



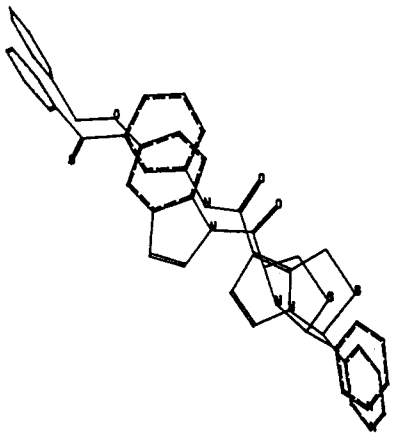
compd	R	K_i, nM[a]	determinations[b]
6a	H	30.0	1
6b	4-Cl	32.7 ± 12.7	3
6c	6-Cl	23.5 ± 2.1	2
6d	6-COC_6H_5	95.0 ± 28.3	2
6e	5-$OCH_2C_6H_5$	14.9 ■ 3.2	2
6f	6-$OCH_2C_6H_5$	51.5 ± 26.2	2
6g	7-$OCH_2C_6H_5$	385 ± 304	2

[a] Binding assay results are reported as geometric means ± standard error. [b] Number of independent determinations performed.

indole ring, which can be reached by some substituents attached at the indole nitrogen as well. Figure 3 illustrates how 3-acylindoles substituted with hydrophobic substituents at the 6-position can be superimposed with the 3-benzoyl group of RP-59227, as exemplified by the superposition of **8d**.

Table 9 includes a number of compounds having multiple substituents on the indole moiety. The structure–activity relationships generally agree with what was observed for the effects of the substituents singly. Thus a compound such as **9w** bearing two "good" substituents displays high receptor affinity, while one such as **8s** loses considerable potency. Exceptions to the pattern are compounds such as **9s**, which is 1,7-disubstituted, and **9x** which is 1,2-disubstituted. Presumably, the groups at neighboring positions are close enough in space to exclude the indole nitrogen substituents from the favorable interactions which they normally achieve. The superposition of **18** with RP-59227, Figure 4, illustrates the proposed bioactive conformation of substituents on the indole nitrogen.

An additional area of study concerned modifications to the cysteine fragment of the general structure (Table 10). Acylation of the thiazolidine nitrogen effectively prevents the diastereomerization at the C-2 center discussed above, allowing, in principle, the isolation and evaluation of the diastereomers independently. Chromatographic separa-



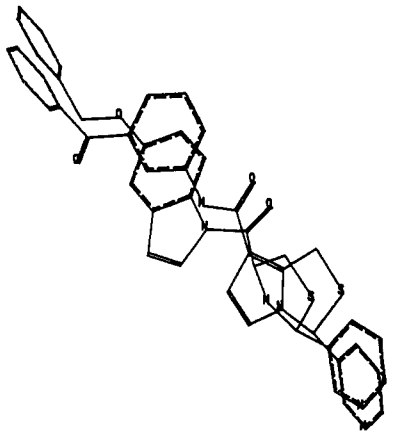


Figure 1. The superposition of **6e** and RP-59227.

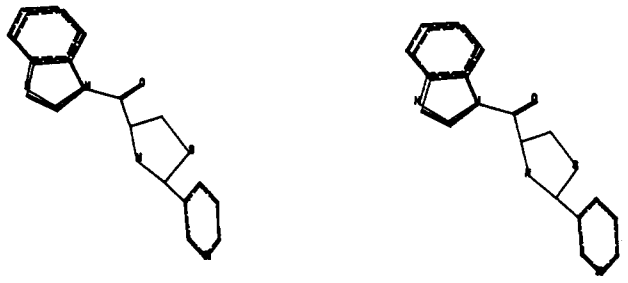


Figure 2. The superposition of **8a** and **6a**.

tion of the *cis* and *trans* isomers was achieved for the trifluoroacetylated compounds **20c** and **20d**. Of the pair, (2*R*,4*R*)-isomer **20c** possessed higher affinity for the PAF receptor. This observation is in agreement with reports that RP-59227, the *R*-enantiomer of RP-58467, possesses greater activity than the corresponding S-enantiomer.[18] Unfortunately, acylation of the thiazolidine nitrogen in compounds **20** consistently led to a loss in binding affinity, a trend which was consistent with earlier observations in the anilide series. Similarly, removal of the ketone group to give **21** led to a 200-fold loss in K_i.

For selected compounds, functional activity was also assessed, using a PAF-induced platelet degranulation assay (see the Experimental Section). All compounds from this study were competitive receptor antagonists, based on a Schild analysis. The results are reported in Table 11 as a K_b. The structure–activity relationships from this functional assay show the same general trends as those found for the receptor binding assay, with a similar rank ordering of potencies. The activities of compounds in the two assays is plotted in Figure 5.

Interestingly, with the exception of a few modifications, most of the analogs of **8a** had similar *in vitro* activity. Of the 70 substituted 3-acylindoles prepared, only 17 differed by more than 4-fold in K_i from **8a**, and only 7 by more than 10-fold. Indeed, detailed analysis of the structure–activity relationships is difficult with the activity of so many compounds falling within the confidence limits of that of the parent structure. In contrast, the differences between compounds *in vivo* was more pronounced.

The compounds were tested in two models which determine the ability of an antagonist to block the effects of exogenously administered PAF 1 h after oral dosing of the test agent. In the mouse, PAF-induced paw edema was monitored, while in the rat PAF-induced skin permeability was used (see the Experimental Section for details). Table 12 presents the ED_{50} values for those compounds for which a dose–response curve was determined.

The rank order of potencies *in vivo* differ from that observed *in vitro* and differ in the two species/models as well. While the complex interplay of intrinsic receptor binding affinity, absorption, distribution, metabolism and clearance make analysis of the results difficult, some general structure–activity relationships can be discerned. The incorporation of hydrophobic substituents at the indole 6-position generally provided an improvement in oral activity, particularly in the rat skin permeability model. Hydrophobic substituents on the indole nitrogen also had a generally positive effect. In particular, the dimethylcarbamoyl substituent was found to be beneficial to activity, especially in the mouse paw edema model. Compounds combining these features, such as **9r**, **9y**, and **18**, provided the best combination of *in vitro* and *in vivo* activity.

Table 13 shows the potencies measured for a number of reference PAF antagonists in our assays, along with values for **9r**. Comparison of these values with those presented above clearly indicates that the 3-(2-(3-pyridinyl)thiazolidin-4-oyl)indoles represent a highly potent new class of PAF receptor antagonists.

Conclusions

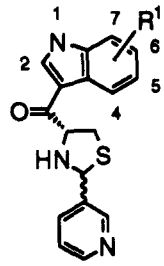
3-(2-(3-Pyridinyl)thiazolidin-4-oyl)indoles have been identified as a class of potent receptor antagonists of platelet activating factor. This series of compounds displayed nanomolar binding affinities *in vitro*, together with generally good oral activity *in vivo*. The introduction of hydrophobic substituents at the 1- and/or 6-positions of the indole ring generally led to improved PAF antagonist activity. This novel series was obtained by employing the 3-indoloyl ketone moiety as a conformationally restrained aryl amide surrogate. Further efforts to exploit this finding will be reported in due course.

Experimental Section

Biological Assays. [^{3}H]PAF Receptor Binding Method. Citrated whole rabbit blood was obtained from Pel-Freez (Rogers, AR). Rabbit platelets were prepared by centrifugation and washing. The platelets were lysed by freeze–thawing and sonication; platelet membranes were prepared by centrifugation and washing. Final membrane preparations were stored frozen in 10 mM Tris/5 mM $MgCl_2$/2 mM EDTA (TME buffer, pH 7.0) with 0.25 M sucrose added for membrane stabilization.

The standard PAF receptor binding assay contained 10 μg of platelet membrane protein, 0.6 nM [^{3}H]C_{18}-PAF (from Amersham or New England Nuclear; specific activity 120–180 Ci/mmol), with and without test compound, in "binding buffer" consisting of TME with 0.25% bovine serum albumin added (Sigma, RIA

Table 8. PAF Receptor Binding: Effects of Substituents on 3-Acylindoles



compd	R	K_i, nM[a]	determinations[b]
8a	H	3.4 ± 1.1	4
8b	4-$OCH_2C_6H_5$	13.0 ● 5.7	2
8c	5-$OCH_2C_6H_5$	26.5 ± 4.9	2
8d	6-$OCH_2C_6H_5$	1.6 ± 0.5	2
8e	7-$OCH_2C_6H_5$	1.1 ± 0.1	2
8f	2-CH_3	22.5 ± 1.4	2
8g	6-CH_3	3.4 ● 0.4	2
8h	7-CH_3	6.5	1
8i	6-OCH_3	9.5 ± 2.8	2
8j	6-C_6H_5	14.2 ± 6.7	2
8k	6(4)-$OCH_2C_6H_4F$	1.6 ● 0.9	2
8l	6(3)-$OCH_2C_5H_4N$	36.5 ± 9.2	2
8m	6(4)-OC_6H_4F	1.9 ● 0.4	2
8n	6-CCC_6H_5	15.0 ● 8.5	2
8o	6-F	5.6 ± 0.8	2
8p	6-Br	6.2 ● 2.9	2
8u	6-OH	225.0	1
9a	1-C_2H_5	5.4 ● 1.6	2
9b	1-$SO_2C_2H_5$	18.0	1
9c	1-$SO_2CH(CH_3)_2$	31.5 ● 7.8	2
9d	1-$CON(CH_3)_2$	0.8 ● 0.1	2
9e	1-$CON(CH_3)C_6H_5$	30.5 ± 7.8	2
9f	1-$CON(C_2H_5)_2$	1.4 ± 0.4	2
9g	1-$CON(CH_2CH_2)_2O$	1.5	1
9h	1-$CONHCH_3$	12.5 ± 7.8	2
9i	1-$CONHC(CH_3)_3$	8.8 ± 5.3	2
9j	1-CO-(4)-C_6H_4Cl	3.4 ± 0.6	2
9k	1-$COC(CH_3)_3$	8.8 ± 1.1	2
9l	1-$CH_2C_6H_5$	49.0 ± 1.4	2
9m	1-$CH_2CO_2C_2H_5$	1.2 ● 0.5	2
9n	1-$CH_2CH_2CO_2CH_3$	4.6 ± 2.0	2
9o	1-$CH_2CON(CH_3)_2$	7.8 ● 3.2	2
9p	1-$CH_2CONHCH_3$	2.4 ● 1.2	2
9q	1-CH_2CF_3	20.5 ± 2.8	2
12	1-$CH_2CH_2NHCONH_2$	5.7 ● 2.1	2
13a	1-CH_2CO_2H	29.8 ± 21.3	2
13b	1-$CH_2CH_2CO_2H$	25.0 ● 18.4	2
14a	1-CH_2CONH_2	5.0 ± 0.2	2
14b	1-$CH_2CH_2CONH_2$	5.7 ● 2.1	2
19a	1-$COOC(CH_3)_3$	1.0 ± 0.4	3
19b	1-$COOCH_3$	2.0 ● 0.7	2
19c	1-$COOC_2H_5$	4.4 ± 0.1	2
19d	1-$COOCH_2C_6H_5$	3.0 ± 0.4	2

[a] Binding assay results are reported as geometric means ● standard error. [b] Number of independent determinations performed.

grade). The final volume of the assay was 100 μL. The assay was conducted in Millititre-GV (Millipore Corp.) filtration plates; incubation time was for 60 min at room temperature (22–23 °C). "Specific binding" was operationally defined as the arithmetic difference between "total binding" of 0.6 nM [^{3}H]C_{18}-PAF (in the absence of added PAF) and "nonspecific binding" (in the presence of 1 μM PAF). After the prescribed incubation, platelet membranes were filtered under vacuum and washed with 1 mL of "binding buffer". The filters were dried and removed. The bound radioactivity was quantitated with a Berthold TLC-Linear Analyzer Model LB2842.

Dose–response curves of inhibition of specific [^{3}H]C_{18}-PAF binding by test compounds were conducted with at least four doses covering the active range. IC_{50} values (concentration producing 50% inhibition) were determined by point-to-point evaluation. K_i values of inhibitory binding constants were calculated according to the method of Cheng and Prusoff,[35] whereby

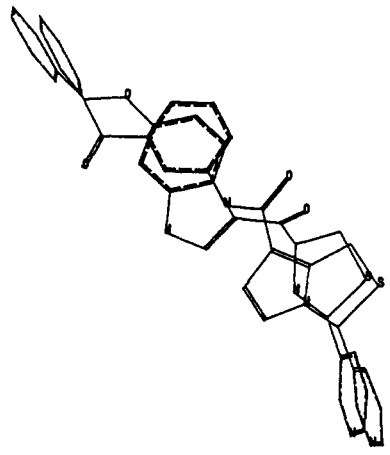
$$K_i = \frac{IC_{50}}{1 + ([[^3H]PAF]/K_d[^3H]PAF)}$$

PAF-Induced Cellular [^{14}C]-5-Hydroxytryptamine Release Assay. Blood was collected via an ear vein from NZW rabbits, diluted with 0.38% sodium citrate, and centrifuged (450*g*, 15 min) to obtain the platelet-rich plasma (PRP) supernatant. The PRP was then incubated with [^{14}C]serotonin (55 mCi/mmol, 0.16 mCi/mL) for 30 min at 37 °C and centrifuged (850*g*, 15 min). The pellet was washed with calcium-free Tyrodes buffer and then resuspended with buffer to original PRP volume. Immediately prior to testing, the platelet suspension was diluted with one volume of 2 mM calcium Tyrodes buffer. The testing protocol was as follows: aliquots of the platelet suspension were incubated with antagonist for 5 min (final DMSO concentration 1%), agonist was added with orbital shaking at 37 °C for 6 min, and the release reaction was terminated by cooling and by adding EDTA in saline (4 °C, final concentration 3 mM). The platelet suspension was then centrifuged (1200*g*, 15 min, 4 °C), and the supernatant was collected for measurement of radioactivity with a liquid scintillation counter.

PAF-Induced Cutaneous Vascular Permeability in the Rat. Male Sprague–Dawley rats (190–220 g) were used, typically in a test group of five. The test compounds were prepared for oral dosing by the stepwise addition of DMSO, PEG400, 45% (hydroxypropyl)-β-cyclodextran, and 0.9% saline (2.5:20:30:47.5, vol/vol). The compounds were administered orally with a dosing volume of 7.0 mL/kg 60 min prior to PAF challenge. Ten minutes prior to PAF challenge, 1% Evans Blue Dye in 0.9% saline was injected (2 mL/kg) iv via the tail vein. The PAF challenge (100 μL of 0.5 μg/mL PAF in PBS containing 0.25% bovine serum albumin, pH 7.3) was injected into the dorsal skin intradermally with a 26-Ga needle. Typically, the rats were injected four times evenly spaced on each side of the midline. Sixty minutes after challenge, the rats were euthanized using CO_2. The dorsal skin was cut and reflected back to reveal the blue spots. Drug effect is expressed as percent inhibition of the mean protein extravasion area for each treatment group relative to areas generated in vehicle-dosed control animals.

PAF-Induced Paw Edema in the Mouse. Male ICR mice (25–30 g) were used, typically in a test group of six. The right hind paw volumes were measured using a mercury plethysmograph. The test compounds were prepared for oral dosing by the stepwise addition of DMSO, PEG400, 45% (hydroxypropyl)-β-cyclodextran, and 0.9% saline (2.5:20:30:47.5 vol/vol). The compounds were administered orally with a dosing volume of 12.5 mL/kg 30 min prior to PAF challenge. The PAF challenge (50 μL of 1 μg/mL PAF in PBS containing 0.25% bovine serum albumin, pH 7.3) was injected into the right hind paw subcutaneously with a 27-Ga needle. The right hind paw volume was then recorded 15 min after PAF challenge. The paw edema was calculated for each mouse by subtracting the initial reading from the postchallenge reading. Drug effect is determined as percent inhibition of paw edema relative to vehicle-dosed controls.

Chemical Synthesis. General. Melting points were determined using an Electrothermal digital melting point apparatus and are uncorrected. Infrared spectra were recorded with a Nicolet 5SXC FT-IR spectrometer and are reported in wavenumbers (cm^{-1}). ^{1}H NMR spectra were recorded on a GE QE300 spectrometer, and chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane as an internal standard. Mass spectra were obtained on a Kratos MS-50 instrument. High-resolution mass spectra were recorded by Midwest Analytical Services. Elemental analyses were performed by Abbott Laboratories Pharmaceutical Products Division Structural Chemistry Department, Oneida Research Services, Inc., Whitesboro, NY, or by Robertson Microlit Laboratories, Inc., Madison, NJ. Spectra are reported only for test compounds and selected intermediates. Flash column chromatography was carried out using silica gel 60 (E. Merck, 230–400 mesh). THF was freshly distilled from sodium benzophenone ketyl. Ethyl ether was purchased as "anhydrous" and used as received. Other solvents



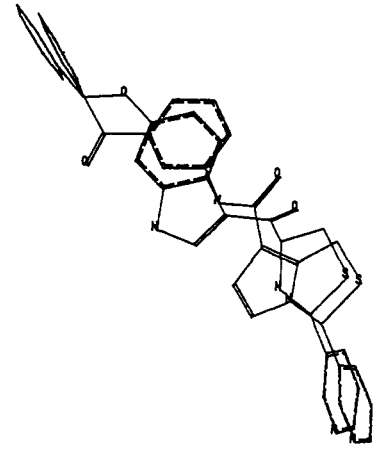
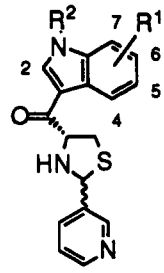


Figure 3. The superposition of **8d** and RP-59227.

Table 9. PAF Receptor Binding: Effects of Multiple Substituents on 3-Acylindoles



compd	R^1	R^2	K_i, nM[a]	n[b]
8q	2,5-CH_3	H	33.0 ± 2.8	2
8r	2-CH_3-6-$OCH_2C_6H_5$	H	15.5 ± 6.4	2
8s	5,6-OCH_3	H	86.5 ± 33.2	2
9r	6-$OCH_2C_6H_5$	$CON(CH_3)_2$	1.4 ± 0.2	2
9s	7-$OCH_2C_6H_5$	$CON(CH_3)_2$	13.7 ± 4.5	3
9t	6-C_6H_5	$CON(CH_3)_2$	3.6 ± 0.5	2
9u	6-$OCH_2C_6H_5$	$CON(CH_2CH_2)_2O$	10.0 ± 7.1	2
9v	6-$OCH_2C_6H_5$	$SO_2C_2H_5$	8.1 ± 2.7	2
9w	6(4)-$OCH_2C_6H_4F$	$CON(CH_3)_2$	1.8 ± 0.2	2
9x	2-CH_3	$CON(CH_2CH_2)_2O$	87.5 ± 31.8	2
9y	6(4)-OC_6H_4F	$CON(CH_3)_2$	2.2 ± 0.6	2
9z	2,5-CH_3	$CON(CH_3)_2$	12.8 ± 6.0	2
9aa	2,5-CH_3	$CON(CH_2CH_2)_2O$	36.2 ± 19.4	2
9bb	6-Cl	$CON(CH_3)_2$	1.0 ± 0.1	2
9cc	6-CCC_6H_5	$CON(CH_3)_2$	1.3 ± 0.6	2
9dd	6(3)-C_5H_4N	$CON(CH_3)_2$	40.0 ± 28.3	2
9ee	6-$OCH_2CH_2OCH_3$	$CON(CH_3)_2$	3.0 ± 0.8	2
9ff	6-Br	$CON(CH_3)_2$	0.6 ± 0.3	2
9gg	5,6-OCH_3	$CON(CH_3)_2$	10.0 ± 0.0	2
9hh	6-F	$CON(CH_3)_2$	1.9 ± 0.7	2
16	6-C_6H_4F	$CON(CH_3)_2$	9.2 ± 9.5	2
18	6-COC_6H_5	$CON(CH_3)_2$	1.0	1
19e	6-$OCH_2C_6H_5$	$CO_2C(CH_3)_3$	1.0 ± 0.4	2
19f	2-CH_3	$CO_2C(CH_3)_3$	9.5 ± 4.2	2
19g	6-CH_3	$CO_2C(CH_3)_3$	2.6	1
19h	6-OCH_3	$CO_2C(CH_3)_3$	8.2 ± 1.1	2
19i	2,5-CH_3	$CO_2C(CH_3)_3$	77.0 ± 53.7	2

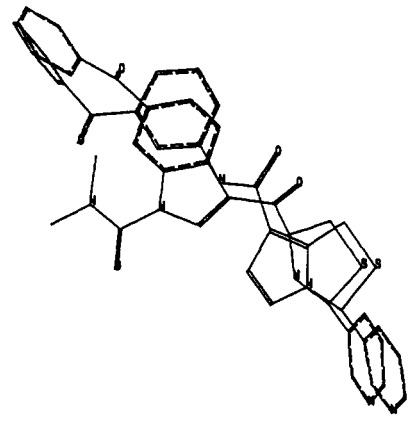
[a] Binding assay results are reported as geometric means ± standard error. [b] Number of independent determinations performed.

were HPLC grade when available and were stored over molecular sieves. Unless otherwise noted, all chemicals and reagents were obtained commercially and used without purification. All chemical yields are unoptimized and generally represent the result of a single experiment. The experimentals given for methods A–N are representative for all compounds listed as prepared by that method and should suffice to reproduce the syntheses; however, in some cases specific reactions were run at differing concentrations and/or for differing lengths of time. Oxalate, hydrochloride, citrate, or trifluoroacetate salts were prepared using standard techniques.

(2*RS*,4*R*)-*N*-(3-Chlorophenyl)-2-(3-pyridinyl)-4-thiazolidinecarboxamide (1). A solution of acid **4a** (2.91 g, 9.4 mmol) and *N*-methylmorpholine (1.42 g, 14 mmol) in CH_2Cl_2 (15 mL) was treated with isobutylchloroformate (1.5 g, 10 mmol) at −15 °C. After 15 min, a solution of 3-chloroaniline (1.4 g, 11 mmol) and DMAP (0.11 g, 0.9 mmol) in CH_2Cl_2 (5 mL) was added. After 1 h, the mixture was warmed to ambient temperature and stirred an additional 17 h. The mixture was quenched with 1 N NaOH, and the organic phase was separated, washed with successive portions of 1 N HCl, saturated $NaHCO_3$, and brine, and then dried ($MgSO_4$). Flash chromatography (2.5:1 hexanes–EtOAc) provided the protected amide (0.65 g, 17% yield). Deprotection according to method D provided **1** (99% yield, 17% yield overall). NMR (DMSO-d_6, 300 MHz): δ 11.08 (s, 0.5H), 11.05 (s, 0.5H), 9.25–9.05 (c, 1H), 9.00–8.85 (c, 1H), 8.80–8.69 (c, 1H), 8.10–8.01 (c, 1H), 7.93–7.83 (c, 1H), 7.67–7.57 (c, 1H), 7.42–7.33 (c, 1H), 7.21–7.14 (c, 1H), 6.12 (s, 0.5H), 6.03 (s, 0.5H), 4.50 (br t, 1H, J = 7.5 Hz), 3.76–3.21 (c, 2H). IR (KBr): 3420, 1690, 1110, 1070. Mass spectrum (DCI/NH_3): 320 $(M + H)^+$. Anal. ($C_{15}H_{14}ClN_3OS$·2HCl) H, N; C: calcd, 49.76; found 49.22.

(2*RS*,4*R*)-*N*-(3-Benzoylphenyl)-2-(3-pyridinyl)-4-thiazolidinecarboxamide (2). A solution of acid **4a** (3.1 g, 10 mmol) and 3-aminobenzophenone (1.97 g, 10 mmol) in CH_2Cl_2 (40 mL) was treated with HOBT (1.35 g, 10 mmol) and DCC (2.06 g, 10 mmol) at −5 °C. After 1 h, the mixture was warmed to ambient temperature and stirred an additional 17 h. The mixture was filtered, and the filtrate washed with successive portions of 1 N NaOH, 10% citric acid, and brine and then dried ($MgSO_4$). Flash chromatography (1:1 EtOAc–hexanes) provided a yellow foam (58% yield). Deprotection according to method D provided **2** (84% yield, 49% yield overall). NMR ($CDCl_3$, 300 MHz): δ 9.28 (s, 0.5 H), 8.80 (bds, 0.5H), 8.62 (dd, 0.5H, J = 2.0, 5.0 Hz), 8.53 (dd, 0.5H, J = 2.0, 5.0 Hz), 8.05–7.76 (c, 6H), 7.62–7.32 (c, 7H), 5.72 (bds, 0.5H), 4.98 (d, 0.5H, J = 12.0 Hz), 4.54 (m, 0.5 H, J = 4.0 Hz), 4.30–4.20 (c, 0.5H), 3.82 (dd, 0.5 H, J = 4.5, 12.0 Hz), 3.62–3.43 (c, 1.5H). Mass spectrum (DCI/NH_3): 390 $(M + H)^+$. Anal. ($C_{22}H_{19}N_3O_2S$·2HCl·$C_4H_8O_2$) C, H, N.

(2*RS*,4*R*)-*N*-[3-(3,4,5-Trimethoxybenzoyl)phenyl]-2-(3-pyridinyl)-4-thiazolidinecarboxamide (3). A solution of acid chloride **4c** (1.95 mmol) and pyridine (0.17 mL, 2.1 mmol) in CH_2Cl_2 (10 mL) was cooled to −5 °C, and a solution of 3-amino-3′,4′,5′-trimethoxybenzophenone hydrochloride (0.68 g, 2.10 mmol) in 5 mL of CH_2Cl_2 was added dropwise over 10 min. The mixture was allowed to warm to ambient temperature and stirred for 17 h. The mixture was washed with successive portions of water, 10% citric acid, saturated $NaHCO_3$, and brine and then dried ($MgSO_4$). Flash chromatography (3:2 EtOAc–hexanes) provided a yellow glass (0.61 g, 54% yield). Deprotection according to method D (*vide infra*) provided **3** (83% yield, 45% yield overall). NMR (DMSO-d_6, 300 MHz): δ 11.02 (br d, 1H, J = 7.5 Hz), 9.11 (m, 1H), 8.86 (d, 1H, J = 4.5 Hz), 8.72 (m, 2H), 8.20 (br s, 0.6H), 8.15 (br s, 0.4H), 8.03 (m, 1H), 7.94 (m, 1H), 7.55 (m, 2H), 7.07 (d, 2H, J = 4.5 Hz), 6.11 (s, 0.6H), 6.00 (s, 0.4H), 4.46 (br t, 1H, J = 7.5 Hz), 3.82 (s, 6H), 3.77 (s, 3H), 3.60 (m, 1H), 3.27 (m, 1H). IR (KBr): 3420, 1690, 1650, 1580, 1550, 1500. Mass



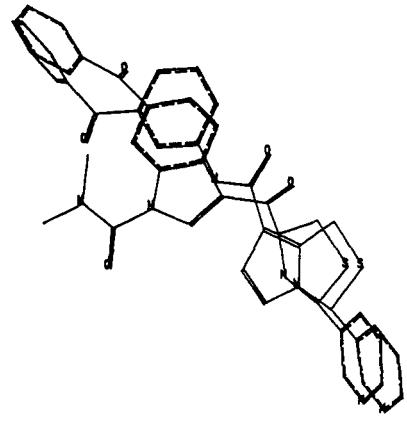
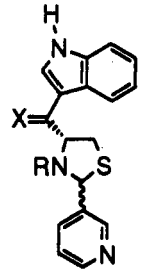


Figure 4. The superposition of 18 and RP-59227.

Table 10. PAF Receptor Binding: Effects of Non-Indole Substituents



compd	X	R	K_i, nM[a]	n[b]
7a	O	$CO_2C(CH_3)_3$	9750.0 ± 3182.0	2
20a	O	CHO	220	1
20b	O	$COCH_3$	17750 ± 6718	2
20c (*cis*)	O	$COCF_3$	1640.0 ± 1499.0	2
20d (*trans*)	O	$COCF_3$	7100.0 ± 5284.0	3
21	H_2	H	600.0 ● 283.0	2

[a] Binding assay results are reported as geometric means ± standard error. [b] Number of independent determinations performed.

spectrum (DCI/NH_3): 480 $(M + H)^+$. Anal. ($C_{25}H_{25}N_3O_5S \cdot 2HCl \cdot 0.25H_2O$) C, H, N.

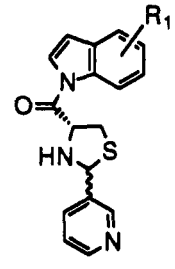
(2*RS*,4*R*)-2-(3-Pyridinyl)-3-(*tert*-butoxycarbonyl)-4-thiazolidinecarboxylic Acid (4a). (*R*)-Cysteine (24.2 g, 0.2 mole) and 3-pyridinecarboxaldehyde (21.4 g, 0.2 mol) were suspended in 60% aqueous EtOH (400 mL), and the mixture was heated at 100 °C for 5 h. The reaction mixture was then cooled and concentrated, and the resulting slurry was washed with EtOH and filtered. This material was dried overnight *in vacuo* at 50 °C to afford the thiazolidine acid (34 g, 81% yield).[18]

To a slurry of the above acid (7.0 g, 33.3 mmol) in 40 mL of dioxane was added 60 mL of 1 M NaOH and di-*tert*-butyl dicarbonate (1.5 equiv, 50 mmol) in dioxane. The mixture was stirred for 19 h. The mixture was concentrated and the resulting liquid partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and dried to yield **4a** (8.27 g, 80% yield, 65% yield overall).

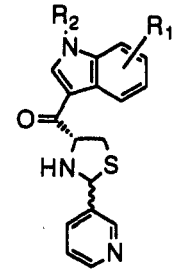
(2*RS*,4*R*)-2-(3-Pyridinyl)-3-(*tert*-butoxycarbonyl)-4-thiazolidinecarboxylate *N*-Hydroxysuccinimide Ester (4b). Acid **4a** (20 g, 64.4 mmol), *N*-hydroxysuccinimide (8.14 g, 7.1 mmol), and DMAP (787 mg, 6.4 mmol) were mixed, and DMF (200 mL) was added with stirring under a N_2 atmosphere at room temperature. The flask was cooled, DCC (13.2 g, 64 mmol) was added, and the mixture was stirred in an ice bath. The reaction mixture was then allowed to slowly warm to room temperature and stirred overnight. The mixture was concentrated under high vacuum, and the residue was extracted with EtOAc and filtered. The material was chromatographed on a silica column (2:1 EtOAc–hexanes) to yield **4b** (16.99 g, 65% yield).

(2*RS*,4*R*)-2-(3-Pyridinyl)-3-(*tert*-butoxycarbonyl)-4-thiazolidinecarboxyl Chloride (4c). Acid **4a** (2.0 g, 64 mmol) was added to a suspension of NaH (0.15 g, 64 mmol) in CH_2Cl_2 (60 mL). The mixture was stirred until gas evolution ceased, oxalyl chloride (0.6 mL, 64 mmol) was added, and the mixture was

Table 11. Inhibition of PAF-induced Platelet Degranulation[a]



6



8, 9, 19

compd	R^1	R^2	K_b, nM	lower	upper
2	*b*		4.14	2.31	7.40
3	*b*		0.415	0.121	1.42
6a	H		9.42	5.98	14.8
6c	6-Cl		6.61	2.45	17.8
6e	5-$OCH_2C_6H_5$		1.95	0.869	4.39
6f	6-$OCH_2C_6H_5$		12.0	1.85	78.6
8c	5-$OCH_2C_6H_5$	H	2.58	1.58	4.19
8d	6-$OCH_2C_6H_5$	H	0.0929	0.00163	1.42
8e	7-$OCH_2C_6H_5$	H	0.571	0.176	1.85
8f	2-CH_3	H	1.99	1.16	3.41
9b	H	$SO_2CH_2CH_3$	1.59	0.325	7.74
9d	H	$CON(CH_3)_2$	0.291	0.00229	37.0
9e	H	$CON(CH_3)C_6H_5$	1.93	1.13	3.32
9l	H	$CH_2C_6H_5$	22.1	4.73	103.
19a	H	$CO_2C(CH_3)_3$	0.111	0.0143	0.853
19e	6-$OCH_2C_6H_5$	$CO_2C(CH_3)_3$	1.19	0.127	11.2

[a] Functional inhibition is reported as the K_b together with the upper and lower 95% confidence limits. [b] See Chart 1 for structure.

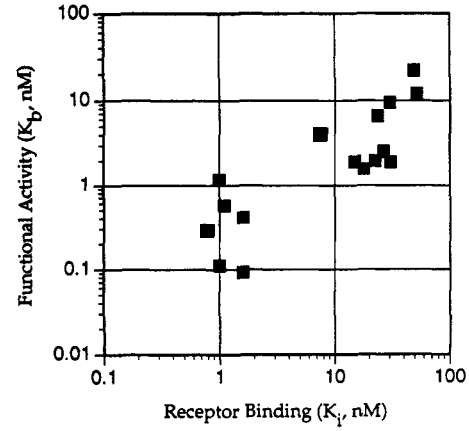
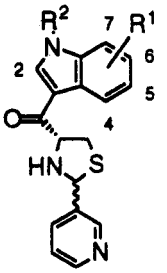


Figure 5. Comparison of functional activity to receptor binding.

Table 12. *In Vivo* Activity of PAF Antagonists[a]



compd	R^1	R^2	mouse ED_{50}	lower	upper	rat ED_{50}	lower	upper
2	*b*		1.727	0.770	4.100	12.880	2.632	28.459
3	*b*		0.476	0.172	1.005	2.065	1.169	3.178
6b	*c*					14.958	6.740	80.519
8a	H	H	5.316	4.199	6.326	3.650	1.490	7.518
8d	6-$OCH_2C_6H_5$	H	1.465	0.887	2.128	0.526	0.260	0.921
8e	7-$OCH_2C_6H_5$	H	6.984	3.295	19.675	1.406	0.433	4.388
8i	6-OCH_3	H	3.703	1.385	8.729			
8j	6-C_6H_5	H	5.391	2.838	10.775	2.296	1.773	2.871
8k	6(4)-$OCH_2C_6H_4F$	H				0.273	0.254	0.294
8o	6-F	H				2.691	2.562	2.838
8p	6-Br	H				1.067	0.979	1.162
8q	2,5-CH_3	H				5.429	4.576	6.188
8r	2-CH_3-6-$OCH_2C_6H_5$	H				1.446	1.404	1.489
9d	H	$CON(CH_3)_2$	0.979	0.520	1.728	1.299	1.202	1.405
9f	H	$CON(C_2H_5)_2$	0.520	0.019	1.511	0.616	0.353	0.987
9g	H	$CON(CH_2CH_2)_2O$	2.632	0.604	5.766			
9h	H	$CONHCH_3$				1.679	1.590	1.774
9i	H	$CONHC(CH_3)_3$				6.279	5.816	6.751
9j	H	CO-(4)-C_6H_4Cl				3.193	1.549	5.403
9k	H	$COC(CH_3)_3$	15.750	8.311	51.698			
9o	H	$CH_2CON(CH_3)_2$				0.384	0.057	1.209
9r	6-$OCH_2C_6H_5$	$CON(CH_3)_2$	0.079	0.011	0.228	0.530	0.191	1.097
9s	7-$OCH_2C_6H_5$	$CON(CH_3)_2$	0.091	0.010	0.551			
9t	6-C_6H_5	$CON(CH_3)_2$	0.808	0.272	1.505	1.118	0.125	2.202
9u	6-$OCH_2C_6H_5$	$CON(CH_2CH_2)_2O$	3.703	2.597	6.160	0.762	0.680	0.852
9v	6-$OCH_2C_6H_5$	$SO_2C_2H_5$				0.862	0.810	0.916
9w	6(4)-$OCH_2C_6H_4F$	$CON(CH_3)_2$				0.355	0.341	0.370
9y	6(4)-OC_6H_4F	$CON(CH_3)_2$				0.108	0.081	0.137
9bb	6-Cl	$CON(CH_3)_2$				1.604	1.420	1.779
9cc	6-CCC_6H_5	$CON(CH_3)_2$				0.885	0.836	0.938
9dd	6(3)-C_5H_4N	$CON(CH_3)_2$				4.477	3.934	5.178
9hh	6-F	$CON(CH_3)_2$				0.945	0.842	1.055
16	6-C_6H_4F	$CON(CH_3)_2$				0.760	0.690	0.844
18	6-COC_6H_5	$CON(CH_3)_2$				0.521	0.490	0.556
19a	H	$CO_2C(CH_3)_3$	0.372	0.263	0.474	4.961	3.586	6.742
19b	H	CO_2CH_3	1.965	0.024	7.327	5.191	4.874	5.489
19d	H	$CO_2CH_2C_6H_5$	1.787	0.215	4.130			
19e	6-$OCH_2C_6H_5$	$CO_2C(CH_3)_3$	1.299	0.170	3.019	0.429	0.264	0.642
19f	2-CH_3	$CO_2C(CH_3)_3$	0.873	0.011	2.628			
19g	6-CH_3	$CO_2C(CH_3)_3$	1.187	0.805	1.606	5.222	0.032	37.078
19h	6-OCH_3	$CO_2C(CH_3)_3$				1.897	1.631	2.146
19i	2,5-CH_3	$CO_2C(CH_3)_3$				9.510	8.922	10.161

[a] Results are presented for the mouse paw edema and rat skin permeability assays (see text). Values represent the dose required to produce 50% inhibition of the response in milligrams per kilogram, along with the lower and upper 95% confidence limits. [b] See Chart 1 for structure. [c] See Figure 1 for structure.

stirred at ambient temperature for 30–60 min, giving a cloudy brown solution of **4c**, which was typically carried on without isolation.

N-Acylation of Indoles. Method A: (2*RS*,4*R*)-5-(Phenylmethoxy)-1-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)-4-thiazolidin-4-oyl]indole (5e). Sodium hydride (60% dispersion, 0.147 g, 3.7 mmol), THF (3 mL), and DMSO (2 mL) were stirred under a N_2 atmosphere and cooled in an ice bath. 5-(Benzyloxy)-indole (0.822 g, 3.7 mmol) in DMSO and THF were added, the resulting suspension was stirred at 0 °C until homogeneous, and **4b** (1.0 g, 2.5 mmol) was added under a N_2 atmosphere. The suspension was stirred at 0 °C for 15 min and then allowed to warm to room temperature with stirring overnight. The reaction was quenched with 10% citric acid and the mixture diluted with EtOAc. The organic layer was washed and dried over $MgSO_4$ and filtered. The filtrate was dissolved in CH_2Cl_2 and chromatographed on silica gel eluting with 2:1 EtOAc–hexanes to yield **5e** (0.884 g, 70% yield).

Also prepared by this method were the following: **(2*RS*,4*R*)-1-[2-(3-Pyridinyl)-3-(*tert*-butoxycarbonyl)-4-thiazolidin-4-oyl]indole (5a)**: carried forward without isolation.

(2*RS*,4*R*)-4-Chloro-1-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)-4-thiazolidin-4-oyl]indole (5b): 33% yield from 4-chloroindole.

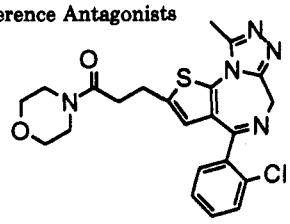
(2*RS*,4*R*)-6-Chloro-1-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)-4-thiazolidin-4-oyl]indole (5c): 28% yield from 6-chloroindole.

(2*RS*,4*R*)-6-Benzoyl-1-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)-4-thiazolidin-4-oyl]indole (5d): carried forward without isolation.

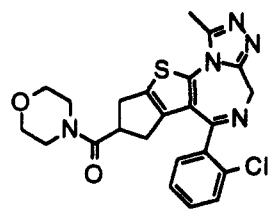
(2*RS*,4*R*)-6-(Phenylmethoxy)-1-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)-4-thiazolidin-4-oyl]indole (5f): 50% yield from 6-(phenylmethoxy)indole.

Indole 3-Acylation. Method B: (2*RS*,4*R*)-3-[2-(3-Pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7a). Indole (7.1 g, 60 mmol) in benzene (250 mL) was treated with

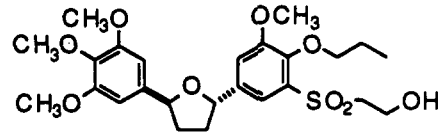
Table 13. Reference Antagonists



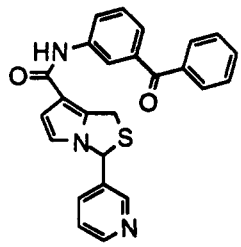
WEB 2086



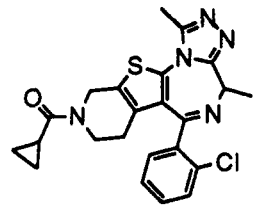
WEB 2170



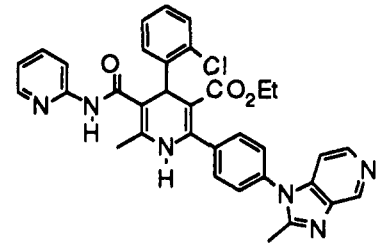
MK-287



RP-58467



E-6123



UK-74505

compd	K_i, nM[a]	n[b]	mouse[c] ED_{50}	lower	upper	rat[d] ED_{50}	lower	upper
9r	1.4 ± 0.2	2	0.079	0.011	0.228	0.530	0.191	1.10
WEB 2086	98.3 ± 54.0	30	2.20	0.100	4.00	22.3	10.6	43.9
WEB 2170	29.2 ± 11.1	3	0.459	0.100	3.37	0.423	0.315	0.561
MK 287	13.5 ± 2.1	2	11.5	3.05	228.	1.89	0.440	13.6
RP 58467	31.8 ± 11.6	8	4.07	1.85	7.77	2.27	1.99	2.55
E 6123	15.7 ● 3.2	3	1.44	1.38	1.49	0.150	0.070	0.330
UK 74505	7.1 ● 0.1	2	ND[e]			0.232	0.222	0.244

[a] PAF receptor binding assay. Results are reported as geometric means ± standard error. [b] Number of independent determinations performed. [c] Mouse paw edema assay (see text). Values represent the dose required to produce 50% inhibition of the response in milligrams per kilogram, along with the lower and upper 95% confidence limits. [d] Rat skin permeability assay. Values represent the dose required to produce 50% inhibition of the response in milligrams per kilogram, along with the lower and upper 95% confidence limits. [e] ND = not determined.

ethylmagnesium chloride (20 mL, 3 M in ether, 60 mmol). The mixture was allowed to stir for 20 min and was then added to a solution of acid chloride **4c** (50 mmol) in benzene (1 L) and CH_2Cl_2 (500 mL). The resulting mixture was stirred for 3 h at ambient temperature, and then the reaction was quenched with saturated NH_4Cl. The organic phase was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated to give a brown solid. Compound **7a** was obtained (2.07 g, 10% yield) following flash chromatography (3:1 EtOAc–hexanes). Anal. ($C_{22}H_{23}N_3O_3S$) C, H, N.

Also prepared by this method were the following: **(2*RS*,4*R*)-4-(Phenylmethoxy)-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7b)**: 5% yield from 4-(phenylmethoxy)indole.

(2*RS*,4*R*)-5-(Phenylmethoxy)-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7c): 7% yield from 5-(phenylmethoxy)indole.

(2*RS*,4*R*)-6-(Phenylmethoxy)-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7d): 16% yield from 6-(phenylmethoxy)indole.

(2*RS*,4*R*)-7-(Phenylmethoxy)-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7e): 9% yield from 7-(phenylmethoxy)indole.

(2*RS*,4*R*)-2-Methyl-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7f): 23% yield from 2-methylindole.

(2*RS*,4*R*)-6-Methyl-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7g): 11% yield from 6-methylindole.

(2*RS*,4*R*)-7-Methyl-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7h): 9% yield from 7-methylindole.

(2*RS*,4*R*)-6-Methoxy-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7i): 25% yield from 6-methoxyindole.

(2*RS*,4*R*)-6-Phenyl-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7j): 16% yield from 6-phenylindole.[37]

(2*RS*,4*R*)-6-[(4-Fluorophenyl)methoxy]-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7k): 20% yield from 6-[(4-fluorophenyl)methoxy]indole, prepared as follows. 6-(Phenylmethoxy)indole (3.93 g, 17.6 mmol) was suspended in acetone (350 mL), under N_2, and cooled in an ice bath. Then 10% palladium on carbon (0.80 g) was added, and the N_2 atmosphere was replaced with H_2 by alternately placing the reaction flask under vacuum and introducing H_2 from a balloon. The cold bath was then removed and the reaction mixture stirred under positive H_2 pressure for 16 h. The reaction mixture was cooled in an ice bath and N_2 reintroduced. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel to give 6-hydroxyindole[38] (1.70 g, 73% yield).

6-Hydroxyindole (0.90 g, 6.8 mmol) and potassium carbonate (1.04 g, 7.5 mmol) were suspended in 13 mL of acetone. 4-Fluorobenzyl bromide (0.93 mL, 7.5 mmol, prefiltered through basic alumina) was added dropwise via syringe. The reaction mixture was heated at reflux under a N_2 atmosphere for 24 h. The reaction mixture was cooled to ambient temperature and partitioned between H_2O and CH_2Cl_2. The aqueous phase was extracted twice with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by chromatography on silica gel to give 6-[(4-fluorophenyl)methoxy]-indole (1.4 g, 88% yield).

(2*RS*,4*R*)-6-(Fluorophenyl)-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7m). A 19% yield from 6-(4-fluorophenoxy)indole, prepared as follows: 4-Bromo-2-nitrotoluene (25.0 g, 116 mmol), 4-fluorophenol (8.70 g, 77.6 mmol), potassium carbonate (21.5 g, 156 mmol), and pyridine (75 mL) were combined under a N_2 atmosphere and heated at 90 °C for 30 min. The reaction mixture was cooled to ambient temperature, CuO (15.4 g, 194 mmol) was added under a stream of N_2, and the resulting dark-brown suspension was heated at reflux for 17 h. The reaction mixture was cooled to ambient temperature and diluted with ether. The solids were removed by filtration through Celite. The ethereal solution was washed

with 1.0 M aqueous NaOH, 1.0 M aqueous HCl, and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a dark-brown oil. The crude product was purified by chromatography on silica gel to give 2-nitro-4-(4-fluorophenoxy)toluene (12.1 g, 63% yield). The 2-nitro-4-(4-fluorophenoxy)toluene (11.8 g, 47.7 mmol) was dissolved in DMF (90.0 mL) under a N_2 atmosphere. DMF dimethyl acetal (20.2 mL, 143 mmol) and pyrrolidine (4.0 mL, 47.4 mmol) were added via syringe, and the reaction mixture was heated at 110 °C for 3 h. The reaction mixture was cooled to ambient temperature and partitioned between H_2O and ether. The organic phase was washed with H_2O. The combined aqueous extracts were washed with ether. The ether extracts were combined and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a viscous oil (16.1 g) which was used without further purification. This material was dissolved in 80% aqueous HOAc (320 mL), and the reaction mixture was warmed to 75 °C. Zinc dust (27 g, 413 mmol) was added in five portions over 1 h. The resulting dark-brown suspension was warmed to 90 °C and heated for 2 h. The reaction mixture was cooled to ambient temperature and diluted with ether. The solids were removed by filtration through Celite. The filter cake was rinsed with H_2O and ether. The layers were separated, and the organic phase was washed with H_2O, with saturated aqueous $NaHCO_3$ until basic, and then once with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel to give 6-(4-fluorophenoxy)indole (1.8 g, 17% yield).

(2*RS*,4*R*)-6-(Phenylethynyl)-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7n). A 15% yield from 6-(phenylethynyl)indole, prepared as follows: 6-bromoindole[37] (3.84 g, 19.6 mmol) was dissolved in triethylamine (40 mL). A few milligrams of phenothiazine was added, and the solution was degassed by bubbling argon through it. Phenylacetylene (8.60 mL, 78.3 mmol) was added via syringe. Bis(triphenylphosphine)palladium(II) chloride (0.69 g, 0.98 mmol) was added, and the reaction mixture was heated at 75–85 °C for 5 h. The reaction mixture was cooled to ambient temperature and filtered. The filtrate was concentrated *in vacuo*. The crude material was purified by chromatography on silica gel to give 6-(phenylethynyl)indole (2.55 g, 60% yield).

(2*RS*,4*R*)-6-Fluoro-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7o): 32% yield from 6-fluoroindole.

(2*RS*,4*R*)-2,5-Dimethyl-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7q): 32% yield from 2,5-dimethylindole.

(2*RS*,4*R*)-6-(Phenylmethoxy)-2-methyl-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7r). A 14% yield from 6-(phenylmethoxy)-2-methylindole, prepared as follows: 6-(Benzyloxy)indole was protected as its [(trimethylsilyl)ethoxy]methyl (SEM) ether according to the method of Muchowski and Solas.[39] 6-(Benzyloxy)indole (2.0 g, 9.0 mmol) in DMF (10 mL) was added to a cooled suspension of NaH (0.226 g, 9.4 mmol) in DMF (15 mL). After 10 min, SEMCl (1.6 mL, 9.0 mmol) was added, and the mixture was stirred for 10 min at 0 °C and 45 min at ambient temperature. The mixture was partitioned between $NaHCO_3$ solution (120 mL) and ether (2 × 125 mL). After drying ($MgSO_4$) and solvent removal, the crude product was chromatographed on silica (5% EtOAc/hexanes) to provide a clear colorless oil (1.37 g, 43% yield). This material (3.7 mmol) was dissolved in DME (4 mL) and cooled to −10 °C under Ar. BuLi (2.5 M in hexanes, 1.6 mL, 4 mmol) was added dropwise, giving a deep red solution. After 10 min, the solution was cooled to −20 °C, and methyl iodide (0.5 mL, 8 mmol) was added by syringe. After 30 min, the crude reaction mixture was partitioned between NH_4Cl solution and ether. After drying ($MgSO_4$) and chromatography on silica (5% EtOAc–hexanes), a clear oil was obtained (0.97 g, 71% yield). Deprotection was carried out using the protocol of Ley *et al.*[40] Freshly dried anhydrous TBAF (1.01 g, 3.87 mmol), ethylenediamine (0.35 mL, 5.25 mmol), and 6-(benzyloxy)-2-methyl-1-[[2-(trimethylsilyl)-ethoxy]methyl]indole (0.47 g, 1.28 mmol) were dissolved in DMF (3 mL) and stirred for 30 h at 45 °C. The mixture was partitioned between ether (70 mL) and 1 M HCl (25 mL). The organic phase was rinsed with $NaHCO_3$ solution and then dried over $MgSO_4$. Purification using a chromatotron device (1 mm SiO_2 rotor, 5% EtOAc–hexanes) gave 2-methyl-6-(phenylmethoxy)indole (0.277 g, 91% yield, 28% yield overall).

(2*RS*,4*R*)-6-[[(2,2-Dimethylethyl)dimethylsilyl]oxy]-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7t). A 5% yield from 6-[[(2,2-dimethylethyl)dimethylsilyl]-oxy]indole, prepared as follows: 6-Hydroxyindole (0.419 g, 3.15 mmol), (see **7k**, above) was dissolved in a mixture of CH_2Cl_2 (12 mL) and 2,6-lutidine (1.0 mL) and cooled in an ice–water bath. *tert*-Butyldimethylsilyl triflate (0.80 mL, 3.50 mmol) was added under N_2, and the reaction mixture was stirred for 2 min, after which the cold bath was removed and stirring was continued for a further 20 min. The reaction mixture was poured into a mixture of aqueous pH 7 buffer (25 mL) and methylene chloride (25 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the desired compound, which was used without further purification.

(2*RS*,4*R*)-6-Chloro-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7u): 32% yield from 6-chloroindole.

(2*RS*,4*R*)-6-Chloro-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7v). A 49% yield from 6-(3-pyridinyl)indole, prepared as follows: To a suspension of hexane-washed KH (35% oil dispersion, 0.85 g, 7.4 mmol) in THF (10 mL) under N_2, cooled in an ice–water bath, was added a solution of 6-bromoindole[37] (1.44 g, 7.34 mmol) in THF (10 mL). After stirring for 15 min, the reaction mixture was cooled further in a dry ice–acetone bath and *tert*-butyllithium (1.7 M in pentane, 8.65 mL, 14.7 mmol) was added *via* syringe. After stirring for 20 min, a solution of tri-*n*-butyl borate (4.00 mL, 14.8 mmol) in THF (5 mL) was added and the suspension allowed to stir in the −78 °C bath for 1 h, then in an ice–water bath for 2 h. The reaction mixture was quenched with 1.0 M HCl (15 mL), stirred in the ice bath for 30 min, and then partitioned between Et_2O and water. The aqueous phase was extracted further with Et_2O (2 × 20 mL). The combined organics were extracted with 1.0 M NaOH (3 × 20 mL). The combined aqueous layers were acidified with 1.0 M HCl (70 mL) and then extracted with Et_2O (3 × 100 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated to afford 6-indolylboronic acid as a yellow solid (0.91 g, 77% yield).

To a solution of 3-bromopyridine (1.84 mL, 19.1 mmol) in DME (20 mL) under N_2 was added tetrakis(triphenylphosphine)-palladium (0.55 g, 0.48 mmol). After the mixture was stirred for 20 min at ambient temperature, a solution of 6-indolylboronic acid (1.54 g, 9.57 mmol) in DME (16 mL) was added. A solution of $NaHCO_3$ (2.41 g, 28.7 mmol) in water (29 mL) was added, and the reaction mixture was heated to reflux under N_2 for 20 h. The organics were removed under reduced pressure, and the residue was partitioned between Et_2O (200 mL) and H_2O (100 mL). The precipitate was removed by vacuum filtration of both phases through a fritted-glass Buchner funnel (10–15 μm). After shaking and separation, the aqueous layer was extracted further with Et_2O (2 × 100 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated to give a yellow crude solid. The collected precipitate, which also contained desired material, was partitioned between Et_2O (40 mL), H_2O (15 mL), and MeOH (5 mL). The aqueous layer was extracted further with Et_2O (4 × 20 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated to give a yellow crude solid. The combined crude samples were purified by flash chromatography on silica gel ($CHCl_3$–MeOH) to give 6-(3-pyridyl)indole as a yellow flaky solid (1.4 g, 75% yield).

(2*RS*,4*R*)-6-(2-Methoxyethoxy)-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7w). A 12% yield from 6-(2-methoxyethoxy)indole, prepared from 6-hydroxyindole and 2-chloroethyl methyl ether as described for the synthesis of 6-[(4-fluorophenyl)methoxy]indole (see **9k**, above) in 91% yield.

Indole 3-Acylation. Method C: (2*RS*,4*R*)-3-[2-(3-Pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7a). Ethylmagnesium bromide (3.0 M in ether, 10.7 mL, 32.1 mmol) was added to a solution of indole (3.77 g, 32.1 mmol) in ether (100 mL). The cloudy yellow-green solution was stirred for 15 min at ambient temperature, $ZnCl_2$ (1.0 M in ether, 32.2 mL, 32.2 mmol) was added, and the resulting heterogeneous solution was stirred for 0.5 h at ambient temperature. A solution of **4c** (16.1 mmol) in CH_2Cl_2 (80 mL) was added quickly, and the reaction

mixture was stirred for 2 h at ambient temperature. The reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted twice with CH_2Cl_2. The aqueous phase was made basic by addition of saturated aqueous $NaHCO_3$ and extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Chromatography on silica gel gave **7a** (3.15 g, 48% yield).

Also prepared by this method were the following: (2*RS*,4*R*)-6-(3-Pyridinylmethoxy)-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (**7l**). A 10% yield from 6-(3-pyridinylmethoxy)indole, prepared from 6-hydroxyindole and 3-picolyl chloride as described for 6-(4-fluorophenoxy)indole (see **7k**, above) in 54% yield.

(2*RS*,4*R*)-6-Bromo-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7p): 39% yield from 6-bromoindole.[37]

(2*RS*,4*R*)-5,6-Dimethoxy-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (7s): 10% yield from 5,6-dimethoxyindole.

Thiazolidine Deprotection. Method D: (2*RS*,4*R*)-5-(Phenylmethoxy)-1-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (6e). Compound **5e** (0.300 g, 0.58 mmol) was stirred with dioxane under a N_2 atmosphere. Hydrochloric acid/dioxane (2.5 mL, 4 M, 10 mmol) was added, and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated and azeotroped with toluene and the solvent removed *in vacuo*. The residue was suspended in ether and washed with $NaHCO_3$. The organic phase was dried over $MgSO_4$ and the solvent evaporated to yield **6e** (0.244 g, 86% yield). NMR ($CDCl_3$, 300 MHz): δ 8.62 (dd, 0.5H, J = 3, 1.5 Hz), 8.53 (dd, 0.5H, J = 3, 1.5 Hz), 8.48 (dd, 1H, J = 4.5, 9 Hz), 7.95 (dt, 0.5H, J = 7.5, 1.5 Hz), 7.87 (d, 0.5H, J = 7.5 Hz), 7.51–7.28 (m, 7H), 7.15–7.05 (m, 2H), 6.68 (d, 0.5H, J = 4.5 Hz), 6.61 (d, 0.5H, J = 4.5 Hz), 6.01 (s, 0.5H), 5.70 (d, 0.5H, J = 10.5 Hz), 5.12 (s, 2H), 4.69–4.55 (m, 1H), 3.59 (dd, 0.5H, J = 3.0, 10.5 Hz), 3.47 (dd, 0.5H, J = 3.0, 10.5 Hz), 3.33–3.23 (m, 1H), 3.19–3.08 (m, 1H). Anal. ($C_{24}H_{21}N_3O_2S$·2HCl·0.5H_2O) C, H, N.

Also prepared by this method the following: (2*RS*,4*R*)-1-[2-(3-Pyridinyl)thiazolidin-4-oyl]indole (**6a**): 16% yield for 2 steps from indole. NMR ($CDCl_3$, 300 MHz): δ 8.84 (m, 1H), 8.66 (m, 1H), 8.50 (br d, 0.5H, J = 5.2 Hz), 8.48 (br d, 0.5H, J = 4.8 Hz), 7.97 (d, 0.5H, J = 8.1 Hz), 7.90 (d, 0.5H, J = 7.7 Hz), 7.58 (m, 1H), 7.54 (d, 0.5H, J = 3.6 Hz), 7.45 (d, 0.5H, J = 4.0 Hz), 7.35 (m, 3H), 6.76 (d, 0.5H, J = 3.5 Hz), 6.70 (d, 0.5H, J = 3.7 Hz), 6.03 (s, 0.5H), 5.72 (s, 0.5H), 4.67 (m, 1H), 3.62 (dd, 0.5H, J = 6.9, 10.3 Hz), 3.49 (dd, 0.5H, J = 6.9, 10.6 Hz), 3.30 (m, 1H). Mass spectrum (DCI/NH_3): 310 [(M + H)$^+$, 100]. Anal. ($C_{17}H_{15}N_3OS$·2HCl·0.25H_2O) C, H; N: calcd, 10.86; found, 10.15.

(2*RS*,4*R*)-4-Chloro-1-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (6b): 91% yield from **5b**. NMR ($CDCl_3$, 300 MHz): δ 8.80 (m, 1H), 8.63 (d, 1H, J = 6.0 Hz), 8.60 (dd, 1H, J = 5.0 Hz), 8.40 (m, 1H), 7.96 (m, 1H), 7.90 (d, 1H, J = 3.0 Hz), 7.60 (d, 1H, J = 3.0 Hz), 7.55 (d, 1H, J = 3.0 Hz), 7.30 (m, 2H), 6.90 (d, 1H, J = 3.0 Hz), 6.85 (d, 1H, J = 3.0 Hz), 6.00 (br s, 1H), 5.80 (br s, 1H), 4.60 (br s, 1H), 3.60 (dd, 1H, J = 7.0, 10.0 Hz), 3.45 (m, 1H), 3.30 (m, 1H). Anal. ($C_{17}H_{14}ClN_3OS$·2HCl·H_2O) C, H; N: calcd, 9.66; found, 8.61.

(2*RS*,4*R*)-6-Chloro-1-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (6c): 61% yield from **5c**. NMR ($CDCl_3$, 300 MHz): δ 8.60–8.40 (m, 2H), 7.65 (m, 1H), 7.30 (m, 2H), 6.90 (m, 1H), 6.40 (m, 1H), 6.18 (m, 1H), 5.60 (m, 1H), 5.40 (m, 1H), 3.80 (dd, 1H, J = 14.0, 7.0 Hz), 3.60–3.20 (m, 2H). Mass spectrum (DCI/NH_3): 344 (M^+), 343, 955. Anal. ($C_{17}H_{15}ClN_3OS$·2HCl·0.25CH_2Cl_2) C, H, N.

(2*RS*,4*R*)-6-Benzoyl-1-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (6d): 6% yield for two steps from 6-benzoylindole.[36] NMR ($CDCl_3$, 300 MHz): δ 8.93 (dd, 1H, J = 1.0, 9.0 Hz), 8.83 (d, 1H, J = 2.0 Hz), 8.67 (d, 1H, J = 3.0 Hz), 8.58 (dd, 1H, J = 2.0, 5.0 Hz), 7.96–7.26 (m, 10H), 6.80 (dd, 1H, J = 6.0 Hz), 5.70 (d, 1H, J = 10.0 Hz), 5.98 (br s, 1H), 4.65 (br m, 1H), 3.60 (dd, 2H, J = 6.0, 10.0 Hz), 3.48 (m, 1H), 3.35 (m, 1H). HRMS: ($C_{24}H_{20}N_3O_2S$) theoretical 414.1276, experimental 414.1282.

(2*RS*,4*R*)-6-(Phenylmethoxy)-1-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (6f): 78% yield from **5f**. NMR ($CDCl_3$, 300 MHz): δ 8.88 (d, 0.75 H, J = 2.0 Hz), 8.81 (m, 0.25 H), 8.63 (m, 0.25H), 8.57 (dd, 0.75 H, J = 0.5, 3.7 Hz), 8.21 (d, 0.75H, J = 2.3 Hz), 8.18 (m, 0.25H), 7.95 (m, 1H), 7.35 (m, 7H), 7.04 (d, 1H, J = 2.6 Hz), 7.01 (d, 1H, J = 2.5 Hz), 6.68 (d, 0.25H), 6.63 (d, 0.75H, J = 4.0 Hz), 6.04 (s, 0.75H), 5.71 (s, 0.25H), 5.16 (s, 1.5H), 5.14 (s, 0.5H), 4.66 (m, 0.75H), 3.64 (m, 0.25H), 3.48 (dd, 0.75H, J = 6.9, 10.6 Hz), 3.29 (m, 0.25H), 3.27 (dd, 0.75H, J = 7.3, 10.6 Hz). IR (KBr): 3450 (br), 3160, 2900, 1695, 1605, 1430, 1380, 1280, 1235, 1205, 905. Mass spectrum (DCI/NH_3): 416 [(M + H)$^+$, 65], 369, 339, 291, 287, 267 (100), 225. HRMS: ($C_{24}H_{22}N_3O_2S$) theoretical 416.1433; experimental 416.1426.

(2*RS*,4*R*)-4-(Phenylmethoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8b): 74% yield from **7b**. NMR ($CDCl_3$, 300 MHz): δ 8.86 (m, 0.5H), 8.78 (m, 0.5H), 8.62 (m, 0.5H), 8.56 (m, 0.5H), 8.00 (m, 0.5H), 7.97 (m, 0.5H), 7.92 (m, 1H), 7.50–7.30 (m, 6H), 7.24 (m, 1H), 7.06 (m, 1H), 6.61 (dd, 0.5H, J = 2.9, 6.8 Hz), 6.58 (dd, 0.5H, J = 1.8, 6.5 Hz), 6.08 (br s, 0.5H), 5.86 (br s, 0.5H), 5.28 (s, 1H), 5.22 (s, 1H), 4.78 (m, 0.5H), 4.60 (m, 0.5H), 3.62 (m, 0.5H), 3.53 (m, 0.5H), 3.24 (m, 1H). Mass spectrum (DCI/NH_3): 416 [(M + H)$^+$, 86], 326 (95), 292 (60), 107 (100). HRMS: ($C_{24}H_{22}N_3O_2S$) theoretical 416.1433, experimental 416.1429.

(2*RS*,4*R*)-5-(Phenylmethoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8c): 92% yield from **7c**. NMR ($CDCl_3$, 300 MHz): δ 8.84 (br s, 0.5H), 8.79 (d, 0.5H, J = 2.2 Hz), 8.61 (dd, 0.5H, J = 1.5, 4.8 Hz), 8.53 (dd, 0.5H, J = 0.7, 4.8 Hz), 8.02 (m, 1H), 7.96 (d, 0.5H, J = 2.9 Hz), 7.89 (d, 0.5H, J = 3.3 Hz), 7.51 (br s, 0.5H), 7.48 (br s, 0.5H), 7.42 (d, 0.5H, J = 1.4 Hz), 7.39 (d, 0.5H, J = 1.5 Hz), 7.33 (m, 5H), 7.05 (m, 2H), 6.03 (s, 0.5H), 5.72 (br s, 0.5H), 5.16 (s, 2H), 4.69 (m, 0.5H), 4.58 (m, 0.5H), 3.52 (dd, 0.5H, J = 7.3, 10.6 Hz), 3.38 (dd, 0.5H, J = 7.0, 10.3 Hz), 3.18 (m, 1H). IR ($CDCl_3$): 3440 (br), 3180, 3050, 2930, 2900, 1620, 1600, 1515, 1470, 1450, 1420, 1375, 1260, 1190, 800, 730, 705. Mass spectrum (DCI/NH_3): 416 [(M + H)$^+$, 90], 313 (85), 250 (100). Anal. ($C_{24}H_{21}N_3O_2S$·0.5H_2O) C, H, N.

(2*RS*,4*R*)-2-Methyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8f): 100% yield from **7f**. NMR ($CDCl_3$, 300 MHz): δ 8.86 (d, 0.4H, J = 2.2 Hz), 8.81 (d, 0.6H, J = 1.9 Hz), 8.68 (br s, 1H (NH)), 8.62 (dd, 0.6H, J = 1.5, 4.8 Hz), 8.54 (dd, 0.4H, J = 1.5, 4.4 Hz), 7.99 (m, 0.6H), 7.92 (m, 0.4H), 7.72 (m, 1H), 7.34 (m, 3H), 7.24 (d, 0.6H, J = 3.3 Hz), 7.22 (d, 0.4 H, J = 2.9 Hz), 6.07 (s, 0.4H), 5.75 (s, 0.6H), 4.92 (dd, 0.6H, J = 7.3, 8.4 Hz), 4.84 (t, 0.4H, J = 7.4 Hz), 3.73 (dd, 0.6H, J = 7.0, 11.8 Hz), 3.55 (dd, 0.4H, J = 7.0, 10.6 Hz), 3.14 (dd, 0.6H, J = 8.5, 10.7 Hz), 3.08 (dd, 0.4H, J = 7.4, 10.7 Hz), 2.82 (s, 1.8H), 2.79 (s, 1.2H). IR (KBr): 3440, 3280, 2920, 2840, 1630, 1455, 1420, 1170. Mass spectrum (FAB): 324 [(M + H)$^+$, 12], 307 (10), 277 (10), 201 (20), 185. HRMS: ($C_{18}H_{18}N_3OS$) theoretical 324.1171, experimental 324.1171.

(2*RS*,4*R*)-7-Methyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8h): 60% yield from **7h**. NMR ($CDCl_3$, 300 MHz): δ 8.82 (m, 0.6H), 8.78 (m, 0.4H), 8.62 (m, 0.4H), 8.60 (m, 0.6H), 8.52 (m, 1H), 8.00 (d, 0.6H, J = 3.3 Hz), 7.97 (m, 0.6H), 7.94 (d, 0.4H, J = 3.3 Hz), 7.87 (m, 0.4H), 7.52 (d, 0.4H, J = 4.1 Hz), 7.44 (d, 0.6H, J = 3.7 Hz), 7.27 (m, 2H), 6.04 (s, 0.4H), 5.73 (s, 0.6H), 4.72 (dd, 0.6H, J = 5.2, 7.4 Hz), 4.61 (dd, 0.4H, J = 5.2, 8.8 Hz), 3.71 (s, 3H), 3.63 (dd, 0.4H, J = 5.2, 10.3 Hz), 3.52 (dd, 0.6H, J = 5.2, 10.2 Hz), 3.34 (dd, 0.4H, J = 8.8, 10.3 Hz), 3.17 (dd, 0.6H, J = 7.4, 10.2 Hz). Mass spectrum (DCI/NH_3): 324 (M + 1$^+$, 100), 239 (15), 132 (45). HRMS: ($C_{18}H_{18}N_3OS$) theoretical 324.1171, experimental 324.1171.

Thiazolidine Deprotection. Method E: (2*RS*,4*R*)-3-[2-(3-Pyridinyl)thiazolidin-4-oyl]indole (8a). Compound **7a** (2.12 g, 5.18 mmol) was dissolved in CH_2Cl_2 (36 mL) and the solution cooled to 0 °C. Trifluoroacetic acid (60 mL) was added and the ice bath removed. After 40 min, the mixture was concentrated and then partitioned between EtOAc (2 × 200 mL) and aqueous $NaHCO_3$ (200 mL). Drying ($MgSO_4$) and solvent removal gave **8a** (1.53 g, 96% yield) as a tan solid. NMR ($CDCl_3$, 300 MHz): δ 8.45 (m, 0.5H), 8.30 (m, 0.5H), 8.75 (br, 1H), 8.61 (m, 1H), 8.52 (m, 1H), 7.89 (m, 0.5H), 7.86 (m, 0.5H), 7.58 (m, 0.5H), 7.53 (d, 0.5H, J = 4.1 Hz), 7.44 (m, 0.5H), 7.39 (m, 0.5H), 7.32 (m, 2H), 6.77 (d, 0.5H, J = 4.1 Hz), 6.03 (br, 0.5H), 5.87 (br, 0.5H), 5.72 (br, 0.5H), 5.57 (br, 0.5H), 4.65 (m, 0.5H), 4.28 (m, 0.5H), 4.12 (m, 0.5H), 4.02 (m, 0.5H), 3.82 (m, 0.5H), 3.71 (m, 0.5H), 3.52 (m, 0.5H), 3.47 (m, 0.5H), 3.34 (m, 0.5H), 3.14 (m, 0.5H). IR ($CHCl_3$): 3500, 3300, 2960, 2940, 1710, 1705, 1450, 1395, 1350, 1205, 805. Mass spectrum (DCI/NH_3): 310 [(M + H)$^+$, 65], 267 (100), 225 (55), 207 (30), 165. Anal. ($C_{17}H_{17}N_3OS$·$C_2H_2O_4$·1.25CH_2Cl_2) C, H, N.

Also prepared by this method were the following:

(2*RS*,4*R*)-7-(Phenylmethoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (6g): 76% yield from **5g**. Mp: 80–86 °C. NMR ($CDCl_3$, 300 MHz): δ 9.10 (d, 0.4H, J = 1.2 Hz), 9.02 (br s, 0.6H), 8.87 (m, 1H), 8.65 (m, 0.6H), 8.56 (m, 0.4H), 8.37 (m, 0.4H), 8.20 (dt, 0.6H, J = 1.9, 5.9 Hz), 7.45 (m, 2H), 7.38 (m, 2H), 7.12 (m, 3H), 7.13 (d, 0.4H, J = 1.8 Hz), 7.11 (d, 0.6H, J = 1.9 Hz), 6.95 (d, 0.6H, J = 5.2 Hz), 6.93 (d, 0.4H, J = 5.1 Hz), 6.69 (d, 0.6H, J = 4.1 Hz), 6.65 (d, 0.4H, J = 3.3 Hz), 6.04 (s, 0.6H), 5.74 (s, 0.4H), 4.72 (dd, 0.4H, J = 4.4, 7.3 Hz), 4.61 (m, 0.6H), 3.62 (m, 0.6H), 3.56 (dd, 0.4H, J = 7.0, 11.0 Hz), 3.40 (dd, 0.6H, J = 8.1, 10.6 Hz), 3.25 (m, 0.4H). IR ($CDCl_3$): 3430, 2920, 1670, 1425, 1360, 1200, 1180. Mass spectrum (DCI/NH_3): 416 (M + 1$^+$, 10), 382 (30), 224 (100). Anal. ($C_{24}H_{21}N_3O_2S \cdot C_2H_2O_4 \cdot 1.5H_2O$) C, H; N: calcd, 7.89; found, 6.16.

(2*RS*,4*R*)-6-(Phenylmethoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8d): 68% yield from **7d**. Mp: 193–195 °C. NMR ($CDCl_3$, 300 MHz): δ 8.85 (d, 0.4H, J = 1.2 Hz), 8.79 (d, 0.6H, J = 1.4 Hz), 8.60 (m, 0.6H), 8.52 (m, 0.4H), 8.28 (s, 0.6H), 8.26 (s, 0.4H), 7.97 (m, 0.6H), 7.91 (d, 0.6H, J = 7.8 Hz), 7.88 (m, 0.4H), 7.83 (d, 0.4H, J = 7.6 Hz), 7.40 (m, 6H), 7.27 (m, 1H), 7.08 (m, 1H), 6.98 (d, 0.6H, J = 2.2 Hz), 6.95 (d, 0.4H, J = 2.3 Hz), 6.03 (s, 0.4H), 5.72 (s, 0.6H), 5.14 (s, 2H), 4.70 (dd, 0.6H, J = 7.0, 7.7 Hz), 4.57 (dd, 0.4H, J = 7.0, 7.2 Hz), 3.52 (dd, 0.6H, J = 7.0, 10.3 Hz), 3.38 (dd, 0.4H, J = 7.0, 9.2 Hz), 3.18 (m, 1H). IR (KBr): 3420, 3250, 2920, 1630, 1525, 1420, 1175. Mass spectrum (DCI/NH_3): 416 [(M + H)$^+$, 35], 185 (100). Anal. ($C_{24}H_{21}N_3O_2S$) C, H, N.

(2*RS*,4*R*)-7-(Phenylmethoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8e): 96% yield from **7e**. NMR (DMSO-d_6, 300 MHz): δ 12.40 (br d, 0.6H, NH), 12.30 (br d, 0.4H, NH), 8.75 (d, 0.6H, J = 2.2 Hz), 8.67 (d, 0.4H, J = 2.5 Hz), 8.57 (dd, 0.6H, J = 1.4, 4.8 Hz), 8.51 (m, 1H), 8.46 (dd, 0.4H, J = 1.4, 4.4 Hz), 8.03 (dt, 0.6H, J = 2.1, 8.1 Hz), 7.88 (m, 0.4H), 7.80 (d, 0.4H, J = 7.6 Hz), 7.79 (d, 0.6H, J = 7.6 Hz), 7.58 (d, 2H, J = 8.0 Hz), 7.42 (m, 4H), 7.13 (m, 1H), 6.93 (d, 0.6H, J = 3.3 Hz), 6.91 (d, 0.4H, J = 3.4 Hz), 5.97 (s, 0.6H), 5.69 (s, 0.4H), 5.31 (s, 1.2H), 5.30 (s, 0.4H), 4.90 (t, 0.6H, J = 7.0 Hz), 4.83 (m, 0.4H), 3.55 (dd, 0.6H, J = 7.6, 10.0 Hz), 3.48 (dd, 0.4H, J = 7.0, 9.9 Hz), 3.06 (dd, 0.6H, J = 9.5, 9.2 Hz), 3.00 (dd, 0.4H, J = 6.9, 9.9 Hz). Mass spectrum (DCI/NH_3): 416 [(M + H)$^+$, 80], 382 (25), 293 (100), 225 (85), 124. Anal. ($C_{24}H_{21}N_3O_2S \cdot 0.75C_2HF_3O_2$) C, H, N.

(2*RS*,4*R*)-6-Methyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8g): 96% yield from **7g**. Mp: 132–138 °C. NMR ($CDCl_3$, 300 MHz): δ 2.48 (s, 1.2H), 2.49 (s, 1.8H), 3.17 (dd, 0.4H, J = 6.9, 10.8 Hz), 3.20 (dd, 0.6H, J = 9.2, 10.3 Hz), 3.38 (dd, 0.4H, J = 7.0, 10.8 Hz), 3.53 (dd, 0.6H, J = 6.9, 10.2 Hz), 4.58 (t, 0.4H, J = 7.0 Hz), 4.69 (dd, 0.6H, J = 6.9, 9.2 Hz), 5.73 (s, 0.6H), 6.04 (s, 0.4H), 7.17 (m, 2H), 7.33 (m, 1H), 7.86 (d, 0.4H, J = 2.9 Hz), 7.94 (d, 0.6H, J = 2.9 Hz), 7.96 (m, 0.6H), 7.99 (m, 0.4H), 8.24 (s, 0.4H), 8.27 (s, 0.6H), 8.53 (dd, 0.4H, J = 2.2, 4.3 Hz), 8.61 (dd, 0.6H, J = 1.5, 4.8 Hz), 8.70 (br s, 1H), 8.79 (d, 0.6H, J = 2.2 Hz), 8.85 (d, 0.4H, J = 2.2 Hz). IR (KBr): 3430, 3240, 2930, 1615, 1525, 1440, 1420. Mass spectrum (DCI/NH_3): 324 (M + H)$^+$, 107. Anal. ($C_{18}H_{17}N_3OS \cdot 0.5H_2O$) C, H; N: calcd, 12.64; found 11.44.

(2*RS*,4*R*)-6-Methoxy-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8i): 80% yield from **7i**. Mp: 86–88 °C. NMR ($CDCl_3$, 300 MHz): δ 8.93–8.90 (m, 0.5H), 8.80–8.78 (m, 0.5H), 8.62–8.54 (m, 2H), 8.12–7.98 (m, 1H), 7.93–7.90 (m, 0.5H), 7.85–7.83 (m, 0.5H), 7.52–7.46 (m, 1H), 7.41–7.33 (m, 2H), 7.02–6.90 (m, 2H), 6.05–5.73 (m, 1H), 4.73–4.50 (m, 1H), 3.86 (s, 3H), 3.58–3.35 (m, 2H). Mass spectrum (DCI/NH_3): 340 (M + H)$^+$, 306. HRMS: ($C_{18}H_{18}N_3O_2S$) theoretical 340.1120, experimental 340.1103.

(2*RS*,4*R*)-6-Phenyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8j): 81% yield from **7j**. Mp: 180–185 °C. NMR ($CDCl_3$, 300 MHz): δ 8.86 (d, 0.4H, J = 2.2 Hz), 8.84 (br s, 1H), 8.81 (d, 0.6H, J = 2.6 Hz), 8.62 (dd, 0.6H, J = 1.4, 4.8 Hz), 8.55 (dd, 0.4H, J = 1.2, 4.6 Hz), 8.45 (s, 0.4H), 8.43 (s, 0.6H), 8.04 (d, 0.6H, J = 2.9 Hz), 7.98 (dd, 0.4H, J = 3.3 Hz), 7.97 (m, 0.6H), 7.89 (m, 0.4H), 7.63 (m, 4H), 7.61 (m, 1H), 7.47 (m, 2H), 7.37 (m, 1H), 6.04 (s, 0.4H), 5.75 (s, 0.6H), 4.73 (dd, 0.6H, J = 7.0, 7.9 Hz), 4.63 (t, 0.4H, J = 7.0 Hz), 3.55 (dd, 0.6H, J = 7.0, 10.3 Hz), 3.41 (dd, 0.4H, J = 7.0, 10.7 Hz), 3.23 (dd, 0.6H, J = 7.9, 10.3 Hz), 3.18 (dd, 0.4H, J = 7.0, 10.7 Hz). IR (KBr): 3420 (br), 3230 (sh), 2920, 1680, 1635, 1605, 1420, 1405, 1205. Mass spectrum (DCI/NH_3): 386 [(M + H)$^+$, 60], 102 (100). Anal. ($C_{23}H_{19}N_3OS \cdot 0.75CH_2Cl_2$) C, H; N: calcd, 9.35; found, 8.90.

(2*RS*,4*R*)-6-[(4-Fluorophenyl)methoxy]-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8k): 58% yield from **7k**. Mp: 185–186 °C. NMR (DMSO-d_6, 300 MHz): δ 12.02 (s, 0.5H), 11.95 (s, 0.5H), 8.73 (d, 0.5H, J = 1.8 Hz), 8.65 (d, 0.5H, J = 2.0 Hz), 8.56 (dd, 0.5H, J = 1.8, 4.8 Hz), 8.48 (t, 1H, J = 3.8 Hz), 8.46 (dd, 0.5H, J = 1.5, 4.5 Hz), 8.07 (dd, 1H, J = 2.4, 8.6 Hz), 8.01 (d, 0.5H, J = 8.1 Hz), 7.85 (d, 0.5H, J = 7.7 Hz), 7.52 (dd, 2H, J = 5.5, 8.8 Hz), 7.44 (dd, 0.5H, J = 4.8, 7.7 Hz), 7.36 (dd, 0.5H, J = 5.2, 7.8 Hz), 7.21 (t, 2H, J = 9.0 Hz), 7.04 (dd, 1H, J = 2.0, 5.0 Hz), 6.94 (dt, 1H, J = 2.1, 8.6 Hz), 5.98 (s, 0.5H), 5.67 (s, 0.5H), 5.12 (s, 2H), 4.82 (c, 1H), 3.52 (dd, 0.5H, J = 7.4, 9.9 Hz), 3.46 (dd, 0.5H, J = 7.0, 9.9 Hz), 3.04 (t, 0.5H, J = 9.4 Hz), 2.96 (dd, 0.5H, J = 7.6, 10.1 Hz). Mass spectrum (DCI/NH_3): 434 (M + H)$^+$. Anal. ($C_{24}H_{20}FN_3OS \cdot 0.5H_2O$) C, H, N.

(2*RS*,4*R*)-6-(3-Pyridinylmethoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8l): 15% yield from **7l**. Mp: 88–93 °C. NMR ($CDCl_3$, 300 MHz): δ 10.09 (s, 0.5H), 9.94 (s, 0.5H), 8.84 (s, 0.5H), 8.79 (s, 0.5H), 8.69 (s, 1H), 8.49–8.64 (c, 2H), 8.28 (d, 1H, J = 8.5 Hz), 8.00–7.76 (m, 3H), 7.40–7.29 (m, 2H), 7.04 (d, 1H, J = 8.8 Hz), 6.95 (s, 1H), 6.03 (s, 0.5H), 5.71 (s, 0.5H), 5.11 (s, 2H), 4.67 (t, 0.5H, J = 8.1 Hz), 4.58 (t, 0.5H, J = 7.4 Hz), 4.43 (br s, 1H), 3.50 (t, 0.5H, J = 8.6 Hz), 3.37 (t, 0.5H, J = 8.6 Hz), 3.19 (t, 0.5H, J = 9.6 Hz), 3.13 (t, 0.5H, J = 9.6 Hz). IR (KBr): 3427 (br), 3287 (br), 1630, 1527, 1448, 1426, 1170, 711. Mass spectrum (DCI/NH_3): 417 (M + H)$^+$. Anal. ($C_{23}H_{20}FN_4O_2S \cdot 0.25H_2O$) C, H; N: calcd, 13.30; found, 12.60.

(2*RS*,4*R*)-6-(4-Fluorophenoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8m): 66% yield from **7m**. Mp: 189–191 °C. NMR (DMSO-d_6, 300 MHz): δ 12.03 (br s, 1H), 8.73 (d, 0.5H, J = 1.8 Hz), 8.65 (d, 0.5H, J = 2.2 Hz), 8.56 (d, 1H, J = 3.3 Hz), 8.55 (dd, 0.5H, J = 1.5, 4.6 Hz), 8.46 (dd, 0.5H, J = 1.6, 4.6 Hz), 8.18 (dd, 1H, J = 2.4, 8.6 Hz), 8.02 (d, 0.5H, J = 7.7 Hz), 7.86 (d, 0.5H, J = 7.7 Hz), 3.00 (dd, 0.5H, J = 7.6, 10.1 Hz), 7.44 (dd, 0.5H, J = 5.0, 7.9 Hz), 7.36 (dd, 0.5H, J = 4.6, 7.9 Hz), 7.21 (t, 2H, J = 8.6 Hz), 7.08–7.01 (m, 3H), 6.96 (dt, 1H, J = 2.4, 8.6 Hz), 5.96 (d, 0.5H, J = 9.2 Hz), 5.68 (d, 0.5H, J = 12.9 Hz), 4.85 (dt, 0.5H, J = 8, 11 Hz), 4.78 (dt, 0.5H, J = 8, 11 Hz), 4.09 (t, 1H, J = 10.0 Hz), 3.46 (dd, 0.5H, J = 7.4, 9.9 Hz), 3.05 (t, 0.5H, J = 9.6 Hz), 3.00 (dd, 0.5H, J = 7.6, 10.1 Hz). IR (KBr): 807 (m), 825 (m), 844 (m), 1196 (s), 1241 (m), 1420 (s), 1449 (s), 1500 (s), 1528 (m), 1638 (s), 3425 (br). Mass spectrum (DCI/NH_3): 420 (M + H)$^+$. Anal. ($C_{23}H_{18}FN_3O_2S \cdot 0.25H_2O$) C, H, N.

(2*RS*,4*R*)-6-(Phenylethynyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8n): 47% yield from **7n**. Mp: 103–107 °C. NMR ($CDCl_3$, 300 MHz): δ 10.15 (s, 0.5H), 10.00 (s, 0.5H), 8.86 (d, 0.5H, J = 2.6 Hz), 8.78 (d, 0.5H, J = 1.5 Hz), 8.60 (dd, 0.5H, J = 1.5, 4.8 Hz), 8.53 (d, 0.5H, J = 4.8 Hz), 8.44 (dd, 0.5H, J = 2.0, 8.3 Hz), 8.34 (dd, 0.5H, J = 2.2, 8.1 Hz), 8.15–7.86 (m, 3H), 7.59 (s, 0.5H), 7.56 (d, 0.5H, J = 2.6 Hz), 7.53 (s, 0.5H), 7.52 (d, 0.5H, J = 1.8 Hz), 7.50 (dd, 0.5H, J = 1.3, 3.8 Hz), 7.46 (dd, 0.5H, J = 1.5, 3.7 Hz), 7.38–7.27 (m, 4H), 6.02 (s, 0.5H), 5.70 (s, 0.5H), 4.66 (t, 0.5H, J = 8.1 Hz), 4.58 (t, 0.5H, J = 7.6 Hz), 3.50 (dd, 0.5H, J = 7.4, 10.3 Hz), 3.38 (dd, 0.5H, J = 6.8, 10.5 Hz), 3.20 (dd, 0.5H, J = 9.2, 10.3 Hz), 3.16 (dd, 0.5H, J = 8.1, 10.3 Hz). IR (KBr): 1417 (s), 1445 (s), 1525 (m), 1622 (s), 1646 (s), 3282 (br), 3402 (br). Mass spectrum (DCI/NH_3): 410 (M + H)$^+$. Anal. ($C_{25}H_{19}N_3OS \cdot 0.75H_2O$) C, H, N.

(2*RS*,4*R*)-6-Fluoro-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8o): 98% yield from **7o**. Mp: 126 °C. NMR ($CDCl_3$, 300 MHz): δ 9.23 (br s, 1H), 9.10–9.04 (m, 1H), 8.83 (dd, 1H, J = 1.5, 3.0 Hz), 8.63–8.60 (m, 0.5H), 8.55–8.52 (m, 0.5H), 8.38–8.32 (m, 1H), 8.00–7.85 (m, 2H), 7.39–7.29 (m, 1H), 7.16–7.05 (m, 2H), 5.72 (s, 1H), 4.59 (t, 2H, J = 6.0 Hz). Mass spectrum (DCI/NH_3): 328 (M + H)$^+$. Anal. ($C_{17}H_{14}FN_3OS$) C, N; H: calcd 4.10; found 4.51.

(2*RS*,4*R*)-6-Bromo-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8p): 96% yield from **7p**. Mp: 106–110 °C. NMR ($CDCl_3$, 300 MHz): δ 10.15 (br s, 0.5H), 9.72 (br s, 0.5H), 8.84 (d, 0.5H, J = 2.2 Hz), 8.80 (d, 0.5H, J = 2.2 Hz), 8.62 (dd, 0.5H, J = 1.6, 5.0 Hz), 8.54 (dd, 0.5H, J = 1.5, 4.8 Hz), 8.26 (dd, 1H, J = 2.6, 8.4 Hz), 8.01–7.95 (m, 1H), 7.94–7.88 (m, 1H), 7.59 (dd, 1H, J = 1.6, 4.2 Hz), 7.44 (dd, 0.5H, J = 1.8, 4.0 Hz), 7.41 (dd, 0.5H, J = 1.5, 4.0 Hz), 7.38 (dd, 0.5H, J = 4.8, 8.1 Hz), 7.34 (dd, 0.5H, J = 4.8, 8.1 Hz), 6.03 (s, 0.5H), 5.72 (s, 0.5H), 4.67 (dd, 0.5H, J = 7.2,

9.0 Hz), 4.58 (t, 0.5H, J = 7.6 Hz), 3.50 (dd, 0.5H, J = 7.4, 10.3 Hz), 3.38 (dd, 0.5H, J = 7.0, 10.3 Hz), 3.19 (dd, 0.5H, J = 10.3, 15.4 Hz), 3.17 (br s, 1H), 3.16 (dd, 0.5H, J = 10.3, 14.7 Hz). IR (KBr): 3421, 3290, 1640, 1521, 1441, 1417. Mass spectrum (DCI/NH_3): 388 and 390 $(M + H)^+$. Anal. ($C_{17}H_{14}BrN_3OS$) C, H, N.

(2*RS*,4*R*)-2,5-Dimethyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8q): 90% yield from **7q**. NMR ($CDCl_3$, 300 MHz: δ 8.81–8.80 (m, 1H), 8.62–8.60 (m, 1H), 8.55–8.51 (m, 0.5H), 8.01–7.97 (m, 1H), 7.92–7.88 (m, 0.5H), 7.71 (s, 1H), 7.39–7.32 (m, 1H), 7.11–7.02 (m, 1H), 6.05 (s, 0.5H), 5.74 (s, 0.5H), 4.91–4.80 (m, 1H), 3.18–3.08 (m, 2H), 2.52 (s, 3H), 2.42 (s, 3H). Mass spectrum (DCI/NH_3): 337 $(M + H)^+$ 146. Anal. ($C_{19}H_{19}N_3OS \cdot 2C_2H_2O_4$) C, H, N.

(2*RS*,4*R*)-6-(Phenylmethoxy)-2-methyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8r): 88% yield from **7r**. NMR ($CDCl_3$, 300 MHz): δ 8.86 (d, 0.5H, J = 1.4 Hz), 8.79 (d, 0.5H, J = 1.5 Hz), 8.60 (dd, 0.5H, J = 1.5, 4.8 Hz), 8.52 (dd, 0.5H, J = 1.4, 4.6 Hz), 8.16 (s, 0.5H), 8.14 (s, 0.5H), 7.93 (m, 3H), 7.47 (d, 1H, J = 7.0 Hz), 7.40 (d, 1H, J = 7.0 Hz), 7.36 (m, 3H), 7.08 (d, 0.5H, J = 2.9 Hz), 7.06 (d, 0.5H, J = 3.3 Hz), 6.03 (s, 0.5H), 5.72 (s, 0.5H), 5.16 (s, 2H), 4.69 (dd, 0.5H, J = 7.0, 7.2 Hz), 4.58 (dd, 0.5H, J = 7.0, 7.1 Hz), 3.52 (dd, 0.5H, J = 7.0, 10.7 Hz), 3.39 (dd, 0.5H, J = 7.0, 10.9 Hz), 3.18 (m, 1H), 2.43 (s, 1.5H), 2.41 (s, 1.5H). IR (KBr): 3430 (br), 3300 (sh), 2930, 1615, 1515, 1410. Mass spectrum (DCI/NH_3): 430 $(M + H)^+$. Anal. ($C_{25}H_{23}N_3O_2S \cdot 1.5H_2O$) C, H, N.

(2*RS*,4*R*)-5,6-Dimethoxy-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (8s): 25% yield from **7s**. Mp: 90–92 °C. NMR ($CDCl_3$, 300 MHz): δ 9.22 (br s, 0.5H), 9.1 (br s, 0.5H), 8.84 (br s, 0.5H), 8.79 (br s, 0.5H), 8.62–8.50 (m, 1H), 7.99–7.93 (m, 1H), 7.88 (dd, 2H, J = 1.5, 3.0 Hz), 7.76 (d, 1H, J = 3.0 Hz), 7.37–7.32 (m, 1H), 6.90 (d, 1H, J = 4.5 Hz), 5.71 (s, 1H), 4.56 (t, 2H, J = 6.0 Hz), 3.98 (s, 3H), 3.90 (s, 3H). Mass spectrum (DCI/NH_3): 370 $(M + H)^+$. Anal. ($C_{19}H_{19}N_3O_3S$) C, H, N.

(2*RS*,4*R*)-6-Hydroxy-3-[2-(3-pyridinyl)thiazolidin-4-oyl]-indole (8t). Compound **7t** (0.071 g, 0.13 mmol) was deBOCed according to method E (100% yield). The resulting green foam was dissolved in THF (2 mL), cooled to 0 °C, and treated with TBAF (1 M in THF, 0.25 mL, 0.25 mmol). After 1 h, the mixture was partitioned between pH 7 buffer solution and ether and then dried over $MgSO_4$. Compound **8t** was obtained as a yellow solid (0.023 g, 56% yield). Mp: 203–205 °C. NMR ($CDCl_3$, 300 MHz): δ 9.28 (s, 0.5H, OH), 9.25 (s, 0.5H, OH), 8.74 (d, 0.5H, J = 1.1 Hz), 8.66 (d, 0.5H, J = 1.3 Hz), 8.56 (dd, 0.5H, J = 1.1, 4.8 Hz), 8.45 (d, 0.5H, J = 1.3, 4.8 Hz), 8.40 (m, 1H), 8.03 (m, 0.5H), 7.98 (d, 0.5H, J = 0.5 Hz), 7.95 (d, 0.5H, J = 0.5 Hz), 7.86 (m, 0.5H), 7.44 (dd, 0.5H, J = 4.8, 6.6 Hz), 7.36 (dd, 0.5H, J = 4.4, 6.2 Hz), 6.84 (d, 0.5H, J = 1.8 Hz), 6.82 (d, 0.5H, J = 2.2 Hz), 6.73 (m, 1H), 6.71 (m, 0.5H), 5.99 (d, 0.5H, J = 8.5 Hz), 5.68 (d, 0.5H, J = 13.2 Hz), 4.78 (m, 1H), 3.49 (m, 1H), 3.03 (m, 0.5H), 2.96 (m, 0.5H). IR (KBr): 3440 (br), 2940, 2920, 1625, 1520, 1420. Mass spectrum (DCI/NH_3): 326 [$(M + H)^+$, 100)] 292 (40). HRMS: ($C_{17}H_{16}N_3O_2S$) theoretical 326.0963, experimental 326.0972.

Indole Functionalization. Method F: Preparation of (2*RS*,4*R*)-1-Ethyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9a). Potassium hexamethyldisilazide (1.2 mL, 0.5 M in toluene, 0.6 mmol) was added to a solution of **7a** (0.254 g, 0.62 mmol) in THF (10 mL) at −78 °C. The mixture was stirred for 20 min, and then ethyl iodide (0.25 mL, 3.1 mmol) was added. After an additional 50 min of stirring the reaction mixture was allowed to warm to room temperature. Sixty minutes later the solvent was removed and the residue partitioned between saturated NH_4Cl solution (20 mL) and ether (2 × 40 mL). The organic phase was dried over $MgSO_4$. The solvent was removed *in vacuo* to give 0.159 g of material (59% yield) which was carried on without further purification.

Deprotection using method D gave **9a** (71% yield, 42% yield overall) after column chromatography. NMR ($CDCl_3$, 300 MHz): δ 8.88 (m, 0.4H), 8.79 (d, 0.6H, J = 1.2 Hz), 8.60 (dd, 0.6H, J = 1.2, 4.8 Hz), 8.55 (m, 0.4H), 8.39 (m, 1H), 7.99 (m, 0.6H), 7.95 (m, 0.4H), 7.93 (s, 0.6H), 7.85 (s, 0.4H), 7.41 (m, 1H), 7.35 (m, 4H), 6.06 (s, 0.4H), 5.74 (s, 0.6H), 4.70 (dd, 0.6H, J = 7.0, 9.8 Hz), 4.58 (dd, 0.4H, J = 8.4, 9.6 Hz), 4.28 (q, 0.6H, J = 7.3 Hz), 4.24 (q, 0.4H, J = 7.3 Hz), 3.54 (dd, 0.6H, J = 6.9, 10.3 Hz), 3.42 (dd, 0.4H, J = 9.6, 16.6 Hz), 3.21 (dd, 0.6H, J = 9.8, 10.3 Hz), 3.12 (dd, 0.4H, J = 8.4, 10.3 Hz), 1.59 (t, 0.6H, J = 7.0 Hz), 1.55 (t, 0.4H, J = 7.3 Hz). IR ($CDCl_3$): 3680, 2960, 2920, 1705, 1635, 1520, 1390, 1130. Mass spectrum (DCI/NH_3): 338 [$(M + H)^+$, 100], 235 (20), 216 (40), 146 (45), 107 (100). HRMS: ($C_{21}H_{21}N_3O_5S$) theoretical 338.1327, experimental 338.1329.

Also prepared by this method were the following:

(2*RS*,4*R*)-1-(1-Morpholinocarbonyl)-3-[2-(3-pyridinyl)-thiazolidin-4-oyl]indole (9g). Carbamylation of **7a** with morpholine carbonyl chloride (28% yield) and subsequent deprotection by method E gave **9g** (96% yield, 27% yield overall). Mp: 102–104 °C. NMR ($CDCl_3$, 300 MHz): δ 8.84–8.78 (m, 2H), 8.63–8.60 (m, 1H), 8.55–8.52 (m, 1H), 8.43–8.38 (m, 2H), 7.97–7.84 (m, 1H), 7.60–7.54 (m, 1H), 7.41–7.36 (m, 2H), 5.73–5.69 (m, 1H), 4.71–4.60 (m, 1H), 3.84–3.60 (m, 8H), 3.30–3.10 (m, 2H). Mass spectrum (DCI/NH_3): 422 $(M + H)^+$. HRMS: ($C_{22}H_{23}N_4O_3S$) theoretical 423.1491, experimental 423.1491.

(2*RS*,4*R*)-1-(2,2-Dimethylpropionyl)-3-[2-(3-pyridinyl)-thiazolidin-4-oyl]indole (9k). Acylation of **7a** with pivaloyl chloride (77% yield) and subsequent deprotection by method E gave **9k** (82% yield, 63% yield overall). Mp: 78–80 °C. NMR ($CDCl_3$, 300 MHz): δ 9.21 (m, 0.5H), 9.10 (m, 0.5H), 8.89 (m, 0.5H), 8.80 (m, 0.5H), 8.60 (m, 1H), 8.55 (m, 1H), 8.49–8.42 (m, 1H), 8.38–8.32 (m, 1H), 8.01–7.95 (m, 1H), 7.48–7.39 (m, 3H), 5.78 (s, 1H), 4.75–4.62 (m, 1H), 3.60–3.21 (m, 2H), 1.22 (s, 9H). Mass spectrum (DCI/NH_3): 394 $(M + H)^+$, 310, 119. Anal. ($C_{22}H_{28}N_3O_2S$) C; H: calcd, 6.23; found 6.67; N: calcd, 9.99; found, 10.69.

(2*RS*,4*R*)-1-(Phenylmethyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9l). Alkylation of **7a** with benzyl bromide (60% yield) and subsequent deprotection by method E gave **9l** (42% yield, 25% yield overall). NMR ($CDCl_3$, 300 MHz): δ 8.90 (m, 1H), 8.75 (m, 1H), 8.67 (m, 1H), 8.58–8.55 (m, 1H), 8.49–8.45 (m, 1H), 8.26–8.21 (m, 1H), 7.91–7.82 (m, 1H), 7.60–7.53 (m, 1H), 7.35–7.31 (m, 3H), 7.26–7.21 (m, 4H), 5.98 (s, 1H), 5.50 (s, 2H), 4.89–4.81 (m, 1H), 3.25–3.00 (m, 2H). Mass spectrum (DCI/NH_3): 400 $(M + H)^+$, 401, 198, 108. HRMS: ($C_{24}H_{22}N_3OS$) theoretical 400.1484, experimental 400.1458.

(2*RS*,4*R*)-1-(Ethylsulfonyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]-6-(phenylmethoxy)indole (9v). Sulfonylation of **7d** with ethanesulfonyl chloride (50% yield) and subsequent deprotection by method E gave **9v** (100% yield, 50% yield overall). Mp: 76–82 °C. NMR ($CDCl_3$, 300 MHz): δ 8.85 (d, 0.5H, J = 2.3 Hz), 8.79 (d, 0.5H, J = 2.2 Hz), 8.62 (dd, 0.5H, J = 1.5, 4.8 Hz), 8.56 (dd, 0.5H, J = 1.3, 4.8 Hz), 8.30 (d, 0.5H, J = 4.4 Hz), 8.27 (d, 0.5H, J = 4.4 Hz), 8.11 (s, 0.5H), 8.06 (s, 0.5H), 7.94 (m, 1H), 7.40 (m, 7H), 7.16 (dd, 0.5H, J = 1.4, 2.2 Hz), 7.14 (dd, 0.5H, J = 1.5, 2.2 Hz), 5.98 (s, 0.5H), 5.71 (s, 0.5H), 5.17 (s, 2H), 4.64 (dd, 0.5H, J = 7.4, 11.7 Hz), 4.60 (t, 0.5H, J = 7.3 Hz), 4.12 (q, 2H, J = 7.0 Hz), 3.54 (dd, 0.5H, J = 7.3, 11.3 Hz), 3.39 (dd, 0.5H, J = 7.0, 11.3 Hz), 3.33 (t, 3H, J = 7.0 Hz), 3.18 (m, 1H). IR (KBr): 3430 (br), 2920, 1660, 1610, 1530, 1375, 1205. Mass spectrum (DCI/NH_3): 508 [$(M + H)^+$, 10], 165 (100). Anal. ($C_{26}H_{25}N_3O_4S_2$) C, H; N: calcd, 8.27; found, 6.84.

(2*RS*,4*R*)-1-(1-Morpholinocarbonyl)-2-methyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9x). Carbamylation of **7f** with morpholinecarbonyl chloride (42% yield) and subsequent deprotection by method E gave **9x** (52% yield, 22% yield overall). NMR ($CDCl_3$, 300 MHz): δ 9.07–9.05 (m, 1H), 8.74–8.69 (m, 1H), 8.62–8.59 (m, 1H), 8.36–8.32 (m, 1H), 8.27–8.21 (m, 1H), 7.72–7.68 (m, 1H), 7.37–7.32 (m, 3H), 6.10 (s, 0.5H), 5.78 (s, 0.5H), 4.33–4.25 (m, 1H), 3.72–3.64 (m, 8H), 3.30–3.25 (m, 2H), 2.84–2.78 (m, 3H). Mass spectrum (DCI/NH_3): 436 $(M + H)^+$, 453. Anal. ($C_{23}H_{24}N_4O_3S \cdot 0.75H_2O$) C, N; H: calcd, 5.71; found, 5.14.

(2*RS*,4*R*)-1-(1-Morpholinocarbonyl)-2,5-dimethyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9aa). Carbamylation of **7q** with morpholinecarbonyl chloride (40% yield) and subsequent deprotection by method E gave **9aa** (85% yield, 36% yield overall). Mp: 87–90 °C. NMR ($CDCl_3$, 300 MHz): δ 8.90–8.78 (m, 1H), 8.63–8.60 (m, 1H), 8.55–8.53 (m, 1H), 8.02–7.97 (m, 1H), 7.70 (s, 1H), 7.40–7.10 (m, 3H), 4.93–4.83 (m, 1H), 3.95–3.62 (m, 8H), 3.62–3.50 (m, 2H), 2.80 (s, 3H), 2.53 (s, 3H). Mass spectrum (DCI/NH_3): 450 $(M + H)^+$, 417. HRMS: ($C_{24}H_{25}N_4O_3S$) theoretical 451.1804, experimental 451.1803.

Method G: (2*RS*,4*R*)-1-(Dimethylcarbamoyl)-6-(phenylmethoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9r). Powdered KOH (0.41 g, 7.3 mmol) was added to a solution of **7d** (0.715 g, 1.39 mmol) in DME (25 mL) at 0 °C. After 10 min,

dimethylcarbamoyl chloride (150 μL, 1.6 mmol) was added, and the mixture was stirred for 30 min at room temperature. Benzene (150 mL) was added to the mixture, and the insoluble materials were removed by filtration. The filtrate was washed with pH 7 buffer solution and dried over $MgSO_4$. The solvent was evaporated to afford 1-(dimethylcarbamoyl)-6-(phenylmethoxy)-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole as a white foam (0.787 g, 97%). Deprotection using method E provided 0.579 g of **9r** (95% yield, 92% yield overall). NMR ($CDCl_3$, 300 MHz): δ 8.86 (br s, 0.5H), 8.80 (br s, 0.5H), 8.61 (d, 0.5H, J = 5.1 Hz), 8.54 (d, 0.5H, J = 4.8 Hz), 8.27 (d, 0.5H, J = 2.3 Hz), 8.24 (d, 0.5H, J = 2.2 Hz), 8.01 (s, 0.5H), 7.96 (s, 0.5H), 7.94 (m, 1H), 7.42 (m, 6H), 7.12 (m, 0.5H), 7.09 (m, 0.5H), 7.05 (m, 1H), 6.01 (s, 0.5H), 5.71 (s, 0.5H), 5.15 (s, 2H), 4.67 (dd, 0.5H, J = 7.7, 8.8 Hz), 4.58 (t, 0.5H, J = 7.0 Hz), 3.53 (dd, 0.5H, J = 7.0, 10.3 Hz), 3.40 (dd, 0.5H, J = 7.7, 9.4 Hz), 3.18 (m, 1H), 3.03 (s, 1.5H), 3.00 (s, 1.5H). IR ($CDCl_3$): 3300, 3030, 2930, 1700, 1660, 1490, 1390, 1220. Mass spectrum (DCI/NH_3): 487 ($M + 1^+$, 50), 108 (100). Anal. ($C_{29}H_{28}N_4O_3S \cdot C_2H_2O_4$) H, N; C: calcd, 55.85; found, 55.26.

Also prepared by this method were the following:

(2*RS*,4*R*)-1-(Ethylsulfonyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9b). Sulfonylation of **7a** with ethanesulfonyl chloride (78% yield) and subsequent deprotection by method E provided **9b** (100% yield, 78% yield overall). NMR ($CDCl_3$, 300 MHz): δ 8.97 (br s, 0.5H), 8.82 (d, 0.5H, J = 1.8 Hz), 8.65–8.59 (m, 1H), 8.46–8.41 (m, 1H), 8.23 (m, 0.5H), 8.06–8.02 (m, 0.5H), 7.68–7.60 (m, 1H), 7.51–7.46 (m, 3H), 7.45–7.35 (m, 2H), 6.50 (s, 0.5H), 5.74 (s, 0.5H), 4.75–4.69 (m, 0.5H), 4.58 (t, 0.5H, J = 7.4 Hz), 3.58–3.45 (m, 2H), 3.25–3.10 (m, 2H), 1.27 (t, 3H, J = 7.4 Hz). Mass spectrum (DCI/NH_3): 401 ($M + H)^+$. Anal. ($C_{19}H_{19}N_3O_3S_2$) C, H, N.

(2*RS*,4*R*)-1-[(2-Methylethyl)sulfonyl]-3-[2-(3-pyridinyl)-thiazolidin-4-oyl]indole (9c). Sulfonylation of **7a** with 2-propanesulfonyl chloride (30% yield), and subsequent deprotection using method E provided **9c** (87% yield, 26% yield overall). NMR ($CDCl_3$, 300 MHz): δ 8.79–8.50 (m, 1H), 8.62–8.61 (m, 1H), 8.60–8.53 (m, 1H), 8.49–8.40 (m, 1H), 7.92–7.86 (m, 2H), 7.50–7.45 (m, 2H), 7.34–7.31 (m, 2H), 5.72 (m, 1H), 4.60–4.75 (m, 1H), 3.68–3.16 (m, 3H), 1.45–1.30 (m, 6H). Mass spectrum (DCI/NH_3): 416 ($M + H)^+$, 310, 320. HRMS: ($C_{20}H_{22}N_3O_3S_2$) theoretical 416.1102, experimental 416.1103.

(2*RS*,4*R*)-1-(Dimethylcarbamoyl)-3-[2-(3-pyridinyl)-thiazolidin-4-oyl]indole (9d). Carbamylation of **7a** with dimethylcarbamoyl chloride (70% yield) and subsequent deprotection using method E provided **9d** (90% yield, 63% yield overall). NMR ($CDCl_3$, 300 MHz): δ 9.10 (d, 0.5H, J = 1.8 Hz), 8.95 (br s, 0.5H), 8.85 (dd, 0.5H, J = 1.8, 5.5 Hz), 8.81 (d, 0.5H, J = 1.8 Hz), 8.62 (dd, 0.5H, J = 1.8, 5.5 Hz), 8.58 (d, 0.5H, J = 5.5 Hz), 8.42–8.38 (m, 1H), 8.21–8.12 (m, 1H), 7.60–7.38 (m, 0.5H), 6.05 (s, 0.5H), 5.72 (s, 0.5H), 4.76–4.69 (m, 0.5H), 4.56 (t, 0.5H, J = 7.4 Hz), 3.60–3.52 (m, 1H), 3.47–3.40 (m, 1H), 3.14 (s, 3H), 3.11 (s, 3H). Anal. ($C_{20}H_{20}N_4O_2S \cdot 0.25H_2O$) C, H, N.

(2*RS*,4*R*)-1-(4-Chlorobenzoyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9j). Acylation of **7a** with 4-chlorobenzoyl chloride (87% yield) and subsequent deprotection using method E provided **9j** (66% yield, 57% yield overall). Mp: 80–84 °C. NMR ($CDCl_3$, 300 MHz): δ 8.81–8.75 (m, 1H), 8.65–8.60 (m, 0.5H), 8.55–8.51 (m, 0.5H), 8.45–8.39 (m, 1H), 8.22–8.16 (m, 1H), 7.95–7.91 (m, 0.5), 7.85–7.81 (m, 0.5H), 7.78–7.69 (m, 3H), 7.65–7.52 (m, 3H), 7.51–7.44 (m, 3H), 5.93 (s, 0.5H), 5.69 (s, 0.5H), 4.36–4.51 (m, 1H), 3.50–3.15 (m, 2H). Mass spectrum (DCI/NH_3): 448 ($M + H)^+$, 310. Anal. ($C_{24}H_{18}ClN_3O_2S \cdot 0.25C_2HF_3O_2$) C, H, N.

(2*RS*,4*R*)-1-(Dimethylcarbamoyl)-7-(phenylmethoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9s). Carbamylation of **7e** with dimethylcarbamoyl chloride (19% yield) and subsequent deprotection using method E provided **9s** (68% yield, 13% yield overall). Mp: 78–84 °C. NMR ($CDCl_3$, 300 MHz): δ 8.86 (d, 0.5H, J = 2.3 Hz), 8.79 (d, 0.5H, J = 1.6 Hz), 8.61 (dd, 0.5H, J = 1.5, 5.9 Hz), 8.54 (dd, 0.5H, J = 2.3, 5.6 Hz), 8.20 (m, 0.5H), 8.18 (m, 0.5H), 8.07 (s, 0.5H), 8.05 (s, 0.5H), 7.98 (m, 1H), 7.5–7.3 (m, 7H), 6.94 (dd, 0.5H, J = 3.4, 6.7 Hz), 6.91 (dd, 0.5H, J = 3.0, 6.5 Hz), 6.02 (d, 0.5H, J = 7.4 Hz), 5.74 (br s, 0.5H), 5.13 (br s, 2H), 4.71 (m, 0.5H), 4.67 (m, 0.5H), 3.57 (dd, 0.5H, J = 7.0, 10.3 Hz), 3.41 (dd, 0.5H, J = 6.7, 8.8 Hz), 3.22 (m, 1H), 2.68 (s, 1.5H), 2.64 (s, 1.5H). IR (KBr): 3440, 3030, 2925, 1705, 1650, 1495, 1395, 1255. Mass spectrum (DCI/NH_3): 487 ($M + H)^+$. HRMS: ($C_{27}H_{27}N_4O_3S$) theoretical 487.1804, experimental 487.1813.

(2*RS*,4*R*)-1-(Dimethylcarbamoyl)-6-phenyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9t). Carbamylation of **7j** with dimethylcarbamoyl chloride (47% yield) followed by deprotection using method E provided **9t** (99% yield, 47% yield overall). Mp: 91–97 °C. NMR ($CDCl_3$, 300 MHz): δ 8.86 (d, 0.4H, J = 1.9 Hz), 8.80 (d, 0.6H, J = 2.2 Hz), 8.62 (dd, 0.6H, J = 1.5, 4.8 Hz), 8.55 (dd, 0.4H, 2.2, 4.2 Hz), 8.45 (d, 0.4H, J = 2.2 Hz), 8.42 (d, 0.6H, J = 2.2 Hz), 8.15 (s, 0.6H), 8.10 (s, 0.4H), 7.97 (m, 0.6H), 7.91 (m, 0.4H), 7.73 (br s, 1H), 7.64 (m, 2H), 7.47 (m, 2H), 7.38 (m, 2H), 7.29 (m, 1H), 6.01 (s, 0.4H), 5.73 (s, 0.6H), 4.71 (dd, 0.6H, J = 7.0, 7.3 Hz), 4.64 (t, 0.4H, J = 7.4 Hz), 3.56 (dd, 0.6H, J = 7.0, 10.3 Hz), 3.44 (dd, 0.4H, J = 7.4, 10.7 Hz), 3.23 (m, 1H), 3.17 (s, 1.8H), 3.13 (s, 1.2H). IR (KBr): 3430, 2920, 1695, 1655, 1470, 1380, 1180. Mass spectrum (DCI/NH_3): 457 [($M + H)^+$, 100], 423 (60), 334 (35). Anal. ($C_{26}H_{24}N_4O_2S \cdot 1.5H_2O$) C, H; N: calcd, 11.58; found, 10.53.

(2*RS*,4*R*)-1-(1-Morpholinocarbonyl)-6-(phenylmethoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9u). Carbamylation of **7d** with morpholinecarbonyl chloride (77% yield) with subsequent deprotection using method E provided **9u** (68% yield, 52% yield overall). NMR ($CDCl_3$, 300 MHz): δ 8.82 (d, 0.6H, J = 2.1 Hz), 8.80 (d, 0.4H, J = 2.1 Hz), 8.63 (m, 0.4H), 8.56 (m, 0.6H), 8.46 (s, 0.4H), 8.41 (s, 0.6H), 8.19 (m, 1H), 7.67 (dd, 0.6H, J = 5.7, 7.1 Hz), 7.58 (dd, 0.4H, J = 5.7, 7.1 Hz), 7.45 (m, 2H), 7.38 (m, 4H), 7.17 (m, 1H), 7.06 (m, 1H), 6.02 (s, 0.6H), 5.78 (s, 0.4H), 5.17 (s, 2H), 4.11 (m, 1H), 3.88 (m, 2H), 3.67 (m, 3H), 3.54 (m, 2H), 3.24 (m, 3H). IR ($CDCl_3$): 3300, 2960, 2920, 2850, 1690, 1660 (sh), 1415, 1220. Mass spectrum (DCI/NH_3): 529 [($M + H)^+$, 25], 201 (100). HRMS: ($C_{29}H_{29}N_4O_4S$) theoretical 529.1909, experimental 529.1891.

(2*RS*,4*R*)-1-(Dimethylcarbamoyl)-6-[(4-fluorophenyl)-methoxy]-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9w). Carbamylation of **7o** with dimethylcarbamoyl chloride (87% yield) with subsequent deprotection using method E provided **9w** (73% yield, 64% yield overall). Mp: 71–74 °C. NMR (DMSO-d_6, 300 MHz): δ 8.75 (s, 1H), 8.75 (d, 0.5H, J = 2.0 Hz), 8.68 (d, 0.5H, J = 2.0 Hz), 8.56 (dd, 0.5H, J = 1.5, 4.8 Hz), 8.48 (dd, 0.5H, J = 1.5, 4.8 Hz), 8.15 (dd, 1H, J = 3.1, 8.6 Hz), 8.04 (d, 0.5H, J = 8.4 Hz), 7.88 (d, 0.5H, J = 7.4 Hz), 7.54 (dd, 2H, J = 5.7, 8.6 Hz), 7.46 (dd, 0.5H, J = 4.8, 7.7 Hz), 7.38 (dd, 0.5H, J = 4.8, 7.7 Hz), 7.24 (t, 2H, J = 8.8 Hz), 7.22 (s, 1H), 7.08 (d, 1H, J = 8.8 Hz), 5.94 (s, 0.5H), 5.70 (s, 0.5H), 5.16 (s, 2H), 4.95 (t, 0.5H, J = 6.8 Hz), 4.82 (t, 0.5H, J = 7.9 Hz), 4.17 (br s, 1H), 3.54 (dd, 0.5H, J = 7.2, 9.8 Hz), 3.48 (dd, 0.5H, J = 7.4, 9.9 Hz), 3.12 (dd, 0.5H, J = 9.8, 13.8 Hz), 3.09 (dd, 0.5H, J = 10.7, 14.3 Hz), 3.05 (s, 3H), 3.02 (s, 3H). Mass spectrum (DCI/NH_3): 505 ($M + H)^+$. Anal. ($C_{27}H_{25}FN_4O_3S$) C, H, N.

(2*RS*,4*R*)-1-(Dimethylcarbamoyl)-6-(4-fluorophenoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9y). Carbamylation of **7m** with dimethylcarbamoyl chloride (65% yield) with subsequent deprotection using method E provided **9y** (70% yield, 46% yield overall). Mp: 72–75 °C. NMR (DMSO-d_6, 300 MHz): δ 8.82 (d, 1H, J = 1.8 Hz), 8.73 (d, 0.5H, J = 1.8 Hz), 8.66 (d, 0.5H, J = 2.2 Hz), 8.54 (dd, 0.5H, J = 1.5, 4.8 Hz), 8.46 (dd, 0.5H, J = 1.6, 4.6 Hz), 8.23 (dd, 1H, J = 4.2, 8.6 Hz), 8.01 (d, 0.5H, J = 8.1 Hz), 7.87 (d, 0.5H, J = 8.1 Hz), 7.36 (dd, 0.5H, J = 4.6, 7.9 Hz), 7.18–7.27 (m, 3H), 7.04–7.12 (m, 3H), 5.92 (d, 0.5H, J = 9.2 Hz), 5.69 (d, 0.5H, J = 12.9 Hz), 4.97 (dt, 0.5H, J = 7, 10 Hz), 4.85 (dt, 0.5H, J = 8, 12 Hz), 4.17 (t, 1H, J = 9 Hz), 3.54 (t, 0.5H, J = 7.7 Hz), 3.47 (dd, 0.5H, J = 8.1, 11 Hz), 3.12 (t, 0.5H, J = 9.6 Hz), 3.03 (s, 3H), 3.00 (s, 3H). Mass spectrum (DCI/NH_3): 491 ($M + H)^+$. Anal. ($C_{28}H_{23}FN_4O_3S \cdot 0.5H_2O$) C, H, N.

(2*RS*,4*R*)-1-(Dimethylcarbamoyl)-2,5-dimethyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9z). Carbamylation of **7q** with dimethylcarbamoyl chloride (30% yield) with subsequent deprotection using method E provided **9z** (42% yield, 13% yield overall). Mp: 79–82 °C. NMR ($CDCl_3$, 300 MHz): δ 8.90 (m, 0.5H), 8.83–8.77 (m, 0.5H), 8.66–8.64 (m, 0.5H), 8.45–8.40 (m, 1H), 8.40–8.32 (m, 0.5H), 7.87–7.78 (m, 1H), 7.75–7.70 (m, 1H), 7.23–7.13 (m, 2H), 5.87 (m, 1H), 4.97 (m, 1H), 3.64–3.55 (m, 2H), 3.31 (s, 6H), 2.70 (s, 3H), 2.43 (s, 3H). Mass spectrum (DCI/NH_3): 408 ($M + H)^+$. Anal. ($C_{22}H_{24}N_4O_2S \cdot 2C_2H_2O_4 \cdot 0.75H_2O$) C, H; N: calcd, 9.30; found, 8.46.

(2*RS*,4*R*)-6-Chloro-1-(dimethylcarbamoyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9bb). Carbamylation of **7u** with dimethylcarbamoyl chloride (10% yield) with subsequent deprotection using method E provided **9bb** (62% yield, 6% yield overall). NMR ($CDCl_3$, 300 MHz): δ 8.71 (m, 1H), 8.66 (s, 0.5H), 8.61 (s, 0.5H), 8.52 (dd, 0.5H, J = 1.5, 2.7 Hz), 8.46 (dd, 0.5H, J = 1.4, 2.8 Hz), 8.31 (d, 0.5H, J = 2.7 Hz), 8.28 (d, 0.5H, J = 2.8 Hz), 8.11 (m, 0.5H), 8.03 (m, 0.5H), 7.68 (d, 0.5H, J = 1.5 Hz), 7.66 (d, 0.5H, J = 1.4 Hz), 7.46 (m, 1H), 7.36 (d, 0.5H, J = 1.7 Hz), 7.31 (d, 0.5H, J = 1.7 Hz), 5.92 (s, 0.5H), 5.73 (s, 0.5H), 4.91 (m, 1H), 3.61 (dd, 0.5H, J = 7.0, 10.3 Hz), 3.53 (dd, 0.5H, J = 7.3, 10.7 Hz), 3.24 (m, 1H), 3.12 (s, 3H), 3.09 (s, 3H). IR ($CDCl_3$): 3440, 2960, 1680, 1600, 1260, 1100. Mass spectrum (DCI/NH_3): 415 [(M + H)$^+$, 100]. Anal. ($C_{20}H_{19}ClN_4O_2S$) C, H, N.

(2*RS*,4*R*)-1-(Dimethylcarbamoyl)-6-(phenylethynyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9cc). Carbamylation of **7n** with dimethylcarbamoyl chloride (80% yield) with subsequent deprotection using method E provided **9cc** (73% yield, 58% yield overall). Mp: 84–88 °C. NMR ($CDCl_3$, 300 MHz): δ 8.83 (s, 0.5H), 8.79 (d, 0.5H, J = 2.2 Hz), 8.61 (dd, 0.5H, J = 1.5, 4.8 Hz), 8.54 (d, 0.5H, J = 4.0 Hz), 8.37 (dd, 1H, J = 3.8, 8.3 Hz), 8.19 (s, 0.5H), 8.15 (s, 0.5H), 7.96 (dt, 0.5H, J = 1.9, 7.8 Hz), 7.88 (d, 0.5H, J = 8.1 Hz), 7.71 (s, 1H), 7.52–7.60 (c, 3H), 7.30–7.40 (c, 4H), 5.98 (s, 0.5H), 5.72 (s, 0.5H), 4.69 (dd, 0.5H, J = 7.0, 8.8 Hz), 4.63 (t, 0.5H, J = 7.6 Hz), 3.56 (dd, 0.5H, J = 7.4, 10.3 Hz), 3.42 (dd, 0.5H, J = 7.4, 10.3 Hz), 3.22 (t, 0.5H, J = 9.6 Hz), 3.16 (s, 3H), 3.13 (t, 0.5H, J = 9.9 Hz), 3.12 (s, 3H). IR (KBr): 1390 (s), 1661 (s), 1700 (s), 3436 (br). Mass spectrum (DCI/NH_3): 481 (M + H)$^+$. Anal. ($C_{28}H_{24}N_4O_2S$·0.5H_2O·0.1$CHCl_3$) C, H, N.

(2*RS*,4*R*)-1-(Dimethylcarbamoyl)-6-(3-pyridyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9dd). Carbamylation of **7v** with dimethylcarbamoyl chloride (44% yield) with subsequent deprotection using method E provided **9dd** (55% yield, 24% yield overall). NMR ($CDCl_3$, 300 MHz): δ 8.90 (s, 1H), 8.84 (s, 0.5H), 8.80 (s, 0.5H), 8.66–8.52 (c, 2H), 8.49 (dd, 1H, J = 2.8, 8.3 Hz), 8.19 (s, 0.5H), 8.14 (s, 0.5H), 7.85–7.99 (c, 2H), 7.76 (s, 1H), 7.60 (dt, 1H, J = 1.9, 8.5 Hz), 7.28–7.43 (m, 2H), 6.00 (s, 0.5H), 5.73 (s, 0.5H), 4.71 (t, 0.5H, J = 8.1 Hz), 4.65 (t, 0.5H, J = 7.4 Hz), 3.56 (dd, 0.5H, J = 7.4, 10.3 Hz), 3.42 (dd, 0.5H, J = 7.0, 10.3 Hz), 3.24 (td, 0.5H, J = 2.2, 9.9 Hz), 3.18 (s, 3H), 3.14 (s, 3H), 3.08–3.00 (m, 0.5H). IR (KBr): 1183 (m), 1390 (s), 1661 (s), 1698 (s), 3442 (br). Mass spectrum (DCI/NH_3): 458 (M + H)$^+$. Anal. ($C_{25}H_{23}N_5O_2S$·0.2H_2O·0.2CH_2Cl_2) C, H, N.

(2*RS*,4*R*)-1-(Dimethylcarbamoyl)-6-(2-methoxyethoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9ee). Carbamylation of **7w** with dimethylcarbamoyl chloride (26% yield) with subsequent deprotection using method E provided **9ee** (48% yield, 12% yield overall). NMR ($CDCl_3$, 300 MHz): δ 8.83 (s, 0.5H), 8.78 (s, 0.5H), 8.60 (d, 0.5H, J = 4.8 Hz), 8.54 (d, 0.5H, J = 4.8 Hz), 8.25 (dd, 1H, J = 2.6, 8.8 Hz), 8.02 (s, 0.5H), 7.96 (d, 0.5H, J = 8.1 Hz), 7.95 (s, 0.5H), 7.88 (d, 0.5H, J = 7.7 Hz), 7.33 (ddd, 1H, J = 4.6, 7.8, 12.3 Hz), 7.10–7.02 (c, 2H), 6.00 (s, 0.5H), 5.71 (s, 0.5H), 4.66 (dd, 0.5H, J = 7.4, 8.8 Hz), 4.58 (t, 0.5H, J = 7.6 Hz), 4.22–4.15 (c, 2H), 3.82–3.76 (c, 2H), 3.52 (dd, 0.5H, J = 7.0, 10.3 Hz), 3.47 (s, 3H), 3.40 (dd, 0.5H, J = 7.0, 10.3 Hz), 3.20 (t, 0.5H, J = 9.8 Hz), 3.13 (s, 3H), 3.09 (s, 3H), 3.08–3.00 (m, 0.5H). IR (KBr): 1230 (s), 1390 (s), 1492 (s), 1657 (s), 1697 (s), 3442. Mass spectrum (DCI/NH_3): 455 (M + H)$^+$. Anal. ($C_{23}H_{26}N_4O_4S$·0.5H_2O) C, H; N: calcd, 12.09; found, 11.51.

(2*RS*,4*R*)-6-Bromo-1-(dimethylcarbamoyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9ff). Carbamylation of **7p** with dimethylcarbamoyl chloride provided **15** in 87% yield. Deprotection using method E provided **9ff** (76% yield, 66% yield overall). NMR ($CDCl_3$, 300 MHz): δ 8.90 (br m, 0.5H), 8.80 (br m, 0.5H), 8.58 (br m, 1H), 8.28 (d, 0.5H, J = 2.9 Hz), 8.11 (s, 0.5H), 8.07 (s, 0.5H), 8.02 (m, 0.5H), 7.98 (m, 0.5H), 7.73 (br s, 1H), 7.49 (m, 1H), 7.43 (m, 0.5H), 7.37 (m, 0.5H), 6.00 (s, 0.5H), 5.72 (s, 0.5H), 4.67 (dd, 0.5H, J = 7.3, 8.8 Hz), 4.59 (dd, 0.5H, J = 7.4, 7.8 Hz), 3.53 (dd, 0.5H, J = 7.3, 10.3 Hz), 3.40 (dd, 0.5H, J = 6.9, 11.3 Hz), 3.18 (m, 1H), 3.14 (s, 1.5H), 3.11 (s, 1.5H). IR ($CDCl_3$): 3300, 3100, 2920, 1700, 1665, 1530, 1465, 1390. Mass spectrum (DCI/NH_3): 461 (M + H$^+$, 25), 459 (M + H$^+$, 28), 108 (100). Anal. ($C_{20}H_{19}N_4O_2S$·$C_6H_8O_7$·H_2O) C, H, N.

(2*RS*,4*R*)-1-(Dimethylcarbamoyl)-5,6-dimethoxy-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9gg). Carbamylation of **7s** with dimethylcarbamoyl chloride (32% yield) with subsequent deprotection using method E provided **9gg** (32% yield, 10% yield overall). Mp: 104 °C NMR ($CDCl_3$, 300 MHz): δ 8.85–8.83 (c, 0.5H), 8.80–8.76 (c, 0.5H), 8.63–8.60 (c, 0.5H), 8.55–8.52 (c, 0.5H), 7.95 (m, 1H), 7.32 (s, 1H), 7.71 (s, 1H), 7.25 (s, 1H), 7.19 (s, 1H), 7.12 (d, 1H, J = 3.0 Hz), 6.00 (br s, 0.5H), 5.71 (br s, 0.5H), 4.70–4.56 (c, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.12 (s, 6H). Mass spectrum (DCI/NH_3): 441 (M + H)$^+$, 523. Anal. ($C_{22}H_{24}N_4O_4S$) C, H, N.

(2*RS*,4*R*)-1-(Dimethylcarbamoyl)-6-fluoro-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9hh). Carbamylation of **7o** with dimethylcarbamoyl chloride (68% yield) with subsequent deprotection using method E provided **9hh** (75% yield, 51% yield overall). Mp: 69–70 °C. NMR ($CDCl_3$, 300 MHz): δ 8.85–8.84 (m, 0.5H), 8.78–8.77 (m, 0.5H), 8.62–8.60 (m, 0.5H), 8.55–8.53 (m, 0.5H), 8.38–8.31 (m, 1H), 8.11 (s, 0.5H), 8.06 (s, 0.5H), 7.97–7.87 (m, 1H), 7.38–7.30 (m, 1H), 7.28–7.26 (m, 0.5H), 7.17–7.15 (m, 0.5H), 7.15–7.10 (m, 2H), 5.98 (s, 0.5H), 5.61 (s, 0.5H), 4.70–4.57 (m, 1H), 3.25–3.17 (m, 2H), 3.15 (s, 6H). Mass spectrum (FAB): 398 (M + H)$^+$, 307. Anal. ($C_{20}H_{19}N_4O_2S$) C, H; N: calcd, 14.06; found, 13.03.

Indole Functionalization. Method H: (2*RS*,4*R*)-1-(Diethylcarbamoyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]-indole (9f). To a suspension of NaH (0.03 g, 1.1 mmol) in THF (5 mL) at 0 °C was added **7a** (0.3 g, 0.733 mmol). After 15 min, diethylcarbamoyl chloride (0.14 mL, 1.1 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 30 more min. After the addition of water (10 mL), the mixture was extracted twice with ethyl acetate and then dried (Na_2SO_4). The solvent was evaporated and the residue chromatographed on silica gel (EtOAc) to provide 1-(diethylcarbamoyl)-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (0.24 g, 65% yield). Deprotection by method E provided **9f** (62% yield, 40% yield overall). Mp: 84 °C. NMR ($CDCl_3$, 300 MHz): δ 9.10 (m, 0.5H), 9.01 (m, 0.5H), 8.86 (m, 0.5H), 8.65 (m, 0.5H), 8.35–8.40 (c, 2H), 8.18 (m, 1H), 8.11 (m, 1H), 7.74 (m, 1H), 7.51 (m, 1H), 7.38 (m, 2H), 6.50–6.32 (c, 1H), 4.54 (m, 1H), 3.51–3.40 (c, 4H), 3.29–3.10 (c, 2H), 1.31–1.20 (c, 6H). Mass spectrum (DCI/NH_3): 409 (M + H)$^+$, 107. HRMS: ($C_{22}H_{25}N_4O_2S$) theoretical 409.1698, experimental 409.1718.

Prepared by the same route was **(2*RS*,4*R*)-1-(*N*-Phenyl-*N*-methylcarbamoyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9e).** Carbamylation of **7a** with *N*-methyl-*N*-phenylcarbamoyl chloride (60% yield) and subsequent deprotection by method E gave **9e** (42% yield, 25% yield overall). Mp: 72–76 °C. NMR ($CDCl_3$, 300 MHz): δ 9.10 (m, 0.5H), 8.90 (m, 0.5H), 8.63 (m, 1H), 8.32–8.22 (c, 2H), 8.30–7.98 (c, 2H), 7.60–7.10 (c, 9H), 6.00–5.61 (c, 1H), 4.30–4.07 (m, 1H), 3.62 (m, 1H), 2.9–2.60 (c, 2H). Mass spectrum (DCI/NH_3): 443 (M + H)$^+$, 310, 311, 107. Anal. ($C_{25}H_{22}N_4O_2S$·0.25H_2O) C, H, N.

Method I: (2*RS*,4*R*)-1-(*N*-Methylcarbamoyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9h). 2,2,6,6-Tetramethylpiperidine (0.09 mL, 0.49 mmol) was dissolved in THF, and BuLi (2.5 M in hexanes, 0.2 mL, 0.50 mmol) was added. The solution was cooled to −78 °C, and a solution in THF of **7a** (0.20 g, 0.49 mmol) was added dropwise. The reaction mixture was stirred for 5 min, after which neat methyl isocyanate (0.03 mL, 0.50 mmol) was added. The cold bath was removed after 15 min, and the reaction mixture was stirred for 16 h at ambient temperature. The THF was removed in vacuo, and the residue was taken up in methylene chloride, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by chromatography on silica gel (40% yield). The resulting material was deprotected by method E (42% yield, 17% yield overall). Mp: 101–102 °C. NMR ($CDCl_3$, 300 MHz): δ 8.83 (m, 1H), 8.63 (m, 1H), 8.57 (m, 1H), 8.36 (m, 1H), 8.32–8.25 (m, 2H), 8.16 (m, 1H), 7.70 (m, 1H), 7.40–7.30 (c, 2H), 5.80 (m, 1H), 4.93 (m, 1H), 3.64–3.56 (m, 2H), 2.96 (s, 3H). Mass spectrum (DCI/NH_3): 366 (M + H)$^+$, 424. Anal. ($C_{23}H_{22}N_4O_2S$·2$C_2H_2O_4$) H, N; C: calcd, 50.55; found, 51.09.

Prepared by the same method was **(2*RS*,4*R*)-1-[*N*-(2,2-Dimethylethyl)carbamoyl]-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9i).** Reaction of **7a** and *tert*-butyl isocyanate (53% yield) with subsequent deprotection (method E, 82% yield, 43% yield overall) gave **9i**. Mp: 101–103 °C. NMR ($CDCl_3$, 300 MHz): δ 8.81 (m, 1H), 8.61 (m, 0.5H), 8.54 (m, 0.5H), 8.44 (m,

2H), 8.39 (s, 0.5H), 8.30 (s, 0.5H), 7.96 (m, 0.5H), 7.88 (m, 0.5H), 7.77 (m, 1H), 7.48–7.30 (c, 4H), 5.74–5.66 (c, 1H), 4.76–4.60 (c, 1H), 3.60–3.53 (m, 1H), 3.43 (m, 1H), 1.57 (br s, 9H). Mass spectrum (DCI/NH_3): 408 (M + H)$^+$. Anal. ($C_{22}H_{24}N_4O_2S$·0.75H_2O) C, H, N.

Method J: Preparation of (2*RS*,4*R*)-1-[(Ethoxycarbonyl)methyl]-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9m). Sodium hydride (60% dispersion, 9.0 mg, 0.38 mmol) and DMF (0.5 mL) were stirred under N_2 and cooled in an ice bath. A solution in 0.5 mL of DMF and **7a** (150 mg, 0.37 mmol) was added over 2 min. The resulting orange solution was stirred at 5 °C for 30 min, and then a solution of ethyl chloroacetate (49 mg, 0.40 mmol) in 0.25 mL of DMF was added over 1 min. The mixture was stirred at 5 °C for 30 min and then at ambient temperature for 1 h. The reaction was quenched with 0.5 mL of H_2O, and the solvents were removed *in vacuo*. The residue was partitioned between H_2O and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give **10b** as a white foamy solid (0.261 g, 78% yield). The crude material was deprotected using method D to give **9m** (91% yield, 74% yield overall). NMR ($CDCl_3$, 300 MHz): δ 8.83 (d, 0.5H, *J* = 3.0 Hz), 8.78 (d, 0.5H, *J* = 3.0 Hz), 8.60 (dd, 0.5H, *J* = 1.5, 4.5 Hz), 8.52 (dd, 0.5H, *J* = 1.5, 4.5 Hz), 8.44–8.37 (m, 1H), 8.00–7.93 (m, 1H), 7.90–7.84 (m, 1H), 7.40–7.24 (m, 4H), 6.02 (s, 0.5H), 5.72 (s, 0.5H), 4.93 (s, 1H), 4.88 (s, 1H), 4.68 (dd, 0.5H, *J* = 1.5, 7.5 Hz), 4.60 (bt, 0.5H, *J* = 7.5 Hz), 4.25 (m, 2H, *J* = 7.5 Hz), 3.61–3.80 (m, 1H), 3.54 (dd, 0.5H, *J* = 3.0, 10.5 Hz), 3.40 (dd, 0.5H, *J* = 3.0, 10.5 Hz), 3.26–3.12 (m, 1H), 1.28 (dd, 3H, *J* = 7.5, 1.5 Hz). IR (KBr): 3440, 1745, 1640, 1530, 1465, 1385, 1210, 1190, 1050, 1020. Mass spectrum (DCI/NH_3): 396 (M + H)$^+$, 125, 108. Anal. ($C_{21}H_{21}N_3O_3S$) C, H; N: calcd, 10.63; found, 10.04.

Also prepared by this method were the following:

(2*RS*,4*R*)-1-Carbomethoxyethyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9n). Alkylation of **7a** with methyl acrylate provided **10a** in 43% yield. Deprotection by method D (79% yield) provided **9n** (34% overall yield). NMR ($CDCl_3$, 300 MHz): δ 8.85 (d, 0.41H, *J* = 0.3 Hz), 8.80 (d, 0.59H, *J* = 0.3 Hz), 8.62 (dd, 0.59H, *J* = 0.3, 0.6 Hz), 8.53 (dd, 0.41H, *J* = 0.3, 0.6 Hz), 8.40 (m, 1H), 8.05–7.85 (m, 2H), 7.30–7.44 (m, 4H), 6.03 (s, 0.38H), 5.72 (s, 0.62H), 4.70–4.50 (m, 3H), 3.70 (s, 2H), 3.65 (s, 1H), 3.60–3.35 (m, 2H), 3.15 (m, 1H), 2.90 (m, 2H). Mass spectrum (DCI/NH_3): 396 (M + H)$^+$. Anal. ($C_{21}H_{21}N_3O_3S$·0.25H_2O) C, H, N.

(2*RS*,4*R*)-1-[(*N*,*N*-Dimethylcarbamoyl)methyl]-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9o). Alkylation of **7a** with *N*,*N*-dimethyl-2-chloroacetamide (60% yield), with subsequent deprotection by method D gave **9n** (58% yield, 35% yield overall). NMR ($CDCl_3$, 300 MHz): δ 8.82 (m, 1H), 8.60 (m, 0.5H), 8.53 (m, 0.5H), 8.40 (m, 1H), 7.98 (m, 1H), 7.88 (s, 1H), 7.30 (m, 4H), 6.02 (s, 0.4H), 5.70 (s, 0.6H), 4.98 (d, 2H, *J* = 0.9 Hz), 4.68 (m, 1H), 4.57 (m, 0.5H), 3.53 (q, 1H, *J* = 0.6, 0.9 Hz), 3.40 (q, 1H, *J* = 0.6, 0.9 Hz), 3.20 (m, 4H), 3.02 (d, 3H, *J* = 0.9 Hz). Mass spectrum (DCI/NH_3): 395 (M + H)$^+$. Anal. ($C_{21}H_{22}N_4O_2S$·0.5H_2O) C, H, N.

(2*RS*,4*R*)-1-[(*N*-Methylcarbamoyl)methyl]-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9p). Alkylation of **7a** with *N*-methyl-2-chloroacetamide (38% yield) followed by deprotection (method D, 50% yield) provided **9p** (19% overall yield). NMR ($CDCl_3$, 300 MHz): δ 8.84 (d, 0.4H, *J* = 0.3 Hz), 8.75 (d, 0.6H, *J* = 0.3 Hz), 8.58 (dd, 0.6H, *J* = 0.3, 0.6 Hz), 8.50 (dd, 0.4H, *J* = 0.3, 0.6 Hz), 8.40 (m, 1H), 7.95 (m, 1H), 7.85 (m, 1H), 7.25–7.45 (m, 4H), 6.00 (s, 0.4H), 5.73 (s, 0.6H), 5.50 (m, 1H), 4.85 (d, 2H, *J* = 1.5 Hz), 4.69 (t, 0.63H, *J* = 0.6, 1.2 Hz), 4.60 (t, 0.37H, *J* = 0.6, 1.2 Hz), 3.53 (dd, 0.5H, *J* = 0.6, 1.2 Hz), 3.40 (dd, 0.5H, *J* = 0.6, 1.2 Hz), 3.20 (m, 2H), 2.78 (d, 3H, *J* = 0.6 Hz). Mass spectrum (DCI/NH_3): 381 (M + H)$^+$. Anal. ($C_{20}H_{20}N_4O_2S$·0.25H_2O) C, H; N: calcd, 14.55; found 14.08.

(2*RS*,4*R*)-1-(2,2,2-Trifluoroethyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (9q). To a solution of **7a** (0.3 g, 0.7 mmol) in DMF was added K_2CO_3 (0.81 g, 5.86 mmol). After stirring for 15 min, 2-iodo-1,1,1-trifluoroethane (0.11 mL, 1.09 mmol) was added, and the mixture was stirred at 40 °C for 20 h. After addition of 20 mL of CH_2Cl_2, a solid was obtained by filtration, rinsing well with CH_2Cl_2. The filtrate was washed with citric acid (0.5 M) and brine and then dried (Na_2SO_4). After concentrating the solution, chromatography (3:7 EtOAc–CH_2Cl_2) provided 1-(2,2,2-trifluoroethyl)-3-[2-(3-pyridinyl)-3-(*tert*-butoxycarbonyl)thiazolidin-4-oyl]indole (0.1 g, 28% yield). Deprotection using method E provided **9q** (53% yield, 15% yield overall). NMR ($CDCl_3$, 300 MHz): δ 3.36–3.57 (2H), 4.56–4.70 (1H), 4.71–4.81 (2H), 5.74 (0.5H), 6.00 (0.5H), 7.30–7.38 (2H), 7.40–7.43 (2H), 7.90–7.94 (2H), 7.95–7.98 (1H), 8.40–8.45 (1H), 8.52–8.55 (0.5H), 8.60–8.63 (0.5H), 8.78–8.79 (0.5H), 8.84–8.85 (0.5H). Mass spectrum (DCI/NH_3): 391 (M + H)$^+$. Anal. ($C_{19}H_{16}F_3N_3OS$·1.5H_2O) C, H; N: calcd, 10.04; found, 9.48.

(2*RS*,4*R*)-1-(3-Amino-3-oxopropyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (12). Acid **11b** (1.80 g, 3.77 mmol) was dissolved in THF (50 mL), and *N*-methylmorpholine (496 μL, 4.5 mmol) was added, followed by the addition of diphenyl phosphorazidate (1.2 mL, 5.65 mmol). The reaction was heated to reflux for 4.5 h and allowed to cool, and 15 mL of water was added. The mixture was extracted three times with ethyl acetate. The organics were dried over $MgSO_4$ and purified on silica gel (97:3 $CHCl_3$/MeOH) to give the isocyanate as a yellow oil (1.23 g, 68% yield). The isocyanate (0.120 g, 0.251 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. The solution was bubbled with ammonia for 5–10 min to give a cloudy suspension. Solvent removal gave the urea as a yellow foam. Deprotection of the crude material by method D, and purification on silica gel (95:5 $CHCl_3$/MeOH) provided **12** as an off-white solid (72% yield). NMR (DMSO-d_6, 300 MHz): δ 8.74 (d, 0.62H, *J* = 3.0 Hz), 8.71 (d, 0.38H, *J* = 3.0 Hz), 8.55 (dd, 0.62H, *J* = 6.0, 1.5 Hz), 8.43 (dd, 0.38H, *J* = 6.0, 1.5 Hz), 8.38 (s, 0.62H), 8.31 (s, 0.38H), 8.29 (d, 2H, *J* = 7.0 Hz), 8.13 (br d, 0.62H, *J* = 7.0 Hz), 8.04 (br d, 0.38H, *J* = 7.0 Hz), 7.58 (t, 1H, *J* = 6.0, 7.0 Hz), 7.50 (m, 0.62H), 7.43 (m, 0.38H), 7.3 (m, 2H), 6.03 (s, 0.38H), 5.63 (s, 0.62H), 4.35 (m, 2H), 3.65 (d, 0.62H, *J* = 7.0 Hz), 3.62 (d, 0.38H, *J* = 7.0 Hz), 3.53 (m, 3H), 3.16 (m, 0.62H), 3.12 (m, 0.38H). Mass spectrum (DCI/NH_3): 396 (M + H$^+$). Anal. ($C_{20}H_{21}N_5O_2S$·0.5H_2O) C, H, N.

Method K: (2*RS*,4*R*)-1-(Carboxymethyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (13a). A solution of **10a** (0.120 g, 0.24 mmol) in THF (0.7 mL) was treated with LiOH (0.028 g, 0.667 mmol) in water (0.7 mL). After 1 h at ambient temperature, the solution was evaporated to dryness, and the residues were partitioned between Et_2O and water. The aqueous phase was acidified to pH 2 and extracted three times with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried (Na_2SO_4), and concentrated to give **11a** as an ivory solid (0.064 g, 57% yield). Deprotection using method D provided **9p** as a pink powder (82% yield, 47% yield for two steps). NMR ($CDCl_3$, 300 MHz): δ 9.20–9.12 (m, 1H), 8.97–8.65 (m, 4H), 8.26–8.18 (m, 1H), 8.12–8.03 (m, 1H), 7.63–7.55 (m, 1H), 7.37–7.28 (m, 2H), 6.32 (s, 0.5H), 6.15 (s, 0.5H), 5.46–5.16 (m, 3H), 3.90–3.77 (m, 1H), 3.51–3.17 (m, 1H). Mass spectrum (FAB): 368, 307, 289, 219, 202. Anal. ($C_{19}H_{17}N_3O_3S$·2HCl·0.5H_2O) C, H; N: calcd, 9.35; found, 8.92.

Also prepared by this method was **(2*RS*,4*R*)-1-(Carboxyethyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (13b).** Hydrolysis of **10b** provided **11b** (92% yield). Deprotection using method D gave **13b** (34% yield, 31% yield overall). NMR ($CDCl_3$, 300 MHz): δ 8.85 (d, 1H, *J* = 0.7 Hz), 8.42 (m, 2H), 8.23 (s, 0.5H), 8.13 (s, 0.5H), 8.90 (d, 0.5H, *J* = 0.7 Hz), 7.98 (d, 0.5H, *J* = 0.7 Hz), 7.35 (m, 5H), 6.00 (s, 0.5H), 5.74 (s, 0.5H), 4.75 (m, 0.5H), 4.55 (m, 2.5H), 3.38 (dd, 0.5H, *J* = 0.6, 1.2 Hz), 3.15 (m, 1H), 2.90 (m, 2H). Mass spectrum (DCI/NH_3): 382 (M + H)$^+$. Anal. ($C_{20}H_{19}N_3O_3S$·0.15$CHCl_3$) C, H; N: calcd, 10.52; found, 9.89.

Method L: (2*RS*,4*R*)-1-(Carbamoylmethyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (14a). To a solution of **13a** (0.5 g, 1 mmol) in methylene chloride (20 mL) at 0 °C was added sodium hydride (46 mg, 1.1 mmol). After 5 min, oxalyl chloride (99 mL, 1.1 mmol) was added and the reaction mixture was stirred for 15 min. Gaseous ammonia was than bubbled through the solution for 30 s. The reaction mixture was concentrated in vacuo and the residue partitioned between saturated aqueous $NaHCO_3$ and chloroform. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 97:3 chloroform–MeOH) to afford **14a** (230 mg, 50% yield). NMR ($CDCl_3$–D_2O, 300 MHz): δ 8.78 (d, 1H, *J* = 0.3 Hz), 8.60 (dd, 0.5H, *J* = 0.2, 0.5 Hz), 8.48 (m, 0.5H), 8.40 (m, 1H), 8.04 (s, 0.5H), 7.95 (m, 1H), 7.83 (m, 0.5H), 7.45 (m, 4H), 6.00 (s, 0.4H), 5.70 (s, 0.6H), 4.65 (t, 1H, *J* = 0.9, 0.7 Hz), 4.55 (m, 3H), 3.75 (m, 0.5H), 3.65 (m, 0.5H), 3.50

(dd, 0.5H, J = 0.9, 0.6 Hz), 3.35 (dd, 0.5H, J = 0.9, 0.6 Hz), 3.14 (m, 1H), 2.75 (m, 2H). Mass spectrum (DCI/NH_3): 381 (M + H)$^+$. Anal. ($C_{19}H_{18}N_4O_2S \cdot H_2O$) C, H; N: calcd, 14.57; found, 13.78.

Also made by this method was **(2*RS*,4*R*)-1-[2-(Aminocarbonyl)ethyl]-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (14b).** Acylation of ammonia with **13b** provided **14b** (50% yield). NMR ($CDCl_3$–D_2O, 300 MHz): δ 8.78 (d, 1H, J = 0.3 Hz), 8.60 (dd, 0.5H, J = 0.2, 0.5 Hz), 8.48 (m, 0.5H), 8.40 (m, 1H), 8.04 (s, 0.5H), 7.95 (m, 1H), 7.83 (m, 0.5H), 7.45 (m, 4H), 6.00 (s, 0.4H), 5.70 (s, 0.6H), 4.65 (t, 1H, J = 0.7, 0.9 Hz), 4.55 (m, 3H), 3.75 (m, 0.5H), 3.65 (m, 0.5H), 3.50 (dd, 0.5H, J = 0.6, 0.6 Hz), 3.35 (dd, 0.5H, J = 0.6, 0.9 Hz), 3.14 (m, 1H), 2.75 (m, 2H). Mass spectrum (DCI/NH_3): 381 (M + H)$^+$. Anal. ($C_{20}H_{20}N_4O_2S \cdot 0.5CH_2Cl_2$) C, H; N: calcd, 13.24; found, 12.74.

(2*RS*,4*R*)-1-(Dimethylcarbamoyl)-6-(4-fluorophenoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (16). Compound 15 (*vide supra*, 0.095 g, 0.17 mmol) and (4-fluorophenyl)boronic acid (0.039 g, 0.28 mmol) were suspended in a deoxygenated solution of 4 mL of DME and 1 mL of aqueous $NaHCO_3$ under N_2. Palladium tetrakis(triphenylphosphine) (0.021 g, 0.02 mmol) was added, and the mixture heated to 85 °C for 7 h. The mixture was partitioned between pH 7 buffer (25 mL) and EtOAc (2 × 50 mL), and the combined organics were dried over $MgSO_4$. The isolated material (0.101 g, 93% yield) was deprotected using method E to provide **16** (0.076 g, 91% yield, 85% yield overall). Mp: 98–102 °C. NMR ($CDCl_3$, 300 MHz): δ 8.87 (m, 1H), 8.68 (m, 1H), 8.42 (m, 1H), 8.15 (s, 0.5H), 8.10 (s, 0.5H), 7.97 (m, 1H), 7.69 (m, 1H), 7.55 (m, 6H), 6.04 (s, 0.5H), 5.75 (s, 0.5H), 4.72 (dd, 0.5H, J = 7.1, 9.7 Hz), 4.54 (t, 0.5H, J = 7.0 Hz), 3.54 (dd, 0.5H, J = 7.0, 10.3 Hz), 3.41 (dd, 0.5H, J = 7.1, 10.7 Hz), 3.22 (m, 1H), 3.18 (s, 3H), 3.11 (s, 3H). IR ($CDCl_3$): 3440 (br), 2920, 1695, 1650, 1595, 1510, 1390, 1150. Mass spectrum (DCI/NH_3): 475 (M + H$^+$, 25), 279 (100). HRMS: calcd for $C_{26}H_{23}F_1N_4O_2S$ 475.1604, found 475.1597.

(2*RS*,4*R*)-1-(Dimethylcarbamoyl)-6-(4-fluorophenoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (18). Compound 15 (*vide supra*, 0.244 g, 0.44 mmol) and hexamethylditin (0.178 g, 0.54 mmol) were dissolved in deoxygenated toluene (8 mL) under Ar. Palladium tetrakis(triphenylphosphine) (0.032 g, 0.03 mmol) was added, and the mixture was heated to reflux for 7 h. The reaction mixture was partitioned between pH 7 buffer (25 mL) and EtOAc (2 × 50 mL), and the combined organics were dried over $MgSO_4$. Solvent removal gave **17** as a yellow wax (0.240 g, 85% yield).

Arylstannane **17** (116 mg, 0.180 mmol) and 1,8-bis(dimethylamino)naphthalene (20 mg, 93 μmol) in THF (1.70 mL) was treated with benzoyl chloride (21 μL, 0.18 mmol). After a few minutes, allylpalladium chloride dimer (3.6 mg, 9.8 μmol, 11 mol % Pd) was added and the reaction mixture stirred for 5 min at ambient temperature, and then reflux was employed for 2 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (2 × 40 mL) and saturated aqueous NaCl. Drying (Na_2SO_4), filtration, and concentration gave a cloudy yellow oil, which was purified by flash chromatography on silica gel ($CHCl_3$–MeOH) to afford a pale green foamy oil (70 mg, 67% yield). Deprotection using method E gave **18** as a yellow foam (76% yield, 51% yield overall). Mp: 81–85 °C. NMR ($CDCl_3$, 300 MHz): δ 9.10 (d, 0.4H, J = 1.5 Hz), 9.00 (br s, 0.6H), 8.89–8.84 (c, 0.4H), 8.64 (m, 1H), 8.47 (dd, 0.6H, J = 4.2, 8.3 Hz), 8.43–8.26 (c, 1.6H), 8.19 (dt, 0.4H, J = 2.0, 7.8 Hz), 8.13–8.03 (c, 1H), 7.82 (dd, 2H, J = 7.6, 9.0 Hz), 7.72–7.60 (c, 2H), 7.51 (dd, 2H, J = 7.0, 8.1 Hz), 7.48–7.37 (c, 1H), 6.06 (s, 0.6H), 5.77 (s, 0.4H), 4.78 (t, 0.4H, J = 7.8 Hz), 4.65 (t, 0.6H, J = 7.4 Hz), 3.60 (dd, 0.4H, J = 7.5, 10.5 Hz), 3.53–3.44 (m, 0.6H), 3.33–3.17 (c, 1H), 3.16 (s, 3H), 3.13 (s, 3H). Mass spectrum (DCI/NH_3): 485 (M + H)$^+$. Anal. ($C_{27}H_{24}N_4O_3S \cdot 0.6H_2O$) C, H; N: calcd, 11.31; found, 11.86.

Indole Functionalization. Method M: (2*RS*,4*R*)-1-(*tert*-Butoxycarbonyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]-indole (19a). Di-*tert*-butyl dicarbonate (0.15 g, 0.69 mmol) was added to a solution of **8a** (0.200 g, 0.65 mmol) and DMAP (0.009 g, 0.07 mmol) in CH_3CN (6.5 mL), and the mixture was stirred for 1 h. The mixture was then partitioned between saturated NH_4Cl and EtOAc. The organic phase was washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$. Solvent removal gave **19a** (0.226 g, 85% yield) as a pale brown gum. NMR ($CDCl_3$, 300 MHz): δ 8.52 (dd, 0.5H, J = 1.5, 4.8 Hz), 8.45 (dd, 0.5H, J = 1.5, 4.8 Hz), 8.34 (s, 0.5H), 8.32 (s, 0.5H), 8.18 (m, 0.5H), 8.15 (m, 0.5H), 8.11 (m, 0.5H), 8.07 (m, 0.5H), 7.46–7.38 (m, 3H), 7.37 (d, 0.5H, J = 1.5 Hz), 7.34 (d, 0.5H, J = 1.0 Hz), 5.90 (bs, 0.5H), 5.75 (bs, 0.5H), 4.93 (m, 1H), 3.60 (dd, 0.5H, J = 7.3, 10.3 Hz), 3.49 (dd, 0.5H, J = 7.4, 10.3 Hz), 3.24 (m, 1H), 1.73 (s, 4.5H), 1.70 (s, 4.5H). IR ($CDCl_3$): 2980, 2920, 1735, 1660, 1445, 1370, 1235, 1045. Mass spectrum (DCI/NH_3): 410 [(M + H)$^+$, 100], 376 (10), 310 (10). HRMS: ($C_{22}H_{24}N_3O_3S$) theoretical 410.1538, experimental 410.1552.

Also prepared by this method were the following:

(2*RS*,4*R*)-1-(Methoxycarbonyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (19b): 32% yield from **8a** and dimethyl dicarbonate. NMR ($CDCl_3$, 300 MHz): δ 8.84 (d, 0.5H, J = 1.2 Hz) 8.80 (d, 0.5H, J = 1.3 Hz), 8.61 (dd, 0.5H, J = 1.2, 4.3 Hz), 8.54 (dd, 0.5H, J = 1.3, 4.5 Hz), 8.42 (s, 0.5H), 8.39 (m, 1H), 8.35 (s, 0.5H), 8.21 (br s, 0.5H (NH)), 8.19 (br s, 0.5H (NH)), 7.95 (m, 0.5H), 7.88 (m, 0.5H), 7.40 (m, 4H), 6.01 (br s, 0.5H), 5.73 (m, 0.5H), 4.70 (m, 1H), 4.16 (s, 1.5H), 4.12 (s, 1.5H), 3.57 (dd, 0.5H, J = 7.4, 10.6 Hz), 3.43 (dd, 0.5H, J = 7.4, 10.3 Hz), 3.17 (m, 1H). IR ($CDCl_3$): 3480, 3300, 3030, 2980, 2920, 1755, 1665, 1540. Mass spectrum (FAB): 368 [(M + H)$^+$, 20], 201 (20), 185 (100). HRMS: ($C_{19}H_{18}N_3O_3S$) theoretical 368.1069, experimental 368.1081.

(2*RS*,4*R*)-1-(Ethoxycarbonyl)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (19c): 76% yield from **8a** and diethyl dicarbonate. NMR ($CDCl_3$, 300 MHz): δ 8.84 (d, 0.5H, J = 1.2 Hz), 8.80 (d, 0.5H, J = 1.3 Hz), 8.61 (dd, 0.5H, J = 1.2, 4.3 Hz), 8.54 (dd, 0.5H, J = 1.3, 4.5 Hz), 8.42 (s, 0.5H), 8.39 (m, 1H), 8.35 (s, 0.5H), 8.21 (br s, 0.5H, (NH)), 8.19 (bds, 0.5H, (NH)), 7.95 (m, 0.5H), 7.88 (m, 0.5H), 7.40 (m, 4H), 6.01 (br s, 0.5H), 5.73 (m, 0.5H), 4.70 (m, 1H), 4.16 (s, 1.5H), 4.12 (s, 1.5H), 3.57 (dd, 0.5H, J = 7.4, 10.6 Hz), 3.43 (dd, 0.5H, J = 7.4, 10.3 Hz), 3.17 (m, 1H). IR ($CDCl_3$): 3480, 3300, 3030, 2980, 2920, 1755, 1665, 1540, 1450, 1440, 1235. Mass spectrum (FAB): 382 [(M + H)$^+$, 20], 201 (20), 185 (100). HRMS: ($C_{20}H_{20}N_3O_3S$) theoretical 382.1225, experimental 382.1241.

(2*RS*,4*R*)-1-[(Phenylmethoxy)carbonyl]-3-[2-(3-pyridinyl)-thiazolidin-4-oyl]indole (19d): 47% yield from **8a** and dibenzyl dicarbonate. NMR ($CDCl_3$, 300 MHz): δ 8.82 (d, 0.5H, J = 1.4 Hz), 8.79 (d, 0.5H, J = 2.2 Hz), 8.61 (dd, 0.5H, J = 1.9, 4.8 Hz), 8.54 (dd, 0.5H, J = 1.1, 4.8 Hz), 8.40 (s, 0.5H), 8.38 (m, 1H), 8.35 (s, 0.5H), 8.18 (m, 1H), 7.95 (m, 0.5H), 7.87 (m, 0.5H), 7.45 (m, 8H), 5.99 (d, 0.5H, J = 8.0 Hz), 5.72 (d, J = 12.9 Hz), 5.55 (br s, 1H), 5.51 (br s, 1H), 4.71 (m, 0.5H), 4.66 (m, 0.5H), 3.55 (dd, 0.5H, J = 7.3, 10.2 Hz), 3.40 (dd, 0.5H, J = 7.0, 10.3 Hz), 3.18 (dd, 0.5H, J = 4.4, 10.8 Hz), 3.14 (dd, 0.5H, J = 3.0, 7.8 Hz). IR ($CDCl_3$): 3480, 3300, 3040, 2960, 2900, 1740, 1670, 1540, 1450, 1225. Mass spectrum (DCI/NH_3): 444 [(M + H)$^+$, 100], 410 (25), 324 (25), 310 (50). Anal. ($C_{25}H_{21}N_3O_3S \cdot C_2H_2O_4$) C, H, N.

(2*RS*,4*R*)-1-(*tert*-Butoxycarbonyl)-6-(phenylmethoxy)-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (19e): 83% yield from **8d** and di-*tert*-butyl dicarbonate. NMR ($CDCl_3$, 300 MHz): δ 8.83 (d, 0.2H), 8.79 (d, 0.8H, J = 1.9 Hz), 8.62 (dd, 0.8H, J = 1.8, 5.1 Hz), 8.55 (dd, 0.2H), 8.26 (s, 0.8H), 8.23 (s, 0.2H), 7.97 (ddd, 0.8H, J = 1.9, 2.3, 7.8 Hz), 7.88 (m, 0.2H), 7.80 (d, 1H, J = 2.3 Hz), 7.41 (m, 7H), 7.10 (dd, 1H, J = 2.2, 8.8 Hz), 6.03 (s, 0.2H), 5.73 (s, 0.8H), 5.15 (s, 2H), 4.70 (dd, 0.8H, J = 7.3, 9.1 Hz), 4.64 (m, 0.2H), 3.56 (dd, 0.8H, J = 7.3, 10.3 Hz), 3.44 (dd, 0.2H), 3.17 (dd, 0.8H, J = 9.2, 10.3 Hz), 3.15 (dd, 0.2H), 1.71 (s, 7.2H), 1.68 (s, 1.8H). KR (KBr): 3440 (br), 2970, 2920, 1740, 1660, 1615, 1490, 1370, 1275, 1210, 1140. Mass spectrum (FAB): 516 [(M + H)$^+$, 7], 307 (15), 154 (100). Anal. ($C_{29}H_{29}N_4O_4S \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H; N: calcd, 6.84; found, 5.35.

(2*RS*,4*R*)-1-(*tert*-Butoxycarbonyl)-2-methyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (19f): 84% yield from **8f** and di-*tert*-butyl dicarbonate. NMR ($CDCl_3$, 300 MHz): δ 8.85 (d, 0.4H, J = 2.1 Hz), 8.81 (d, 0.6H, J = 1.5 Hz), 8.62 (dd, 0.6H, J = 1.5, 4.8 Hz), 8.55 (dd, 0.4H, J = 2.1, 4.1 Hz), 8.12 (m, 1H), 7.98 (m, 0.6H), 7.86 (m, 0.4H), 7.32 (m, 4H), 6.00 (s, 0.4H), 5.52 (s, 0.6H), 4.90 (dd, 0.6H, J = 7.0, 7.5 Hz), 4.83 (t, 0.4H, J = 7.0 Hz), 3.53 (dd, 0.6H, J = 7.0, 10.7 Hz), 3.40 (dd, J = 7.0, 10.7 Hz), 3.11 (m, 1H), 2.92 (s, 1.2H), 2.88 (s, 1.8H). IR ($CDCl_3$): 3440, 2980, 2920, 1735, 1455. 1370, 1320, 1255, 1145, 1120. Mass spectrum

(FAB): 424 [(M + H)$^+$, 60], 154 (100). Anal. ($C_{25}H_{27}N_3O_3S \cdot C_2H_2O_4 \cdot 0.5C_4H_{10}O$) C, H, N.

(2*RS*,4*R*)-1-(*tert*-Butoxycarbonyl)-6-methyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (19g): 56% yield from **8g** and di-*tert*-butyl dicarbonate. Mp: 95–98 °C. NMR ($CDCl_3$, 300 MHz): δ 8.83 (d, 0.7H, J = 2.2 Hz), 8.80 (d, 0.3H, J = 1.9 Hz), 8.62 (dd, 0.3H, J = 1.6, 4.8 Hz), 8.53 (dd, 0.7H, J = 1.1, 4.7 Hz), 8.29 (s, 0.7H), 8.25 (s, 0.3H), 8.23 (m, 1H), 7.98 (m, 1.3H), 7.87 (m, 0.7H), 7.45 (dd, 0.3H, J = 4.2, 5.5 Hz), 7.30 (dd, 0.7H, J = 0.8, 5.5 Hz), 7.22 (m, 1H), 6.02 (br s, 0.7H), 5.74 (br s, 0.3H), 4.63 (m, 1H), 3.56 (dd, 0.3H, J = 7.0, 10.3 Hz), 3.42 (dd, 0.7H, J = 7.0, 10.7 Hz), 3.17 (m, 1H), 2.50 (s, 2.1H), 1.73 (s, 2.7H), 1.70 (s, 6.3H), 1.56 (s, 0.9H). IR ($CDCl_3$): 3300, 3150, 2980, 2930, 1735, 1665, 1540, 1375, 1240. Mass spectrum (DCI/NH_3) 424 (M + H)$^+$, 392. HRMS: ($C_{23}H_{26}N_3O_3S$) theoretical 424.1695, experimental 424.1687.

(2*RS*,4*R*)-1-(*tert*-Butoxycarbonyl)-6-methoxy-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (19h): 90% yield from **8i** and di-*tert*-butyl dicarbonate. Mp: 99–100 °C. NMR ($CDCl_3$, 300 MHz): δ 9.00–8.97 (m, 0.5H), 8.85–8.83 (m, 0.5H), 8.67–8.64 (m, 1H), 8.26 (s, 0.5H), 8.24–8.18 (m, 2H), 8.12–8.06 (m, 0.5H), 7.67 (s, 1H), 7.63–7.56 (m, 0.5H), 7.50–7.44 (m, 0.5H), 7.30–6.98 (m, 1H), 7.57 (s, 1H), 4.75–4.60 (m, 1H), 3.89 (s, 3H), 3.60–3.42 (m, 2H), 1.71 (s, 9H). Mass spectrum (DCI/NH_3): 439 (M + H)$^+$, 340. Anal. ($C_{23}H_{25}N_3O_4S \cdot C_2H_2O_4$) C, N; H: calcd, 5.14; found, 5.83.

(2*RS*,4*R*)-1-(*tert*-Butoxycarbonyl)-2,5-dimethyl-3-[2-(3-pyridinyl)thiazolidin-4-oyl]indole (19i): 99% yield from **8q** and di-*tert*-butyl dicarbonate. NMR ($CDCl_3$, 300 MHz): δ 8.81–8.80 (m, 1H), 8.62–8.60 (m, 1H), 8.55–8.51 (m, 0.5H), 8.01–7.97 (m, 1H), 7.88 (m, 0.5H), 7.71 (s, 1H), 7.39–7.32 (m, 1H), 7.11–7.02 (m, 1H), 6.05 (s, 0.5H), 5.74 (s, 0.5H), 4.91–4.80 (m, 1H), 3.18–3.08 (m, 1H), 2.52 (s, 3H), 2.42 (s, 3H), 1.71 (s, 9H). Mass spectrum (DCI/NH_3): 437 (M + H)$^+$, 434, 380. Anal. ($C_{24}H_{27}N_3O_3S \cdot C_2H_2O_4$) H, N; C: calcd, 59.19; found, 59.83.

Method N: (2*RS*,4*R*)-3-[2-(3-Pyridinyl)-3-fomylthiazolidin-4-oyl]indole (20a). Amine **19a** (0.30 g, 0.73 mmol) was dissolved in THF (15 mL) and cooled to −20 °C. Acetic formic anhydride (1.1 mL, 14.7 mmol) was then added in one portion and allowed to stir for 45 min. The ice bath was removed and the reaction allowed to warm to room temperature. The mixture was partitioned between saturated $NaHCO_3$ and EtOAc. The organics were washed with brine and dried over $MgSO_4$. Chromatography (80:20 ethyl acetate–hexanes) provided a light yellow foam (0.287 g, 90% yield). Removal of the BOC group by method E provided **20a** (34% yield, 31% yield overall). NMR ($CDCl_3$, 300 MHz): δ 8.90 (d, 1H, J = 1.5 Hz), 8.70 (s, 0.25H), 8.63 (d, 0.25H, J = 0.3 Hz), 8.55 (d, 0.5H, J = 0.3 Hz), 8.40 (m, 1H), 8.30–8.00 (m, 2H), 7.90–7.70 (m, 1H), 7.40–7.10 (m, 4H), 6.30 (s, 0.5H), 6.14 (s, 0.5H), 6.08 (s, 0.5H), 5.90 (s, 0.5H), 5.60–5.40 (m, 0.75H), 5.33 (t, 0.25H), 3.35–3.00 (m, 2H). Mass spectrum (DCI/NH_3): 338 (M + 1). HRMS: calcd for $C_{18}H_{16}N_3O_2S$ 338.0963, found 338.0955.

Prepared by the same method were the following:

(2*RS*,4*R*)-3-[2-(3-Pyridinyl)-3-acetylthiazolidin-4-oyl]indole (20b). Acylation of **19a** with acetic anhydride followed by deprotection by method E gave an oil, which was purified on silica gel (97:3 chloroform–methanol followed by 95:5 chloroform/methanol) to give **20b** (65% yield) as a tan solid. NMR (DMSO-d_6, 300 MHz): δ 12.31 (br s, 1H), 9.05 (d, 0.75H, J = 0.3 Hz), 8.93 (d, 0.25H, J = 0.3 Hz), 8.70 (d, 0.5H, J = 0.3 Hz), 8.68 (d, 0.5H, J = 0.3 Hz), 8.55–8.39 (m, 2H), 8.30–8.20 (m, 1H), 7.31–7.20 (m, 4H), 6.63 (s, 0.75H), 6.49 (s, 0.25H), 5.95 (m, 0.5H), 5.65 (m, 0.5H), 3.70 (dd, 0.5H, J = 0.4, 0.9 Hz), 3.60 (dd, 0.5H, J = 0.4, 0.9 Hz), 3.18 (m, 0.5H), 3.00 (m, 0.5H), 1.90 (d, 3H, J = 0.6 Hz). Mass spectrum (DCI/NH_3): 352 (M + 1). Anal. ($C_{19}H_{17}N_3O_2S \cdot 0.25H_2O$) C, H, N.

(2*R*,4*R*)-3-[2-(3-Pyridinyl)-3-(trifluoroacetyl)thiazolidin-4-oyl]indole (20c) and (2*S*,4*R*)-3-[2-(3-Pyridinyl)-3-(trifluoroacetyl)thiazolidin-4-oyl]indole (20d). Acylation of **19a** with trifluoroacetic anhydride proceeded in 57% yield. Deprotection using method E provided a mixture of diastereomers, which were separated by silica gel chromatography (98:2 chloroform–methanol, then 95:5 chloroform–methanol) providing *cis* isomer **20c** (0.058 g, 34% yield) [Mp: 196–198 °C. NMR (DMSO-d_6, 300 MHz): δ 12.30 (br s, 1H), 8.97 (d, 0.75H, J = 0.3 Hz), 8.96 (d, 0.25H, J = 0.3 Hz), 8.78 (s, 0.75H), 8.70 (s, 0.25H), 8.53 (m, 1H), 8.35 (m, 1H), 8.25 (m, 1H), 7.55–7.44 (m, 2H), 7.30–7.20 (m, 2H), 6.90 (s, 0.75H), 6.45 (s, 0.25H), 6.15 (m, 0.25H, thiazolidine C-4H, minor rotamer), 5.85 (m, 0.75H, thiazolidine C-4H, major rotamer), 3.94 (m, 1H), 3.75 (m, 1H). Mass spectrum (DCI/NH_3): 406 (M + 1). Anal. ($C_{19}H_{14}F_3N_3O_2S$) C, H, N] and **20d** (0.016 g, 10% yield). Mp: 270–274 °C. NMR (DMSO-d_6, 300 MHz): δ 12.28 (br s, 1H), 8.68–8.50 (m, 3H), 8.17 (d, 1H, J = 0.66 Hz), 7.82 (d, 1H, J = 0.65 Hz), 7.57–7.40 (m, 2H), 7.30–7.20 (m, 2H), 6.89 (bs, 0.25H), 6.60 (s, 0.75H), 6.45 (m, 1H, thiazolidine C-4H), 3.90 (m, 1H), 3.70 (m, 1H), 3.52 (m, 1H). Mass spectrum (DCI/NH_3): 406 (M + 1). Anal. ($C_{19}H_{14}F_3N_3O_2S$) C, H, N.

(2*RS*,4*R*)-3-[[2-(3-Pyridinyl)thiazolidin-4-yl]methyl]indole (21). Borane–tetrahydrofuran (165 mL, 1 M in THF, 0.165 mol) was added to a solution of BOC-D-tryptophan (10 g, 0.033 mol) in THF (250 mL) at 0 °C. The reaction mixture was stirred overnight and then quenched with MeOH (50 mL). The mixture was poured into water (200 mL), the organic layer was separated and dried over Na_2SO_4, and the solvent was removed *in vacuo*. The resulting residue was purified by chromatography on silica gel eluting with 1:1 EtOAc–hexanes to yield 5.13 g (54% yield) of the desired alcohol.

Diisopropyl azodicarboxylate (3.48 mL, 17 mmol) was added to a solution of triphenylphosphine (4.63 g, 17 mmol) in THF (75 mL). The mixture was stirred at 0 °C for 30 min, and then a solution of the alcohol (5.1 g, 17 mmol) and thioacetic acid (1.26 mL, 17.6 mmol) in THF was added. The reaction mixture was stirred overnight, and then the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel eluting with 2:1 EtOAc–hexanes to yield the desired product (4.97 g, 84% yield).

This material (3.0 g, 0.0086 mol) in MeOH (20 mL) was heated at 60 °C for 30 min. The mixture was poured into saturated citric acid (200 mL) and then extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and the solvent evaporated. The residue was dissolved in HOAc (10 mL), and HCl in HOAc (10 mL) was added. The mixture was allowed to stand at room temperature for 45 min, and the desired material precipitated with the addition of 200 mL of ether. The precipitate was collected by filtration and partitioned between saturated $NaHCO_3$ solution and CH_2Cl_2. The organic phase was separated and dried over Na_2SO_4, and the solvent was evaporated to give the desired compound as a gray oil which was carried on to the next step without further purification.

3-Pyridine aldehyde (0.30 mL, 0.0032 mol) was added to a solution of crude 1-indol-3-yl-2-amino-3-mercaptopropane (650 mg) in EtOH (10 mL) and the mixture stirred overnight. The solvent was removed *in vacuo* and the residue chromatographed on silica gel eluting with 2:1 EtOAc/hexanes to provide **12** (6% yield for two steps, 3% yield overall). NMR ($CDCl_3$, 300 MHz): δ 10.13 (s, 1H), 9.08–8.82 (m, 1H), 8.80–8.50 (m, 2H), 8.21–8.19 (m, 1H), 7.90–7.62 (m, 2H), 7.52–7.38 (m, 1H), 7.30–7.10 (m, 3H), 5.77 (s, 0.33H), 5.60 (s, 0.67H), 3.73 (m, 1H), 3.20 (m, 3H), 2.87 (m, 1H). Mass spectrum (DCI/NH_3): 296 (M + H)$^+$. Anal. ($C_{17}H_{17}N_3S \cdot 2HCl \cdot H_2O$) C, N; H: calcd, 5.47; found, 4.93.

Acknowledgment. We wish to acknowledge the contributions of Mr. Paul Tapang in performing *in vivo* assays and of Ms. Sonya Ratliff and Mr. Chris Limberakis in preparing compounds.

References

(1) This material was presented, in part, at the 205th ACS National Meeting, Denver, CO, March 28–April 2, 1993: Sheppard, G. S.; Pireh, D.; Carrera, G. M., Jr.; Bures, M. G.; Heyman, H. R.; Steinman, D. H.; Davidsen, S. K.; Phillips, J. G.; Guinn, D. E.; May, P. D.; Conway, R. G.; Rhein, D. A.; Calhoun, W. C.; Albert, D. H.; Magoc, T. J.; Carter, G. W.; Summers, J. B., Jr. 3-(2-(3-Pyridinyl)thiazolidin-4-oyl)indoles, a Novel Series of Platelet Activating Factor Antagonists. Abstract MEDI-102.

(2) (a) Benveniste, J. Characterization and Semipurification of Platelet Activating Factor from Human and Rabbit Leukocytes. *Fed. Proc.* **1974**, *33*, 797. (b) Benveniste, J. Platelet Activating Factor, a New Mediator of Anaphylaxis and Immune Complex Deposition from Rabbit and Human Basophils. *Nature (London)* **1974**, *249*, 581. (c) Benveniste, J. H.; Tencé, M.; Varenne, P.; Bidault, J.; Boullet, C.; Polonsky, J. Semisynthesis and Proposed Structure of Platelet Activating Factor. *C.R.C. Acad. Sci.* **1979**, *289D*, 1037.

(3) Snyder, F., Ed. *Platelet-Activating Factor and Related Lipid Mediators*; Plenum Press: New York, 1987.
(4) Honda, Z.-I.; Nakamura, M.; Miki, I.; Minami, M.; Watanabe, T.; Seyama, Y.; Okado, H.; Toh, H.; Ito, K.; Miyamoto, T.; Shimizu, T. Cloning by Functional Expression of Platelet-Activating Factor from Guinea-pig Lung. *Nature* **1991**, *349*, 342–346.
(5) Nakamura, M.; Honda, Z.-I.; Izumi, T.; Sakanaka, C.; Mutoh, H.; Minami, M.; Bito, H.; Seyama, Y.; Matsumoto, T.; Noma, M.; Shimizu, T. Molecular Cloning and Expression of PAF Receptor from Human Leukocytes. *J. Biol. Chem.* **1991**, *266*, 20400–20405.
(6) Kung, D.; Gerard, N. P.; Gerard, C. The Human Leukocyte PAF Receptor. *J. Biol. Chem.* **1992**, *267*, 9101.
(7) Hwang, S.-B.; Lam, M.-H. L-659,989: A Useful Probe in the Detection of Multiple Conformational States of PAF Receptors. *Lipids* **1991**, *26*, 1148–1153.
(8) Voelkel, N. F.; Chang, S.-W.; Pfeffer, K.; Worthen, S. G.; McMurtry, I. F.; Henson, P. M. PAF Antagonists: Different Effects on Platelets, Neutrophils, Guinea Pig Ileum, and PAF-induced Vasodilation in Isolated Rat Lung, *Prostaglandins* **1986**, *32*, 359–372.
(9) Lambrecht, G.; Parnham, M. J. Kadsurenone Distinguishes Between Different Platelet Activating Factor Receptor Subtypes on Macrophages and Polymorphonuclear Leukocytes. *Br. J. Pharmacol.* **1986**, *87*, 287–289.
(10) O'Flaherty, J. T.; Surles, J.; Redman, J.; Jacobson, D.; Piantodosi, C.; Wykle, R. Binding and Metabolism of Platelet-Activating Factor by Human Neutrophils. *J. Clin. Invest.* **1986**, *78*, 381–388.
(11) Pinckard, R. N.; Showell, H. J.; Castillo, R.; Lear, C.; Breslow, R.; McManus, L. M.; Woodard, D. S.; Ludwig, J. C. Differential Responsiveness of Human Neutrophils to the Autocrine Actions of 1-*O*-Alkyl-homologs and 1-Acyl Analogs of Platelet Activating Factor. *J. Immunol.* **1992**, *148*, 3528–3535.
(12) For recent general review of the area, see: Venabe, M. E.; Zimmerman, G. A.; McIntyre, T. M.; Prescott, S. M. Platelet-Activating Factor: a Phospholipid Autacoid with Diverse Actions. *J. Lipid. Res.* **1993**, *34*, 691–702.
(13) For a recent review, see: Sanchez-Crespo, M. Potential of PAF Receptor Antagonists in the Treatment of Septic Shock. *Drug News Perspect.* **1993**, *6*, 78–87.
(14) Parsons, W. H.; Chabala, J. C. Platelet-Activating Factor, Hyperreactivity and Asthma. In *Airways Hyperresponsiveness: Is it really Important for Asthma*?; Page, C., Gardiner, P., Eds.; Blackwell Scientific Publications: Oxford, 1991.
(15) Braquet, P.; Paubert-Braquet, M.; Koltai, M.; Bourgain, R.; Bussolino, F.; Hosford, D. Is there a Case for PAF Antagonists in the Treatment of Ischemic States? *Trends Pharm. Sci.* **1991**, *10*, 23–30.
(16) For an excellent summary, see: Whittaker, M. PAF Receptor Antagonists: Recent Advances. *Curr. Opin. Ther. Pat.* **1992**, *2*, 583–623.
(17) Guinn, D. E.; Summers, J. B.; Heyman, H. R.; Conway, R. G.; Rhein, D. A.; Albert, D. H.; Magoc, T.; Carter, G. W. Synthesis and Structure-Activity Relationships of a Series of Novel Benzopyran-Containing Platelet Activating Factor Antagonists. *J. Med. Chem.* **1992**, *35*, 2055–2061.
(18) Lavé, D.; James, C.; Rajoharison, H.; Bost, P. E.; Cavero, I. Pyrrolo-[1,2-*c*]thiazole Derivatives: Potent PAF Receptor Antagonists. *Drugs Future* **1989**, *14*, 891–898.
(19) Summers, J. B.; Davidsen, S. K.; Guinn, D. E.; Steinman, D. H.; May, P. D. Benzoylphenyl Pyridinyl Compounds as Platelet Activating Factor Antagonists. U.S. Patent 5,120,751, issued June 9, 1992.
(20) Yamada, T.; Tomioka, K.; Saito, M.; Horie, M.; Mase, T.; Hara, H.; Nagaoka, H. Pharmacological Properties of YM264, a Potent and Orally Active Antagonist of Platelet-Activating Factor. *Arch. Int. Pharmacodyn.* **1990**, *308*, 123–128. Yamada, T.; Saito, M.; Mase, T.; Hara, H.; Nagaoka, H.; Murase, K.; Tomioka, K. Pharmacological Properties of YM461, a New Orally Active Platelet-Activating Factor Antagonist. *Lipids* **1991**, *26*, 1179–1183.
(21) Although a full binding curve was not obtained, this compound provided 70% inhibition at 10^{-4} M.
(22) Faggiani, R.; Howard-Lock, H. E.; Lock, C. J. L.; Orgias, R. 2*R*,4*S*-2-(2′-Methyl-3′-hydroxymethylenepyridine-C4′)-5,5-dimethylthiazolidine-4-carboxylic Acid, the Product of the Reaction of *D*-Penicillamine and Vitamin B6. *Can. J. Chem.* **1991**, *69*, 1–7.
(23) The relative stereochemistry across the thiazolidine ring was assigned based on the work of McMillan and Stoodley, who reported that the chemical shift of the C-4 methine proton consistently appeared at lower field in the *trans* isomer in a series of thiazolidine-4-carboxylic acid derivatives, due to shielding from the *cis* substituent. McMillan, I.; Stoodley, R. J. The Absolute Stereochemistry at C-2 of Thiazolidines Derived from *R*-Penicillamine and Aldehydes. *J. Chem. Soc., Chem. Commun.* **1968**, 11–12.
(24) Fife, T. H.; Natarajan, R.; Shen, C. C.; Bembi, R. Mechanism of Thiazolidine Hydrolysis. Ring Opening and Hydrolysis of 1,3-Thiazolidine Derivatives of *p*-(Dimethylamino)cinnamaldehyde. *J. Am. Chem. Soc.* **1991**, *113*, 3071–3079 and references cited therein.
(25) Kuchinskas, E. J.; du Vigneaud, V. An Increased Vitamin B_6 Requirement in the Rat on a Diet Containing *L*-Penicillamine. *Arch. Biochem. Biophys.* **1957**, *66*, 1–9.
(26) Davidsen, S. K.; Summers, J. B.; Conway, R. G.; Rhein, D. A.; Carter, G. W. Synthesis of Bicyclic Thiazolidine PAF Antagonists. *Biorg. Med. Chem. Lett.* **1993**, *3*, 2729–2732.
(27) The incorporation of the anilide phenyl ring and nitrogen into an indole eliminates rotation about the *N*-phenyl bond. This conformational restriction is distinct from the restricted rotation about the amide bond of the anilide. While the *N*-acylindoles and 3-acylindoles are not amides, they do contain an sp^2-hybridized atom linked to a carbonyl, and therefore adopt a similar orientation. We are grateful to a referee for suggesting that we point out this difference.
(28) Heacock, R. A.; Kasparek, S. The Indole Grignard Reagents. *Adv. Heterocycl. Chem.* **1969**, *10*, 60–85.
(29) Bergman, J.; Venemalm, L. Acylation of the Zinc Salt of Indole. *Tetrahedron* **1990**, *46*, 6061–6066.
(30) Samples of **7a** obtained by both methods B and C were recrystallized, and the major (*cis*) diastereomer confirmed to have the 2*R*,4*R* configuration by X-ray crystallography. While this does not exclude epimerization at C-4 under the reaction conditions, as recrystallization could remove the enantiomer, we feel it supports our contention that extensive epimerization did not occur. Pireh, D.; Henry, R. Unpublished results.
(31) These conditions had been previously reported for BOC protection of simple indole systems: Grehn, L.; Ragnarsson, U. A Convenient Method for the Preparation of 1-(*tert*-Butyloxycarbonyl)pyrroles. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 296–297; *Angew. Chem.* **1984**, *96*, 291–292.
(32) For example, see the series of reports from Zeneca Pharmaceutical's peptidoleukotriene antagonist program: Jacobs, R. T.; Brown, F. J.; Cronk, L. A.; Aharony, D.; Buckner, C. K.; Kusner, E. J.; Kirkland, K. M.; Neilson, K. L. Substituted 3-(Phenylmethyl)-1*H*-indole-5-carboxamides and 1-(Phenylmethyl)indole-6-carboxamides as Potent, Selective, Orally Active Antagonists of the Peptidoleukotrienes. *J. Med. Chem.* **1993**, *36*, 394–409 and references cited therein.
(33) DGEOM, Quantum Chemical Program Exchange, Indiana University, Bloomington, IN 47405.
(34) AMPAC, Quantum Chemical Program Exchange, Indiana University, Bloomington, IN 47405. The AM1 Hamiltonian was used, along with GNORM=1.0.
(35) Cheng, Y. C.; Prusoff, W. H. Relationship Between the Inhibition Constant (K_i) and the Concentration of Inhibitor Which Causes 50 Percent Inhibition (IC_{50}) of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.
(36) Tishler, A. N.; Lanza, T. J. 6-Substituted Indoles from *o*-Halonitrobenzenes. *Tetrahedron Lett.* **1986**, *27*, 1653–1656.
(37) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. R. Metal-Halogen Exchange of Bromoindoles. A Route to Substituted Indoles. *J. Org. Chem.* **1986**, *51*, 5106–5110.
(38) Brown, F. J.; Cronk, L. A.; Aharony, D.; Snyder, D. W. 1,3,6-Trisubstituted Indoles as Peptidoleukotriene Antagonists: Benefits of a Second, Polar, Pyrrole Substituent. *J. Med. Chem.* **1992**, *35*, 2419–2439.
(39) Muchowski, J. M.; Solas, D. R. Protecting Groups for the Pyrrole and Indole Nitrogen Atom. The [2-(Trimethylsilyl)ethoxy]methyl Moiety. Lithiation of 1-[[2-(Trimethylsilyl)ethoxy]methyl]pyrrole. *J. Org. Chem.* **1984**, *49*, 203–205.
(40) Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M. Preparation of 2-Substituted Pyrroles and Indoles by Regioselective Alkylation and Deprotection of 1-(2-Trimethylsilylethoxymethyl)pyrrole and 1-(2-Trimethylsilylethoxymethyl)indole. *Tetrahedron* **1986**, *42*, 3723–3729.