Indole Inhibitors of Human Nonpancreatic Secretory Phospholipase A_2. 2. Indole-3-acetamides with Additional Functionality

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As reported in our previous paper, a series of indole-3-acetamides which possessed potency and selectivity as inhibitors of human nonpancreatic secretory phospholipase A_2(hnps-PLA_2) was developed. The design of these compounds was based on information derived from x-ray crystal structures determined for complexes between the enzyme and its inhibitors. We describe here the further implementation of this structure-based design strategy and continued SAR development to produce indole-3-acetamides with additional functionalities which provide increased interaction with important residues within the enzyme active site. These efforts led to inhibitors with substantially enhanced potency and selectivity.

Introduction

The first paper in this series described the X-ray structure-based development of an indole-3-acetic acid lead from a screening program, into a series of indole-3-acetamides which were potent and selective inhibitors of hnps-PLA_2. In order to provide direction to the continued SAR development and improve upon the potency of this initial series of inhibitors, the available crystal structures of sPLA_2 enzyme−inhibitor complexes were further studied. X-ray crystal structures of the complex between a phosphonate transition state analogue (TSA)[2] and hnps-PLA_2 and of that between an amide substrate analogue (ASA)[3] and a mutant porcine PLA_2 enzyme were compared to the complex between 5-methoxy-2-methyl-1*H*-indole-3-acetamide (**1d**) and hnps-PLA_2. Examination of these complexes indicated that two other interactions between enzyme and inhibitor noted for both ASA and TSA could be mimicked by proper substitution on the carbocyclic portion of the indole ring. The phosphate group in both TSA and ASA provides an oxygen as an additional ligand for the calcium in the active site and also a hydrogen bond to the side chain of residue 69 (Lys 69 for hnps-PLA_2 and Tyr 69 for the mutant porcine enzyme). It was concluded that an acidic group linked to the 5-position of the indole could add these two interactions to those already observed for **1d**. This observation was the basis for the modifications of indole-3-acetamides reported in this paper. As new inhibitors with the additional functionalities were prepared, X-ray crystal structures of selected compounds, along with the determination of their hnps-PLA_2 inhibitory activity, further contributed to our understanding of the enzyme active site, and derivatives with substantially enhanced potency and selectivity were obtained.

Chemistry

The methoxylated indole-3-acetamides (**1**) prepared as described in the previous paper[1] were convenient starting materials for the syntheses of many indoles with new substituents on the carbocyclic portion of the ring system. Demethylation[4] was efficiently carried out using boron tribromide in dichloromethane at room temperature or below (Scheme 1), providing 4-, 5-, or 6-phenolic indoles (**2**), which were used to prepare compounds with functionalities linked to these positions of the indole ring.

Treatment of the sodium salt of 2-ethyl-5-hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (**2g**) with allyl bromide gave the 5-allyloxy intermediate. This intermediate undergoes a thermal Claisen[5] rearrangement to providie 4-allyl-5-hydroxyindole, **2i**. The exclusive formation of the 4-allyl isomer is explicable on the basis of the stability of the possible intermediates in the rearrangement (Figure 1). The 4-allyl-4*H*-indol-5-one retains the aromaticity of the pyrrole ring and allows extended conjugation from the unshared pair of electrons on the nitrogen through to the indol-5-one. The other possible intermediate, 6-allyl-6*H*-indol-5-one, would lose all aromaticity and retain only less significant conjugated structures. An identical stereospecificity has been observed for the Claisen rearrangement of a 5-(allyloxy)indole-3-glyoxamide.[6]

Indoles having a functional group linked to the phenolic oxygen via an alkyl chain were generally prepared by reacting the sodium salt of the phenol with an ω-bromoalkanoate or alkylphosphonate, followed by deesterification with aqueous sodium hydroxide, or with trimethylsilyl bromide followed by methanol for the phosphonates (Schemes 2 and 3). In the case of the ethylene-linked derivative **5f**, Michael addition[7] of the phenol to an acrylic ester in the presence of mild base afforded this derivative. The ready reversibility of this reaction under more basic conditions required the use of benzyl acrylate as the acceptor. This permitted conversion of the ester to the acid using the neutral conditions of reductive debenzylation.

In cases where the functional group was linked to the phenolic oxygen via an arylalkyl group, compounds were prepared by alkylation of the sodium salt of the phenol using (bromomethyl)benzoic acid esters. Aryl-linked derivatives were prepared by Ullman coupling of the cuprous phenoxide[8] with iodobenzoic acid esters.

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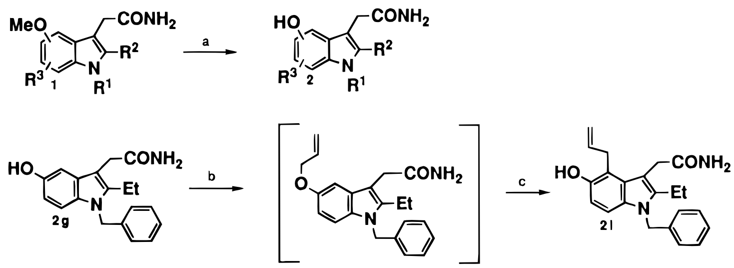
Scheme 1. Preparation of Hydroxyindoles[a]



compound	R^1	R^2	R^3	HO-position
2a	$C_6H_5CH_2$	H	H	4
2b	$C_6H_5CH_2$	H	H	5
2c	$C_6H_5CH_2$	CH_3	H	4
2d	$C_6H_5CH_2$	CH_3	H	5
2e	$C_6H_5CH_2$	CH_3	H	6
2f	$C_6H_5CH_2$	CH_3CH_2	H	4
2g	$C_6H_5CH_2$	CH_3CH_2	H	5
2h	$C_6H_5CH_2$	CH_3CH_2	6-iPr	5
2i	$C_6H_5CH_2$	CH_3CH_2	4-allyl	5
2j	$C_6H_5CH_2$	$CH_3CH_2CH_2$	H	5
2k	$C_6H_5CH_2$	cyclopropyl	H	5
2l	$C_6H_5CH_2$	Cl	H	5
2m	$C_6H_5CH_2$	Br	H	5
2n	$C_6H_5CH_2$	Br	6-Cl	5
2o	$C_6H_5CH_2$	CH_3S	H	5
2p	3-$ClC_6H_4CH_2$	CH_3	H	4
2q	3-$ClC_6H_4CH_2$	CH_3CH_2	H	4
2r	3-$ClC_6H_4CH_2$	CH_3CH_2	H	5
2s	2-$(C_6H_5)C_6H_4CH_2$	CH_3	H	4
2t	2-$(C_6H_5)C_6H_4CH_2$	CH_3	H	5
2u	cyclohexylCH_2	CH_3	H	5
2v	$CH_3(CH_2)_9$	CH_3	H	5

[a] Reagents: (a) BBr_3, CH_2Cl_2; (b) NaH, allyl bromide, DMF; (c) *N*,*N*-dimethylaniline, heat.

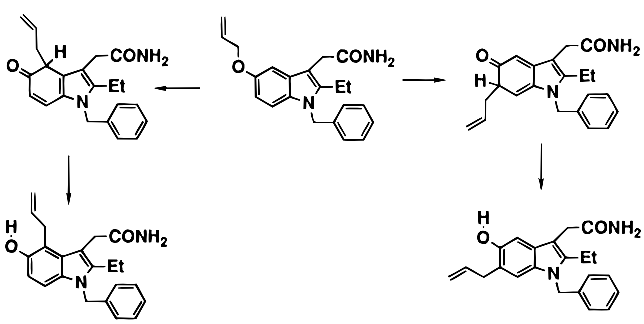


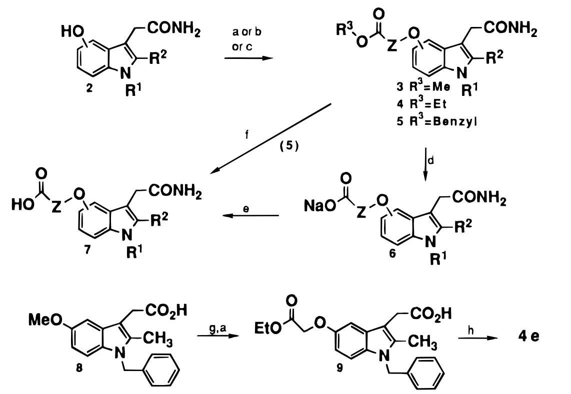
Figure 1.

The (indolyloxy)alkanoic acid esters were reacted with hydrazine to give the hydrazides **19**, which were reductively cleaved to produce amides **20** (Scheme 4). Alternatively, for those compounds, such as **4s**, containing functional groups not compatible with the reductive procedure, the esters were converted directly to amides by treatment with methylchloroaluminum amide.[9] Alkylation of the phenoxide with bromobutyronitrile followed by reaction with tributyltin azide[10] afforded the tetrazole **18**. Reacting the phenoxide with 1,3-propyl sultone gave the (indolyloxy)propanesulfonic acids **16a** and **16b**.

Functionalities linked to the indole system by a nitrogen atom were prepared as outlined in Scheme 5. The previously reported[1] 5-aminoindole **27** was reacted with methyl acrylate in Michael fashion to give a product which was sufficiently resistant to reversal that it could be hydrolyzed in aqueous base to the corresponding acid. Direct alkylation of the 5-aminoindole gave substantial amounts of N,N-dialkylation along with the monoalkylated compound **28**. Access to the 4-aminoindoles was made via the 4-nitroindole, **21**.[1] The diminished reactivity of the 3-position of 4-nitroindoles was evidenced by its reaction with oxalyl chloride,[11] which required prolonged reaction time at room temperature to reach completion. The 4-nitro group and the keto group of the glyoxamide were both reduced by low-pressure hydrogenation with palladium on barium sulfate as catalyst to give the glycolic amide (**23**), which was further reduced to the indole-3-acetamide by triethylsilane and trifluoroacetic acid.[12] Alkylation of the amino group of **24** produced the *tert*-butyl ester **25** which on treatment with trifluoroacetic acid gave the acid **26**.

The all-carbon-linked carboxyl derivative **35** was prepared as shown in Scheme 6. The crude product from the Friedel-Crafts acylation of the *N*-acylindoline using aluminum chloride and succinic anhydride[13] was esterified and solvolyzed to the indoline **31** by heating in ethanol containing sulfuric acid. N-Alkylation followed by oxidation with dichlorodicyanoquinone[14] gave the 5-acylindole (**32**) which was easily converted to the indole-3-glyoxamide by sequential treatment with oxalyl chloride and ammonia. It was assumed that sodium borohydride reduction of **33** would lead to undesired lactonization of the side chain and that proceeding to the indole-3-acetamide by way of the indole-3-glycolamide would be inappropriate. Both keto functions of the compound were efficiently reduced to methylenes (compound **34**) by use of excess triethylsilane and trifluoroacetic acid in refluxing dichloroethane without effect on the ester, amide, or indole functionalities.

Scheme 2. Oxygen-Linked Carboxyl Functionalities[a]



starting material	compound	R1	R2	Z	indole position
2a	3a, 7a	$C_6H_5CH_2$	H	CH_2	4
2b	4b, 7b	$C_6H_5CH_2$	H	$(CH_2)_3$	5
2c	3c, 6c, 7c	$C_6H_5CH_2$	CH_3	CH_2	4
2c	4d, 7d	$C_6H_5CH_2$	CH_3	$(CH_2)_3$	4
8	4e, 7e	$C_6H_5CH_2$	CH_3	CH_2	5
2d	5f, 7f	$C_6H_5CH_2$	CH_3	$(CH_2)_2$	5
2d	4g, 7g	$C_6H_5CH_2$	CH_3	$(CH_2)_3$	5
2d	3h, 7h	$C_6H_5CH_2$	CH_3	$(CH_2)_4$	5
2d	3i, 7i	$C_6H_5CH_2$	CH_3	$(2\text{-}C_6H_4)CH_2$	5
2d	3j, 7j	$C_6H_5CH_2$	CH_3	$(3\text{-}C_6H_4)CH_2$	5
2e	4k, 7k	$C_6H_5CH_2$	CH_3	$(CH_2)_3$	6
2e	4l, 7l	$C_6H_5CH_2$	CH_3	$(CH_2)_4$	6
2f	3m,7m	$C_6H_5CH_2$	CH_3CH_2	CH_2	4
2g	4n, 7n	$C_6H_5CH_2$	CH_3CH_2	$(CH_2)_3$	5
2g	3o, 7o	$C_6H_5CH_2$	CH_3CH_2	$(2\text{-}C_6H_4)CH_2$	5
2k	3p, 7p	$C_6H_5CH_2$	cyclopropyl	$(CH_2)_3$	5
2l	4q, 7q	$C_6H_5CH_2$	Cl	$(CH_2)_3$	5
2m	4r, 7r	$C_6H_5CH_2$	Br	$(CH_2)_3$	5
2o	4s, 7s	$C_6H_5CH_2$	CH_3S	$(CH_2)_3$	5
2p	4t, 6t	$3\text{-}ClC_6H_4CH_2$	CH_3	CH_2	4
2q	3u, 7u	$3\text{-}ClC_6H_4CH_2$	CH_3CH_2	CH_2	4
2s	3v, 6v	$2\text{-}(C_6H_5)C_6H_4CH_2$	CH_3	CH_2	4
2u	4w, 7w	cyclohexylCH_2	CH_3	$(CH_2)_3$	5
2v	4x, 7x	$CH_3(CH_2)_9$	CH_3	$(CH_2)_3$	5
2d	4y, 7y	$C_6H_5CH_2$	CH_3	$3\text{-}C_6H_4$	5

[a] Reagents: (a) NaH, $BrZCO_2R^3$, DMF/THF; (b) K_2CO_3, benzyl acrylate, 2-butanone, heat; (c) Ullman; (d) NaOH, EtOH/H_2O; (e) HCl, H_2O; (f) 10% Pd/C, H_2, EtOH; (g) BBr_3, CH_2Cl_2; (h) (1) methyl chloroformate, Et_3N, CH_2Cl_2, (2) ammonia.

Replacement of the oxygen link by a sulfur link was accomplished by subjecting the hydroxyindoles to the known phenol to thiophenol conversion methodology[15] as illustrated in Scheme 7. The vigorous reaction conditions involved in carrying out this conversion prevented the early insertion of useful 3-substituents, so the desired 3-acetamides were prepared by way of the 3-glyoxamides subsequent to the elaboration of the groups attached to the carbocyclic ring of the indoles.

Scheme 8 shows the route selected for the preparation of 5,7-disubstituted indole-3-acetamides. The selective lithiation at the 7-position[16] of the *N*-BOC-indoline **47** is an example of the ability of an acyl nitrogen function to direct aromatic metalation even in the presence of other good directing groups such as methoxy.[17] After alkylation of the 7-lithioindoline, the N-BOC was removed, the nitrogen alkylated, and the indoline oxidized to the indole with dichlorodicyanoquinone. Demethylation produced the phenol **52**, which was converted to the thiophenol **55** as described above. Both the phenol and the thiophenol were converted to the desired compounds, **60a** and **60b**, by the series of steps used previously.

The preparation of 4,5- and 5,6-disubstituted indole-3-acetamides are shown in Scheme 9. These compounds were easily available by the routes used for the corresponding 5-substituted analogues, uncomplicated by the additional 4- or 6-substituent.

In the first paper[1] of this series, replacement of the 3-acetamide by several related functionalities was reported. Schemes 10 and 11 show the synthesis of some 3-acetic acid, 3-acetic acid hydrazide, and 3-propionamide derivatives with the additional functionalities of the current series using methodologies as reported before. The unexpected decarbonylation observed on treatment of the 4-methoxy indole-3-glyoxamide, **79**, with boron tribromide has some precedence[18] in a reported metal-catalyzed decarbonylation of glyoxylic acid esters. A cyclic boronate intermediate is probably involved since the decarbonylation is not observed on reaction of the analogous 5-methoxyindole-3-glyoxamides.

Pharmacology

The initial pharmacological evaluation of all reported compounds was accomplished using a chromogenic assay system, with followup testing of selected compounds in the hnps-PLA$_2$-induced tissue contraction assay. The specific methods employed are described in the first paper of this series. The relative inhibitory activities of the reported compounds, as indicated by these two assay systems, are shown in Table 1.

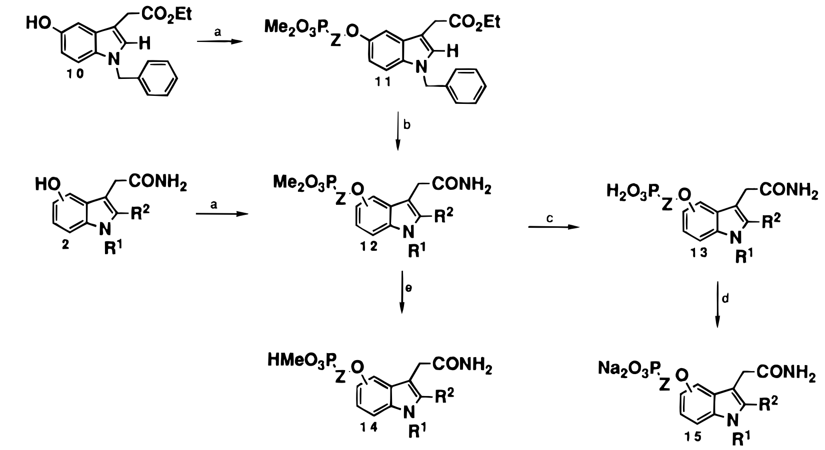
Information on selectivity of the inhibitors for hnps-PLA$_2$ was derived from comparisons of chromogenic assay results using different types of secretory PLA$_2$'s. Relative inhibitory activities against hnps-PLA$_2$, human pancreatic secretory PLA$_2$, and porcine pancreatic secretory PLA$_2$ are shown in Table 2.

Discussion

In the first paper of this series we described the initiation of a screening program to identify potential inhibitors of hnps-PLA$_2$. 5-Methoxy-2-methyl-1*H*-indole-3-acetic acid was selected from the hits produced by this screen for further development. This lead compound had an IC_{50} of 13.6 μM (mole fraction 1×10^{-2}). Using a structure-based design approach with information gathered from X-ray crystallographic studies[19] of complexes between various inhibitors and hnps-PLA$_2$, this lead progressed to a series of indole-3-acetamides having a wide variety of simple substituents at other positions of the indole nucleus. These derivatives were potent inhibitors of the enzyme with IC_{50} values as low as 120 nM (mole fraction 1×10^{-4}) in the primary chromogenic assay screen. The compounds reported here exhibit a further enhancement in potency, with IC_{50}'s as low as 10 nM (mole fraction less than 1×10^{-5}).

This improved activity resulted from a continuation of a structure-based design strategy applied to the developing SAR. X-ray crystal structures of complexes of TSA[2] with hnps-PLA$_2$ and ASA[3] with a mutant porcine PLA$_2$ enzyme were compared to the complex between 5-methoxy-2-methyl-1*H*-indole-3-acetamide (**1d**) and hnps-PLA$_2$. These comparisons[19] made it clear that the indole-based inhibitor overlapped both the glycerol backbone and one of the aliphatic side chains of the substrate analog inhibitors very nicely, but it had no substituent that corresponded to the phosphate head groups of ASA and TSA. The phosphate group provides

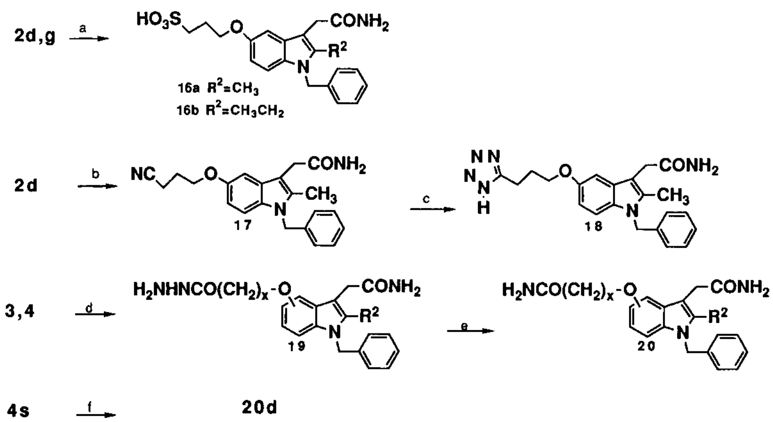
Scheme 3. Oxygen-Linked Phosphonate Functionalities[a]



starting material	compound	R1	R2	Z	indole position
10	**11a[a],12a,15a**	$C_6H_5CH_2$	H	CH_2	5
10	**11b-13b**	$C_6H_5CH_2$	H	$(CH_2)_3$	5
2c	**12c[a],13c**	$C_6H_5CH_2$	CH_3	CH_2	4
2d	**12d,13d**	$C_6H_5CH_2$	CH_3	$(CH_2)_3$	5
2g	**12e-14e**	$C_6H_5CH_2$	CH_3CH_2	$(CH_2)_3$	5
2j	**12f,13f**	$C_6H_5CH_2$	$CH_3CH_2CH_2$	$(CH_2)_3$	5
2k	**12g,13g**	$C_6H_5CH_2$	cyclopropyl	$(CH_2)_3$	5
2m	**12h,13h,15h**	$C_6H_5CH_2$	Br	$(CH_2)_3$	5
2r	**12i,13i**	3-$ClC_6H_4CH_2$	CH_3CH_2	$(CH_2)_3$	5
2t	**12j,13j**	2-$(C_6H_5)C_6H_4CH_2$	CH_3	$(CH_2)_3$	5

[a] Reagents: (a) NaH, $ICH_2PO_3R_2$ or $BrZPO_3Me_2$, DMF; (b) $MeClAlNH_2$, benzene/toluene, 50 °C; (c) (1) Me_3SiBr, CH_2Cl_2, (2) MeOH; (d) NaOH, chromatography, HP-20 column; (e) (1) NaOH, MeOH, H_2O, heat, (2) HCl, H_2O. a. Diethyl ester instead of dimethyl ester.

Scheme 4. Other Oxygen-Linked Functionalities[a]



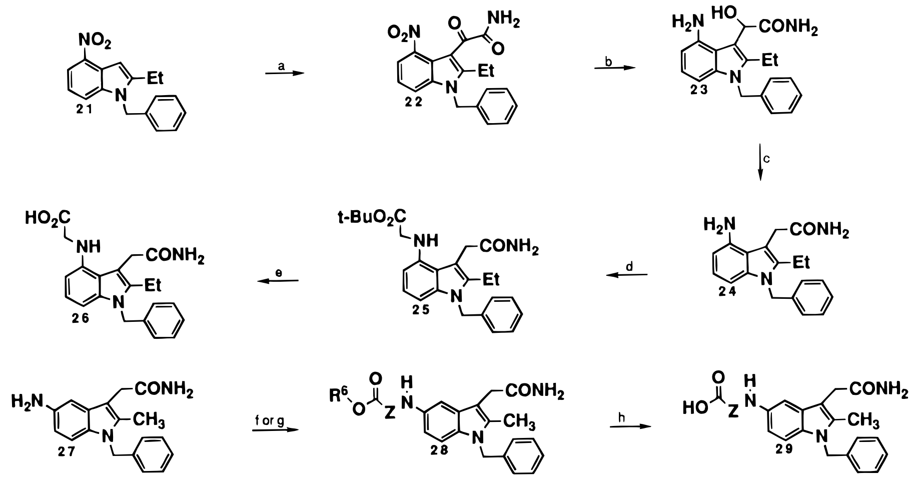
starting material	compound	R2	X	indole position
3c	**19a, 20a**	CH_3	1	4
3m	**19b, 20b**	CH_3CH_2	1	4
4k	**19c, 20c**	CH_3	3	6
4s	**20d**	CH_3S	3	5

[a] Reagents: (a) NaH, THF, 1,3-propane sultone; (b) NaH, $Br(CH_2)_3CN$, DMF; (c) $Et_3N{\cdot}HCl$, NaN_3, DMF, 105 °C; (d) hydrazine, EtOH, heat; (e) Raney Ni, EtOH, heat; (f) $MeClAlNH_2$, benzene/toluene, 50 °C.

one oxygen to the coordination sphere of the catalytic calcium while another oxygen atom hydrogen bonds to residue 69. Consequently, the next synthetic goal for potency improvement in the indole series of inhibitors was to append a side chain that would emulate these interactions.

As an initial attempt we chose to append a carboxyl-terminated side chain to the indole nucleus. This was synthetically attractive since numerous methoxyindoles were available from our previous work[1] and boron tribromide treatment of these readily provided a phenol functionality that facilitated introduction of the requisite appendage. Since the crystallographic information indicated that the 5-methoxy group of **1d** was positioned in a direction which overlapped well with that portion of the substrate analog inhibitors containing the phosphate head group, our first derivatives were prepared with the carboxyl group linked to the indole 5-position. The activity observed for a methyleneoxy linker, **7e** (IC_{50} 1.79 ± 0.17 μM), was somewhat less than that observed for **1d** (IC_{50} 0.84 ± 0.17 μM). Activity began to increase with the addition of another methylene to the linker (**7f**,

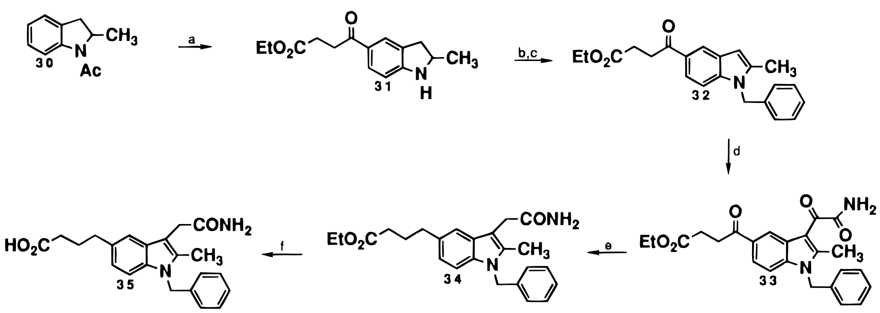
Scheme 5. Nitrogen-Linked Carboxyl Functionalities[a]



compound	Z	R6	compound	Z
28a	$(CH_2)_2$	CH_3	**29a**	$(CH_2)_2$
28b	$(CH_2)_3$	CH_3CH_2	**29b**	$(CH_2)_3$

[a] Reagents: (a) (1) oxalyl chloride, CH_2Cl_2, (2) ammonia; (b) Pd/BaSO$_4$, H$_2$, THF/EtOH; (c) Et$_3$SiH, TFA; (d) Na$_2$CO$_3$, *t*-BuO$_2$CCH$_2$Br, DMF; (e) TFA; (f) methyl acrylate, MeOH, room temperature; (g) NaH, Br(CH$_2$)$_3$CO$_2$Et, DMF; (h) (1) NaOH, EtOH, H$_2$O, (2) HCl, H$_2$O.

Scheme 6. Carbon-Linked Carboxyl Functionalities[a]



[a] Reagents: (a) (1) AlCl$_3$, succinic anhydride, CH$_2$Cl$_2$, (2) H$_2$SO$_4$, EtOH, heat; (b) K$_2$CO$_3$, benzyl bromide, DMF, 85 °C; (c) DDQ, dioxane, 85 °C; (d) (1) oxalyl chloride, CH$_2$Cl$_2$, (2) ammonia; (e) Et$_3$SiH, TFA, 1,2-dichloroethane, heat; (f) (1) NaOH, EtOH, H$_2$O, (2) HCl, H$_2$O.

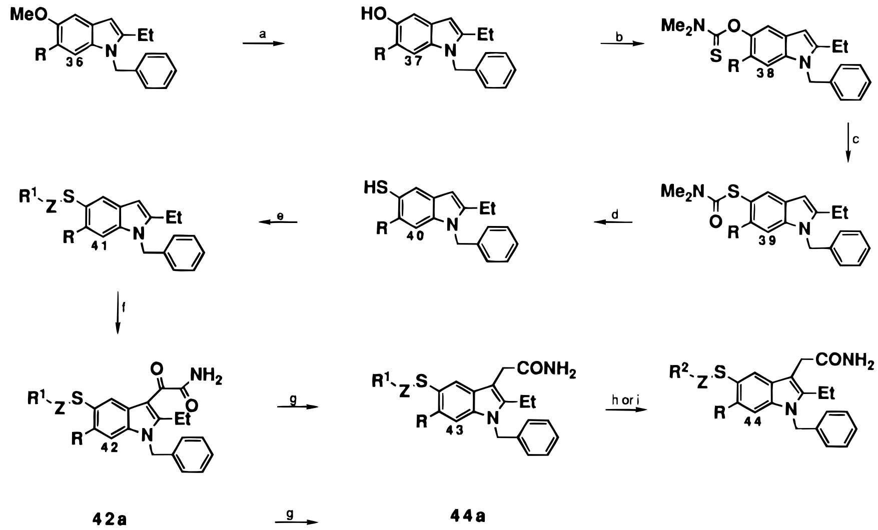
IC$_{50}$ 0.53 ± 0.06 μM) and peaked with the propyleneoxy linker, **7g** (IC$_{50}$ 0.15 ± 0.03 μM). Extending the chain with a fourth methylene provided a side chain that was too long and diminished activity (**7h**, IC$_{50}$ 1.15 ± 0.09 μM).

The X-ray structure[19] of **7g** in the active site of hnps-PLA$_2$ showed that its carboxylate does coordinate to the primary calcium as desired. However, the trigonal array of the carboxylate's oxygens prevented any interaction with Lys 69. With the expectation that a phosphonate would better mimic the interactions observed for the phosphate groups of TSA and ASA, the corresponding 5-propyleneoxy phosphonic acid derivative **13d** was prepared. This compound displayed improved activity in the chromogenic assay (IC$_{50}$ 0.06 ± 0.01 μM). A crystallographic determination of this inhibitor's binding to the active site[19] indicated a water-mediated hydrogen bond to Lys 69 that may contribute to the observed improvement in activity.

Systematic alterations of side chain functionality were carried out. Amides (**20d**) and sulfonic acids (**16**) displayed activity similar to that of the corresponding carboxylic acids. Interestingly, use of a tetrazole as a carboxy replacement resulted in a large loss of activity (**18**, IC$_{50}$ 2.24 ± 0.24 μM), suggesting that this anionic heterocycle cannot substitute for the carboxylate in the coordination sphere of the catalytic calcium. Changes in linker atoms had effects consistent with the geometric requirements of the system. The 5-[(2-carboxyphenyl)-methylene]oxy compound **7i** is larger and less flexible than **7g**, but it has the proper length to coordinate to calcium and consequently retains good activity. Moving the carboxy group one position on the phenyl ring, as in **7j**, provides a spatial arrangement that is more reminiscent of **7h** and leads to a corresponding loss of activity. Replacement of the oxygen of the linker by nitrogen, sulfur, and carbon was also accomplished. The nitrogen substitution (**29**) resulted in a large decrease in activity. Sulfur (**44**) and carbon (**35**) substitution provided compounds that retained activity, with some of these showing improved activity relative to their oxygen-containing equivalents. It seems likely that this would be a result of more precise positioning of the carboxylate in the coordination sphere of the calcium, but further work is required to investigate this question.

The three-dimensional structures of these inhibitors in the active site of hnps-PLA$_2$ suggested that positioning a shorter carboxy-terminated group at the 4-position of the indole, rather than at the 5-position as described above, would also achieve a favorable ligation of the catalytic calcium. This was indeed demonstrated with the synthesis of the oxyacetic acid derivative **7c** (IC$_{50}$ 0.052 ± 0.01 μM), which showed better activity than the 5-oxybutyric acid compound **7g**. Changes to **7c** by lengthening the linker (**7d**), substituting nitrogen for oxygen (**26**), or replacing the carboxy with amide

Scheme 7. Sulfur-Linked Functionalities[a]



compound	R
36a-40a	H
36b-40b	CH_3
36c-40c	i-Pr

compound	R	Z	R^1 or R^2
41a,42a	H	$(CH_2)_2$	t-BuO_2C
41b-43b	H	$(CH_2)_3$	EtO_2C
41c-43c	CH_3	$(CH_2)_3$	EtO_2C
41d-43d	i-Pr	$(CH_2)_3$	EtO_2C
41e-43e	H	$(CH_2)_3$	Me_2O_3P
44a	H	$(CH_2)_2$	HO_2C
44b	H	$(CH_2)_3$	HO_2C
44c	CH_3	$(CH_2)_3$	HO_2C
44d	i-Pr	$(CH_2)_3$	HO_2C
44e	H	$(CH_2)_3$	Na_2O_3P

[a] Reagents: (a) BBr_3, CH_2Cl_2; (b) NaH, dimethylthiocarbamoyl chloride, DMF; (c) phenyl ether, heat; (d) (1) NaOH, EtOH, H_2O, heat, (2) HCl, H_2O; (e) NaH, $BrZR^1$, DMF or K_2CO_3, *tert*-butyl acrylate; (f) (1) oxalyl chloride, CH_2Cl_2, (2) ammonia; (g) (1) $NaBH_4$, EtOH, (2) Et_3SiH, TFA; or Et_3SiH, TFA, dichloromethane, heat; (h) (1) NaOH, EtOH, H_2O, (2) HCl, H_2O, or (1) Me_3SiBr, CH_2Cl_2, (2) MeOH; (i) NaOH, H_2O, HP-20 chromatography.

(**20a**,**b**), hydrazide (**19a**,**b**), or phosphonate (**13c**) groups resulted in decreased activity. Thus, it appears that substitution at the 4-position of the indole ring is tightly constrained with regard to the proper positioning of a ligand to the catalytic calcium atom.

In contrast to the 4- and 5-positions of the indole ring, the 6-position points out of the active site. Addition of substituents at this site would not be expected to provide significant enhancements of activity. This is dramatically seen in **7k** and **7l**, which have IC_{50} values of greater than 5 μM. Addition of 6-alkyl groups to compounds containing a carboxy-terminated side chain in the 5-position had only modest effects on activity. This is in contrast to 4-allyl substitution, as in **62c**, that leads to much diminished activity presumably by preventing the 5-side chain from coordinating favorably with the calcium.

The SAR produced by substituent changes at the 1- and 2-positions of the indole were similar to those observed for such changes on the structures reported in the previous paper.[1] As before, an ethyl group at the 2-position optimally fit the hydrophobic cleft in this region of the protein. Addition of a substituent at the 7-position enhanced activity somewhat (**60a**, IC_{50} 0.075 $\pm$ 0.018 μM) compared to **7g**. This probably is a consequence of a favorable restriction on the conformational flexibility of the 1-benzyl group which has an important role in the binding of the inhibitor through enlarging the catalytic site by displacing His 6 in a manner similar to that of TSA.[2]

The compounds described in this report displayed excellent selectivity for hnps-PLA_2. As shown in Table 1, many of these inhibitors effectively blocked hnps-PLA_2-induced contraction of guinea pig lung pleural strips while they showed little or no effect on the arachidonic acid-induced contraction of the tissue at the concentration tested. This indicates that the activity is a result of a direct effect on the enzyme rather than any effect as inhibitors of agents formed subsequent to the action of the PLA_2. The results in Table 2 demonstrate selectivity for the human, nonpancreatic enzyme because IC_{50} values for the inhibition of this enzyme are several hundred-fold lower than the IC_{50} values for inhibition of human, pancreatic $sPLA_2$.

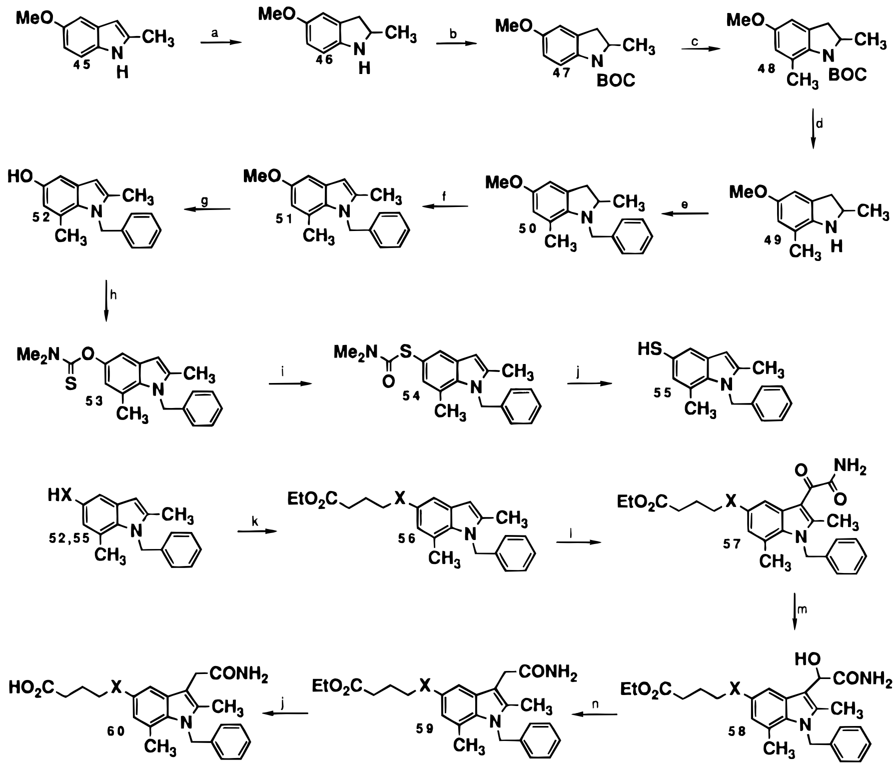
Summary

Addition of a tethered acidic group to either the 4- or 5-position of the indole ring has made a further improvement to the potency of the indole series of hnps-PLA_2 inhibitors. The most active inhibitors described in this paper (IC_{50} of ca. 10 nM) approach the stoichiometric limit of the chromogenic assay (16 nM enzyme). Additional improvement to the inherent potency of this series was still possible, however, and these activities are described in the following paper.

Experimental Section

Melting points were obtained on a Thomas-Hoover Mel Temp and are uncorrected. The NMR data were recorded on a QE300 instrument. The FD mass spectral data were obtained on a VG Analytical 70-SE instrument and the FAB spectra were recorded on a ZAB 2-SE instrument. Syntheses of indoles **1**, **8**, **10**, **21**, **27**, **36**, **63**, **69**, **73**, and **77** are described in the preceding paper. Compound **45** was commercially available.

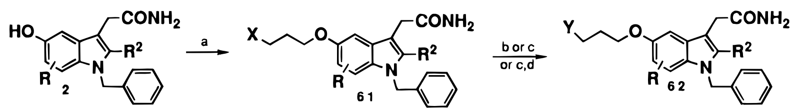
Scheme 8. Oxygen- and Sulfur-Linked Functionalities: 7-Alkyl[a]



compound	X
52, 56a-60a	O
55, 56b-60b	S

[a] Reagents: (a) NaCNBH$_3$, HOAc; (b) (BOC)$_2$O, THF, heat; (c) (1) *n*-BuLi, THF, −70 °C, (2) MeI; (d) NaOH, EtOH, H$_2$O, heat; (e) NaH, benzyl bromide, DMF; (f) DDQ, dioxane, 85 °C; (g) BBr$_3$, CH$_2$Cl$_2$; (h) NaH, dimethylthiocarbamoyl chloride, DMF; (i) phenyl ether, 195 °C; (j) (1) NaOH, EtOH, H$_2$O, heat, (2) HCl, H$_2$O; (k) NaH, Br(CH$_2$)$_3$CO$_2$Et, DMF; (l) (1) oxalyl chloride, CH$_2$Cl$_2$, (2) ammonia; (m) NaBH$_4$, MeOH; (n) Et$_3$SiH, TFA.

Scheme 9. Oxygen-Linked Functionalities: 4- or 6-Substituted[a]



starting material	compound	R^2	R	X or Y
2h	**61a**	CH$_3$CH$_2$	6-i-Pr	Me$_2$O$_3$P
2n	**61b**	Br	6-Cl	EtO$_2$C
2i	**61c**	CH$_3$CH$_2$	4-allyl	Me$_2$O$_3$P
	62a	CH$_3$CH$_2$	6-i-Pr	H$_2$O$_3$P
	62b	Br	6-Cl	HO$_2$C
	62c	CH$_3$CH$_2$	4-allyl	Na$_2$O$_3$P
	62d[20]	CH$_3$CH$_2$	6-Me	HO$_2$C
	62e[20]	CH$_3$CH$_2$	6-Me	H$_2$O$_3$P

[a] Reagents: (a) NaH, Br(CH$_2$)$_3$X, DMF; (b) (1) NaOH, EtOH, H$_2$O, (2) HCl, H$_2$O; (c) (1) Me$_3$SiBr, CH$_2$Cl$_2$, (2) MeOH; (d) NaOH, H$_2$O, HP-20 chromatography.

5-Hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (2b). A solution of 375 mg (1.23 mmol) of **1b** and 5 mL of 1 M BBr$_3$/CH$_2$Cl$_2$ in 75 mL of CH$_2$Cl$_2$ was stirred for 1.25 h and poured into 1 N HCl. The CH$_2$Cl$_2$ layer was separated, washed with brine, and dried (Na$_2$SO$_4$). The solvent was removed at reduced pressure to give as residue 310 mg (90% yield) of **2b**, mp 158−160 °C. Anal. (C$_{17}$H$_{16}$N$_2$O$_2$·0.5H$_2$O) C, H, N.

Using the above procedure, the following hydroxyindoles (**2**) were prepared from the corresponding methoxyindole (**1**).

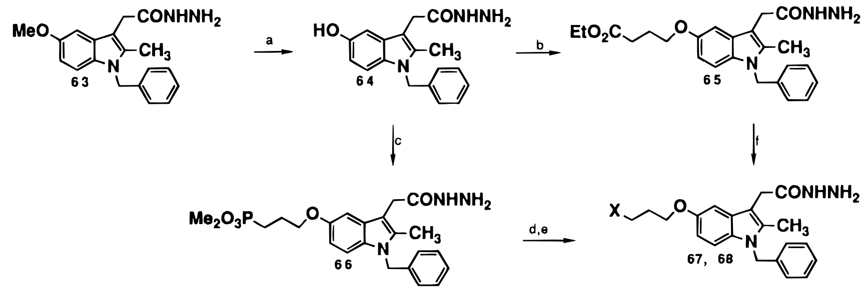
4-Hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (2a) (chromatography on silica gel, 50% EtOAc/hexane): yield 35%; ^{1}H NMR (CDCl$_3$) ∂ 9.50 (br s, 1H), 7.62−6.87 (m, 8H), 6.64 (d, 1H), 6.08−5.82 (m, 2H), 5.30 (s, 2H), 5.17 (s, 2H); MS (FD) 280 (M$^+$).

4-Hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (2c) (chromatography on silica gel, 50% EtOAc/hexane, then EtOAc): yield 66%; mp 200−208 °C; ^{1}H NMR (CDCl$_3$) ∂ 7.35−6.92 (m, 9H), 6.81 (d, 1H), 6.60 (d, 1H), 5.27 (s, 2H), 3.78 (s, 2H), 2.31 (s, 3H); MS (FD$^+$) 294 (M$^+$). Anal. (C$_{18}$H$_{18}$N$_2$O$_2$) C, H, N.

5-Hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (2d) (chromatography on silica gel, 20% EtOAc/hexane, then 50% EtOAc/hexane, then EtOAc): yield 80%; ^{1}H NMR (CDCl$_3$) ∂ 7.45−6.82 (m, 8H), 6.37 (br s, 1H), 5.82 (br s, 1H), 5.57 (br s, 1H), 5.40 (s, 2H), 3.81 (s, 2H), 2.42 (s, 3H).

6-Hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (2e) (chromatography on silica gel, 5% MeOH/CH$_2$Cl$_2$): yield 45%; mp 174−179 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.80 (s, 1H), 7.35−7.18 (m, 4H), 7.15 (br s, 1H), 7.00 (d, 2H), 6.78 (br s, 1H), 6.61 (s, 1H), 6.51 (d, 1H), 5.25 (s, 2H), 3.39 (s, 2H), 2.25 (s, 3H); MS (FD) 294 (M$^+$). Anal. (C$_{18}$H$_{18}$N$_2$O$_2$) H, N; C: calcd, 73.45; found, 72.43.

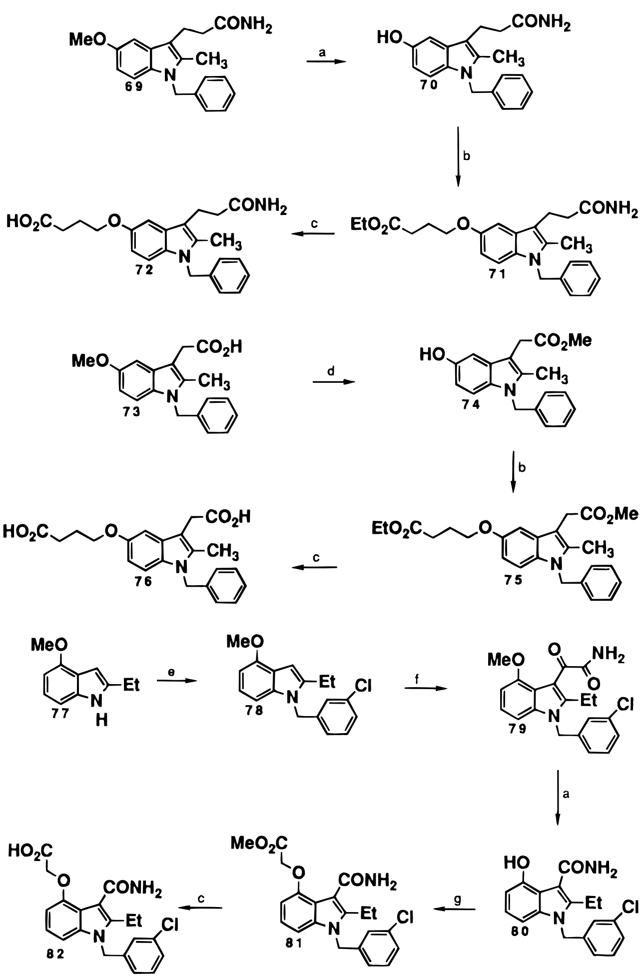
Scheme 10. Indole-3-acetic Acid Hydrazides[a]



compound	X
67	HO_2C
68	Na_2O_3P

[a] Reagents: (a) BBr_3, CH_2Cl_2; (b) NaH, $Br(CH_2)_3CO_2Et$, DMF; (c) NaH, $Br(CH_2)_3PO_3Me_2$, DMF; (d) (1) Me_3SiBr, CH_2Cl_2, (2) MeOH; (e) NaOH, H_2O, HP-20 chromatography; (f) (1) NaOH, EtOH, H_2O, (2) HCl, H_2O.

Scheme 11. Other 3-Substituents[a]



[a] Reagents: (a) BBr_3, CH_2Cl_2; (b) NaH, $Br(CH_2)_3CO_2Et$, DMF; (c) (1) NaOH, EtOH, H_2O, (2) HCl, H_2O; (d) (1) BBr_3, CH_2Cl_2, (2) $MeSO_3H$, MeOH, heat; (e) NaH, 3-chlorobenzyl bromide, DMF; (f) (1) oxalyl chloride, CH_2Cl_2, (2) ammonia; (g) NaH, $BrCH_2CO_2Me$, DMF.

2-Ethyl-4-hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (2f) (chromatography on silica gel, EtOAc, then 5% MeOH/EtOAc): yield 34%; foam; ^{1}H NMR ($CDCl_3$) ∂ 7.36−6.86 (m, 7H), 6.14 (br s, 1H), 5.80 (br s, 1H), 5.28 (s, 2H), 3.79 (s, 2H), 2.72 (q, 2H), 1.12 (t, 3H); MS (FD$^+$) 308 (M$^+$). Anal. ($C_{19}H_{20}N_2O_2$) C, calcd 74.00, found 69.23; H, calcd 6.54, found 6.09; N, calcd 9.08, found 8.24.

2-Ethyl-5-hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (2g) (chromatography on silica gel, 50% EtOAc/hexane, then EtOAc): yield 45%; mp 174−179 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.36−6.70 (m, 9H), 5.73 (br s, 1H), 5.44 (br s, 1H), 5.31 (s, 2H), 5.50 (s, 2H), 2.72 (q, 2H), 1.12 (t, 3H); MS (FD$^+$) 308 (M$^+$). Anal. ($C_{19}H_{20}N_2O_2$·0.2H_2O) C, H, N.

2-Ethyl-5-hydroxy-6-isopropyl-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (2h) (crystallization, EtOAc/hexane): yield 79%; mp 163−164 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.57 (s, 1H), 7.32−6.96 (m, 7H), 6.85 (s, 1H), 6.82 (br s, 1H), 5.32 (s, 2H), 3.37 (s, 2H), 3.30−3.16 (m, 1H), 2.67 (q, 2H), 1.12 (d, 6H), 1.02 (t, 3H); MS (FD$^+$) 350 (M$^+$). Anal. ($C_{22}H_{26}N_2O_2$) C, H, N.

5-Hydroxy-1-(phenylmethyl)-2-propyl-1*H*-indole-3-acetamide (2j) (chromatography on silica gel, EtOAc, then 10% MeOH/EtOAc): yield 65%; glass; ^{1}H NMR ($CDCl_3$) ∂ 7.35−6.68 (m, 9H), 5.74 (br s, 1H), 5.46 (br s, 1H), 5.29 (s, 2H), 3.69 (s, 2H), 2.65 (t, 2H), 1.60−1.44 (m, 2H), 0.93 (t, 3H); MS (FD$^+$) 322 (M$^+$). Anal. ($C_{20}H_{22}N_2O_2$·H_2O) C, H, N.

2-Cyclopropyl-5-hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (2k) (crystallization, EtOAc): yield 79%; mp 174−175 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.62 (s, 1H), 7.32−7.16 (m, 3H), 7.12 (br s, 1H), 7.04−6.96 (m, 3H), 6.86 (br s, 1H), 6.80 (d, 1H), 6.54 (dd, 1H), 5.44 (s, 2H), 3.50 (s, 2H), 1.70−1.60 (m, 1H), 0.94-0.84 (m, 2H), 0.74−0.64 (m, 2H); MS (FD$^+$) 320 (M$^+$). Anal. ($C_{20}H_{20}N_2O_2$) C, H, N.

2-Chloro-5-hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (2l) (crude product).

2-Bromo-5-hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (2m) (chromatography on silica gel, gradient, 1−4% MeOH/CH_2Cl_2): yield 20%; oil; ^{1}H NMR (DMSO-d_6/D_2O) ∂ 7.25−7.10 (m, 4H), 7.00 (d, 2H), 6.80 (d, 1H), 6.10 (dd, 1H), 5.30 (s, 2H), 3.40 (s, 2H); MS (FD$^+$) 358 (M − 1), 360 (M + 1).

2-Bromo-6-chloro-5-hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (2n) (chromatography on silica gel, gradient, 2−4% MeOH/CH_2Cl_2): yield 45%; mp 195 °C dec; ^{1}H NMR (DMSO-d_6/D_2O) ∂ 7.35 (s, 1H), 7.25−7.15 (m, 3H), 6.95 (s, 1H), 6.90 (d, 2H), 5.30 (s, 2H), 3.40 (s, 2H); MS (FD) 392 (M − 1, 75), 394 (M + 1, 100). Anal. ($C_{17}H_{14}BrClN_2O_2$·0.1CH_2Cl_2) C, H, N, Br; Cl: calcd, 10.58; found, 9.49.

5-Hydroxy-2-(methylthio)-1-(phenylmethyl)-1*H*-indole-3-acetamide (2o) (crude product): yield 64%; wax; MS (FD$^+$) 326 (M$^+$). Anal. ($C_{18}H_{18}N_2O_2S$) C, H, N, S.

1-[(3-Chlorophenyl)methyl]-4-hydroxy-2-methyl-1*H*-indole-3-acetamide (2p) (chromatography on silica gel, gradient, 50% EtOAc/hexane−EtOAc): yield 48%; mp 173−177 °C; ^{1}H NMR ($CDCl_3$) ∂ 8.65 (br s, 1H), 7.41−6.74 (m, 6H), 6.59 (d, 1H), 6.07 (br s, 1H), 5.66 (br s, 1H), 5.21 (s, 2H), 3.80 (s, 2H), 2.33 (s, 3H); MS (FD$^+$) 328 (M − 1, 100), 330 (M + 1, 32). Anal. ($C_{18}H_{17}ClN_2O_2$) C, H, N.

1-[(3-Chlorophenyl)methyl]-2-ethyl-4-hydroxy-1*H*-indole-3-acetamide (2q) (chromatography on silica gel, EtOAc): yield 76%; ^{1}H NMR ($CDCl_3$) ∂ 8.75 (br s, 1H), 7.41−6.57 (m, 7H), 5.12 (br s, 1H), 5.78 (br s, 1H), 5.25 (s, 2H), 3.81 (s, 2H), 2.73 (q, 2H), 1.15 (t, 3H); MS (FD) 343 (M − 1, 100), 345 (M + 1, 43).

1-[(3-Chlorophenyl)methyl]-2-ethyl-5-hydroxy-1*H*-indole-3-acetamide (2r) (chromatography on silica gel, EtOAc): yield 81%; ^{1}H NMR ($CDCl_3$) ∂ 7.33−6.74 (m, 7H), 6.39

Table 1. Inhibitory Activity against hnps-PLA$_2$ and Arachidonic Acid

compd	inhibition of human secreted PLA$_2$ chromogenic assay: IC$_{50}$ (μM)	mole fraction[a]	contraction of GP lung tissue: PLA$_2$-induced apparent K_B (μM) ($n = 4$)	AA-induced ED$_{50}$ (μM) ($n = 4$)	compd	inhibition of human secreted PLA$_2$ chromogenic assay: IC$_{50}$ (μM)	mole fraction[a]	contraction of GP lung tissue: PLA$_2$-induced apparent K_B (μM) ($n = 4$)	AA-induced ED$_{50}$ (μM) ($n = 4$)
2b	3.68 ± 0.15	3.0×10^{-3}			**13c**	1.29 ± 0.16	1.0×10^{-3}	6.94 ± 1.03	>10
2c	8.28 ± 2.34	6.7×10^{-3}			**13d**	0.057 ± 0.004	4.6×10^{-5}	0.85 ± 0.13	>10
2d	1.02 ± 0.38	8.3×10^{-4}			**13e**	0.023 ± 0.005	1.9×10^{-5}	0.27 ± 0.05	>10
2e	3.61 ± 0.62	2.9×10^{-3}			**13f**	6.13 ± 1.46	5.0×10^{-3}		
2g	0.342 ± 0.070	2.8×10^{-4}			**13g**	0.074 ± 0.008	6.0×10^{-5}	0.90 ± 0.30	
2i	0.143 ± 0.031	1.2×10^{-4}			**13h**	0.033 ± 0.004	2.7×10^{-5}	0.44 ± 0.09	>10
2j	34.0 ± 14.6	2.8×10^{-2}			**13i**	0.016 ± 0.01	1.3×10^{-5}	0.24 ± 0.05	
2k	0.118 ± 0.011	9.6×10^{-5}			**13j**	0.022 ± 0.006	1.8×10^{-5}	0.26 ± 0.04	>10
2n	0.085 ± 0.010	6.9×10^{-5}			**14e**	0.040 ± 0.004	3.2×10^{-5}	0.34 ± 0.04	>10
2o	0.379 ± 0.101	3.1×10^{-4}			**15a**	3.68 ± 0.12	3.0×10^{-3}		
2p	5.88 ± 0.95	4.8×10^{-3}			**15h**	0.165 ± 0.040	1.3×10^{-4}	1.55 ± 0.27	
3c	1.38 ± 0.23	1.1×10^{-3}			**16a**	0.195 ± 0.050	1.6×10^{-4}		
4k	0.450 ± 0.060	3.7×10^{-4}			**16b**	0.050 ± 0.015	4.1×10^{-5}	0.26 ± 0.07	>10
4l	0.306 ± 0.096	2.5×10^{-4}	22.46 ± 5.95	>30	**18**	2.45 ($n = 1$)	2.0×10^{-3}		
4n	1.27 ($n = 1$)	1.0×10^{-3}			**19a**	0.422 ± 0.084	3.4×10^{-4}	1.95 ± 0.17	
6c	0.044 ± 0.008	3.6×10^{-5}	0.42 ± 0.11		**19b**	0.121 ± 0.056	9.8×10^{-5}		
6t	0.052 ± 0.012	4.2×10^{-5}	0.19 ± 0.02		**19c**	1.27 ± 0.52	1.0×10^{-3}		
6v	0.010 ± 0.001	8.1×10^{-6}	0.14 ± 0.04		**20a**	0.360 ± 0.085	2.9×10^{-4}		
7a	0.321 ± 0.016	2.6×10^{-4}			**20b**	0.154 ± 0.050	1.3×10^{-4}	4.44 ± 0.95	
7b	0.180 ± 0.007	1.5×10^{-4}			**20c**	5.83 ($n = 1$)	4.7×10^{-3}		
7c	0.052 ± 0.010	4.2×10^{-5}	0.37 ± 0.06	>10	**20d**	0.093 ± 0.053	7.6×10^{-5}		
7d	0.399 ± 0.045	3.2×10^{-4}			**26**	0.619 ± 0.741	5.0×10^{-4}		
7e	1.79 ± 0.17	1.5×10^{-3}	8.22 ± 1.07	>30	**29a**	3.37 ± 0.46	2.7×10^{-3}		
7f	0.527 ± 0.056	4.3×10^{-4}	3.76 ± 0.87	>30	**29b**	1.83 ($n = 1$)	1.5×10^{-3}		
7g	0.152 ± 0.033	1.2×10^{-4}	2.38 ± 0.59	>30	**35**	0.155 ± 0.029	1.3×10^{-4}	0.332 ± 0.04	
7h	1.15 ± 0.09	9.3×10^{-4}	8.80 ± 1.95	>30	**44a**	0.059 ± 0.027	4.8×10^{-5}		
7i	0.147 ± 0.009	1.2×10^{-4}	0.72 ± 0.10	>10	**44b**	0.023 ± 0.005	1.9×10^{-5}	0.124 ± 0.02[b]	
7j	1.90 ± 0.40	1.5×10^{-3}			**44c**	0.022 ± 0.005	1.8×10^{-5}		
7k	12.21 ± 0.44	9.9×10^{-3}			**44d**	0.033 ± 0.015	2.7×10^{-5}		
7l	7.96 ± 0.99	6.5×10^{-3}			**44e**	0.058 ± 0.006	4.7×10^{-5}		
7m	0.024 ± 0.001	2.0×10^{-5}	0.20 ± 0.04	>3	**60a**	0.075 ± 0.013	6.1×10^{-5}		
7n	0.189 ± 0.006	1.5×10^{-4}	0.52 ± 0.12	>10	**60b**	0.051 ± 0.012	4.1×10^{-5}		
7o	0.555 ± 0.182	4.4×10^{-4}			**62a**	0.040 ± 0.011	3.3×10^{-5}	0.698 ± 0.15	
7p	0.044 ± 0.005	3.6×10^{-5}			**62b**	0.020 ± 0.003	1.6×10^{-5}	2.74 ± 1.04	>10
7q	0.077 ± 0.018	6.3×10^{-5}	0.61 ± 0.07	>30	**62c**	0.612 ± 0.065	5.0×10^{-4}		
7r	0.073 ± 0.016	5.9×10^{-5}	0.53 ± 0.07	>10	**62d**	0.033 ± 0.005	2.7×10^{-5}	0.206 ± 0.05	
7s	0.162 ± 0.143	1.3×10^{-4}	0.63 ± 0.21	>10	**62e**	0.015 ± 0.006	1.2×10^{-5}	0.202 ± 0.02	
7u	0.039 ± 0.003	3.2×10^{-5}			**67**	1.02 ± 0.15	8.3×10^{-4}	2.17 ± 0.29	>30
7w	0.654 ± 0.114	5.3×10^{-4}			**68**	0.462 ± 0.132	3.8×10^{-4}	1.07 ± 0.11	>10
7x	0.683 ± 0.003	5.6×10^{-4}			**72**	6.93 ± 1.81	5.6×10^{-3}		
7y	>110				**76**	25.9 ± 4.2	2.1×10^{-2}		
12e	0.266 ($n = 1$)	2.2×10^{-4}			**82**	16.8 ($n = 1$)	1.4×10^{-2}		
13b	0.203 ± 0.061	1.7×10^{-4}							

[a] Mole fraction is the IC$_{50}$ concentration value divided by the total lipid concentration (1230 μM). [b] Intrinsic contractile activity was exhibited by the compound during the incubation period.

Table 2. Inhibitory Activity against Selected sPLA$_2$'s (μM)

compd	human nonpancreatic PLA$_2$	human pancreatic PLA$_2$	porcine pancreatic PLA$_2$
6t	0.052 ± 0.012	1.2	0.02
6v	0.010 ± 0.001	4.09(1.4)	0.014
7c	0.052 ± 0.010	1.4	0.15
7d	0.399 ± 0.045	3.66	0.61
7g	0.152 ± 0.033	69(76)	25(18.7)
7i	0.147 ± 0.009	22.5	7.5
7m	0.024 ± 0.001	1.8	0.13
7n	0.189 ± 0.006	94	13.5
7r	0.073 ± 0.016	15.9	2.86
13c	1.29 ± 0.16	73.5	5.55
13d	0.057 ± 0.004	67	27
13e	0.023 ± 0.005	91.1	35.5
13h	0.033 ± 0.004	6.2	2.2
13i	0.016 ± 0.01	46.2	
13j	0.022 ± 0.006	39	7.6
16b	0.050 ± 0.015	135	5.8
35	0.155 ± 0.029	94	
44b	0.023 ± 0.005	16	
62b	0.020 ± 0.003	3.2	1.3
67	1.02 ± 0.15	no activity	no activity

(s, 1H), 5.72 (br s, 1H), 5.48 (br s, 1H), 5.25 (s, 2H), 3.70 (s, 2H), 2.70 (q, 2H), 1.13 (t, 3H); MS (FD) 342 (M − 1, 100%), 344 (M + 1, 43%).

1-([1,1′-Biphenyl]-2-ylmethyl)-4-hydroxy-2-methyl-1*H*-indole-3-acetamide (2s) (chromatography on silica gel, EtOAc): yield 98%; ^{1}H NMR (CDCl$_3$) ∂ 8.62 (br s, 1H), 7.70−6.43 (m, 12H), 6.06 (br s, 1H), 5.74 (br s, 1H), 5.14 (s, 2H), 3.74 (s, 2H), 2.16 (s, 3H); MS (FD) 370 (M$^+$).

1-([1,1′-Biphenyl]-2-ylmethyl)-5-hydroxy-2-methyl-1*H*-indole-3-acetamide (2t) (chromatography on silica gel, EtOAc, then 5% MeOH/EtOAc): yield 85%; ^{1}H NMR (CDCl$_3$) ∂ 7.62−6.69 (m, 12H), 6.47 (d, 1H), 6.72 (br s, 1H), 5.64 (br s, 1H), 5.15 (s, 2H), 3.66 (s, 2H), 2.15 (s, 3H); MS (FD) 371 (M$^+$).

1-(Cyclohexylmethyl)-5-hydroxy-2-methyl-1*H*-indole-3-acetamide (2u) (crude product): yield 95%; mp 75−85 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.54 (br s, 1H), 7.17−7.04 (br s, 2H), 6.82 (d, 1H), 6.77 (br s, 1H), 6.54 (dd, 1H), 3.84 (d, 2H), 2.29 (s, 3H), 1.80−1.45 (m, 6H), 1.25−0.90 (m, 5H); MS (FD$^+$) 300 (M$^+$). Anal. ($C_{18}H_{24}N_2O_2$) C, calcd 71.97, found 69.14; H, calcd 8.05, found 7.60; N, calcd 9.33, found 8.69.

1-Decyl-5-hydroxy-2-methyl-1*H*-indole-3-acetamide (2v) (crude product): yield 60%; oil; ^{1}H NMR (DMSO-d_6) ∂ 8.54 (s, 1H), 7.08 (d, 1H), 7.06 (br s, 1H), 6.80 (d, 1H), 6.74 (br s, 1H), 6.54 (dd, 1H), 4.00 (t, 2H), 3.80 (s, 2H), 2.30 (s, 3H), 1.70−1.50 (m, 2H), 1.36−1.16 (m, 14H), 0.82 (t, 3H); MS (FD$^+$) 344 (M$^+$).

4-Allyl-2-ethyl-5-hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (2i). To a solution of **2g** (620 mg, 2.0 mmol) in

10 mL of THF and 40 mL of DMF was added 90 mg (2.2 mmol) of 60% NaH/mineral oil, and after the mixture was stirred for 0.17 h, 0.2 mL (2.3 mmol) of allyl bromide was added. After 2 h, the mixture was diluted with water and extracted with EtOAc. The EtOAc solution was washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica gel, eluted with a gradient of 1−3% MeOH/CH_2Cl_2, to give 770 mg of 5-(allyloxy)-2-ethyl-1-(phenylmethyl)-1*H*-indole-3-acetamide. This material (2.21 mmol) in 20 mL of *N*,*N*-dimethylaniline was heated in an oil bath at 190 °C for 20 h. The mixture was cooled, diluted with EtOAc, washed with 1 N HCl and brine, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica gel, eluted with a gradient of 1−3% MeOH/CH_2Cl_2, to give 295 mg (38% yield) of **2i** as a wax: MS (FD^+) 348 (M^+). Anal. ($C_{22}H_{24}N_2O_2$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]butanoic Acid Ethyl Ester (4d). A solution of 294 mg (1 mmol) of 4-hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (**2c**) in 5 mL of DMF was treated with 40 mg (1 mmol) of 60% NaH/mineral oil, and after 1 h, 0.15 mL (1 mmol) of ethyl 4-bromobutyrate was added. The mixture was stirred for 2 h, diluted with water, and extracted with EtOAc. The EtOAc solution was washed with a saturated NaCl solution, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was crystallized from MeOH/hexane to give a total of 235 mg (58% yield) of **4d**: mp 115−116 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.38−6.90 (m, 6H), 6.87 (d, 1H), 6.52 (d, 1H), 6.02 (br s, 1H), 5.29 (s, 2H), 5.22 (br s, 1H), 4.21−4.09 (m, 4H), 3.85 (s, 2H), 2.57 (t, 2H), 2.32 (s, 3H), 2.26−2.15 (m, 2H), 1.26 (s, 3H); MS (FD^+) 408 (M^+). Anal. ($C_{24}H_{28}N_2O_4$) C, H, N.

Using the preceding method, the following were prepared by reaction of the properly substituted hydroxyindole (**2**) (see Scheme 2) with the appropriate bromo ester.

2-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid methyl ester (3a) (chromatography on silica gel, 2% MeOH/EtOAc): yield 34%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.53 (br s, 1H), 7.38−7.02 (m, 9H), 6.94 (d, 1H), 6.40 (d, 1H), 5.85 (br s, 1H), 5.25 (s, 2H), 4.78 (s, 2H), 3.88 (s, 3H); MS (FD) 353 (M^+).

4-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid ethyl ester (4b) (chromatography on silica gel, gradient, CH_2Cl_2−3% MeOH/CH_2Cl_2): yield 66%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.35−7.25 (m, 3H), 7.15 (d, 1H), 7.10 (d, 2H), 7.05 (s, 2H), 6.85 (dd, 1H), 6.35 (br s, 1H), 5.85 (br s, 1H), 5.20 (s, 2H), 4.15 (q, 2H), 4.05 (t, 2H), 3.65 (s, 2H), 2.60−2.50 (m, 2H), 2.20−2.05 (m, 2H), 1.30 (t, 3H).

2-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid methyl ester (3c) (chromatography on silica gel, 50%EtOAc/hexane, then EtOAc, then 2% MeOH/EtOAc): yield 76%; mp 206−208 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.34−6.92 (m, 7H), 6.89 (d, 1H), 6.22 (d, 1H), 5.29 (s, 2H), 5.22 (br s, 1H), 4.79 (s, 2H), 3.88 (s, 2H), 3.86 (s, 3H), 2.40 (s, 3H); MS (FD) 366 (M^+). Anal. ($C_{21}H_{22}N_2O_4$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid ethyl ester (4g) (chromatography on silica gel, gradient, CH_2Cl_2−3% MeOH/CH_2Cl_2): yield 51%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.30−7.15 (m, 3H), 7.05 (d, 1H), 6.95 (d, 1H), 6.90 (d, 2H), 6.75 (dd, 1H), 6.40 (br s, 1H), 5.75 (br s, 1H), 5.25 (s, 2H), 4.10 (q, 2H), 4.00 (t, 2H), 3.65 (s, 2H), 2.50 (t, 2H), 2.25 (s, 3H), 2.15−2.00 (m, 2H), 1.25 (t, 3H).

5-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]pentanoic acid methyl ester (3h) (chromatography on silica gel, gradient, CH_2Cl_2−2% MeOH/CH_2Cl_2): yield 46%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.30−7.15 (m, 3H), 7.05 (d, 1H), 6.95 (d, 1H), 6.90 (d, 2H), 6.75 (dd, 1H), 6.30 (br s, 1H), 5.70 (br s, 1H), 5.20 (s, 2H), 3.95 (t, 2H), 3.65 (s, 3H), 3.60 (s, 2H), 2.35 (t, 2H), 2.25 (s, 3H), 1.85−1.75 (m, 4H).

2-[[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]methyl]benzoic acid methyl ester (3i) (chromatography on silica gel, gradient, CH_2Cl_2−2% MeOH/CH_2Cl_2): yield 69%; mp 178−180 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.85 (d, 1H), 7.70 (d, 1H), 7.60 (t, 1H), 7.40 (t, 1H), 7.35−7.15 (m, 5H), 7.10 (d, 1H), 6.95 (d, 2H), 6.75 (br s, 1H), 6.65 (dd, 1H), 5.35 (s, 2H), 5.10 (s, 2H), 3.75 (s, 3H), 3.40 (s, 2H), 2.25 (s, 3H); MS (FD^+) 442 (M^+). Anal. ($C_{27}H_{26}N_2O_4$·0.4H_2O) C, H, N.

3-[[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]methyl]benzoic acid methyl ester (3j) (chromatography on silica gel, gradient, 1−3% MeOH/CH_2Cl_2, crystallization, CH_2Cl_2/EtOH): yield 69%; mp 147−149 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.05 (s, 1H), 7.85 (d, 1H), 7.70 (d, 1H), 7.50 (t, 1H), 7.30−7.10 (m, 6H), 6.95 (d, 2H), 6.75 (br s, 1H), 6.70 (dd, 1H), 5.30 (s, 2H), 5.10 (s, 2H), 3.80 (s, 3H), 3.40 (s, 2H), 2.25 (s, 3H); MS (FD^+) 442 (M^+). Anal. ($C_{27}H_{26}N_2O_4$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-6-yl]oxy]butanoic acid ethyl ester (4k) (chromatography on silica gel, EtOAc, crystallization, CH_2Cl_2/MeOH/hexane): yield 76%; mp 126−133 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.41 (d, 1H), 7.34−6.94 (m, 5H), 6.81 (d, 1H), 6.75 (d, 1H), 5.69 (br s, 1H), 5.49 (br s, 1H), 5.25 (s, 2H), 4.13 (q, 2H), 3.99 (t, 2H), 3.69 (s, 2H), 2.50 (t, 2H), 2.29 (s, 3H), 2.09 (t, 2H), 1.23 (t, 3H); MS (FD^+) 408 (M^+). Anal. ($C_{24}H_{28}N_2O_4$) C, H, N.

5-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-6-yl]oxy]pentanoic acid ethyl ester (4l) (chromatography on silica gel, 50% EtOAc/hexane, then EtOAc): yield 71%; mp 123−135 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.40 (d, 1H), 7.34−6.60 (m, 9H), 5.34 (s, 2H), 4.03 (q, 2H), 3.91 (t, 2H), 3.40 (s, 2H), 2.33 (t, 2H), 2.25 (s, 3H), 1.16 (t, 3H); MS (FD^+) 422 (M^+). Anal. ($C_{25}H_{30}N_2O_4$) C, H, N.

2-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid methyl ester (3m) (crude product): yield 71%; ^{1}H NMR (DMSO-d_6) ∂ 7.32−6.83 (m, 8H), 6.77 (br s, 1H), 6.45 (d, 1H), 5.39 (s, 2H), 4.87 (s, 2H), 3.76 (s, 3H), 3.68 (s, 2H), 2.72 (q, 2H), 1.03 (t, 3H); MS (FD^+) 380 (M^+). Anal. ($C_{22}H_{24}N_2O_4$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid ethyl ester (4n) (chromatography on silica gel, 50% EtOAc/hexane): yield 55%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.45−6.84 (m, 8H), 6.09 (br s, 1H), 5.89 (br s, 1H), 5.40 (s, 2H), 4.25 (q, 2H), 4.14 (t, 2H), 3.78 (s, 2H), 2.83 (q, 2H), 2.64 (t, 2H), 2.21 (t, 2H), 1.38 (t, 3H), 1.24 (t, 3H); MS (FD^+) 422 (M^+). Anal. ($C_{25}H_{30}N_2O_4$) C, H, N.

2-[[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]methyl]benzoic acid methyl ester (3o) (chromatography on silica gel, gradient, 1−2% MeOH/CH_2Cl_2): yield 18%; mp 132−134 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.85 (d, 1H), 7.70 (d, 1H), 7.55 (t, 1H), 7.40 (t, 1H), 7.35−7.10 (m, 5H), 6.90 (d, 2H), 6.80 (br s, 1H), 6.65 (dd, 1H), 5.30 (s, 2H), 5.25 (s, 2H), 3.80 (s, 3H), 3.40 (s, 2H), 2.65 (q, 2H), 1.00 (t, 3H); MS (FD) 456 (M^+). Anal. ($C_{28}H_{28}N_2O_4$) H, N; C: calcd, 73.66; found, 74.36.

4-[[3-(2-Amino-2-oxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid methyl ester (3p) (chromatography on silica gel, 3% MeOH/CH_2Cl_2): yield 23%; oil.

4-[[3-(2-Amino-2-oxoethyl)-2-chloro-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid ethyl ester (4q) (chromatography on silca gel, gradient, CH_2Cl_2−3% MeOH/CH_2Cl_2): yield 57%; ^{1}H NMR ($CDCl_3$) ∂ 7.35−7.20 (m, 3H), 7.15 (dd, 1H), 7.00 (t, 2H), 6.95 (t, 1H), 6.80 (dd, 1H), 5.60 (br s, 1H), 5.65 (br s, 1H), 5.35 (d, 2H), 4.15 (q, 2H), 4.05 (t, 2H), 3.70 (s, 2H), 2.50 (t, 2H), 2.20−2.05 (m, 2H), 1.25 (t, 3H).

4-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid ethyl ester (4r) (chromatography on silica gel, gradient, 1−3% MeOH/CH_2Cl_2): yield 61%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.30−7.15 (m, 3H), 7.05 (d, 1H), 7.00 (d, 2H), 6.95 (d, 1H), 6.75 (dd, 1H), 5.50 (br s, 2H), 5.35 (s, 2H), 4.10 (q, 2H), 3.95 (t, 2H), 2.50 (t, 2H), 2.10−2.00 (m, 2H), 1.20 (t, 3H).

4-[[3-(2-Amino-2-oxoethyl)-2-(methylthio)-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid ethyl ester (4s) (crude product, washed with EtOH/Et_2O): yield 83%; mp 109−111 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.50 (br s, 1H), 7.40−7.25 (m, 4H), 7.20 (d, 1H), 7.10 (d, 2H), 7.00 (br s, 1H), 6.85 (dd, 1H), 5.60 (s, 2H), 4.10 (q, 2H), 4.05 (t, 2H), 3.75 (s, 2H), 2.55 (t, 2H), 2.15 (s 3H), 2.10−2.00 (m, 2H), 1.25 (t, 3H); MS (FD^+) 440 (M^+). Anal. ($C_{24}H_{28}N_2O_4S$) C, H, N.

2-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-methyl-1*H*-indol-4-yl]oxy]acetic acid ethyl ester (4t) (crude product, washed with MeOH): yield 73%; mp 180−183 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.36−6.84 (m, 7H), 6.78 (br s, 1H), 6.46 (d, 1H), 5.20 (s, 2H), 4.87 (s, 2H), 3.75 (s, 3H), 3.69 (s, 2H), 2.27 (s, 3H); MS (FD$^+$) 400 (M − 1, 100), 402 (M + 1, 36). Anal. ($C_{21}H_{21}ClN_2O_4$) C, H, N, S.

2-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (3u) (chromatography on silica gel, EtOAc): yield 71%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.25−6.74 (m, 7H), 6.43 (d, 1H), 5.40 (br s, 1H), 5.27 (s, 2H), 4.81 (s, 2H), 3.89 (s, 2H), 3.88 (s, 3H), 2.84 (q, 2H), 1.16 (t, 3H); MS (FD) 415 (M − 1, 100), 417 (M + 1, 45).

2-[[3-(2-Amino-2-oxoethyl)-1-([1,1′-biphenyl]-2-ylmethyl)-2-methyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (3v) (chromatography on silica gel, 50% EtOAc/hexane): yield 67%; ^{1}H NMR ($CDCl_3$) ∂ 7.66−6.90 (m, 10H), 6.78 (d, 1H), 6.47 (d, 1H), 6.40 (d, 1H), 5.16 (s, 3H), 4.80 (s, 2H), 3.86 (s, 5H), 2.28 (s, 3H); MS (FD$^+$) 442 (M$^+$).

4-[[3-(2-Amino-2-oxoethyl)-1-(cyclohexylmethyl)-2-methyl-1*H*-indol-5-yl]oxy]butanoic acid ethyl ester (4w) (chromatography on silica gel, 2% MeOH/CH_2Cl_2): yield 46%; mp 92−94 °C; MS (FD) 414 (M$^+$). Anal. ($C_{24}H_{34}N_2O_4$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-1-decyl-2-methyl-1-H-indol-5-yl]oxy]butanoic acid ethyl ester (4x) (chromatography on silica gel, 3% MeOH/CH_2Cl_2): yield 55%; mp 93−95 °C; MS (FD$^+$) 458 (M$^+$). Anal. ($C_{27}H_{42}N_2O_4$) C, H, N.

5-[3-(Ethoxycarbonyl)phenoxy]-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (4y). A mixture of 590 mg (2.0 mmol) of 5-hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (**2d**), 290 mg (2.0 mmol) of CuBr, and 90 mg (2.2 mmol) of NaH (60% in mineral oil) in 40 mL of pyridine was stirred for 10 min and then treated with 830 mg (3 mmol) of ethyl 3-iodobenzoate at reflux for 15.5 h. The mixture was cooled, diluted with EtOAc, washed with water, washed with brine, dried (Na_2SO_4), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of CH_2Cl_2−4% MeOH/CH_2Cl_2 and crystallized with Et_2O to give **4z**: 120 mg (yield 14%); mp 199−200 °C; ^{1}H NMR (DMSO-d_6) ∂ 10.40 (s, 1H), 8.80 (s, 1H), 8.40 (s, 1H), 8.05 (d, 1H), 7.80 (d, 1H), 7.50 (t, 1H), 7.45−7.25 (m, 3H), 7.20 (d, 1H), 7.10 (d, 2H), 7.05 (d, 1H), 6.70 (dd, 1H), 5.40 (s, 2H), 4.40 (q, 2H), 3.80 (s, 2H), 2.40 (s, 3H), 1.40 (t, 3H); MS (FD) 442 (M$^+$). Anal. ($C_{27}H_{26}N_2O_4$·0.5EtOAc) C, H, N.

3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propionic Acid Benzyl Ester (5f). 5-Hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (**2d**) (270 mg, 0.92 mmol), 500 mg of K_2CO_3, and 1.0 mL of benzyl acrylate in 30 mL of methyl ethyl ketone was heated to maintain reflux for 100 h (additional benzyl acrylate was added at various times). After cooling, the mixture was diluted with water and extracted with EtOAc, and the EtOAc solution was washed with a saturated NaCl solution and dried (Na_2SO_4). After the mixture was concentrated the residue was chromatographed on silica gel, eluting with a gradient of CH_2Cl_2−7% MeOH/CH_2Cl_2 to give 130 mg of **5f**.

2-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]acetic Acid Ethyl Ester (4e). A solution of 1.78 g (5.3 mmol) of 5-methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid (**8**) in 125 mL of CH_2Cl_2 and 21 mL of 1 M boron tribromide in CH_2Cl_2 was stirred for 4 h, the boron complex was decomposed by the addition of 10 mL of methanol over 0.5 h, and the resulting crude 5-hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid was concentrated at reduced pressure. A solution of 590 mg of this material in 30 mL of THF and 10 mL of DMSO was treated with 180 mg (4.5 mmol) of 60% NaH/mineral oil, and after 10 min, 0.25 mL (2.25 mmol) of ethyl 2-bromoacetate was added. The mixture was stirred for 0.5 h, acidified with 1 N HCl, and extracted with EtOAc. The EtOAc solution was washed with water and a saturated NaCl solution, dried (Na_2SO_4), and concentrated at reduced pressure. After chromatography on silica gel, eluted with a gradient of CH_2Cl_2−3% MeOH/CH_2Cl_2, there was obtained 590 mg (77% yield) of 5-(carbethoxymethoxy)-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid (**9**). While cooling at −5 °C, 0.16 mL (2.1 mmol) of methyl chloroformate was added to 630 mg (1.6 mmol) of **9** and 0.3 mL (2.2 mmol) of triethylamine in 30 mL of CH_2Cl_2, and the mixture was stirred for 10 min. Anhydrous ammonia was bubbled into the reaction mixture for 0.5 h, and then the mixture was washed with water and a saturated NaCl solution, dried (Na_2SO_4) and concentrated at reduced pressure. The residue was chromatographed on silica gel, eluted with a gradient of CH_2Cl_2−3% MeOH/CH_2Cl_2, to give after crystallization from Et_2O, 270 mg (yield 44%) of **4e**: mp 160−161 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.30−7.15 (m, 5H), 7.05 (d, 1H), 6.95 (d, 2H), 6.75 (br s, 1H), 6.65 (dd, 1H), 6.35 (br s, 1H), 5.30 (s, 2H), 4.70 (s, 2H), 4.10 (q, 2H), 3.40 (s, 2H), 2.25 (s, 3H), 1.20 (t, 3H); MS (FD$^+$) 380 (M$^+$). Anal. ($C_{22}H_{24}N_2O_4$) C, H, N.

2-[[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-methyl-1*H*-indol-4-yl]oxy]methyl]acetic Acid Sodium Salt (6t). A mixture of 155 mg (0.39 mmol) of **4t** and 4 mL of 1 N NaOH in 10 mL of EtOH was heated 0.5 h and allowed to cool, and the precipitate was filtered to give 140 mg (88% yield) of **6t**: mp >250 °C; ^{1}H NMR (DMSO-d_6) ∂ 9.42 (br s, 1H), 7.34−6.82 (m, 6H), 6.38 (t, 1H), 6.31 (br s, 1H), 5.36 (s, 2H), 4.12 (s, 2H), 3.63 (s, 2H), 2.32 (s, 3H); MS (FAB+) 409 (M − 1, 100), 411 (M + 1, 45). Anal. ($C_{20}H_{18}ClN_2O_4Na$) C, H, N.

Using the preceding method, **6c** was prepared from **3c** and **6v** was prepared from **3v**.

2-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid sodium salt (6c) (crystallized from reaction mixture): yield 92%; mp >250 °C; ^{1}H NMR (DMSO-d_6) ∂ 9.33 (br s, 1H), 7.32−6.32 (m, 8H), 6.31 (br s, 1H), 5.33 (s, 2H), 4.13 (s, 2H), 3.62 (s, 2H), 2.32 (s, 3H); MS (FD$^+$) 352 (M$^+$). Anal. ($C_{20}H_{19}N_2O_4Na$) C, H, N.

2-[[3-(2-Amino-2-oxoethyl)-1-([1,1′-biphenyl]-2-ylmethyl)-2-methyl-1*H*-indol-4-yl]oxy]acetic acid sodium salt (6v) (crystallized from reaction mixture): yield 75%; mp >250 °C; ^{1}H NMR (DMSO-d_6) ∂ 9.18 (br s, 1H), 7.40−6.80 (m, 9H), 6.65 (d, 1H), 6.38−6.26 (m, 3H), 5.21 (s, 2H), 4.11 (s, 2H), 3.61 (s, 2H), 2.21 (s, 3H); MS (FAB+) 451 (M$^+$). Anal. ($C_{26}H_{23}N_2O_4$-Na) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-6-yl]oxy]butanoic Acid (7k). A solution of 100 mg (0.245 mmol) of **4k** and 2 mL of 1 N NaOH in 5 mL of EtOH was stirred for 1.5 h, diluted with water, and extracted with EtOAc. The aqueous layer was made acidic to pH 6 with 1 N HCl and extracted with EtOAc; the EtOAc was dried ($MgSO_4$) and concentrated at reduced pressure. The residue was crystallized from MeOH/CH_2Cl_2 to give 44 mg (yield 47%) of **7k**: mp 180−184 °C; ^{1}H NMR (DMSO-d_6) ∂ 12.08 (br s, 1H), 7.40 (d, 1H), 7.33−7.20 (m, 3H), 7.18 (br s, 1H), 6.99 (d, 1H), 6.12 (s, 1H), 6.78 (br s, 1H), 6.64 (d, 1H), 5.34 (s, 2H), 3.93 (t, 2H), 3.41 (s, 2H), 2.37 (t, 2H), 2.25 (s, 3H); MS (FD$^+$) 380 (M$^+$). Anal. ($C_{22}H_{24}N_2O_4$) C, H, N.

Using the procedure above or a similar procedure where the reaction was heated at reflux in ethanol, the following conversions were made: **3a** to **7a**; **4b** to **7b**; **3c** to **7c**; **4d** to **7d**; **4e** to **7e**; **4g** to **7g**; **3h** to **7h**; **3i** to **7i**; **3j** to **7j**; **4l** to **7l**; **3m** to **7m**; **4n** to **7n**; **3o** to **7o**; **3p** to **7p**; **4q** to **7q**; **4r** to **7r**; **4s** to **7s**; **3u** to **7u**; **4w** to **7w**; **4x** to **7x**; **4y** to **7y**; **4z** to **7z**:

2-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid (7a) (crude product, washed with CH_2Cl_2): yield 56%; mp 207−208 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.34−6.92 (m, 9H), 6.81 (br s, 1H), 6.42 (d, 1H), 5.33 (s, 2H), 4.72 (s, 2H), 3.64 (s, 2H); MS (FD) 339 (M$^+$). Anal. ($C_{19}H_{18}N_2O_4$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid (7b) (crystallization, CH_2Cl_2/EtOH): yield 46%; mp 160−163 °C; ^{1}H NMR (DMSO-d_6/D_2O) ∂ 7.30−7.10 (m, 4H), 7.05 (d, 2H), 7.00 (d, 1H), 6.65 (dd, 1H), 5.20 (s, 2H), 3.90 (t, 2H), 3.40 (s, 2H), 2.35 (t, 2H), 1.95−1.80 (m, 2H); MS (FD$^+$) 366 (M$^+$). Anal. ($C_{21}H_{22}N_2O_4$) C, H, N.

2-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid (7c) (crystallization, MeOH): yield 57%; mp 225−227 °C; ^{1}H NMR (DMSO-d_6) ∂ 13.19 (br s, 1H), 7.35−6.85 (m, 8H), 6.77 (br s, 1H), 6.42 (d, 1H), 5.37 (s, 2H), 4.75 (s, 2H), 3.66 (s, 2H), 2.28 (s, 3H); MS (FD) 352 (M$^+$). Anal. ($C_{20}H_{20}N_2O_4$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]butanoic acid (7d) (crude product, washed with MeOH): yield 42%, mp 192−193 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) ∂ 7.42−6.92 (m, 6H), 6.85 (d, 1H), 6.49 (d, 1H), 6.06 (br s, 1H), 5.82 (br s, 1H), 5.28 (s, 2H), 4.16 (t, 2H), 3.83 (s, 2H), 2.60−2.52 (m, 2H), 2.30 (s, 3H), 2.23−2.14 (m, 2H); MS (FD$^+$) 380 (M$^+$). Anal. ($C_{22}H_{24}N_2O_4$) H, N; C: calcd, 69.46; found, 68.17.

2-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]acetic acid (7e) (crude product, washed with Et_2O): yield 90%; mp 196−198 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.40−7.25 (m, 5H), 7.15 (d, 1H), 7.05 (d, 2H), 6.85 (br s, 1H), 6.75 (dd, 1H), 5.40 (s, 2H), 4.65 (s, 2H), 3.50 (s, 2H), 2.35 (s, 3H); MS (FD$^+$) 352 (M$^+$). Anal. ($C_{20}H_{20}N_2O_4$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid (7g) (crystallization, EtOAc): yield 38%; mp 218−221 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.35−7.20 (m, 5H), 7.10 (d, 1H), 7.00 (d, 2H), 6.80 (br s, 1H), 6.65 (dd, 1H), 5.35 (s, 2H), 3.95 (t, 2H), 3.45 (s, 2H), 2.40 (t, 2H), 2.30 (s, 3H), 2.00−1.90 (m, 2H); MS (FD$^+$) 380 (M$^+$). Anal. ($C_{22}H_{24}N_2O_4$) C, H, N.

5-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]pentanoic acid (7h) (crystallization, MeOH/CH_2Cl_2/Et_2O): yield 100%; mp 168−169 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.25−7.10 (m, 5H), 7.05 (d, 1H), 6.90 (d, 2H), 6.75 (br s, 1H), 6.60 (dd, 1H), 5.25 (s, 2H), 3.90 (t, 2H), 3.35 (s, 2H), 2.15 (t, 2H), 2.15 (s, 3H), 1.75−1.55 (m, 4H); MS (FD$^+$) 394 (M$^+$). Anal. ($C_{23}H_{26}N_2O_4$) C, H, N.

2-[[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]methyl]benzoic acid (7i) (crystallization, CH_2Cl_2): yield 59%; mp 173−176 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.90 (d, 1H), 7.70 (d, 1H), 7.55 (t, 1H), 7.40 (t, 1H), 7.35−7.15 (m, 5H), 7.10 (d, 1H), 6.95 (d, 2H), 6.75 (br s, 1H), 6.65 (dd, 1H), 5.40 (s, 2H), 5.30 (s, 2H), 3.40 (s, 2H), 2.25 (s, 3H); MS (FD) 428 (M$^+$). Anal. ($C_{26}H_{24}N_2O_4$·0.4 H_2O) C, H, N.

3-[[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]methyl]benzoic acid (7j) (crystallization, CH_2Cl_2/EtOH): yield 72%; mp 176−179 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.05 (s, 1H), 7.85 (d, 1H), 7.70 (d, 1H), 7.50 (t, 1H), 7.30−7.15 (m, 6H), 6.95 (d, 2H), 6.75 (br s, 1H), 6.70 (dd, 1H), 5.30 (s, 2H), 5.15 (s, 2H), 3.40 (s, 2H), 2.25 (s, 3H); MS (FD$^+$) 428 (M$^+$). Anal. ($C_{26}H_{24}N_2O_4$.H_2O) C, H, N.

5-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-6-yl]oxy]pentanoic acid (7l) (crystallization, MeOH/CH_2Cl_2): yield 56%; mp 103−107 °C; ^{1}H NMR (DMSO-d_6) ∂ 12.00 (br s, 1H), 7.44−6.80 (m, 10H), 5.27 (s, 2H), 3.92 (t, 2H), 3.41 (s, 2H), 2.30−2.22 (m, 2H), 2.25 (s, 3H), 1.80−1.52 (m, 4H); MS (FD$^+$) 394 (M$^+$). Anal. ($C_{23}H_{26}N_2O_4$) C, H, N.

2-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid (7m) (crystallized from reaction mixture): yield 95%; mp 220−222 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.32−6.40 (m, 10H), 5.38 (s, 2H), 4.75 (s, 2H), 3.66 (s, 2H), 2.74 (q, 2H), 1.05 (t, 2H); MS (FD$^+$) 366 (M$^+$). Anal. ($C_{21}H_{22}N_2O_4$) H; C: calcd, 68.84; found, 67.52; N: calcd, 7.65; found, 8.46.

4-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1-H-indol-5-yl]oxy]butanoic acid (7n) (crude product, washed with Et_2O/MeOH): yield 61%; mp 196−199 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.37−6.59 (m, 10H), 5.32 (s, 2H), 3.92 (t, 2H), 3.41 (s, 2H), 2.71 (q, 2H), 2.39 (t, 2H), 2.00−1.85 (m, 2H), 1.03 (t, 3H); MS (FD$^+$) 394 (M$^+$). Anal. ($C_{23}H_{26}N_2O_4$) C, H, N.

2-[[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]methyl]benzoic acid (7o) (crystallization, CH_2Cl_2/Et_2O): yield 92%; mp ∼100 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.90 (d, 1H), 7.70 (d, 1H), 7.55 (t, 1H), 7.40 (t, 1H), 7.30−7.10 (m, 6H), 6.95 (d, 2H), 6.75 (br s, 1H), 6.65 (dd, 1H), 5.35 (s, 2H), 5.25 (s, 2H), 3.35 (s, 2H), 2.65 (q, 2H), 1.00 (t, 3H); MS (FD) 442 (M$^+$). Anal. ($C_{27}H_{26}N_2O_4$·0.9CH_2Cl_2) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid (7p) (crude product): yield 15%; mp 192−196 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.32−7.18 (m, 3H), 7.12 (d, 1H), 7.02 (br s, 1H), 7.00 (d, 2H), 6.85 (br s, 1H), 6.70 (dd, 1H), 5.45 (s, 2H), 3.96 (t, 2H), 3.54 (s, 2H), 2.90 (t, 2H), 2.00−1.86 (m, 2H), 1.70−1.60 (m, 1H), 0.98−0.88 (m, 2H), 0.78−0.68 (m, 2H); MS (FD) 406 (M$^+$). Anal. ($C_{24}H_{26}N_2O_4$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2-chloro-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid (7q) (crystallization, MeOH/CH_2Cl_2): yield 80%; mp 198−200 °C; MS (FD$^+$) 400 (M − 1, 100), 402 (M + 1, 38). Anal. ($C_{21}H_{21}ClN_2O_4$·0.4CH_2Cl_2) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid (7r) (crystallization, EtOH/Et_2O): yield 80%; mp 184−186 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.60 (br s, 1H), 7.30−7.15 (m, 4H), 7.05 (d, 1H), 6.95 (d, 2H), 6.85 (br s, 1H), 6.70 (dd, 1H), 5.35 (s, 2H), 3.90 (t, 2H), 3.30 (s, 2H), 2.35 (t, 2H), 1.95−1.80 (m, 2H); MS (FD$^+$) 444 (M − 1), 446 (M + 1). Anal. ($C_{21}H_{21}BrN_2O_4$) C, calcd 56.64, found 42.71; H, calcd 4.75, found 3.76; N, calcd 6.29, found 4.50; Br, calcd 17.94, found 12.77; residue 17.00%.

4-[[3-(2-Amino-2-oxoethyl)-2-(methylthio)-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid (7s) (crude product, washed with EtOH/Et_2O): yield 85%; mp 187−188 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.40 (br s, 1H), 7.30−7.10 (m, 4H), 7.05 (s, 1H), 6.95 (d, 2H), 6.90 (br s, 1H), 6.70 (d, 1H), 5.45 (s, 2H), 3.95 (t, 2H), 3.65 (s, 2H), 2.35 (t, 2H), 2.00−1.85 (m, 2H); MS (FD) 411 (M − 1)$^+$. Anal. ($C_{22}H_{24}N_2O_4S$) C, H, N, S.

2-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid (7u) (crude product, washed with EtOAc): yield 80%; mp 216−217 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.34−6.74 (m, 8H), 6.46 (t, 1H), 5.41 (s, 2H), 4.75 (s, 2H), 3.67 (s, 2H), 2.74 (q, 2H), 1.04 (t, 3H); MS (FD) 401 (M − 1, 100), 403 (M + 1, 39). Anal. ($C_{21}H_{21}ClN_2O_4$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-1-(cyclohexylmethyl)-2-methyl-1*H*-indol-5-yl]oxy]butanoic acid (7w) (crystallization, MeOH): yield 28%; mp 212−214 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.25 (d, 1H), 7.20 (br s, 1H), 7.02 (d, 1H), 6.78 (br s, 1H), 6.66 (dd, 1H), 3.96 (t, 2H), 3.88 (d, 2H), 3.40 (s, 2H), 2.40 (t, 2H), 2.32 (s, 3H), 2.00−1.88 (m, 2H), 1.78−1.46 (m, 6H), 1.20−0.88 (m, 5H); MS (FD) 386 (M$^+$). Anal. ($C_{22}H_{30}N_2O_4$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-1-decyl-2-methyl-1*H*-indol-5-yl]oxy]butanoic acid (7x) (crystallization, MeOH): yield 77%; mp 163−165 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.25 (d, 1H), 7.20 (br s, 1H), 7.04 (d, 1H), 6.78 (br s, 1H), 6.64 (dd, 1H), 4.04 (t, 2H), 3.95 (t, 2H), 3.36 (s, 2H), 2.40 (t, 2H), 2.32 (s, 3H), 2.00−1.88 (m, 2H), 1.66−1.50 (m, 6H), 1.36−1.16 (m, 14H), 0.86 (t, 3H); MS (FD) 430 (M$^+$). Anal. ($C_{25}H_{38}N_2O_4$) H; C: calcd, 69.74; found, 70.63; N: calcd, 6.51; found, 6.98.

5-(3-Carboxyphenoxy)-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (7y) (crude product): yield 32%; amorphous solid; MS (FD$^+$) 414 (M$^+$). Anal. ($C_{25}H_{22}N_2O_4$·H_2O) C, H, N.

3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propionic Acid (7f). A mixture of 130 mg (0.29 mmol) of **5f** and 0.2 g of 10% Pd/C in 100 mL of EtOH was hydrogenated at 40 psi of hydrogen for 4.5 h. The mixture was filtered and concentrated until the product crystallized. The crystals were washed with Et_2O to give 80 mg (75% yield) of **7f**; mp 201−203 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.30−7.10 (m, 5H), 7.05 (d, 1H), 6.90 (d, 2H), 6.75 (br s, 1H), 6.60 (dd, 1H), 5.25 (s, 2H), 3.90 (t, 2H), 3.40 (s, 2H), 2.65 (t, 2H), 2.25 (s, 3H). Anal. ($C_{21}H_{22}N_2O_4$·H_2O) C, H; N: calcd, 7.29; found, 6.68.

[3-(2-Ethoxy-2-oxoethyl)-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]methyl]phosphonic Acid Diethyl Ester (11a). 5-Hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetic acid ethyl ester (**10**, 730 mg, 2.4 mmol) was dissolved in 20 mL of THF and 75 mL of DMF, and 115 mg (2.8 mmol) of 60% NaH/mineral oil was added. After 0.17 h, 1.1 g (4.0 mmol) of (iodomethyl)phosphonic acid dimethyl ester was added and stirring maintained for 5.5 h. The mixture was diluted with water and EtOAc, and the organic layer was separated, washed with water and brine, and dried (Na_2SO_4). The solution was evaporated at reduced pressure and the residue chromatographed on silica gel, eluting with Et_2O to give 150 mg (14% yield) of **11a**: ^{1}H NMR ($CDCl_3$) ∂ 7.35−7.00 (m, 8H), 6.85 (dd, 1H), 5.15 (s, 2H), 4.45 (d, 2H), 4.20 (q, 4H), 4.10 (q, 2H), 3.65 (s, 2H), 1.30 (t, 6H), 1.20 (t, 3H).

[3-[[3-(2-Ethoxy-2-oxoethyl)-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic Acid Dimethyl Ester (11b). A solution of **10** (560 mg, 1.8 mmol) in 25 mL of THF and 75 mL of DMF was treated with 80mg (2.0 mmol) of 60% NaH/mineral oil. After 0.17 h, 465 mg (2.0 mmol) of (3-bromopropyl)phosphonic acid dimethyl ester was added and stirring maintained for 3 h. The mixture was diluted with water and EtOAc, and the organic layer was separated, washed with water and brine, and dried (Na_2SO_4). The solution was evaporated at reduced pressure and the residue chromatographed on florisil, eluting with a gradient of 1−3% MeOH/CH_2Cl_2, to give 590 mg (71% yield) of **11b**: ^{1}H NMR ($CDCl_3$) ∂ 7.30−7.20 (m, 3H), 7.10−7.05 (m, 5H), 6.75 (dd, 1H), 5.15 (s, 2H), 4.15 (q, 2H), 4.00 (t, 2H), 3.75 (s, 3H), 3.70 (s, 3H), 3.65 (s, 2H), 2.15−1.85 (m, 4H), 1.25 (t, 3H).

[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]methyl]phosphonic Acid Diethyl Ester (12a). The phosphonic acid ester **11a** (150 mg, 0.3 mmol) was dissolved in 25 mL of toluene, and 10 mL of 0.67 M $CH_3ClAlNH_2$ in benzene/toluene was added. The mixture was heated at 50 °C for 1.25 h, and water and 1 N HCl were added. The mixture was extracted with a large volume of EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 1−3% MeOH/CH_2Cl_2, to give 120 mg (93% yield) of **12a**: ^{1}H NMR ($CDCl_3$) ∂ 7.30−7.20 (m, 3H), 7.15−7.00 (m, 5H), 6.85 (dd, 1H), 6.20 (br s, 1H), 6.00 (br s, 1H), 5.15 (s, 2H), 4.30 (d, 2H), 4.25−4.10 (m, 4H), 3.60 (s, 2H), 1.30 (t, 6H).

Using the preceding method, **12b** was prepared from **11b**:

[3-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester (12b) (chromatography on silica gel, gradient, 1−4% MeOH/CH_2Cl_2): yield 80%; oil.

[[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]methyl]phosphonic Acid Diethyl Ester (12c). 4-Hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (**2c**, 294 mg, 1 mmol) was added to 40 mg (1 mmol) of 60% NaH/mineral oil (previously washed with hexane) in 2 mL of DMF, the mixture was stirred 0.33 h, and then 1.1 g (4 mmol) of (iodomethyl)phosphonic acid diethyl ester was added. The mixture was stirred 72 h, 1.1 g (4 mmol) more (iodomethyl)phosphonic acid diethyl ester was added, and stirring was continued 24 h. The mixture was diluted with water and extracted with EtOAc, and the EtOAc was washed with brine, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was chromatographed on silica gel, eluting with EtOAc and then 10% MeOH/EtOAc, to give 206 mg (yield 46%) of **12c**: ^{1}H NMR ($CDCl_3$) ∂ 7.38−7.04 (m, 7H), 7.01 (d, 1H), 6.63 (d, 1H), 5.41 (s, 2H), 5.26 (br s, 1H), 4.52 (d, 2H), 4.41−4.33 (m, 4H), 3.97 (s, 2H), 2.53 (s, 3H), 1.50 (t, 6H).

[3-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic Acid Dimethyl Ester (12e). 2-Ethyl-5-hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (**2g**, 308 mg, 1.0 mmol) was added to 40 mg (1.0 mmol) of NaH/mineral oil (washed with hexanes) in 4 mL of DMF, the mixture was stirred for 0.5 h, 196 mg (0.85 mmol) of (3-bromopropyl)phosphonic acid dimethyl ester was added, and stirring was maintained for 6.5 h. The mixture was diluted with water and extracted with EtOAc, and the EtOAc was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel, eluting with EtOAc, 5% MeOH/EtOAc, and then 10% MeOH/EtOAc, to give 269 mg (59% yield) of **12e**: ^{1}H NMR ($CDCl_3$) ∂ 7.49−6.86 (m, 8H), 5.80 (br s, 1H), 5.48 (br s, 1H), 5.43 (s, 2H), 4.16 (t, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.82 (s, 2H), 2.85 (q, 2H), 2.33−2.04 (m, 4H), 1.25 (t, 3H); MS (FD) 458 (M^+).

The following were made by the above procedure from the appropriately substituted hydroxyindole (see Scheme 3).

[3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester (12d) (crystallization, MeOH/hexane): yield 57%; mp 136−138 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.36−6.76 (m, 9H), 5.67 (br s, 1H), 5.29 (s, 2H), 4.05 (t, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.68 (s, 2H), 2.32 (s, 3H), 2.20−1.90 (m, 4H); MS (FD) 444 (M^+). Anal. ($C_{23}H_{29}N_2O_5P$) H, N; C: calcd, 62.15; found, 61.09.

[3-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-2-propyl-1*H*-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester (12f) (chromatography on silica gel, gradient, EtOAc−5% MeOH/EtOAc): yield 60%; wax; ^{1}H NMR ($CDCl_3$) ∂ 7.32−6.74 (m, 8H), 5.81 (br s, 1H), 5.43 (br s, 1H), 5.31 (s, 2H), 4.05 (t, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.71 (s, 2H), 2.69 (t, 2H), 2.18−1.90 (m, 4H), 1.60−1.44 (m, 2H), 0.93 (t, 3H); MS (FD^+) 472 (M^+). Anal. ($C_{25}H_{33}N_2O_5P$) C, H, N.

[3-[[3-(2-Amino-2-oxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester (12g) (chromatography on silica gel, gradient, 1−5% MeOH/CH_2Cl_2): yield 71%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.20−7.05 (m, 3H), 6.95 (d, 1H), 6.90−6.80 (m, 3H), 6.70 (dd, 1H), 6.35 (br s, 1H), 5.65 (br s, 1H), 5.40 (s, 2H), 3.98 (t, 2H), 3.75 (s, 2H), 3.70 (s, 3H), 3.65 (s, 3H), 2.05−1.80 (m, 4H), 1.60−1.50 (m, 1H), 0.90−0.80 (m, 2H), 0.65−0.60 (m, 2H).

[3-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester (12h) (chromatography on silica gel, gradient, 1−3% MeOH/CH_2Cl_2, crystallization, CH_2Cl_2/Et_2O): yield 27%; mp ∼100 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.30−7.10 (m, 3H), 7.05 (d, 1H), 7.00 (d, 2H), 6.95 (d, 1H), 6.75 (dd, 1H), 6.15 (br s, 1H), 5.70 (br s, 1H), 5.30 (s, 2H), 3.95 (t, 2H), 3.75 (s, 3H), 3.70 (s, 3H), 3.65 (s, 2H), 2.10−1.85 (m, 4H); MS (FD^+) 508 (M − 1), 510 (M + 1). Anal. ($C_{22}H_{26}BrN_2O_5P\cdot 0.8CH_2Cl_2$) C, H, N.

[3-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1*H*-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester (12i) (chromatography on silica gel, EtOAc, then 10% MeOH/EtOAc): yield 40%; ^{1}H NMR ($CDCl_3$) ∂ 7.33−6.77 (m, 7H), 5.72 (br s, 1H), 5.62 (br s, 1H), 5.29 (s, 2H), 4.07 (t, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.71 (s, 2H), 2.74 (q, 2H), 2.21−1.94 (m, 4H), 1.16 (t, 3H); MS (FD) 493 (M − 1, 100), 491 (M + 1, 38).

[3-[[3-(2-Amino-2-oxoethyl)-1-([1,1′-biphenyl]-2-ylmethyl)-2-methyl-1*H*-indol-5-yl]oxy]propyl]phosphonic acid dimethyl ester (12j) (chromatography on silica gel, gradient, EtOAc−10% MeOH/EtOAc): yield 34%; ^{1}H NMR ($CDCl_3$) ∂ 7.58−6.73 (m, 11H), 5.62 (br s, 1H), 5.34 (br s, 1H), 5.17 (s, 2H), 4.04 (t, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.66 (s, 2H), 2.28−1.90 (m, 2H), 2.17 (s, 3H); MS (FD) 520 (M^+). Anal. ($C_{29}H_{33}N_2O_5P$) H, N; C: calcd, 66.91; found, 68.34.

[3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic Acid (13d). A solution of 100 mg (0.23 mmol) of **12d** and 0.24 mL (1.8 mmol) of bromotrimethylsilane in 2 mL of CH_2Cl_2 was stirred for 18 h. The reaction mixture was concentrated at reduced pressure, 5 mL of MeOH was added, and the mixture was stirred for 0.5 h and concentrated. The residue was crystallized from EtOAc/MeCN/HOAc/H_2O to give 40 mg (42% yield) of **13d**: mp 201−203 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.35−6.60 (m, 10H), 5.34 (s, 2H), 4.00 (t, 2H), 3.41 (s, 2H), 2.29 (s, 3H), 2.00−1.82 (m, 2H), 1.75−1.60 (m, 2H); MS (FD^+) 416 (M^+). Anal. ($C_{21}H_{25}N_2O_5P$) C, H, N.

Using the above procedure, the following conversions were made: **12b**,**c**,**e**−**j** to **13b**,**c**,**e**−**j**.

[3-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic acid (13b) (crystallization, EtOAc/MeOH): yield 81%; solid; ^{1}H NMR (DMSO-d_6) ∂ 7.35 (br s, 1H), 7.30−7.10 (m, 5H), 7.15 (d, 2H), 7.05 (d, 1H), 6.80 (br s, 1H), 6.70 (dd, 1H), 5.25 (s, 2H), 3.95 (t, 2H), 3.40 (s, 2H), 1.95−1.75 (m, 2H), 1.70−1.55 (m, 2H). Anal. ($C_{20}H_{23}N_2O_5P\cdot 0.8H_2O$) C, H, N.

[[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]methyl]phosphonic acid (13c) (crystallization EtOAc/MeCN/HOAc/ H_2O): yield 29%; mp 195−198 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.38 (br s, 1H), 7.32−6.86 (m, 8H), 6.80 (br s, 1H), 6.56 (d, 1H), 5.35 (s, 2H), 4.17 (d, 2H), 3.65 (s, 2H), 2.32 (s, 3H); MS (FD^+) 388 (M^+). Anal. ($C_{19}H_{21}N_2O_5P$) C, H, N.

[3-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic acid (13e) (crystallization, EtOAc/MeCN/HOAc/ H_2O): yield 97%; mp 194−196 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.41−6.57 (m, 10H), 5.33 (s, 2H), 3.98 (t, 2H), 3.42 (s, 2H), 2.81 (q, 2H), 2.00−1.82 (m, 2H), 1.75−1.57 (m, 2H), 1.04 (t, 3H); MS (FD^+) 430 (M^+). Anal. ($C_{22}H_{27}N_2O_5P$) C, H, N.

[3-[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-2-propyl-1*H*-indol-5-yl]oxy]propyl]phosphonic acid (13f) (crystallization, EtOAc/MeCN/HOAc/ H_2O): yield 66%; mp 213−215 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.35−6.62 (m, 10H), 5.34 (s, 2H), 3.99 (t, 2H), 3.44 (s, 2H), 2.68 (t, 2H), 2.00−1.80 (m, 2H), 1.74−

1.58 (m, 2H), 1.50−1.34 (m, 2H), 0.87 (t, 3H); MS (FD$^+$) 444 (M$^+$). Anal. ($C_{23}H_{29}N_2O_5P$) C, H, N.

[3-[[3-(2-Amino-2-oxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic acid (13g) (crystallization, MeCN/ EtOAc/Et$_2$O): yield 94%; wax. Anal. ($C_{23}H_{27}N_2O_5P\cdot H_2O\cdot 1.2\ CH_2Cl_2$) C, H, N.

[3-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic acid (13h) (crystallization, EtOAc/EtOH/CH$_2$Cl$_2$): yield 39%; mp 188−190 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.35 (br s, 1H), 7.30−7.15 (m, 4H), 7.10−6.95 (m, 3H), 6.90 (br s, 1H), 6.70 (dd, 1H), 5.40 (s, 2H), 3.95 (t, 2H), 3.40 (s, 2H), 1.95−1.80 (m, 2H), 1.70−1.55 (m, 2H); MS (FD) 481 (M − 1), 483 (M + 1). Anal. ($C_{20}H_{22}BrN_2O_5P\cdot 0.5CH_2Cl_2$) C, H, N.

[3-[[3-(2-Amino-2-oxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1*H*-indol-5-yl]oxy]propyl]phosphonic acid (13i) (crystallization, EtOAc/MeCN/HOAc/H$_2$O): yield 65%; mp 203−205 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.37−6.63 (m, 9H), 5.38 (s, 2H), 3.99 (t, 2H), 3.44 (s, 2H), 2.74 (q, 2H), 2.00−1.84 (m, 2H), 1.76−1.60 (m, 2H), 1.03 (t, 3H); MS (FD$^+$) 464 (M − 1, 100), 466 (M + 1, 27). Anal. ($C_{22}H_{26}ClN_2O_5P$) C, H, N.

[3-[[3-(2-Amino-2-oxoethyl)-1-([1,1′-biphenyl]-2-ylmethyl)-2-methyl-1*H*-indol-5-yl]oxy]propyl]phosphonic acid (13j) (crystallization, EtOAc/MeCN/HOAc/H$_2$O): yield 33%; mp 200−202 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.58−6.60 (m, 13H), 6.31 (d, 1H), 5.22 (s, 2H), 3.98 (t, 2H), 3.40 (s, 2H), 2.15 (s, 3H), 2.00−1.80 (m, 2H), 1.75−1.60 (m, 2H); MS (FD) 493 (M + 1). Anal. ($C_{27}H_{29}N_2O_5P$) C, H, N.

[3-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic Acid Monomethyl Ester (14e). A mixture of 162 mg (0.35 mmol) of **12e** and 5 mL of 1 N NaOH in 10 mL of MeOH was heated to maintain reflux for 5 h, diluted with water, and extracted with EtOAc. The aqueous layer was made acidic to pH 2−3 with 1 N HCl and extracted with EtOAc. The EtOAc solution was washed with brine, dried (MgSO$_4$), and concentrated at reduced pressure to give 120 mg (yield 77%) of **14e**: oil; ^{1}H NMR (DMSO-d_6) ∂ 7.36−6.62 (m, 10H), 5.36 (s, 2H), 3.99 (t, 2H), 3.56 (d, 3H), 3.33 (s, 2H), 2.72 (q, 2H), 2.00−1.66 (m, 4H), 1.04 (t, 3H); MS (FD$^+$) 444 (M$^+$). Anal. ($C_{23}H_{29}N_2O_5P$) H; C: calcd, 62.15; found, 63.15; N: calcd, 6.30; found, 4.81.

[[[3-(2-Amino-2-oxoethyl)-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]methyl]phosphonic Acid Disodium Salt (15a). A solution of 120 mg (0.28 mmol) of **12a** and 0.5 mL of trimethylsilyl bromide in 20 mL of CH$_2$Cl$_2$ was stirred for 17 h and concentrated at reduced pressure. The residue was dissolved in 10 mL of MeOH, and the mixture was stirred for 2 h and concentrated. The residue was chromatographed on a C-18 reverse phase column, eluting with 20% (5%HOAc/H$_2$O)/MeOH, then dissolved in 0.05 N NaOH and chromatographed on an HP-20 column, eluting with 10% MeCN/H$_2$O and then 50% MeCN/H$_2$O, to give 15 mg (14% yield) of **15a**: ^{1}H NMR (DMSO-d_6) ∂ 7.30−6.95 (m, 9H), 6.75 (dd, 1H), 5.15 (s, 2H), 3.65 (d, 2H), 3.40 (s, 2H).

[3-[[3-(2-Amino-2-oxoethyl)-2-bromo-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic Acid Disodium Salt (15h). The filtrate from the crystallization of **13h** was concentrated at reduced pressure and the residue chromatographed on a C-18 reverse phase column, eluting with 5% (5%HOAc/H$_2$O)/MeOH. The product was dissolved in 0.05 N NaOH and put on a medium pressure HP-20 column, eluted with a gradient of 10−50% MeCN/H$_2$O, to give 195 mg of **15h**. Anal. ($C_{20}H_{20}BrN_2O_5PNa_2$) C, H, Br; N: calcd, 5.42; found, 4.83.

3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propanesulfonic Acid (16a). 5-Hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (**2d**, 300 mg, 1.0 mmol) was dissolved in 50 mL of THF, 40 mg (1.0 mmol) of 60% NaH/mineral oil was added, the mixture was stirred for 0.25 h, 125 mg (1.0 mmol) of sultone was added, and the mixture was stirred for 24 h. The mixture was made acidic with 5 N HCl and then concentrated at reduced pressure. The residue was crystallized from EtOH/water to give 145 mg (yield 35%) of **16a**: mp 218−222 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.30 (br s, 1H), 7.28−7.10 (m, 4H), 7.05 (s, 1H), 6.95 (d, 2H), 6.75 (br s, 1H), 6.60 (d, 1H), 5.25 (s, 2H), 4.00 (t, 2H), 3.40 (s, 2H), 2.55 (t, 2H), 2.25 (s, 3H), 2.05−1.90 (m, 2H). Anal. ($C_{21}H_{24}N_2O_5S$) Calcd: C, 60.56; H, 5.81; N, 6.73; S, 7.70. Found: C, 53.36; H, 5.66; N, 5.44; S, 3.30; residue, 15.32%.

Using the above procedure, **16b** was prepared from **2g**.

3-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propanesulfonic Acid (16b) (chromatography on C-18 RP column, 10% (5% HOAc/H$_2$O)/MeOH): yield 60%; solid; ^{1}H NMR (DMSO-d_6) ∂ 7.40 (br s, 1H), 7.30−7.15 (m, 4H), 7.10 (s, 1H), 6.90 (d, 2H), 6.75 (br s, 1H), 6.60 (d, 1H), 5.30 (s, 2H), 4.00 (t, 2H), 3.35 (s, 2H), 2.70 (q, 2H), 2.55 (t, 2H), 2.00−1.85 (m, 2H), 0.95 (t, 3H); MS (FD$^+$) 430 (M$^+$). Anal. ($C_{22}H_{26}N_2O_5S$) H; C: calcd, 61.38; found, 56.00; N: calcd, 6.51; found, 5.52; S: calcd, 7.45; found, 3.85; residue, 11.60%.

4-[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylethyl)-1*H*-indol-5-yl]butyronitrile (17). 5-Hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (**2d**, 295 mg, 1.0 mmol) was dissolved in 25 mL of DMSO and 5 mL of THF, 45 mg (1.1 mmol) of 60% NaH/mineral oil was added, the mixture was stirred for 10 min, 0.11 mL (1.1 mmol) of 4-bromobutyronitrile was added, and the mixture was stirred for 2 h at 60 °C. The mixture was cooled, diluted with water, and extracted with EtOAc. The EtOAc solution was separated, washed with brine, dried (Na$_2$SO$_4$), and concentrated. The residue was chromatographed on silica gel, eluting with a gradient of CH$_2$Cl$_2$−2% MeOH/CH$_2$Cl$_2$, and recrystallized from CH$_2$Cl$_2$/EtOH to give **17**: 200 mg (yield 55%); mp 144−146 °C; ^{1}H NMR (CDCl$_3$) ∂ 7.30−7.15 (m, 3H), 7.10 (d, 1H), 6.95 (d, 1H), 6.90 (d, 2H), 6.75 (dd, 1H), 6.20 (br s, 1H), 5.70 (br s, 1H), 5.25 (s, 2H), 4.05 (t, 2H), 3.65 (s, 2H), 2.55 (t, 2H), 2.30 (s, 3H), 2.15−2.05 (m, 2H); MS (FD$^+$) 361 (M$^+$). Anal. ($C_{22}H_{23}N_3O_2$) C, H, N.

1-(1*H*-Tetrazol-5-yl)-3-[3-(2-amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]propane (18). A mixture of **17** (165 mg, 0.46 mmol) and 2 mL of *n*-Bu$_3$SnN$_3$ was heated at 95 °C for 19 h, cooled, stirred with 50 mL of CH$_3$CN, 10 mL of THF, and 20 mL of HOAc for 2 h, and washed several times with hexane, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 3−8% MeOH/CH$_2$Cl$_2$, to give **18** [160 mg (yield 87%)] as a glass: ^{1}H NMR (DMSO-d_6) ∂ 7.20−7.10 (m, 4H), 7.10 (d, 1H), 6.95 (d, 1H), 6.85 (d, 2H), 6.80 (br s, 1H), 6.60 (dd, 1H), 5.25 (s, 2H), 3.95 (t, 2H), 3.35 (s, 2H), 2.95 (t, 2H), 2.20 (s, 3H), 2.10−2.00 (m, 2H); MS (FD) 404 (M$^+$). Anal. ($C_{22}H_{24}N_6O_2\cdot 0.4H_2O$) C, H, N.

4-(2-Hydrazino-2-oxoethoxy)-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (19a). A mixture of 484 mg (1.3 mmol) of **3c** and 2 mL of hydrazine in 10 mL of EtOH was heated to maintain reflux for 16 h, 10 mL of EtOH was added, and the mixture was heated an additional 4 h and cooled. Ethyl acetate and water were added, and the insoluble material was filtered. The EtOAc solution was separated, washed with brine, dried (MgSO$_4$), and concentrated. The residue was combined with the precipitate above to give 435 mg (91% yield) of **19a**: mp 207−210 °C; ^{1}H NMR (DMSO-d_6) ∂ 9.57 (br s, 1H), 7.36−6.82 (m, 9H), 6.43 (d, 1H), 5.37 (s, 2H), 4.60 (s, 2H), 4.56 (br s, 2H), 3.64 (s, 2H), 2.34 (s, 3H); MS (FD$^+$) 366 (M$^+$). Anal. ($C_{20}H_{22}N_4O_3$) C, H, N.

Also by this method, the following conversions were made: **3m** to **19b** and **4k** to **19c**.

2-Ethyl-5-(4-hydrazino-4-oxobutoxy)-1-(phenylmethyl)-1*H*-indole-3-acetamide (19b) (crude product, washed with MeOH): yield 87%; mp 176−179 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.99 (br s, 1H), 7.32−6.62 (m, 10H), 5.35 (s, 2H), 4.17 (br s, 2H), 3.93 (t, 2H), 3.43 (s, 2H), 2.73 (q, 2H), 2.21 (t, 2H), 2.00−1.90 (m, 2H), 1.04 (t, 3H); MS (FD) 408 (M$^+$). Anal. ($C_{23}H_{28}N_4O_3$) C, H, N.

6-(4-Hydrazino-4-oxobutoxy)-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (19c) (crystallization, MeOH/CH$_2$Cl$_2$): yield 81%; mp 132−138 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.96 (br s, 1H), 7.41 (d, 1H), 7.34−6.60 (m, 9H), 5.34 (s, 2H), 4.14 (br s, 2H), 3.90 (t, 2H), 3.40 (s, 2H), 2.25 (s, 3H), 2.18 (t, 2H), 1.96−1.84 (m, 2H); MS (FD$^+$) 394 (M$^+$). Anal. ($C_{22}H_{26}N_4O_3$) C, H, N.

4-(2-Amino-2-oxoethoxy)-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (20a). A mixture of 230 mg (0.63

mmol) of **19a** and 300 mg of Raney nickel in 40 mL of EtOH was heated to maintain reflux for 4 h. The mixture was cooled, the EtOH was poured off the catalyst, and the catalyst was washed twice with CH_2Cl_2. The combined solvents were filtered and concentrated, and the residue was chromatographed on silica gel, eluting with 10% MeOH/EtOAc, to give 25 mg (yield 11%) of **20a**. This material melted at 190−207 °C: ^{1}H NMR (DMSO-d_6) ∂ 7.44−6.40 (m, 12H), 5.37 (s, 2H), 4.52 (s, 2H), 3.66 (s, 2H), 2.30 (s, 3H). Anal. ($C_{20}H_{21}N_3O_3$) C; H: calcd, 6.02; found, 6.55; N: calcd, 11.96; found, 13.28.

Using the same method, the following conversions were made: **19b** to **20b** and **19c** to **20c**.

5-(4-Amino-4-oxobutoxy)-2-ethyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (20b) (chromatography on silica gel, EtOAc, then 10% MeOH/EtOAc): yield 47%; mp 176−179 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.38−6.62 (m, 12H), 5.36 (s, 2H), 3.93 (t, 2H), 3.43 (s, 2H), 2.73 (q, 2H), 2.43 (t, 2H), 1.98−1.85 (m, 2H), 1.03 (t, 3H); MS (FD$^+$) 393 (M$^+$). Anal. ($C_{23}H_{27}N_3O_3$) C, H, N.

6-(4-Amino-4-oxobutoxy)-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (20c) (chromatography on silica gel, EtOAc, then 5% MeOH/EtOAc): yield 11%; MS (FD$^+$) 379 (M$^+$).

5-(4-Amino-4-oxobutoxy)-2-(methylthio)-1-(phenylmethyl)-1*H*-indole-3-acetamide (20d). Ten milliliters of 0.6 M (CH_3)ClAlNH$_2$/benzene was added to 200 mg (0.45 mmol) of **4s** in 25 mL of benzene, and the mixture was heated at 50 °C for 1.75 h. After cooling, the mixture was decomposed with ice and 1 N HCl added. The mixture was extracted with EtOAc, and the EtOAc solution was washed with a saturated NaCl solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was crystallized from EtOH/CH_2Cl_2 to give 155 mg (yield 84%) of **20d**: mp 185 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.40 (br s, 1H), 7.30−7.00 (m, 5H), 7.10 (d, 1H), 6.95 (d, 2H), 6.90 (br s, 1H), 6.70 (dd, 1H), 5.50 (s, 2H), 3.90 (t, 2H), 3.65 (s, 2H), 3.30 (s, 3H), 2.15 (t, 2H), 2.00−1.80 (m, 2H); MS (FD) 411 (M$^+$). Anal. ($C_{22}H_{25}N_3O_3S$) C; H: calcd, 6.12; found, 6.54; N: calcd, 10.21; found, 8.97; S: calcd, 7.79; found, 7.11.

3-(2-Amino-1,2-dioxoethyl)-2-ethyl-4-nitro-1-(phenylmethyl)-1*H*-indole (22). A solution of 6.36 g (22.7 mmol) of **21** in 30 mL of CH_2Cl_2 was treated with 1.98 mL (22.7 mmol) of oxalyl chloride for 24 h, and the mixture was evaporated at reduced pressure, diluted with 30 mL of CH_2Cl_2, treated with ammonia gas for 15 min, and then evaporated at reduced pressure. The residue was dissolved in EtOAc, washed with water and brine, dried over $MgSO_4$, and evaporated at reduced pressure. The residue was triturated with EtOAc/hexane and the product removed by filtration. The filtrate was evaporated at reduced pressure and the residue chromatographed on silica gel, eluting with 20% EtOAc/hexane, to give additional product. Combined product of **22** weighed 6.0 g (yield 75%): mp 207−208 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.01 (br s, 1H), 7.96−7.84 (m, 2H), 7.65 (br s, 1H), 7.39−7.23 (m, 4H), 7.03 (d, 2H), 5.67 (s, 2H), 2.91 (q, 2H), 1.09 (t, 3H); MS (FD$^+$) 351 (M$^+$). Anal. ($C_{19}H_{17}N_3O_4$) C, H, N.

2-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]amino]acetic Acid (26). The nitro derivative **22** (6.0 g) and 1.0 g of 5% Pd/BaSO$_4$ in 70 mL of THF and 70 mL of EtOH was hydrogenated at 60 psi for 4 h, filtered and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with 50% EtOAc/hexane to give a 30% yield of 4-amino-3-(3-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indole and a 23% yield of **23**. A solution of 969 mg (3 mmol) of **23** in 15 mL of trifluoroacetic acid was stirred with 0.54 mL (3.3 mmol) of triethylsilane for 18 h, triturated with EtOAc−H_2O, and filtered to give 751 mg (yield 82%) of **24** as its trifluoroacetic acid salt. A solution of 523 mg (1.7 mmol) of **24** in 5 mL of DMF and 0.28 mL (1.7 mmol) of *tert*-butyl bromoacetate was stirred with 714 mg (8.5 mmol) of NaHCO$_3$ for 2 h, diluted with water, and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 50−67% EtOAc/hexane, to give 410 mg (yield 57%) of **25**. A solution of 400 mg (0.95 mmol) of **25** in 5 mL of trifluoroacetic acid was stirred for 1 h, evaporated at reduced pressure, and dissolved in EtOAc/H_2O. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was triturated with CH_2Cl_2 and filtered to give 72 mg (yield 16%) of **26** as its trifluoroacetic acid salt: ^{1}H NMR (DMSO-d_6) ∂ 7.79 (br s, 1H), 7.32−6.72 (m, 9H), 6.18 (br s, 1H), 5.35 (s, 2H), 3.94 (s, 2H), 3.64 (s, 2H), 2.78 (q, 2H), 1.00 (t, 3H); MS (FD) 355 (M$^+$). Anal. ($C_{21}H_{23}N_3O_3$·CF_3CO_2H) Calcd: C, 57.62; H, 5.04; N, 8.76. Found: C, 56.61; H, 5.09; N, 8.33.

3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]amino]propionic Acid Methyl Ester (28a). A solution of 147 mg (0.5 mmol) of 5-amino-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (**27**) and 2 mL of methyl acrylate in 5 mL of MeOH was stirred for 65 h and concentrated at reduced pressure. The residue was a mixture of **28a** and a minor (bisalkylated) product, which were separated by chromatography on silica gel, eluting with a gradient of EtOAc−5% MeOH/EtOAc to give 105 mg (yield 55%) of **28a**: ^{1}H NMR (CDCl$_3$) ∂ 7.38−6.85 (m, 9H), 5.77 (br s, 1H), 5.58 (br s, 1H), 5.26 (s, 2H), 3.69 (s, 3H), 3.66 (s, 2H), 3.54 (t, 2H), 2.79 (t, 2H), 2.31 (s, 3H); MS (FD) 379 (M$^+$). Anal. ($C_{22}H_{25}N_3O_3$) C, H, N.

3-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]amino]propionic Acid (29a). One milliliter of 1 N NaOH was added to a solution of 110 mg (0.3 mmol) of **28a** in 5 mL of MeOH, the mixture was stirred for 1 h, 1 mL of 1 N NaOH was added, and the mixture was stirred for 0.5 h. Water was added, 2 mL of 1 N HCl was then added, and the mixture was extracted with EtOAc. This was dried ($MgSO_4$) and concentrated at reduced pressure to give 21mg (20% yield) of **29a**: ^{1}H NMR (DMSO-d_6) ∂ 7.41−7.02 (m, 8H), 6.87 (br s, 1H), 6.74 (s, 1H), 6.53 (d, 1H), 5.35 (s, 2H), 3.46 (s, 2H), 3.33 (t, 2H), 2.64 (s, 2H), 2.34 (s, 3H); MS (FD$^+$) 365 (M$^+$).

4-[[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]amino]butanoic Acid (29b). To a solution of 293 mg (1.0 mmol) of **27** in 5 mL DMF was added 420 mg (5 mmol) of NaHCO$_3$ and 0.15 mL (1 mmol) of ethyl 4-bromobutyrate, and the mixture was heated at 80 °C for 18 h, diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was a mixture of **28b** and the bisalkylated product, which were separated by chromatography on silica gel, eluted with a gradient of 25−50%EtOAc/hexane, to give 76 mg (yield 14%) of the bisalkylated product and 88 mg (0.21 mmol, yield 22%) of **28b**. This material (**28b**) was stirred with 1 mL of 1 N NaOH in 2 mL of EtOH for 4 h, diluted with water, and extracted with EtOAc. The aqueous portion was acidified to pH 6 with 1 N HCl and then extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure, and then the mixture was stirred with EtOAc/MeCN/HOAc/H_2O for 16 h and filtered to give 10 mg (yield 13%) of **29b**: ^{1}H NMR (DMSO-d_6) ∂ 7.41−7.08 (m, 8H), 6.86 (br s, 1H), 6.71 (s, 1H), 6.53 (d, 1H), 4.34 (s, 2H), 3.45 (s, 2H), 3.08 (t, 2H), 2.43 (t, 2H), 2.33 (s, 3H), 1.87 (t, 2H); MS (FD$^+$) 379 (M$^+$).

4-(2-Methylindolin-5-yl)-4-oxobutanoic Acid Ethyl Ester (31). A solution of 10 g (57 mmol) of 1-acetyl-2-methylindoline (**30**) in 400 mL of CH_2Cl_2 was treated in portions with 24 g (180 mmol) of aluminum chloride and then with 6 g (60 mmol) of succinic anhydride. The mixture was refluxed for 3 h, cooled, poured onto ice/hydrochloric acid, and extracted with CH_2Cl_2/2-propanol (3:1). The organic phase was washed with brine, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was dissolved in 300 mL of EtOH containing 5 mL of concentrated sulfuric acid, refluxed for 15 h, cooled, concentrated at reduced pressure, diluted with EtOAc, washed with aqueous NaHCO$_3$, dried over Na_2SO_4, and evaporated. The residue was chromatograped on silica gel, eluting with a gradient of 25−50% Et_2O/hexane, to give, after crystallizing from EtOH, 8.8 g (yield 59%) of **31**: mp 92−94 °C; ^{1}H NMR (CDCl$_3$) ∂ 7.65 (d, 1H), 7.60 (s, 1H), 6.35 (d, 1H), 4.05 (q, 2H), 3.15 (t, 2H), 2.65 (t, 2H), 1.20 (d, 3H), 1.15 (t, 3H); MS (FD$^+$) 261 (M$^+$). Anal. ($C_{15}H_{19}NO_3$) C, H, N.

4-[2-Methyl-1-(phenylmethyl)-1*H*-indol-5-yl]-4-oxobutanoic Acid Ethyl Ester (32). A mixture of 2.8 g (11 mmol) of the **31**, 1.6 mL (14 mmol) of benzyl bromide, 2.2 g (16 mmol) of potassium carbonate, and 125 mL of DMF was heated at

85 °C for 4 h, diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 20−50% Et_2O/hexane, to give 3.5 g (yield 91%) of an oil (1-(phenylmethyl)indoline derivative). This material was mixed with 2.5 g (11 mmol) of dichlorodicyanoquinone in 120 mL of dioxane, and the mixture was heated at 85 °C for 0.5 h, cooled, diluted with EtOAc, washed with brine, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was chromatographed on fluorisil, eluting with CH_2Cl_2, to give, after crystallizing from Et_2O, 2.1 g (yield 55%) of **32**: mp 78−79 °C; ^{1}H NMR ($CDCl_3$) ∂ 8.15 (s, 1H), 7.65 (d, 1H), 7.25−7.05 (m, 4H), 6.80 (d, 2H), 6.30 (s, 1H), 5.15 (s, 2H), 4.05 (q, 2H), 3.25 (t, 2H), 2.65 (t, 2H), 2.20 (s, 3H), 1.15 (t, 3H); MS (FD$^+$) 349 (M$^+$). Anal. ($C_{22}H_{23}NO_3$·$0.5H_2O$) C, H, N.

4-[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]-4-oxobutanoic Acid Ethyl Ester (33). A solution of 790 mg (2.3 mmol) of **32** in 40 mL of CH_2Cl_2 was cooled to −5 °C and treated with 0.22 mL (2.5 mmol) of oxalyl chloride. The cooling bath was removed, and the solution was stirred for 0.5 h, saturated with ammonia gas, washed with water and brine, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 1−3% MeOH/CH_2Cl_2, to give, after crystallizing from Et_2O, 770 mg (yield 80%) of **33**: mp 122−123 °C; ^{1}H NMR ($CDCl_3$) ∂ 8.75 (s, 1H), 7.80 (d, 1H), 7.35−7.05 (m, 5H), 6.90 (d, 2H), 6.55 (br s, 1H), 5.25 (s, 2H), 4.05 (q, 2H), 3.30 (t, 2H), 2.65 (t, 2H), 2.55 (t, 2H), 2.55 (s, 3H), 1.15 (t, 3H); MS (FD) 421 (M$^+$). Anal. ($C_{24}H_{24}N_2O_5$) C, H, N.

4-[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]butanoic Acid Ethyl Ester (34). A solution of 770 mg (1.83 mmol) of **33**, 5 mL of triethylsilane, 5 mL of trifluoroacetic acid, and 40 mL of 1,2-dichloroethane was refluxed for 23 h. After cooling, the mixture was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with EtOAc, and crystallized from Et_2O to give 450 mg (yield 63%) of **34**: mp 88−90 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.35 (s, 1H), 7.30−7.15 (m, 4H), 7.10 (d, 1H), 6.95 (d, 2H), 6.30 (br s, 1H), 5.70 (br s, 1H), 5.25 (q, 2H), 4.05 (q, 2H), 3.60 (s, 2H), 2.70 (t, 2H), 2.30 (t, 2H), 2.25 (s, 3H), 2.05−1.85 (m, 2H), 1.20 (t, 3H); MS (FD) 392 (M$^+$). Anal. ($C_{24}H_{28}N_2O_3$) C, H, N.

4-[3-(2-Amino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]butanoic Acid (35). A solution of 450 mg (1.15 mmol) of **34** in 30 mL of EtOH and 2 mL of 2 N NaOH was stirred 15 h, diluted with water, and washed with Et_2O. The aqueous phase was acidified with 5 N HCl and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was crystallized from CH_2Cl_2/EtOH to give 300 mg (yield 72%) of **35**, mp 167−168 °C. Anal. ($C_{22}H_{24}N_2O_3$) H; C: calcd, 72.51; found, 72.08; N: calcd, 7.69; found, 7.14.

5-[[(Dimethylamino)thiocarbamoyl]oxy]-2-ethyl-1-(phenylmethyl)-1*H*-indole (38a). A solution of 1.8 g (6.8 mmol) of **36a** in 125 mL of CH_2Cl_2 was stirred with 20 mL of 1 M boron tribromide in CH_2Cl_2 for 2 h, decomposed with ice/water, washed with brine, dried over Na_2SO_4, and evaporated at reduced pressure. The crude 2-ethyl-5-hydroxy-1-(phenylmethyl)-1*H*-indole (**37a**, 1.8 g) was dissolved in 75 mL of DMSO and 10 mL of THF and stirred with 300 mg of NaH (60% in mineral oil; 7.5 mmol) for 10 min and then with 930 mg (7.5 mmol) of dimethylthiocarbamoyl chloride for 2.5 h, diluted with water, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 10−25% Et_2O/hexane, to give, after crystallizing from EtOH, 1.9 g (yield 83%) of **38a**: mp 135−138 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.35−7.20 (m, 4H), 7.15 (d, 1H), 7.00 (d, 2H), 6.85 (dd, 1H), 6.40 (s, 1H), 5.25 (s, 2H), 3.45 (s, 3H), 3.35 (s, 3H), 2.70 (q, 2H), 1.35 (t, 3H); MS (FD) 399 (M + 1)$^+$. Anal. ($C_{20}H_{22}N_2OS$) C, H, N.

2-Ethyl-5-hydroxy-6-methyl-1-(phenylmethyl)-1*H*-indole (37b). To a solution of 3.01 g (10.8 mmol) of 2-ethyl-5-methoxy-6-methyl-1-(phenylmethyl)-1*H*-indole (**36b**) in 50 mL of CH_2Cl_2 was added 16 mL (16 mmol) of a 1 M solution of boron tribromide in 50 mL of CH_2Cl_2. The mixture was stirred for 3 h and then evaporated at reduced pressure. The residue was diluted with water and extracted with EtOAc, washed with brine, dried ($MgSO_4$), evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 10% EtOAc/hexane, to give 1.69 g (yield 59%) of **37b** as an oil: ^{1}H NMR ($CDCl_3$) ∂ 7.37−6.89 (m, 8H), 6.19 (s, 1H), 5.25 (s, 2H), 2.64 (q, 2H), 2.31 (s, 3H), 1.30 (t, 3H); MS (FD$^+$) 265 (M$^+$). Anal. ($C_{18}H_{19}NO$) H, N; C: calcd, 81.47; found, 82.38.

Using the preceding method, 2-ethyl-5-methoxy-6-isopropyl-1-(phenylmethyl)-1*H*-indole (**36c**) was converted to **37c**.

2-Ethyl-5-hydroxy-6-isopropyl-1-(phenylmethyl)-1*H*-indole (37c) (chromatography on silica gel, 10% EtOAc/hexane): yield 65%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.39−6.90 (m, 8H), 6.18 (s, 1H), 5.26 (s, 2H), 3.35−3.24 (m, 1H), 2.64 (q, 2H), 1.41−1.18 (m, 9H); MS (FD) 293 (M$^+$). Anal. ($C_{20}H_{23}NO$) C, H, N.

5-[[(Dimethylamino)thiocarbamoyl]oxy]-2-ethyl-6-methyl-1-(phenylmethyl)-1*H*-indole (38b). To a solution of 1.69 g (6.4 mmol) of **37b** in 20 mL of DMF was added 256 mg (6.4 mmol) of 60% NaH/mineral oil and 791 mg (6.4 mmol) of dimethylthiocarbamoyl chloride. The mixture was stirred for 22 h, and then water and EtOAc were added. The EtOAc extract was washed with brine, dried ($MgSO_4$), evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 10% EtOAc/hexane, to give 1.78 g (yield 79%) of **38b**: ^{1}H NMR ($CDCl_3$) ∂ 7.41−6.90 (m, 7H), 6.31 (s, 1H), 5.26 (s, 2H), 3.49 (s, 3H), 3.39 (s, 3H), 2.64 (q, 2H), 2.24 (s, 3H), 1.30 (t, 3H); MS (FD$^+$) 352 (M$^+$). Anal. ($C_{21}H_{24}N_2OS$) H; C: calcd, 71.56; found, 72.07; N: calcd, 7.95; found, 7.14.

Using the preceding method, **38c** was prepared from **37c**.

5-[[(Dimethylamino)thiocarbamoyl]oxy]-2-ethyl-6-isopropyl-1-(phenylmethyl)-1*H*-indole (38c) (chromatography on silica gel, 17% EtOAc/hexane): yield 73%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.33−6.98 (m, 7H), 6.28 (s, 1H), 5.27 (s, 2H), 3.50 (s, 3H), 3.39 (s, 3H), 2.63 (q, 2H), 1.27 (t, 3H), 1.22 (d, 6H); MS (FD$^+$) 293 (M$^+$). Anal. ($C_{23}H_{28}N_2OS$) H, N; C: calcd, 72.59; found, 73.72.

5-[[(Dimethylamino)carbamoyl]thio]-2-ethyl-1-(phenylmethyl)-1*H*-indole (39a). A solution of 1.9 g of **38a** in 50 mL of phenyl ether was refluxed for 28 h, cooled, and chromatographed on silica gel, eluting with a gradient of 10−40% Et_2O/hexane and crystallized from EtOH to give 1.5 g (yield 80%) of **39a**: mp 148−151 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.75 (s, 1H), 7.30−7.15 (m, 5H), 6.95 (d, 2H), 6.35 (s, 1H), 5.25 (s, 2H), 3.05 (br s, 6H), 2.65 (q, 2H), 1.30 (t, 3H); MS (FD$^+$) 338 (M$^+$). Anal. ($C_{20}H_{22}N_2OS$) C, H, N.

Using the preceding method, **38b** was converted to **39b** and **38c** was converted to **39c**.

5-[[(Dimethylamino)carbamoyl]thio]-2-ethyl-6-methyl-1-(phenylmethyl)-1*H*-indole (39b) (chromatography on silica gel, 10% EtOAc/hexane, then 20% EtOAc/hexane): yield 82%; ^{1}H NMR ($CDCl_3$) ∂ 7.75 (s, 1H), 7.45−6.90 (m, 6H), 6.31 (s, 1H), 5.30 (s, 2H), 3.29−2.92 (m, 6H), 2.66 (q, 2H), 2.47 (s, 3H), 1.31 (t, 3H); MS (FD$^+$) 352 (M$^+$). Anal. ($C_{21}H_{24}N_2OS$)H, N; C: calcd, 71.56; found, 72.43.

5-[[(Dimethylamino)carbamoyl]thio]-2-ethyl-6-isopropyl-1-(phenylmethyl)-1*H*-indole (39c) (chromatography on silica gel, 10% EtOAc/hexane, then 20% EtOAc/hexane): yield 50%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.75 (s, 1H), 7.34−7.22 (m, 3H), 7.18 (s, 1H), 7.02 (d, 2H), 6.28 (s, 1H), 5.31 (s, 2H), 3.59−3.44 (m, 1H), 3.17 (br s, 3H), 3.05 (br s, 3H), 2.64 (q, 2H), 1.29 (t, 3H), 1.23 (d, 6H); MS (FD$^+$) 352 (M$^+$). Anal. ($C_{23}H_{28}N_2OS$) H, N; C: calcd, 72.59; found, 70.23.

4-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic Acid Ethyl Ester (41b). A mixture of 1.5 g of **39a** and 25 mL of 5 N NaOH in 125 mL of EtOH was refluxed for 5 h, cooled, acidified with 5 N HCl, and extracted with CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 10−15% Et_2O/hexane to give 930 mg (yield 84%) of 2-ethyl-5-mercapto-1-(phenylmethyl)-1*H*-indole (**40a**) as a glass. A solution of 400 mg (1.5 mmol) of **40a** in 70 mL of DMF and 10 mL of THF was treated with 70 mg of NaH (60% in mineral oil; 1.7 mmol) for 5 min and then with 0.25 mL (1.8 mmol) of ethyl 4-bromobutyrate for 0.5 h, diluted with water, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 10−15% Et_2O/hexane to give 480 mg (yield 84%) of **41b** as an oil: ^{1}H NMR ($CDCl_3$) ∂ 7.75 (s, 1H), 7.35−7.15 (m, 4H), 7.10 (d, 1H), 6.95 (d, 2H), 6.35 (br s, 1H), 5.25 (s, 2H), 4.15 (q, 2H), 2.95 (t, 2H), 2.70 (q, 2H), 2.50 (t, 2H), 2.05−1.95 (m, 2H), 1.35 (t, 3H), 1.05 (t, 3H); MS (FD$^+$) 381 (M$^+$). Anal. ($C_{23}H_{27}NO_2S$) H, N; C: calcd, 72.41; found, 73.27; S: calcd, 8.40; found, 7.96.

4-[[2-Ethyl-6-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]-thio]butanoic Acid Ethyl Ester (41c). A solution of 1.46 g (4.1 mmol) of **39b** and 20 mL of 5 N NaOH in 60 mL of EtOH was heated at reflux for 5 h and cooled to room temperature, water was added, and the mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure to give 1.2 g of crude 2-ethyl-5-mercapto-6-methyl-1-(phenylmethyl)-1*H*-indole (**40b**), which was immediately dissolved in 20 mL of DMF and stirred with 160 mg (4 mmol) of 60% NaH/mineral oil and 0.56 mL (4 mmol) of ethyl bromobutyrate. The mixture was stirred for 18 h, water was added, and the mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), concentrated, and then chromatographed on silica gel, eluting with 10% EtOAc/hexane, to give 947 mg (yield 60%) of **41c** as an oil: ^{1}H NMR ($CDCl_3$) ∂ 7.66 (s, 1H), 7.33−6.90 (m, 6H), 6.27 (s, 1H), 5.27 (s, 2H), 4.13 (q, 2H), 2.88 (t, 2H), 2.65 (q, 2H), 2.49 (s, 3H), 2.49−2.41 (m, 2H), 1.93 (t, 2H), 1.36−1.22 (m, 6H); MS (FD$^+$) 396 (M$^+$). Anal. ($C_{24}H_{29}NO_2S$) H, N; C: calcd, 72.87; found, 74.72.

Using the preceding method, **39c** was converted to **41d**.

4-[[2-Ethyl-6-isopropyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic acid ethyl ester (41d) (chromatography on silica gel, 10% EtOAc/hexane): yield 81%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.28 (s, 1H), 7.37−7.22 (m, 3H), 7.11 (s, 1H), 7.01 (d, 1H), 5.26 (s, 1H), 5.29 (s, 2H), 4.12 (q, 2H), 3.82−3.66 (m, 1H), 2.86 (t, 2H), 2.64 (q, 2H), 2.47 (t, 2H), 2.00−1.86 (m, 2H), 1.37−1.16 (m, 12H); MS (FD$^+$) 423 (M$^+$).

[3-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]propyl]phosphonic Acid Dimethyl Ester (41e). A solution of 530 mg (2.0 mmol) of **40a** in 90 mL of DMF and 10 mL of THF was treated with 70 mg (2.2 mmol) of 60%NaH/mineral oil. The mixture was stirred for 5 min, 510 mg (2.2 mmol) of dimethyl 3-bromopropyl phosphonate was then added, and the mixture was stirred for 30 min. The solution was diluted with water and EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), and then evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with EtOAc, to give 400 mg (yield 48%) of **41e** as an oil: ^{1}H NMR ($CDCl_3$) ∂ 7.60 (s, 1H), 7.25−7.00 (m, 5H), 6.80 (d, 2H), 6.25 (s, 1H), 5.20 (s, 2H), 3.65 (s, 3H), 3.60 (s, 3H), 2.85 (t, 2H), 2.60 (q, 2H), 1.95−1.70 (m, 4H), 1.20 (t, 3H).

3-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]propionic Acid *tert*-Butyl Ester (42a). To **40a** (1.91g, 7.15 mmol) and 3.9 g of potassium carbonate in 50 mL of MEK was added 1.6 mL of *tert*-butyl acrylate. The mixture was heated at reflux for 24 h, diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with 20% EtOAc/hexane, to give 2.47 g (6.25 mmol, yield 84%) of **41a** as an oil. This material was stirred with 0.55 mL (6.25 mmol) of oxalyl chloride in 40 mL of CH_2Cl_2 for 1 h and then evaporated at reduced pressure. The residue was redissolved in 40 mL of CH_2Cl_2, saturated with ammonia gas, stirred an additional 20 min, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with 50% EtOAc/hexane, to give 1.81 g (yield 62%) of **42a** as an oil: ^{1}H NMR ($CDCl_3$) ∂ 8.24 (s, 1H), 7.34−6.99 (m, 7H), 6.75 (br s, 1H), 5.71 (br s, 1H), 5.39 (s, 2H), 3.16−3.04 (m, 4H), 2.50 (t, 2H), 1.45 (s, 9H), 1.27 (t, 3H); MS (FD$^+$) 466 (M$^+$). Anal. ($C_{26}H_{30}N_2O_4S$) C, H; N: calcd, 6.00; found, 5.21.

4-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic Acid Ethyl Ester (42b). A solution of 480 mg (1.3 mmol) of **41b** in 100 mL of CH_2Cl_2 was cooled to −5 °C, and 0.14 mL (1.6 mmol) of oxalyl chloride was added. The cooling bath was removed, and the solution was stirred for 1 h, recooled to −5 °C, saturated with ammonia, washed with brine, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 40% Et_2O/hexane−100% Et_2O, to give 325 mg (yield 56%) of **42b** as a glass: MS (FD$^+$) 452 (M$^+$). Anal. ($C_{25}H_{28}N_2O_4S$) C, H, N, S.

4-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-6-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic Acid Ethyl Ester (42c). To a solution of 945 mg (2.4 mmol) of **41c** in 15 mL of CH_2Cl_2 was added 0.21 mL (2.4 mmol) of oxalyl chloride. The mixture was stirred for 3 h and then evaporated at reduced pressure, 15 mL of CH_2Cl_2 and saturated with ammonia gas was added, and the mixture was stirred 16 h and evaporated at reduced pressure. Water was added, and the mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 20% EtOAc/hexane, to give 620 mg (yield 55%) of **42c** as an oil: ^{1}H NMR ($CDCl_3$) ∂ 8.16 (s, 1H), 7.34−6.97 (m, 6H), 6.72 (br s, 1H), 5.77 (br s, 1H), 5.35 (s, 2H), 4.14 (q, 2H), 3.10 (q, 2H), 2.98 (t, 2H), 2.51 (t, 2H), 2.43 (s, 3H), 2.08−1.96 (m, 2H), 1.33−1.18 (m, 6H); MS (FD$^+$) 466 (M$^+$). Anal. ($C_{26}H_{30}N_2O_4S$) H; C: calcd, 66.93; found, 67.90; N: calcd, 7.00; found, 6.34.

Using the preceding method, **41d** was converted to **42d**.

4-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-6-isopropyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic acid ethyl ester (42d) (chromatography on silica gel, 20% EtOAc/hexane; yield 77%; oil; ^{1}H NMR ($CDCl_3$) ∂ 8.18 (s, 1H), 7.35−7.00 (m, 6H), 6.70 (br s, 1H), 5.74 (br s, 1H), 5.39 (s, 2H), 4.14 (q, 2H), 3.67−3.55 (m, 1H), 3.10 (q, 2H), 2.98 (t, 2H), 2.51 (t, 2H), 2.08−1.98 (m, 2H), 1.30−1.15 (m, 12H); MS (FD$^+$) 494 (M$^+$).

4-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic Acid Ethyl Ester (43b). A solution of 325 mg of **42b**, 2 mL of triethylsilane, and 2 mL of trifluoroacetic acid in 40 mL of 1,2-dichloroethane was refluxed for 18 h, cooled, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 1−5% $MeOH/CH_2Cl_2$ to give 200 mg (yield 64%) of **43b** as an oil which crystallized on standing: mp 90−92 °C; ^{1}H NMR ($CDCl_3$) ∂ 8.15 (s, 1H), 7.30−7.15 (m, 4H), 7.10 (d, 1H), 6.95 (d, 2H), 6.90 (br s, 1H), 6.25 (br s, 1H), 5.30 (s, 2H), 4.05 (q, 2H), 3.05 (q, 2H), 2.90 (t, 2H), 2.40 (t, 2H), 1.95−1.80 (m, 2H), 1.15 (t, 6H); MS (FD$^+$) 438 (M$^+$). Anal. ($C_{25}H_{30}N_2O_3S$) C, H, N, S.

4-[[3-(2-Amino-2-oxoethyl)-2-ethyl-6-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic Acid Ethyl Ester (43c). To a solution of 615 mg (1.32 mmol) of **42c** in 15 mL of EtOH was added 62.4 mg (1.65 mmol) of $NaBH_4$. The mixture was stirred for 20 h and then evaporated at reduced pressure, water was added, and the mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and evaporated to give 537 mg (yield 87%) of 4-[[3-(2-amino-1-hydroxy-2-oxoethyl)-2-ethyl-6-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic acid ethyl ester as an oil (532mg, 1.14 mmol). This oil was dissolved in 20 mL of CH_2Cl_2 and 0.23 mL (1.65 mmol) of triethylsilane, and 2 mL of trifluoroacetic acid was added. The mixture was stirred for 2 h and then evaporated at reduced pressure, water was added, and the mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 50% EtOAc/hexane, to give 290 mg (yield 56%) of **43c**: mp 135−137 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.60 (s, 1H), 7.33−7.22 (m, 3H), 7.07 (s, 1H), 6.97 (d, 2H), 5.71 (br s, 1H), 5.40 (br s, 1H), 5.31 (s, 2H), 4.12 (q, 2H), 3.72 (s, 2H), 2.89 (t, 2H), 2.73 (q, 2H), 2.51−2.46 (m, 2H), 2.49 (s, 3H), 1.93 (t, 2H), 1.26 (t, 3H), 1.12 (t, 3H); MS (FD$^+$) 452 (M$^+$). Anal. ($C_{26}H_{32}N_2O_3S$) C, H, N.

Using the preceding method, **42d** was converted to **43d**.

4-[[3-(2-Amino-2-oxoethyl)-2-ethyl-6-isopropyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic acid ethyl ester (43d) (crude product): yield 78%; ^{1}H NMR ($CDCl_3$) ∂ 7.37−7.23 (m, 3H), 7.10 (s, 1H), 7.00 (d, 2H), 5.80 (br s, 1H), 5.67 (br s, 1H), 5.32 (s, 2H), 4.11 (q, 2H), 3.82−3.60 (m, 1H), 3.72 (s, 2H), 2.89 (t, 2H), 2.73 (q, 2H), 2.47 (t, 2H), 2.00−1.84 (m, 2H), 1.35−1.07 (m, 12H); MS (FD$^+$) 480 (M$^+$).

[3-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]propyl]phosphonic Acid Dimethyl Ester (43e). To a solution of 400 mg (1.0 mmol) of **41e** in 100 mL of CH_2Cl_2 at −5 °C was added 0.11 mL (1.2 mmol) of oxalyl chloride. The cooling bath was removed, and the solution was stirred for 1 h. After being cooled to −5 °C, the solution was saturated with ammonia gas, washed with water, dried (Na_2SO_4), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 1−5% $MeOH/CH_2Cl_2$, to give 280 mg (yield 57%) of **42e**, which was dissolved in 40 mL of 1,2-dichloroethane, 2 mL of TFA, and 2 mL of triethylsilane and refluxed for 18 h. The cooled solution was washed with a saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 1−5% $MeOH/CH_2Cl_2$, to give 175 mg (yield 64%) of **43e**: ^1H NMR ($CDCl_3$) ∂ 7.60 (s, 1H), 7.25−7.00 (m, 4H), 7.05 (d, 1H), 6.95 (d, 2H), 6.30 (br s, 1H), 5.95 (br s, 1H), 5.25 (s, 2H), 3.65 (s, 3H), 3.60 (s, 3H), 2.80 (t, 2H), 2.70 (q, 2H), 1.95−1.70 (m, 4H), 1.05 (t, 3H).

3-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]propionic Acid (44a). To **42a** (1.81 g, 3.9 mmol) in 30 mL of EtOH was added 184 mg (4.9 mmol) of sodium borohydride. The mixture was stirred for 16 h, the solvent was evaporated at reduced pressure, and the residue was dissolved in EtOAc/water. The organic layer was washed with water and with brine, dried ($MgSO_4$), and evaporated at reduced pressure to give 1.34 g (3 mmol) of the α-hydroxy intermediate. This crude product was stirred with triethylsilane (0.6 mL, 3.75 mmol) in trifluoroacetic acid (10 mL) for 2 h. The solvent was evaporated at reduced pressure. The residue was dissolved in EtOAc, washed with water and brine, dried ($MgSO_4$), and evaporated at reduced pressure to give 1.0 g (yield 84%) of **44a**. This product was purified on a C-18 reverse phase column eluting with 10% (5% $HOAc/H_2O$)/MeOH: ^1H NMR ($CDCl_3$) ∂ 7.66 (s, 1H), 7.33−7.20 (m, 4H), 7.14 (d, 1H), 7.08 (br s, 1H), 6.95 (d, 1H), 5.80 (br s, 1H), 5.33 (s, 2H), 3.72 (s, 2H), 3.11 (t, 2H), 2.72 (q, 2H), 2.57 (t, 2H), 1.12 (t, 2H); MS (FD) 396 (M^+). Anal. ($C_{22}H_{24}N_2O_3S$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic Acid (44b). A mixture of 200 mg of **43b** and 2 mL of 2 N NaOH in 25 mL of EtOH was stirred for 19 h, acidified with 5 N HCl, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The residue was crystallized from EtOH to give 65 mg (yield 89%) of **44b**: mp 117−119 °C; MS (FD) 410 (M^+). Anal. ($C_{23}H_{26}N_2O_3S$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2-ethyl-6-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic Acid (44c). To a solution of 280 mg (0.62 mmol) of **43c** in 10 mL of MeOH was added 4 mL of 1 N NaOH, the mixture was heated at reflux for 1 h, water was then added,and the mixture was extracted with EtOAc. The aqueous portion was acidified to pH 2, extracted with EtOAc, washed with brine, dried ($MgSO_4$), evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 50% EtOAc/hexane to give 214 mg (yield 81%) of **44c**: ^1H NMR ($CDCl_3$) ∂ 7.59 (s, 1H), 7.33−7.21 (m, 4H), 7.03 (s, 1H), 6.97 (d, 2H), 6.03 (br s, 1H), 5.30 (s, 2H), 3.72 (s, 2H), 2.91 (t, 2H), 2.72 (q, 2H), 2.49 (t, 2H), 2.44 (s, 3H), 1.96 (t, 2H), 1.11 (t, 3H); MS (FD^+) 424 (M^+). Anal. ($C_{24}H_{28}N_2O_3S$) C, H, N.

Using the preceding method, **43d** was converted to **44d**.

4-[[3-(2-Amino-2-oxoethyl)-2-ethyl-6-isopropyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic acid (44d) (crystallization, EtOH/water): yield 37%; mp 138−140 °C; ^1H NMR ($CDCl_3$) ∂ 7.66 (s, 1H), 7.41−7.21 (m, 3H), 7.10 (s, 1H), 7.01 (d, 2H), 6.97 (br s, 1H), 6.03 (br s, 1H), 5.33 (s, 2H), 3.73−3.57 (m, 1H), 3.66 (s, 2H), 2.89 (t, 2H), 2.69 (q, 2H), 2.47 (t, 2H), 2.00−1.88 (m, 2H), 1.23 (d, 6H), 1.12 (t, 3H); MS (FD^+) 452 (M^+). Anal. ($C_{26}H_{32}N_2O_3S$) C, H, N.

[3-[[3-(2-Amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]propyl]phosphonic Acid (44e). A solution of 175 mg (0.37 mmol) of **43e** in 25 mL of CH_2Cl_2 was stirred with 0.5 mL of trimethylsilyl bromide for 19 h, evaporated at reduced pressure, dissolved in 25 mL of MeOH, stirred for 3 h, and evaporated at reduced pressure. The residue, dissolved in dilute NaOH, was chromatographed on an HP-20 column, eluting with a gradient of 5−15% $MeCN/H_2O$ to give 70 mg (yield 43%) of **44e** as a solid: MS (FAB) 469 $(M + 1 - Na)^+$, 470 $(M + 2 - Na)^+$, 491 $(M + 1)^+$, 492 $(M + 2)^+$. Anal. ($C_{22}H_{25}Na_2N_2O_4PS{\cdot}1.8H_2O$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-5-methoxy-2-methylindoline (47).** To a solution of 19 g (118 mmol) of 5-methoxy-2-methylindole (**45**) in 500 mL of acetic acid at 0 °C was added 37 g (590 mmol) of sodium cyanoborohydride in portions. The cooling bath was removed, and the reaction mixture was stirred for 4 h and then diluted with water. The acetic acid was evaporated at reduced pressure, the residue was made basic with 2 N NaOH, and then the product was extracted with Et_2O, washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure to give 16.9 g (104 mmol) of 5-methoxy-2-methylindoline (**46**). The crude product was heated at reflux with 27.2 g (124 mmol) of di-*tert*-butyl dicarbonate in 150 mL of THF for 22 h. The solvent was evaporated at reduced pressure, and the residue was diluted with water, extracted with EtOAc, washed with brine, dried ($MgSO_4$), evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 20% EtOAc/hexane, to give 16 g (yield 58%) of **47** as an oil: ^1H NMR ($CDCl_3$) ∂ 6.75−6.66 (m, 3H), 4.49 (br s, 1H), 3.78 (s, 3H), 3.34 (dd, 1H), 2.57 (br d, 1H), 1.58 (s, 9H), 1.30 (d, 3H); MS (FD^+) 263 (M^+). Anal. ($C_{15}H_{21}NO_3$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-2,7-dimethyl-5-methoxyindoline (48).** To a solution of 16 g (61 mmol) of **47** and 11.9 mL (79 mmol) of *N*,*N*,*N′*,*N′*-tetramethylethylenediamine in 300 mL of Et_2O at −78 °C was added 56 mL of a 1.3 M solution of *sec*-butyllithium in cyclohexane. The mixture was stirred for 1 h, 5.7 mL (91 mmol) of methyl iodide was then added, the cooling bath was removed, and the mixture was stirred for an additional 16 h. Water was added, and the product was extracted with Et_2O, washed with brine, dried ($MgSO_4$), evaporated at reduced pressure, and chromatographed on silica gel, eluting with 20% EtOAc/hexane, to give 15.4 g (yield 91%) of **48** as an oil: ^1H NMR ($CDCl_3$) ∂ 6.61 (s, 1H), 6.55 (s, 1H), 4.72−4.59 (m, 1H), 3.78 (s, 3H), 3.37 (dd, 1H), 2.34 (d, 1H), 2.26 (s, 3H), 1.51 (s, 9H), 1.18 (d, 3H); MS (FD^+) 277 (M^+). Anal. ($C_{16}H_{23}NO_3$) C, H, N.

2,7-Dimethyl-5-methoxy-1-(phenylmethyl)indoline (50). A solution of 15.7 g (56.7 mmol) of **48** in 25 mL of trifluoroacetic acid was stirred for 17 h. The TFA was evaporated at reduced pressure, the residue was dissolved in EtOAc/water and neutralized with 2 N NaOH, and then the EtOAc layer was separated, washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel, eluting with 20% EtOAc/hexane, to give 3.0 g (17 mmol, yield 30%) of 2,7-dimethyl-5-methoxyindoline (**49**). This material was dissolved in 15 mL of DMF and treated with 680 mg (17 mmol) of 60% NaH/mineral oil, followed by 2 mL (17 mmol) of benzyl bromide, and then the mixture was stirred for 1 h, diluted with water, and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), evaporated, and then chromatographed on a silica gel column, eluting with 20% EtOAc/hexane to give 4.1 g (yield 90%) of **50** as an oil: ^1H NMR ($CDCl_3$) ∂ 7.53−7.20 (m, 5H), 6.59 (s, 1H), 6.49 (s, 1H), 4.29 (AB q, 2H), 3.76 (s, 3H), 3.57-3.46 (m, 1H), 3.26 (dd, 1H), 2.44 (dd, 1H), 2.26 (s, 3H), 1.14 (d, 3H); MS (FD^+) 267 (M^+). Anal. ($C_{18}H_{21}NO$) C, H, N.

2,7-Dimethyl-5-methoxy-1-(phenylmethyl)-1*H*-indole (51). A solution of 4.1 g (15.4 mmol) of **50** in 50 mL of dioxane was treated with 3.5 g (15.4 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, and the mixture was heated at 90 °C for 15 min, diluted with water, and extracted with EtOAc. Some insoluble material was filtered off, the EtOAc layer was washed with brine, dried ($MgSO_4$), evaporated, and then chromatographed on silica gel, eluting with 20% EtOAc/hexane to give 3.25 g (yield 80%) of **51**: mp 98−108 °C; ^1H NMR ($CDCl_3$) ∂ 7.41−6.80 (m, 6H), 6.49 (s, 1H), 6.26 (s, 1H), 5.49 (s, 2H), 3.82 (s, 3H), 2.44 (s, 3H), 2.31 (s, 3H); MS (FD^+) 265 (M^+). Anal. ($C_{18}H_{19}NO$) C, H, N.

2,7-Dimethyl-5-hydroxy-1-(phenylmethyl)-1*H*-indole (52). A solution of 3.25 g (12.3 mmol) of **51** in 50 mL of CH_2Cl_2 was treated with 18.4 mL (18.4 mmol) of a 1 M solution of boron tribromide in CH_2Cl_2. The mixture was stirred for 1 h, the solvent was evaporated, and the residue was diluted with water, extracted with EtOAc, washed with brine, dried ($MgSO_4$), evaporated, and then chromatographed on silica gel, eluting with 20% EtOAc/hexane, to give 2.28 g (yield 74%) of **52**: mp 113−116 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.37−6.78 (m, 7H), 6.40 (s, 1H), 6.23 (s, 1H), 5.48 (s, 2H), 3.42 (s, 3H), 2.29 (s, 3H); MS (FD) 251 (M^+). Anal. ($C_{17}H_{17}NO$) C, H, N.

2,7-Dimethyl-5-[[(dimethylamino)thiocarbamoyl]oxy]-1-(phenylmethyl)-1*H*-indole (53). To a solution of 1.7 g (6.8 mmol) of **52** in 20 mL of DMF were added 272 mg (6.8 mmol) of 60% NaH/mineral oil and 841 mg (6.8 mmol) of dimethylthiocarbamoyl chloride. The mixture was stirred 72 h, water was added, and the mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was stirred with EtOAc, and the insoluble portion was filtered off to give 1.9 g (yield 83%) of **53**: ^{1}H NMR ($CDCl_3$) ∂ 7.33−7.19 (m, 4H), 7.08 (s, 1H), 6.89 (d, 1H), 6.56 (s, 1H), 6.33 (s, 1H), 5.51 (s, 1H), 3.48 (s, 3H), 3.34 (s, 3H), 2.49 (s, 3H), 2.31 (s, 3H); MS (FD$^+$) 338 (M^+). Anal. ($C_{20}H_{22}N_2OS$) H, N; C: calcd, 70.97; found, 68.65; residue 2.95%.

2,7-Dimethyl-5-[[(dimethylamino)carbamoyl]thio]-1-(phenylmethyl)-1*H*-indole (54). A solution of 1.9 g (5.6 mmol) of **53** in 120 mL of phenyl ether was heated at reflux for 16 h and cooled to room temperature, and then the entire solution was chromatographed on silica gel, eluting with 20% EtOAc/hexane and then 50% EtOAc/hexane, to give 1.51 g (yield 80%) of **54**: mp 171−173 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.57 (s, 1H), 7.37−7.16 (m, 4H), 6.94 (s, 1H), 6.84 (d, 1H), 6.33 (s, 1H), 5.53 (s, 2H), 3.09 (br s, 3H), 3.03 (br s, 3H), 2.47 (s, 3H), 2.29 (s, 3H); MS (FD$^+$) 338 (M^+). Anal. ($C_{20}H_{22}N_2OS$) C, H, N.

2,7-Dimethyl-5-mercapto-1-(phenylmethyl)-1*H*-indole (55). A solution of 744 mg (2.2 mmol) of **54** was heated with 10 mL of 5 N NaOH in 30 mL of EtOH at reflux for 5 h and cooled to room temperature, water was added, and the mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 20% EtOAc/hexane to give 545 mg (yield 93%) of **55** as an oil: ^{1}H NMR ($CDCl_3$) ∂ 7.41 (s, 1H), 7.32−7.74 (m, 6H), 6.25 (s, 1H), 5.49 (s, 2H), 3.41 (s, 1H), 2.43 (s, 3H), 2.30 (s, 3H); MS (FD$^+$) 267 (M^+). Anal. ($C_{17}H_{17}NS$) C, H, N.

4-[[2,7-Dimethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic Acid Ethyl Ester (56a). To a solution of 480 mg (1.9 mmol) of **52** in 15 mL of DMF were added 76 mg (1.9 mmol) of 60% NaH/mineral oil and 0.27 mL (1.9 mmol) of ethyl 4-bromobutyrate. The mixture was stirred for 16 h, diluted with water, extracted with EtOAc, washed with brine, dried ($MgSO_4$), evaporated, and then chromatographed on silica gel, eluting with 20% EtOAc/hexane to give 502 mg (yield 72%) of **56a** as an oil: ^{1}H NMR ($CDCl_3$) ∂ 7.34−6.80 (m, 6H), 6.49 (s, 1H), 6.26 (s, 1H), 5.49 (s, 2H), 4.14 (q, 2H), 4.00 (t, 2H), 2.52 (t, 2H), 2.43 (s, 3H), 2.31 (s, 3H), 2.25−2.08 (m, 2H), 1.25 (t, 3H); MS (FD$^+$) 365 (M^+). Anal. ($C_{23}H_{27}NO_3$) C, H, N.

4-[[3-(2-Amino-1-hydroxy-2-oxoethyl)-2,7-dimethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic Acid Ethyl Ester (58a). To a solution of 490 mg (1.34 mmol) of **56a** in 10 mL of CH_2Cl_2 was added 0.12 mL (1.34 mmol)of oxalyl chloride. The mixture was stirred for 45 min and then evaporated at reduced pressure, 10 mL of CH_2Cl_2 was added, and the mixture was saturated with ammonia gas, stirred for 30 min, and evaporated at reduced pressure. Water was added, and the mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was stirred with EtOAc, and the insoluble material was filtered off to give 441 mg (1 mmol, yield 75%) of 4-[[3-(2-amino-1,2-dioxoethyl)-2,7-dimethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid ethyl ester (**57a**), mp 169−171 °C. This crude product was stirred with 47.2 mg (1.25 mmol) of sodium borohydride in 20 mL of EtOH for 24 h. The solvent was evaporated, and the residue was dissolved in EtOAc/water. The EtOAc layer was separated, washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure to give 397 mg (yield 91%) of **58a**: ^{1}H NMR ($CDCl_3$) ∂ 7.37−6.78 (m, 6H), 6.51 (s, 1H), 6.04 (br s, 1H), 5.57 (br s, 1H), 5.49 (AB q, 2H), 5.39 (d, 1H), 4.07 (q, 2H), 4.00 (t, 2H), 3.59 (d, 1H), 2.51 (t, 2H), 2.43 (s, 3H), 2.33 (s, 3H), 2.10 (t, 2H), 1.25 (t, 3H); MS (FD$^+$) 438 (M^+). Anal. ($C_{25}H_{30}N_2O_5$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2,7-dimethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic Acid (60a). A solution of 389 mg (0.89 mmol) of **58a** in 0.18 mL (1.1 mmol) of triethylsilane and 3 mL of trifluoroacetic acid was stirred for 2 h and then evaporated at reduced pressure. Water was added, and the mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 50% EtOAc/hexane, and then EtOAc, to give 235 mg (yield 63%) of **59a**, which was dissolved in 10 mL of MeOH and heated 10 min at reflux with 4 mL of 1 N NaOH. Water was then added and the mixture extracted with EtOAc. The aqueous portion was acidified to pH 2, extracted with EtOAc, washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was stirred with EtOAc, and the insoluble product was filtered off and vacuum-dried to give 41 mg (yield 19%) of **60a** (reaction was not complete, recovered 160 mg of **59a**): mp 207−209 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.33−6.77 (m, 8H), 6.41 (s, 1H), 5.49 (s, 2H), 3.93 (t, 2H), 3.43 (s, 2H), 2.39 (t, 2H), 2.35 (s, 3H), 2.23 (s, 3H), 1.93 (t, 2H); MS (FD$^+$) 394 (M^+). Anal. ($C_{23}H_{26}N_2O_4$) C, H, N.

4-[[2,7-Dimethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic Acid Ethyl Ester (56b). A solution of 545 mg (2 mmol) of **55** in 10 mL of DMF was treated with 80 mg (2 mmol) of 60% NaH/mineral oil and 0.29 mL (2 mmol) of ethyl bromobutyrate. The mixture was stirred for 18 h, water was added, and the mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 20% EtOAc/hexane, to give 625 mg (yield 82%) of **56b** as an oil: ^{1}H NMR ($CDCl_3$) ∂ 7.51 (s, 1H), 7.34−7.21 (m, 4H), 6.91 (s, 1H), 6.84 (d, 1H), 6.31 (s, 1H), 5.51 (s, 2H), 4.12 (q, 2H), 2.92 (t, 2H), 2.48 (s, 3H), 2.47 (t, 2H), 2.33 (s, 3H), 1.93 (t, 2H), 1.26 (t, 3H); MS (FD$^+$) 381 (M^+). Anal. ($C_{23}H_{27}NO_2S$) H; C: calcd, 72.41; found, 73.48; N: calcd, 3.67; found, 3.26.

4-[[3-(2-Amino-1,2-dioxoethyl)-2,7-dimethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic Acid Ethyl Ester (57b). To a solution of 620 mg (1.6 mmol) of **56b** in 10 mL of CH_2Cl_2 was added 0.14 mL (1.6 mmol) of oxalyl chloride. The mixture was stirred for 1.5 h and then evaporated at reduced pressure, 10 mL of CH_2Cl_2 was added, and the mixture was saturated with ammonia gas with stirring over 15 min and evaporated at reduced pressure. Water was added, and the mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 50% EtOAc/hexane and then EtOAc, to give 520 mg (yield 72%) of **57b** as an oil: ^{1}H NMR ($CDCl_3$) ∂ 8.08 (s, 1H), 7.37−7.25 (m, 4H), 6.99 (s, 1H), 6.91 (d, 1H), 6.79 (br s, 1H), 5.76 (br s, 1H), 5.57 (s, 2H), 4.12 (t, 2H), 2.97 (t, 2H), 2.59 (s, 3H), 2.47 (t, 2H), 2.48 (s, 3H), 1.97 (t, 2H), 1.25 (t, 3H); MS (FD$^+$) 452 (M^+). Anal. ($C_{25}H_{28}N_2O_4S$) C, H, N.

4-[[3-(2-Amino-1-hydroxy-2-oxoethyl)-2,7-dimethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic Acid Ethyl Ester (58b). To a solution of 510 mg (1.13 mmol) of **57b** in 20 mL of EtOH was added 53.4 mg (1.4 mmol) of $NaBH_4$. The mixture was stirred for 16 h and then evaporated at reduced pressure, water was added, and the mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and evaporated to give 486 mg (yield 95%) of **58b** as an oil: ^{1}H NMR ($CDCl_3$) ∂ 7.56 (s, 1H), 7.34−7.18 (m, 4H), 6.92 (s, 1H), 6.86 (d, 1H), 6.11 (br s, 1H), 5.72 (br s, 1H), 5.52 (AB q, 2H), 5.39 (d, 1H), 4.12 (q, 2H), 3.63 (d, 1H), 2.89 (t, 2H), 2.48 (s, 3H), 2.47 (t, 2H), 2.35 (s, 3H), 1.95−1.82 (m, 2H), 1.26 (t, 3H); MS (FD$^+$) 454 (M^+). Anal. ($C_{25}H_{30}N_2O_4S$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2,7-dimethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic Acid Ethyl Ester (59b). A solution of 475 mg (1.05 mmol) of **58b**, 0.21 mL (1.3 mmol) of triethylsilane, and 3 mL of trifluoroacetic acid was stirred for 2 h. The solvent was evaporated at reduced pressure, water was added to the residue, and it was extracted with EtOAc, washed with brine, dried ($MgSO_4$), evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 50% EtOAc/hexane, to give 340 mg (yield 74%) of **59b**: ^{1}H NMR ($CDCl_3$) ∂ 7.48 (s, 1H), 7.41−7.16 (m, 4H), 6.95 (s, 1H), 6.83 (d, 1H), 5.67 (br s, 1H), 5.56 (s, 2H), 5.51 (br s, 1H), 4.11 (q, 2H), 3.69 (s, 2H), 2.91 (t, 2H), 2.48 (s, 3H), 2.46 (t, 2H), 2.26 (s, 3H), 1.92 (t, 2H), 1.25 (t, 3H); MS (FD) 438 (M^+). Anal. ($C_{25}H_{30}N_2O_3S$) C, H, N.

4-[[3-(2-Amino-2-oxoethyl)-2,7-dimethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic Acid (60b). To a solution of 330 mg (0.75 mmol) of **59b** in 10 mL of EtOH was added 5 mL of 1 N NaOH. The mixture was heated at reflux for 20 min, water was then added, and the mixture was extracted with EtOAc. The aqueous portion was acidified to pH 2, extracted with EtOAc, washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was stirred with EtOAc, and the insoluble material was filtered off and vacuum-dried to give 245 mg (yield 80%) of **60b**: ^{1}H NMR ($CDCl_3$) ∂ 7.45 (s, 1H), 7.33−7.16 (m, 4H), 6.91 (s, 1H), 6.83 (d, 1H), 6.66 (br s, 1H), 5.88 (br s, 1H), 5.53 (s, 2H), 3.71 (s, 2H), 2.96 (t, 2H), 2.49 (s, 3H), 2.49 (t, 2H), 2.29 (s, 3H), 1.94 (t, 2H); MS (FD) 410 (M^+). Anal. ($C_{23}H_{26}N_2O_3S$) C, H, N.

[3-[[3-(2-Amino-2-oxoethyl)-2-ethyl-6-isopropyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic Acid Dimethyl Ester (61a). To a suspension of 40 mg (1 mmol) of 60% NaH/mineral oil (previously washed with hexane) in 4 mL of DMF was added 350 mg (1mmol) of 2-ethyl-5-hydroxy-6-isopropyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (**2h**). The mixture was stirred for 50 min, 231 mg (1 mmol) of (3-bromopropyl)phosphonic acid dimethyl ester was added, the mixture was stirred an additional 4 h, water was added, and the product was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and evaporated. The crystalline residue was triturated with EtOAc/hexane, filtered, and dried to give 367 mg (yield 73%) of **61a**: mp 143−145 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.32−7.20 (m, 6H), 7.09 (d, 1H), 6.98 (d, 1H), 6.80 (br s, 1H), 5.35 (s, 2H), 4.01 (t, 2H), 3.66 (s, 1H), 3.62 (s, 1H), 3.41 (s, 2H), 3.38−3.22 (m, 1H), 2.71 (q, 2H), 2.04−1.84 (m, 4H), 1.14 (d, 6H), 1.03 (t, 3H); MS (FD^+) 500 (M^+). Anal. ($C_{27}H_{37}N_2O_5P$) C, H, N.

Using the preceding method, **61c** was prepared from **2i**.

[3-[[4-Allyl-3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic Acid Dimethyl Ester (61c) (chromatography on silica gel, gradient, 1−4% MeOH/CH_2Cl_2): yield 78%; ^{1}H NMR ($CDCl_3$) ∂ 7.25−7.10 (m, 3H), 6.95 (d, 1H), 6.85 (d, 2H), 6.75 (d, 1H), 6.55 (br s, 1H), 6.05−6.95 (br s, 1H), 5.25 (s, 2H), 4.95−4.75 (m, 2H), 3.90 (t, 2H), 3.65 (s, 5H), 3.60 (s, 3H), 2.60 (q, 2H), 2.10−1.85 (m, 4H), 1.05 (t, 3H).

4-[[3-(2-Amino-2-oxoethyl)-2-bromo-6-chloro-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic Acid Ethyl Ester (61b). A solution of 235 mg (0.6 mmol) of 2-bromo-6-chloro-5-hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (**2n**) in 30 mL of DMSO and 10 mL of THF was treated with 25 mg (0.6 mmol) of 60% NaH/mineral oil, the mixture was stirred for 5 min, and then 0.1 mL (0.7 mmol) of ethyl 4-bromobutyrate was added. The solution was heated at 60 °C for 2 h, cooled, diluted with water, and extracted with EtOAc. The extract was washed with water and brine, dried (Na_2SO_4), and chromatographed on silica gel, eluting with a gradient of CH_2Cl_2−2% MeOH/CH_2Cl_2, to give 210 mg (yield 69%) of **61b**: ^{1}H NMR ($CDCl_3$) ∂ 7.35−7.15 (m, 4H), 7.10−6.95 (m, 3H), 6.10 (br s, 1H), 5.85 (br s, 1H), 5.30 (s, 2H), 4.10 (q, 2H), 4.05 (t, 2H), 3.65 (s, 2H), 2.55 (t, 2H), 2.15−2.05 (m, 2H), 1.25 (t, 3H).

[3-[[3-(2-Amino-2-oxoethyl)-2-ethyl-6-isopropyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic Acid (62a). A solution of 350 mg (0.7 mmol) of **61a** and 0.74 mL (5.6 mmol) of trimethylsilyl bromide in 5 mL of CH_2Cl_2 was stirred for 16 h and concentrated at reduced pressure. The residue was dissolved in 5 mL of MeOH, stirred for 2 h, and concentrated. The residue was crystallized from EtOAc/MeCN/HOAc/H_2O to give 330 mg (yield 100%) of **62a**: mp 176−178 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.32−7.14 (m, 4H), 7.06 (s, 2H), 6.97 (d, 2H), 6.80 (br s, 1H), 5.36 (s, 2H), 4.01 (t, 2H), 3.41 (s, 2H), 3.32−3.02 (m, 1H), 2.70 (q, 2H), 2.03−1.88 (m, 2H), 1.80−1.64 (m, 2H), 1.13 (d, 6H), 1.03 (t, 3H); MS (FD^+) 472 (M^+). Anal. ($C_{25}H_{33}N_2O_5P$) H, N; C: calcd, 63.55; found, 61.98.

4-[[3-(2-Amino-2-oxoethyl)-2-bromo-6-chloro-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic Acid (62b). A mixture of 210 mg (0.41 mmol) of **61b** and 2 mL of 2 N NaOH in 5 mL of THF and 25 mL of EtOH was stirred for 10.5 h, and the mixture was made acidic with 5 N HCl and extracted with EtOAc. The EtOAc solution was washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was crystallized from CH_2Cl_2/EtOH to give 60 mg (yield 31%) of **62b**, mp 220 °C dec. Anal. ($C_{21}H_{20}BrClN_2O_4$) H, N; C: calcd, 52.57; found, 54.03; Br: calcd, 16.65; found, 11.57; Cl: calcd, 7.39; found, 8.96; residue, 1.35%.

[3-[[4-Allyl-3-(2-amino-2-oxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic Acid Disodium Salt (62c). A solution of 310 mg (0.62 mmol) of **61c** and 1.0 mL (7.6 mmol) of trimethylsilyl bromide in 20 mL of CH_2Cl_2 was stirred for 18.5 h and concentrated at reduced pressure. The residue was dissolved in 20 mL of MeOH, stirred for 2.5 h, and concentrated. This residue was chromatographed on a C-18 reverse phase column, eluted with 10% (5% HOAc/H_2O)/MeOH. Material from this column was dissolved in 1 N NaOH and chromatographed on a HP-20 column. The product was eluted with 10% MeCN/H_2O and then 25% MeCN/H_2O to give 165 mg (yield 52%) of **62c**. Anal. ($C_{25}H_{29}N_2O_5PNa_2{\cdot}3H_2O$) N; C: calcd, 52.82; found, 52.15; H: calcd, 6.21; found, 5.50.

5-Hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic Acid Hydrazide (64). A solution of 5-methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid hydrazide (**63**, 162 mg, 0.5 mmol) was stirred with 1.5 mL of 1 M BBr_3/CH_2Cl_2 for 3 h and poured into aqueous $NaHCO_3$, and the CH_2Cl_2 solution was separated, washed with brine, dried (Na_2SO_4), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 2−5% MeOH/CH_2Cl_2 to give 60 mg (yield 38%) of **64**: mp 216−219 °C; ^{1}H NMR (DMSO-d_6) ∂ 9.00 (s, 1H), 8.55 (s, 1H), 7.25−7.10 (m, 3H), 7.05 (d, 1H), 6.95 (d, 2H), 6.85 (d, 1H), 6.50 (dd, 1H), 5.25 (s, 2H), 4.10 (br s, 2H), 3.30 (s, 2H), 2.25 (s, 3H); MS (FD^+) 309 (M^+). Anal. ($C_{18}H_{19}N_3O_2$) C, H, N.

4-[3-(2-Hydrazino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]butanoic Acid (67). A solution of **64** (310 mg, 1.0 mmol) in 25 mL of DMSO and 5 mL of THF was treated with 45 mg (1.1 mmol) of 60%NaH/ mineral oil for 10 min and then with 0.16 mL (1.1 mmol) of ethyl 4-bromobutyrate for 7.5 h. The mixture was diluted with water and extracted with EtOAc. The EtOAc solution was washed with brine, dried (Na_2SO_4), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of CH_2Cl_2−4% MeOH/CH_2Cl_2 to give **65**, as an oil, 320 mg (yield 75%). A solution of 290 mg of **65** in 5 mL of THF, 25 mL of EtOH, and 2 mL of 2N NaOH was stirred for 22.5 h, diluted with water, acidified with 1 N HCl, and extracted with EtOAc. The EtOAc solution was evaporated at reduced pressure, and the residue was dissolved in EtOH and precipitated by diluting with Et_2O to give **67**, 50 mg (yield 18%), as an amorphous solid: ^{1}H NMR (DMSO-d_6/D_2O) ∂ 7.25−7.05 (m, 4H), 7.00 (d, 1H), 6.90 (d, 2H), 6.60 (dd, 1H), 5.20 (s, 2H), 3.85 (t, 2H), 3.35 (s, 2H), 2.30 (t, 2H), 2.20 (s, 3H), 1.90−1.75 (m, 2H). Anal. ($C_{22}H_{25}N_3O_4$) H; C: calcd:, 66.82; found, 66.19; N: calcd, 10.63; found, 9.32.

[3-[[3-(2-Hydrazino-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]propyl]phosphonic Acid Disodium Salt (68). A solution of 420 mg (1.4 mmol) of **64** in 25 mL of DMSO and 5 mL of THF was treated with 65 mg (1.6 mmol) of 60%NaH/mineral oil for 10 min and then with 370 mg (1.6 mmol) of dimethyl (3-bromopropyl)phosphonate for 3.5 h, diluted with water, and extracted with EtOAc. The EtOAc solution was washed with brine, dried (Na_2SO_4), and evaporated at reduced pressure to give the crude dimethyl ester (**66**), 170 mg (yield 35%). This material (0.4 mmol) was dissolved in 20 mL of CH_2Cl_2 and treated with 0.5 mL (3.9 mmol) of Me_3SiBr for 16 h. The solvent was evaporated, and the residue was dissolved in 25 mL of MeOH, stirred for 1 h, and evaporated at reduced pressure. The residue, dissolved in 0.05 N NaOH, was chromatographed on an HP-20 column, eluting with a gradient of 15−30% CH_3CN/H_2O to give **68**, 105 mg (yield 53%), as a powder: ^{1}H NMR (DMSO-d_6/D_2O) ∂ 7.25−

7.05 (m, 5H), 6.90 (d, 2H), 6.55 (d, 1H), 5.20 (s, 2H), 3.90 (t, 2H), 3.55 (s, 2H), 2.20 (s, 3H), 1.90−1.75 (m, 2H), 1.45−1.25 (m, 2H); MS (FAB+) 476 (M + 1 + Na), 454 (M + 1). Anal. ($C_{21}H_{24}Na_2N_3O_5P \cdot 2.4H_2O$) C, H, N.

4-[[3-(3-Amino-3-oxopropyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic Acid (72). A solution of 504 mg (1.6 mmol) of 3-[5-methoxy-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]propionamide (**69**) in 20 mL of CH_2Cl_2 and 6.3 mL of a 1 M solution of BBr_3/CH_2Cl_2 was stirred for 2.5 h. The boron complex was decomposed with water, and the product was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with EtOAc and then 5% MeOH/EtOAc, to give 377 mg (yield 78%) of **70** as a solid. A solution of 170 mg (0.55 mmol) of **70** in 6 mL of DMF was treated with 22 mg (0.55 mmol) of 60%NaH/mineral oil for 30 min and then with 0.08 mL (0.55 mmol) of ethyl 4-bromobutyrate for 2.5 h, diluted with water, and extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with EtOAc and then 5% MeOH/EtOAc, to give 71 mg (yield 31%) of 4-[[3-(3-amino-3-oxopropyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid ethyl ester (**71**). A solution of 65 mg (0.15 mmol) of **71** and 2 mL of 1 N NaOH in 5 mL of EtOH was stirred 1.5 h, diluted with water, and washed with EtOAc. The aqueous phase was acidified with 1 N HCl and extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was crystallized from MeOH to give 55 mg (yield 93%) of **72**: mp 169−171 °C; ^{1}H NMR (DMSO-d_6) ∂ 12.10 (s, 1H), 7.32−6.80 (m, 9H), 5.31 (s, 2H), 4.98 (t, 2H), 2.87 (t, 2H), 2.41 (t, 2H), 2.29 (t, 2H), 2.27 (s, 3H), 2.00−1.88 (m, 2H); MS (FD$^+$) 394 (M$^+$). Anal. ($C_{23}H_{26}N_2O_4$) C, H, N.

5-Hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic Acid Methyl Ester (74). A solution of 1.78 g (5.3 mmol) of 5-methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid (**73**) in 125 mL of CH_2Cl_2 and 21 mL of a 1 M solution of BBr_3/CH_2Cl_2 was stirred for 4 h. The boron complex was decomposed by the addition of 10 mL of MeOH over 30 min, and the resulting crude 5-hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid was concentrated at reduced pressure. The residue was dissolved in 100 mL of MeOH containing 10 mL of methanesulfonic acid, and the mixture was stirred for 16 h, poured into water, and extracted with EtOAc. The organic phase was washed with water, dried (Na_2SO_4), evaporated at reduced pressure, and then chromatographed on silica gel, eluting with a gradient of 10−30% EtOAc/toluene, to give **74**, 1.30 g (yield 79%), as a wax: ^{1}H NMR (DMSO-d_6) ∂ 8.64 (s, 1H), 7.36−7.16 (m, 3H), 7.12 (d, 1H), 6.96 (d, 2H), 6.74 (d, 1H), 6.55 (dd, 1H), 5.36 (s, 2H), 3.58 (s, 3H), 3.30 (s, 2H), 2.26 (s, 3H), 2.00−1.88 (m, 2H); MS (FD) 309 (M$^+$). Anal. ($C_{19}H_{19}NO_3$) C, H, N.

4-[[3-(2-Methoxy-2-oxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic Acid Ethyl Ester (75). A solution of 0.31 g (1.0 mmol) of **74** in 15 mL of DMF and 15 mL of THF was treated with 40 mg (1.0 mmol) of 60%NaH/mineral oil for 30 min, and then 0.143 mL (1.0 mmol) of ethyl 4-bromobutyrate was added. The mixture was stirred for 96 h, poured into water, and extracted with EtOAc. The organic phase was washed with water, dried (Na_2SO_4), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of toluene−10% EtOAc/toluene to give 0.22 g (yield 52%) of **75** as an oil: ^{1}H NMR (DMSO-d_6) ∂ 7.36−7.16 (m, 4H), 7.00−6.92 (m, 3H), 6.66 (dd, 1H), 5.36 (s, 2H), 4.04 (q, 2H), 3.96 (t, 2H), 3.60 (s, 3H), 3.32 (s, 2H), 2.46 (t, 2H), 2.26 (s, 3H), 2.04−1.80 (m, 2H), 1.14 (t, 3H); MS (FD) 423 (M$^+$). Anal. ($C_{25}H_{29}NO_5$) C, H, N.

4-[[3-(Carboxymethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic Acid (76). A solution of 0.22 g (0.52 mmol) of **75** in 40 mL of MeOH and 1.5 mL of 5 N NaOH was refluxed for 3 h, cooled, acidified with 1 N HCl, and extracted with EtOAc. The organic phase was washed with water, dried (Na_2SO_4), and evaporated at reduced pressure. The residue was crystallized from MeOH/water to give 90 mg (yield 45%) of **76**: mp 190−192 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.36−7.16 (m, 4H), 7.04−6.88 (m, 3H), 6.66 (dd, 1H), 5.30 (s, 2H), 3.96 (t, 2H), 3.58 (s, 3H), 2.38 (s, 2H), 2.28 (s, 3H), 2.00−1.88 (m, 2H); MS (FD$^+$) 381 (M$^+$). Anal. ($C_{22}H_{23}NO_5$) C, H, N.

3-(2-Amino-1,2-dioxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-4-methoxy-1*H*-indole (79). A solution of 7.65 g (44 mmol) of 2-ethyl-4-methoxy-1*H*-indole (**77**) in 50 mL of DMF was treated with 1.76 g (44mmol) of 60% NaH/mineral oil for 0.75 h and then with 5.6 mL (44 mmol) of 3-chlorobenzyl chloride for 18 h. The solution was diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with 25% EtOAc/hexane to give 1.6 g (yield 12%) of **78**. This material (5.3 mmol) was dissolved in 20 mL of CH_2Cl_2, and 0.5 mL of oxalyl chloride was added. The solution was stirred for 5.5 h, saturated with ammonia, and stirred for 18 h. The suspension was diluted with EtOAc, the insoluble product was filtered off, and the filtrate was concentrated at reduced pressure. The residue was chromatographed on silica gel, eluting with 50% EtOAc/hexane, and the product fractions were combined with the insoluble material from above to give 1.47 g (yield 75%) of **79**: mp 186−189 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.73 (br s, 1H), 7.41 (br s, 1H), 7.36−6.88 (m, 6H), 6.68 (d, 1H), 5.54 (s, 2H), 3.78 (s, 3H), 2.88 (q, 2H), 1.07 (t, 3H); MS (FD) 370 (M − 1, 100), 372 (M + 1, 40). Anal. ($C_{20}H_{19}ClN_2O_3$) C, H, N.

4-(Carboxymethoxy)-1-[(3-chlorophenyl)methyl]-2-ethyl-1*H*-indole-3-carboxamide (82). A solution of 503 mg (1.35 mmol) of **79** in 20 mL of CH_2Cl_2 and 6 mL of a 1 M solution of BBr_3/CH_2Cl_2 was stirred for 21 h. The solvent was evaporated, and the residue was dissolved in EtOAc, washed with water and brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 50−67% EtOAc/hexane to give 178 mg (yield 41%) of **80** as a solid. This material (0.5 mmol) was dissolved in 15 mL of DMF and stirred with 20 mg (0.5 mmol) of 60%NaH/mineral oil for 1.5 h and and then with 0.5 mL (0.5 mmol) of methyl bromoacetate for 3 h. The solution was diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with EtOAc, to give 73 mg (yield 43%) of **81**. This material was dissolved in 6 mL of MeOH by warming and then stirred with 2 mL of 1 N NaOH for 2 h. The solution was diluted with water and washed with EtOAc. The aqueous phase was acidified with 1 N HCl, extracted with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was triturated with CH_2Cl_2 and the insoluble material filtered to give 17 mg (yield 23%) of **82**: ^{1}H NMR (DMSO-d_6) ∂ 8.15 (br s, 1H), 7.34−6.80 (m, 7H), 6.68 (d, 1H), 5.50 (s, 2H), 4.86 (s, 2H), 3.09 (q, 2H), 1.05 (t, 3H); MS (FD) 386 (M − 1, 100), 388 (M + 1, 9). Anal. ($C_{20}H_{19}ClN_2O_4$) H, N; C: calcd, 62.10; found, 61.38.

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References

(1) Dillard, R. D.; Bach, N. J.; Draheim, S. E.; Berry, D. R.; Carlson, D. G.; Chirgadze, N. Y.; Clawson, D. K.; Hartley, L. W.; Johnson, L. M.; Jones, N. D.; McKinney, E. R.; Mihelich, E. D.; Olkowski, J. L.; Schevitz, R. W.; Smith, A. C.; Snyder, D. W.; Sommers, C. D.; Wery, J.-P. Indole Inhibitors of Human Nonpancreatic Secretory Phospholipase A$_2$. 1. Indole-3-acetamides. *J. Med. Chem.* **1996**, *39*, 5119−5136.

(2) Scott, D. L.; et al. Structures of free and inhibited human secretory phospholipase A$_2$ from inflammatory exudate. *Science* **1991**, *254*, 1007−1010.

(3) Thunnissen, M. M. G. M.; Eiso, A. B.; Kalk, K. H.; Drenth, J.; Dijkstra, B. W.; Kuipers, O. P.; Dijkman, R.; de Hass, G. H.; Verheij, H. M. X-ray structure of phospholipase A$_2$ complexed with a substrate-derived inhibitor. *Nature* **1990**, *347*, 689−691.

(4) Shen, T.-Y.; Winter, C. A. Indomethacin, Sulindac and Anologs. In *Advances in Drug Research*; Harper, N. J., Simmonds, A. B., Eds.; Academic Press: New York, 1977; Vol. 12, pp 89−245.

(5) Ho, D. K.; McKenzie, A. T.; Byrn, S. R.; Cassady, J. M. O^5-Methyl-(+/−)-(2′*R*,3′*S*)-psorospermin. *J. Org. Chem.* **1987**, *52*, 342−347.

(6) Macor, J. E.; Ryan, K.; Newman, M. E. The synthesis of pyrano-[3,2-e]indoles and pyrano[2,3-f]indoles as rotationally restricted phenolic analogues of the neurotransmitter serotonin. *Tetrahedron* **1992**, *48*, 1039−1052.
(7) Cremins, P. J.; Hayes, R.; Wallace, T. W. Heteroannulation of 4-oxo-4H-1-benzopyrans (chromones) via the conjugate addition of haloalkanols in the presence of base. *Tetrahedron* **1991**, *47*, 9431−9438.
(8) Afzali, A.; Firouzabadi, H.; Kahlafi-nejad, A. Improved Ullman synthesis of diaryl ethers. *Synth. Commun.* **1983**, *13*, 335−339.
(9) Levin, J. I.; Turos, E.; Weinreb, S. M. An alternative procedure for the aluminum-mediated conversion of esters to amides. *Synth. Commun.* **1982**, *12*, 989−993.
(10) Duncia, J. V.; Pierce, M. E.; Santella, J. B., III. Three synthetic routes to a sterically hindered tetrazole. A new one-step mild conversion of an amide into a tetrazole. *J. Org. Chem.* **1991**, *56*, 2395−2400.
(11) (a) Speeter, M. E.; Anthony, W. C. The action of oxalyl chloride on indoles: A new approach to tryptamines. *J. Am. Chem. Soc.* **1954**, *76*, 6208−6210. (b) Domschke, D.; Furst, H. Notiz zur darstellung einiger [1-benzyl-2-methyl-5-methoxy-indolyl-(3)]-glyoxylsaureamide. *Ber.* **1961**, *94*, 2353−2355.
(12) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. Silane reductions in acidic media. II. Reductions of aryl aldehydes and ketones by trialkylsilanes in trifluoroacetic acid. A selective method for converting the carbonyl group to methylene. *J. Org. Chem.* **1973**, *38*, 2675−2681.
(13) Thyes, M.; Lehmann, H. D.; Gries, J.; Konig, H.; Kretzschmar, R.; Kunze, J.; Lebkucher, R.; Lenke, D. 6-Aryl-4, 5-dihydro-3(2H)-pyridazinones. A new class of compounds with platelet aggregation inhibiting and hypotensive activities. *J. Med. Chem.* **1983**, *26*, 800−807.
(14) Siddiqui, M. A.; Snieckus, V. Concise synthesis of the amaryllidaceae alkaloids ungermine and hippadine via the Suzuki aryl-aryl cross coupling reaction. *Tetrahedron Lett.* **1990**, *31*, 1523−1526.
(15) Newman, M. S.; Karnes, H. A. The conversion of phenols to thiophenols *via* dialkylthiocarbamates. *J. Org. Chem.* **1966**, *31*, 3980−3984.
(16) Iwao, M.; Kuraishi, T. Directed lithiation of 1-(*tert*-butoxycarbonyl)indolines. A convenient route to 7-substituted indolines. *Heterocycles* **1992**, *34*, 1031−1038.
(17) Beak, P.; Snieckus, V. Directed lithiation of aromatic tertiary amides: An evolving synthetic methodology for polysubstituted aromatics. *Acc. Chem. Res.* **1982**, *15*, 306−312.
(18) Snyder, H. R.; Brooks, L. A.; Shapiro, S. H. Pimelic acid. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, pp 531−538.
(19) (a)Schevitz, R. W.; Bach, N. J.; Carlson, D. G.; Chirgadze, N. Y.; Clawson, D. K.; Dillard, R. D.; Draheim, S. E.; Hartley, L. W.; Jones, N. D.; Mihelich, E. D.; Olkowski, J.L.; Snyder, D. W.; Sommers, C. D.; Wery, J.-P. Structure-based design of the first potent and selective inhibitor of human non-pancreatic secretory phospholipase A_2. *Nat. Struct. Biol.* **1995**, *2*, 458−465. (b) See the above reference for a complete description of this and other X-ray structures referred to in this publication.
(20) Martinelli et al. Lilly Research Laboratories, Eli Lilly and Company. Manuscript in preparation.

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