Indole Inhibitors of Human Nonpancreatic Secretory Phospholipase A_2. 3. Indole-3-glyoxamides

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The preceding papers of this series detail the development of functionalized indole-3-acetamides as inhibitors of hnps-PLA_2. We describe here the extension of the structure−activity relationship to include a series of indole-3-glyoxamide derivatives. Functionalized indole-3-glyoxamides with an acidic substituent appended to the 4- or 5-position of the indole ring were prepared and tested as inhibitors of hnps-PLA_2. It was found that the indole-3-glyoxamides with a 4-oxyacetic acid substituent had optimal inhibitory activity. These inhibitors exhibited an improvement in potency over the best of the indole-3-acetamides, and LY315920 (**6m**) was selected for evaluation clinically as an hnps-PLA_2 inhibitor.

Introduction

As detailed in the preceding papers of this series, variation of the indole 3-substituent had been explored in developing the structure−activity relationship (SAR) of the indole hnps-PLA_2 inhibitors. The preferred 3-substituent was a 3-acetamide functionality, and our reported modifications of this group had generally resulted in diminished activity. The exception was the 3-glyoxamide derivatives, some of which had shown activity similiar to their 3-acetamide counterparts. Chromogenic assay results comparing methoxy-substituted indole-3-acetamides and -3-glyoxamides are shown in Figure 1. There were obvious differences between 4- and 5-methoxy substitution of the indoles having a 3-glyoxamide substituent in place of the 3-acetamide. Applying the SAR information gained in the previous papers of this series, we sought to further elaborate these indole-3-glyoxamides to include an acidic substituent appended at an optimal length for interaction with the calcium in the enzyme active site.

As the SAR of this series developed, the exceptional potency of the compounds brought into question whether the chromogenic assay was adequate to differentiate them. A deoxycholate/phosphatidylcholine (DOC/PC) mixed micelle system, which allowed accurate determination of IC_{50} values for inhibitors with a mole fraction below 10^{-5}, was implemented.

Chemistry

Substituted indoles with a 3-glyoxamide functionality and an acidic group appended to a 4- or 5-oxygen substituent were prepared starting with 4- or 5-methoxyindoles (**1**) (Scheme 1). The sodium salt of **1** was first reacted with an alkyl halide to give the N-alkylated product (**2**) or with an acyl halide to give the N-acylated product (**2q**). Boron tribromide demethylation[2] of **2** gave the hydroxy indoles (**3**), which were treated with sodium hydride and an ω-bromoalkanoic ester in DMF to give the O-alkylated products (**4**). The glyoxamide group was then introduced into the 3-position by reaction with oxalyl chloride in dichloromethane, followed by treatment with ammonia gas. The ester of the 4- or 5-substituent was hydrolyzed, providing the free acid or its sodium salt (**6**).

4-MeO	1.18 ± 0.39 μM	4-MeO	0.551 ± 0.228 μM
5-MeO	0.26 ± 0.11 μM	5-MeO	2.56 ± 0.55 μM

Figure 1. Chromogenic assay results of methoxy-substituted acetamides and glyoxamides.

The 5-allyl-4-hydroxyindole **3u** was prepared by treatment of the 4-hydroxyindole **3m** with NaH and allyl bromide in DMF to give an intermediate *O*-allyl product, which, when refluxed in *N*,*N*-dimethylaniline, gave the Claisen rearrangement[3] product **3u**. This product was then treated with sodium hydride and ethyl bromoacetate, and the resulting O-alkylated product (**4u**) was treated with oxalyl chloride and ammonia as above to give **5u**. Hydrogenation of the 5-allyl group of **5u** gave the 5-propyl compound **5ab**. Basic hydrolysis of **5u** and **5ab** gave **6u** and **6ab**, respectively.

The amide **4aa** was prepared from **4m**, which was first heated with hydrazine in ethanol to give the hydrazide and then was reduced to the amide by refluxing in ethanol with Raney nickel catalyst. Treatment of **4aa** with oxalyl chloride and ammonia as above gave **5aa**.

For the preparation of compound **5ac**, the reaction sequence was altered. 2-Ethyl-5-methoxy-1*H*-indole **1g** was reacted with oxalyl chloride and ammonia prior to alkylation of the indole nitrogen. With the usual sequence, some 1,3-dialkylation was often seen. The 3-glyoxylindole **7** was cleanly N-alkylated with sodium hydride and benzyl bromide in DMF. Subsequent boron tribromide demethylation and alkylation of the resulting hydroxy indole with *tert*-butyl 4-bromobutyrate, followed by trifluoroacetic acid deprotection, gave **6ac**. This

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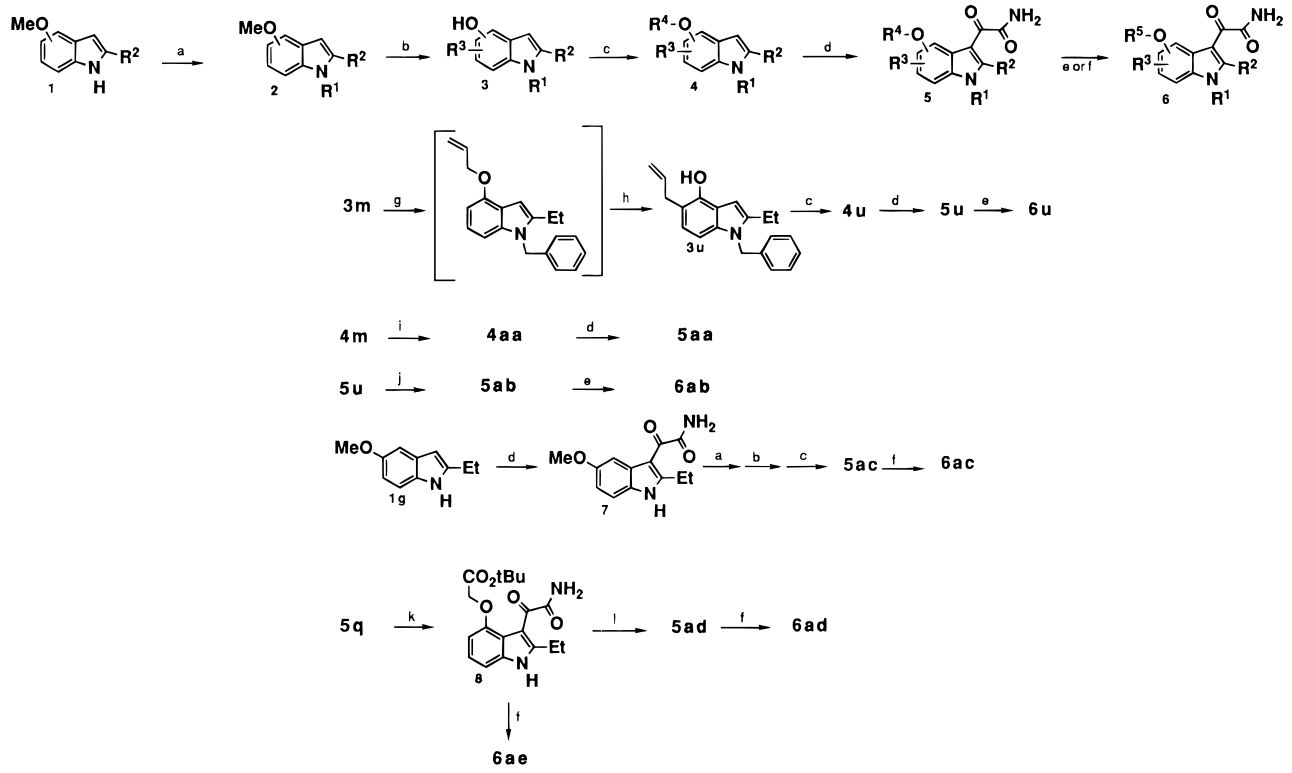
Scheme 1. Oxygen-Linked Functionalities[a]

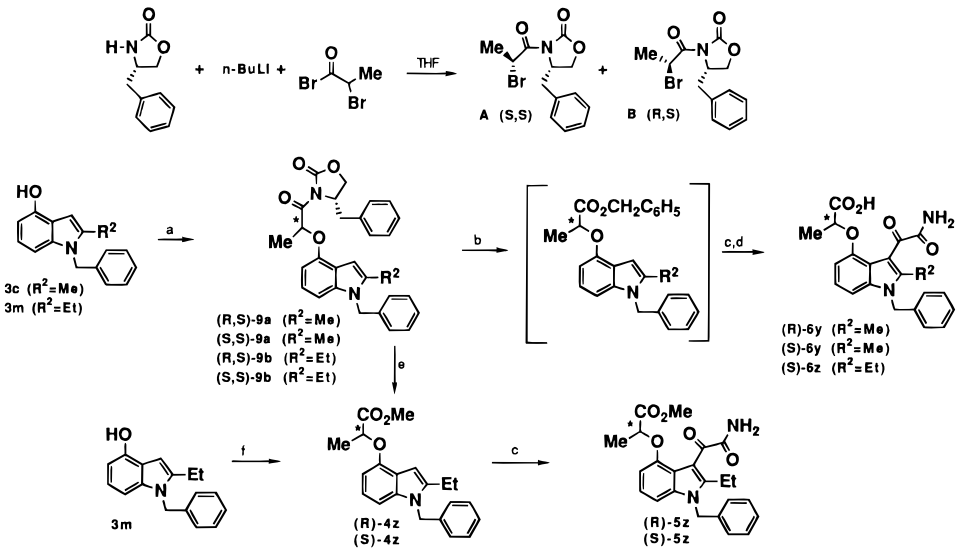


starting material	compound	R^1	R^2	position of O-substitution	R^3	R^4	R^5
1a	**2a-6a**	$C_6H_5CH_2$	H	5	H	$(CH_2)_3CO_2Et$	$(CH_2)_3CO_2H$
1b	**2b-6b**	$C_6H_5CH_2$	H	4	H	CH_2CO_2t-Bu	CH_2CO_2H
1c	**2c-6c**	$C_6H_5CH_2$	CH_3	4	H	CH_2CO_2Me	CH_2CO_2H
1c	**2d-6d**	2-$(C_6H_5)C_6H_4CH_2$	CH_3	4	H	CH_2CO_2Me	CH_2CO_2H
1c	**2e-6e**	3-$(C_6H_5)C_6H_4CH_2$	CH_3	4	H	CH_2CO_2Me	CH_2CO_2H
1c	**2f-6f**	4-$(C_6H_5)C_6H_4CH_2$	CH_3	4	H	CH_2CO_2Me	CH_2CO_2H
1c	**2g-6g**	4-$FC_6H_4CH_2$	CH_3	4	H	CH_2CO_2Me	CH_2CO_2H
1c	**2h-6h**	2,6-$Cl_2C_6H_3CH_2$	CH_3	4	H	CH_2CO_2Me	CH_2CO_2H
1c	**2i-6i**	1-NaphthylCH_2	CH_3	4	H	CH_2CO_2Me	CH_2CO_2H
1c	**2j-6j**	2-$ClC_6H_4CH_2$	CH_3	4	H	CH_2CO_2Me	CH_2CO_2H
1c	**2k-6k**	2-$MeC_6H_4CH_2$	CH_3	4	H	CH_2CO_2Me	CH_2CO_2H
1c	**2l-6l**	n-C_8H_{17}	CH_3	4	H	CH_2CO_2Me	CH_2CO_2H
1d	**2m-6m**	$C_6H_5CH_2$	CH_3CH_2	4	H	CH_2CO_2Me	CH_2CO_2H
1d	**2n-6n**	2-$(C_6H_5)C_6H_4CH_2$	CH_3CH_2	4	H	CH_2CO_2Me	CH_2CO_2H
1d	**2o-6o**	2-$(C_6H_5CH_2)C_6H_4CH_2$	CH_3CH_2	4	H	CH_2CO_2Me	CH_2CO_2H
1d	**2p-6p**	3-$ClC_6H_4CH_2$	CH_3CH_2	4	H	CH_2CO_2Me	CH_2CO_2H
1d	**2q-6q**	$C_6H_5C{=}O$	CH_3CH_2	4	H	CH_2CO_2t-Bu	CH_2CO_2H
1e	**2r-6r**	2-$(C_6H_5)C_6H_4CH_2$	n-propyl	4	H	CH_2CO_2Me	CH_2CO_2H
1f	**2s-6s**	$C_6H_5CH_2$	cyclopropyl	4	H	CH_2CO_2Me	CH_2CO_2H
1f	**2t-6t**	2-$(C_6H_5)C_6H_4CH_2$	cyclopropyl	4	H	CH_2CO_2Me	CH_2CO_2H
3m	**3u-6u**	$C_6H_5CH_2$	CH_3CH_2	4	5-allyl	CH_2CO_2Et	CH_2CO_2H
3c	**4v-6v**	2-$(C_6H_5)C_6H_4CH_2$	CH_3	4	H	$(CH_2)_3CO_2Et$	$(CH_2)_3CO_2H$
3m	**4w-6w**	$C_6H_5CH_2$	CH_3CH_2	4	H	$C(Me)_2CO_2Me$	$C(Me)_2CO_2H$
3m	**4x-6x**(dl)	$C_6H_5CH_2$	CH_3CH_2	4	H	$CH(CH_2CH_2Ph)$-CO_2Me	$CH(CH_2CH_2Ph)$-CO_2H
3c	**4y-6y**(dl)	$C_6H_5CH_2$	CH_3	4	H	$CH(Me)CO_2Me$	$CH(Me)CO_2H$
3m	**4z-6z**(dl)	$C_6H_5CH_2$	CH_3CH_2	4	H	$CH(Me)CO_2Me$	$CH(Me)CO_2H$
4m	**4aa, 5aa**	$C_6H_5CH_2$	CH_3CH_2	4	H	CH_2CONH_2	
5u	**5ab, 6ab**	$C_6H_5CH_2$	CH_3CH_2	4	5-propyl	CH_2CO_2Et	CH_2CO_2H
1g	**5ac, 6ac**	$C_6H_5CH_2$	CH_3CH_2	5	H	$(CH_2)_3CO_2t$-Bu	$(CH_2)_3CO_2H$
5q	**5ad, 6ad**	$C_6H_5SO_2$	CH_3CH_2	4	H	CH_2CO_2t-Bu	CH_2CO_2H
5q	**6ae**	H	CH_3CH_2	4	H		CH_2CO_2H
	6af[16]	$C_6H_5CH_2$	CH_3CH_2	4	6-methyl		CH_2CO_2H

[a] Reagents: (a) NaH, R^1X, DMF; (b) BBr_3, CH_2Cl_2; (c) NaH, BrR_4, DMF; (d) 1 oxalyl chloride, CH_2Cl_2, (2) ammonia; (e) 1 NaOH, ROH, H_2L, (2) HCl, H_2O; (f) TFA, CH_2Cl_2; (g) allyl bromide, NaH; (h) $PhNMe_2$, heat; (i) (1) H_2NNH_2, (2) RaNi; (j) H_2, Pd/C; (k) NaOH, MeOH; (l) $PhSO_2Cl$, NaH, DMF.

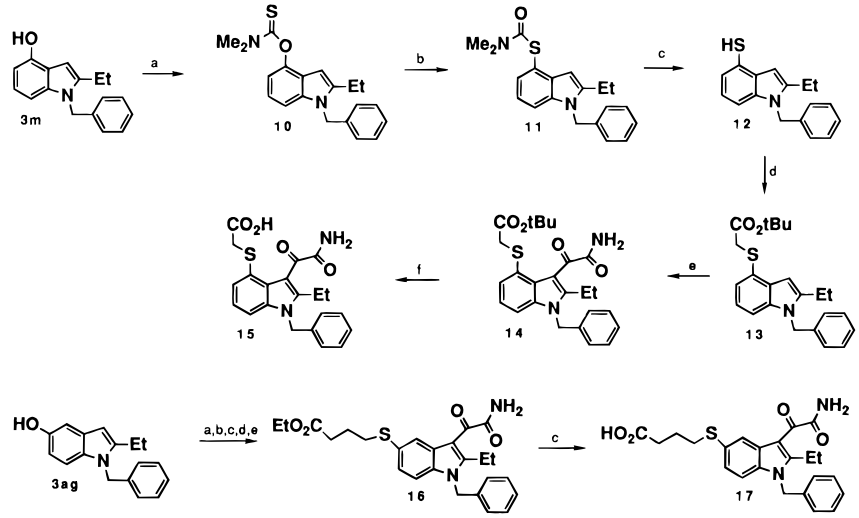
reaction sequence, however, was not useful for the preparation of the 4-functionalized indoles, because the boron tribromide demethylation of 4-methoxy indoles having a 3-glyoxamide functionality can lead to the decarbonylation described in the previous paper of this series.

Scheme 2. Enantiomeric Oxygen-Linked Carboxyl Functionalities[a]



[a] Reagents: (a) NaH, A or B, DMF; (b) $LiOCH_2Ph$, THF, 0 °C; (c) 1 oxalyl chloride, (2) ammonia; (d) H_2, Pd/C, EtOH; (e) MeOMgBr, MeOH, THF; (f) NaH, (*R*)- or (*S*)-$CH_3CH(Cl)CO_2CH_3$, DMF.

Scheme 3. Sulfur-Linked Carboxyl Functionalities[a]



[a] Reagents: (a) NaH, dimethylthiocarbamoyl chloride, DMF; (b) phenyl ether, heat; (c) (1) NaOH, H_2O, EtOH, (2) HCl, H_2O; (d) NaH, $BrCH_2CO_2tBu$ or $Br(CH_2)_3CO_2Et$, DMF; (e) (1) oxalyl chloride, CH_2Cl_2, (2) ammonia; (f) TFA.

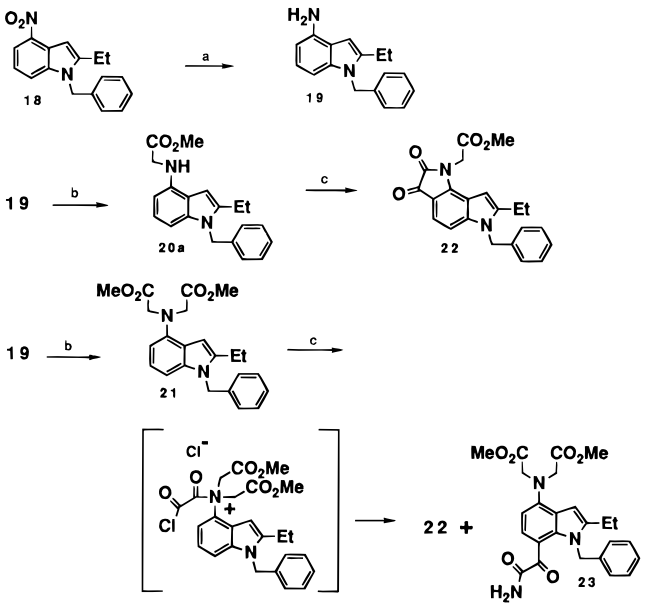
The 1-benzoyl group of **5q** is extremely labile to base, providing **8**, which was a useful starting material for other indoles that could not be prepared by our usual route, such as the 1-(phenylsulfonyl)indole **6ad** and the N-unsubstituted indole **6ae**.

The racemic compounds (*dl*)-**6y** and (*dl*)-**6z** (Scheme 1) were prepared as single enantiomers in Scheme 2. Acylation of the lithium salt of (*S*)-4-benzyl-2-oxazolidine by 2-bromopropionyl bromide provided a mixture of diastereomers (**A** and **B**), which were separated by chromatography. Compounds **3c** and **3m** were each alkylated separately with **A** and **B** in DMF at room temperature. These alkylation reactions gave some minor racemization, but the individual diastereomers were readily separable by chromatography. Both diastereomers of **9a** and one of the diastereomers of **9b** were converted to their benzyl esters by treatment with lithium benzyl oxide in THF,[4] the 3-glyoxamide functionality was then added, and hydrogenation of the benzyl esters provided the single enantiomers of **6y** and **6z**.

To establish the absolute configuration of these enantiomers, the other diastereomer of **9b** was converted to **4z** by treatment with MeOMgBr[5] in MeOH/THF, and then the 3-glyoxamide functionality was added to give **5z**. The optical rotation of this product was −80.5°. As a standard for comparison, the sodium salt of **3m** was alkylated with the pure *S*- and *R*-enantiomers of methyl 2-chloropropionate, resulting in inversion of the optical center to give the *R*- and *S*-isomers of **4z**, and these isomers were carried on to the 3-glyoxamide compounds, **5z**. Optical rotations were measured for each of these **5z** isomers and found to be −13.3° for the *R*-isomer and +13.9° for the *S*-isomer. The low rotation of these two samples indicates that some racemization occurred during the alkylation procedure, but the direction of rotation allowed assignment of the *R*- and *S*-isomers of **5z**, **6y**, and **6z**.

The preparation of 4- or 5-mercaptoindoles, and their elaboration to indole 3-glyoxamides with an acidic group appended to the sulfur is shown in Scheme 3. The oxygen to sulfur conversion of the 4- and 5-hydroxyindoles **3m** and **3ag** was accomplished by the dialkyl thiocarbamate conditions reported by Newman et al.[6] The mercaptoindoles were S-alkylated and then treated

Scheme 4. Nitrogen-Linked Carboxyl Functionalities[a]



[a] Reagents: (a) H_2, 5% Pt/C, EtOH; (b) $NaHCO_3$, $BrCH_2CO_2Me$, DMF; (c) (1) oxalyl chloride, CH_2Cl_2, (2) ammonia.

with oxalyl chloride and ammonia as above, and the ester products were hydrolyzed to give **15** and **17**.

An early attempt to produce 4-aminoindole-3-glyoxamide derivatives with an acidic substituent on the amino nitrogen is depicted in Scheme 4. Catalytic hydrogenation of the 4-nitro group of **18** provided the 4-aminoindole, **19**, which was treated with 1 equiv of methyl bromoacetate to give **20a**, or with an excess to give the N,N-dialkylated product **21**. Reaction of **20a** with oxalyl chloride occurred exclusively at the 4-amino group with no reaction at the 3-position of the indole. This reflects the exceptional nucleophilicity of a 4-amino substituent consequent to the enhanced electron density at this position of the indole system. No catalyst was required for the subsequent cyclization to **22**. Similar observations have been made with anilines having exceptional electron density due to multiple oxygen substituents.[7] Treatment of **21** with oxalyl chloride produced compounds **22** and **23**. These were presumed to have been formed from the intermediate shown, which leads to **23** by a Fries[8] type rearrangement and to **22** by a von Braun[9] dealkylation, followed by an internal cyclization.

As shown in Scheme 5, hydrogenation of a 4-nitroindole with the 3-glyoxamide functionality already in place provided the 4-aminoindole-3-glyoxamide **25**, which was readily converted to the ester **26** and to the desired *N*-acetic acid compound **27**. Treatment of the 4-N-alkylated indole-3-glyoxamide **26** with oxalyl chloride and ammonia resulted in acylation of the 4-nitrogen, but the electron density of the carbocyclic ring of the indole was so diminished by the 3-acyl group that the spontaneous cyclization seen with compound **22** did not occur. Only compound **28** was isolated.

N,N-Disubstituted indole-3-glyoxamides with an *N*-acetyl group in addition to the N-acidic substituent on the 4-nitrogen were prepared by acylation of **20a** and **20b** with acetic anhydride and then further elaborated to the 3-glyoxamides as described previously.

Indole-3-glyoxamides with an acidic group attached to the 4-position of the indole via an all-carbon chain (**39** and **40**) were prepared from 2-methylindoline (Scheme 6). Bromination of the indoline with bromine and silver salts in H_2SO_4[10] followed by N-alkylation gave a mixture of the 4- and 6-bromoindolines, **33a** and **33b**. The bromine was subjected to halogen−metal exchange using *n*-butyllithium, and the mixture of lithio derivatives was reacted with DMF to give **34a** and **34b**, which were separable by chromatography. Wittig reaction of the aldehyde **34a** with methyl (triphenylphosphoranylidene)acetate gave the indoline **35**, which could be oxidized by DDQ[11] to the indole **36**. Compound **36** and compound **38** (obtained by hydrogenation of **36**) were each treated with oxalyl chloride and ammonia and then with aqueous base to give **39** and **40**, respectively.

Pharmacology

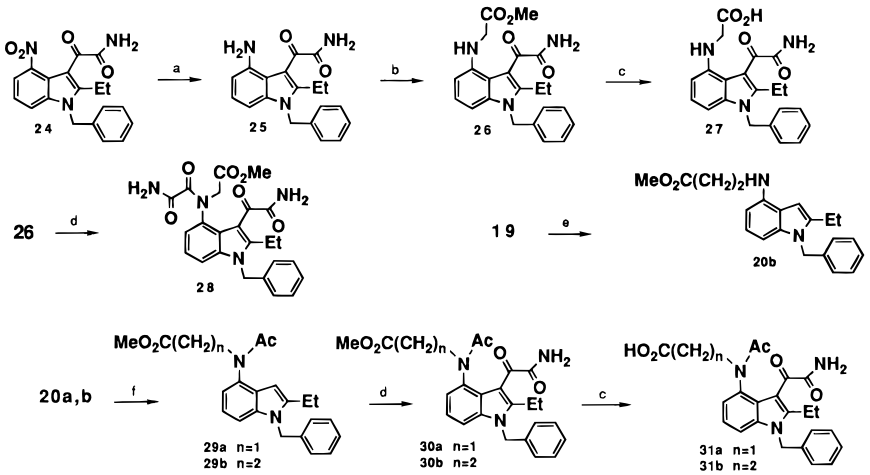
All compounds were evaluated in the chromogenic assay system described in the previous papers of this series. The most interesting compounds were tested for potency and selectivity in secondary assays that used either hnps-PLA_2 or arachidonic acid to stimulate a contraction of guinea pig lung pleural strips. These results are summarized in Table 1.

The exceptional potency of a number of these inhibitors raised some questions with regard to the meaning of the chromogenic assay results. The concentration of hnps-PLA_2 in this system is 16 nM, and many of the IC_{50} values determined for the indole-3-glyoxamide inhibitors are at or below this concentration. In particular, a number of the most potent compounds displayed half-maximal inhibition within experimental error of 8 nM. This concentration is exactly half that of the enzyme in the assay and suggests that the stoichiometric limit may have been attained.

To address this concern, we used a slightly modified deoxycholate/phosphatidyl choline (DOC/PC) assay that had been developed for the evaluation of patient samples of hnps-PLA_2.[12] The lipid concentration in this assay (4 mM) is higher than that of the chromogenic (1.23 mM), and less enzyme was required (3 nM). These differences allow accurate determination of IC_{50} values below 10^{-5} mole fraction. The use of mole fraction terminology in the description of inhibitory constants is important for the PLA_2 enzymes since they operate on aggregated substrate.[13] Briefly, an IC_{50} presented in molar terms for any inhibitor will vary depending on the concentration of lipid used in the assay. This makes it difficult to compare inhibitors evaluated in different assays. However, if the IC_{50} determined for a compound is divided by the lipid concentration that is being used in the assay, a dimensionless number results that is independent of the lipid concentration and may be used to compare results generated under quite different conditions. The symbol commonly used to express the mole fraction for 50% inhibition is Xi_{50}.

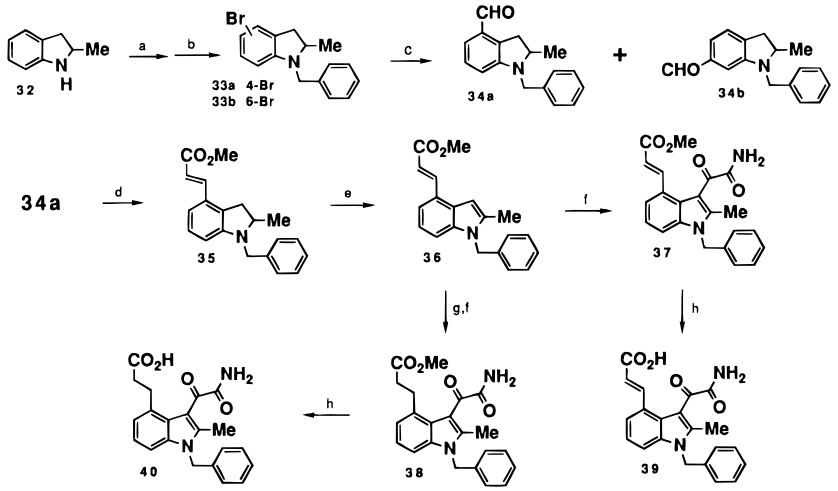
A significant number of the indole-3-glyoxamide inhibitors were evaluated in the DOC/PC assay (Table 1). For those compounds whose IC_{50} values had not dropped below the 16 nM concentration of PLA_2 in the chromogenic assay, there was generally excellent agreement between the Xi_{50}'s observed in the two assays. Representative examples are **6f**, **6g**, and **6k**. For some compounds at the stoichiometric limit of the chromogenic assay, such as **6h**, **6i**, **6j**, and **6p**, comparable results were obtained in the DOC/PC assay when mole fraction comparisons were made. The most potent compounds, such as **6d**, **6m**, **6n**, and **6o**, had truly "bottomed out"

Scheme 5. Nitrogen-Linked Carboxyl Functionalities[a]



[a] Reagents: (a) H_2, Pd/$BaSO_4$, EtOH; (b) $NaHCO_3$, $BrCH_2CO_2Me$, DMF; (c) (1) NaOH, H_2O, EtOH, (2) HCl, H_2O; (d) (1) oxalyl chloride, CH_2Cl_2, (2) ammonia; (e) methyl acrylate, MeOH; (f) Ac_2O, CH_2Cl_2.

Scheme 6. Carbon-Linked Carboxyl Functionalities[a]



[a] Reagents: (a) Ag_2SO_4, H_2SO_4, Br_2; (b) K_2CO_3, benzyl bromide, DMF, 85 °C; (c) (1) *n*-BuLi, THF, −75 °C, (2) DMF; (d) $Ph_3P{=}CHCO_2Me$, THF; (e) DDQ, dioxane, 95 °C; (f) (1) oxalyl chloride, CH_2Cl_2, (2) ammonia; (g) 10% Pd/C, H_2, EtOH; (h) (1) NaOH, H_2O, EtOH, (2) HCl, H_2O.

in the chromogenic assay. As shown in Table 1, these inhibitors were 3−6-fold more potent in the DOC/PC assay than had been indicated by the chromogenic numbers. The best inhibitors show Xi_{50} values of 10^{-6} or below. This improved potency was reflected in generally improved activity in the tissue bath secondary assay (Table 1).

Discussion

The structure−activity relationship of the indole-3-acetamide hnps-PLA$_2$ inhibitors discussed in the preceding papers[1] was extended to include a series of indole-3-glyoxamides. The information gained from the 3-acetamide SAR and the X-ray crystal structures[14] of the 3-acetamide inhibitors in the enzyme active site was applied. Indole-3-glyoxamides with an acidic group linked by a carbon chain to a 4- or 5-heteroatom substituent on the indole ring, or directly linked to the indole by an all-carbon chain, were prepared. In general, the 4-substituted indole-3-glyoxamides were significantly more active than the corresponding acetamides, while the 5-substituted indole-3-glyoxamides were somewhat less active.

Within the glyoxamide series, 4-substitution was generally preferred over 5-substitution. Comparison of mole fraction values generated for a pair of 2-ethyl-1-(phenylmethyl)-1*H*-indole-3-glyoxamides with an acidic substituent appended at an optimal length for interaction with the calcium in the enzyme active site (determined in the preceding paper) showed the indole-3-glyoxamide with a 4-oxyacetic acid substituent, **6m** (1.8×10^{-6}), was approximately 100-fold more active than **6ac** (1.7×10^{-4}), which has a 5-oxybutanoic acid substituent. The carboxy group of the 4-substituent and the carboxamido group of the glyoxamide, which provide ligands for the calcium in the active site, are held in a distinct relation to each other in the 4-substituted glyoxamides. This arrangement is apparently very suitable for the geometry of the ligand shell. The 5-substituted analogues require a longer alkyl chain for the carboxy ligand to reach the calcium in the enzyme active site and therefore have more conformational flexibility.

The most potent inhibitors were substituted with a 3-glyoxamide and 4-oxyacetic acid function. The optimal substitution at the 1-position of these indoles mimicked the SAR of the indole-3-acetamides. Compounds with a benzyl, substituted benzyl, or a long alkyl chain at the 1-position showed the best activity, while compounds with a 1-benzoyl or 1-benzenesulfonyl were

Table 1. Inhibitory Activity Against hnps-PLA_2 and Arachidonic Acid

	inhibition of human secreted PLA_2				contraction of GP lung tissue	
	chromogenic assay		DOC/PC assay		PLA_2-induced	AA-induced
compd	IC_{50} (μM)	mole fraction[a]	IC_{50} (μM)	mole fraction	apparent K_B (μM) ($n = 4$)	ED_{50} (μM) ($n = 4$)
5aa	0.124 ± 0.013	1.0×10^{-4}				
6a	62.0 ± 2.9	4.8×10^{-2}				
6b	0.096 ± 0.015	8.0×10^{-5}				
6c	0.011 ± 0.004	8.9×10^{-6}	0.019	4.8×10^{-6}	0.14 ± 0.07	>10
6d	0.006 ± 0.001	5.0×10^{-6}	0.003	7.5×10^{-7}	0.068 ± 0.01	>10
6e	0.009 ± 0.001	7.3×10^{-6}	0.008	2.0×10^{-6}		
6f	0.043 ± 0.003	3.6×10^{-5}	0.150	3.8×10^{-5}		
6g	0.030 ± 0.003	2.5×10^{-5}	0.074	1.9×10^{-5}	0.11 ± 0.02	>30
6h	0.006 ± 0.001	5.0×10^{-6}	0.022	5.5×10^{-6}	0.077 ± 0.01	>30
6i	0.009 ± 0.004	7.3×10^{-6}	0.017	4.3×10^{-6}	0.128 ± 0.04	>30
6j	0.009 ± 0.002	7.3×10^{-6}	0.025	6.3×10^{-6}	0.100 ± 0.02	>30
6k	0.015 ± 0.004	1.3×10^{-5}	0.045	1.1×10^{-5}	0.154 ± 0.05	>30
6l	0.008 ± 0.003	6.5×10^{-6}	0.018	4.5×10^{-6}	0.061 ± 0.01	>30
6m	0.009 ± 0.001	7.3×10^{-6}	0.007	1.8×10^{-6}	0.083 ± 0.01	>10
6n	0.006 ± 0.002	5.0×10^{-6}	0.006	1.5×10^{-6}	0.057 ± 0.01	>30
6o	0.004 ± 0.001	3.3×10^{-6}	0.004	1.0×10^{-6}	0.052 ± 0.01	
6p	0.007 ± 0.002	5.8×10^{-6}	0.025	6.3×10^{-6}	0.11 ± 0.01	5 ± 1
6q	0.081 ± 0.009	6.6×10^{-5}	0.039	9.8×10^{-6}	0.34 ± 0.12	
6r	0.082 ± 0.014	6.7×10^{-5}				
6s	0.028 ± 0.010	2.3×10^{-5}	0.041	1.0×10^{-5}		
6t	0.006 ± 0.002	5.0×10^{-6}	0.023	5.8×10^{-6}	0.075 ± 0.01	>10
6u	1.62 ± 0.085	1.3×10^{-3}				
6v	0.243 ± 0.075	2.0×10^{-4}				
6w	0.025 ± 0.002	2.1×10^{-5}	0.029	7.3×10^{-6}	0.143 ± 0.02	>30
(*dl*)-**6x**	0.046 ± 0.001	3.8×10^{-5}	0.026	6.5×10^{-6}	0.293 ± 0.04	>30
(*dl*)-**6y**	0.010 ± 0.002	8.1×10^{-6}	0.009	2.3×10^{-6}	0.145 ± 0.04	>30
(*R*)-**6y**	0.011 ± 0.002	8.9×10^{-6}	0.006	1.5×10^{-6}		
(*S*)-**6y**	0.188 ± 0.055	1.5×10^{-4}	0.136	3.4×10^{-5}		
(*dl*)-**6z**	0.011 ± 0.001	8.9×10^{-6}	0.013	3.3×10^{-6}	0.21 ± 0.09	>30
(*S*)-**6z**	0.141 ± 0.030	1.1×10^{-4}				
6ab	2.07 ± 0.12	1.7×10^{-3}				
6ac	0.210 ± 0.046	1.7×10^{-4}				
6ad	0.028 ± 0.013	2.3×10^{-5}			0.316 ± 0.12	
6ae	1.600 ± 0.200	1.3×10^{-3}			3.41 ± 0.64	
6af	0.008 ± 0.001	6.5×10^{-6}	0.008	2.0×10^{-6}	0.124 ± 0.029	3.16 ± 0.5
15	0.145 ± 0.008	1.2×10^{-4}	0.210	5.3×10^{-5}		
17	0.049 ± 0.01	4.0×10^{-5}				
27	1.0 ± 0.28	8.1×10^{-4}				
31a	>100					
31b	>100					
39	46	3.6×10^{-2}				
40	0.145 ± 0.006	1.2×10^{-4}			0.614 ± 0.18	

[a] Mole fraction is the IC_{50} concentration value divided by the total lipid concentration (chromogenic assay, 1230 μM; DOC/PC assay, 4000 μM).

less active. *Ortho*- or *meta*-substitution of the benzyl was preferred; in particular, compounds with an *o*-phenyl or *o*-benzyl substituent were very active. The optimal indole 2-substituent also paralleled the indole-3-acetamide SAR. An ethyl group was generally best, but compounds with a 2-methyl or 2-cyclopropyl group were also very active.

An additional 5-substituent such as the 5-allyl or 5-propyl group of **6u** and **6ab** caused a large loss of activity compared to **6m**, presumably a consequence of steric interference with the positioning of the 4-substituent. The additional 6-methyl substituent of **6af** caused no loss of activity.

Substitution on the α-carbon of the oxyacetic acid (**6w**−**z**) was well tolerated. Even groups as large as a phenethyl substituent or dimethyl substitution of the α-carbon retained considerable activity. When the enantiomers of the α-methyl compound, **6y**, were prepared and tested, the *R*-isomer was 20-fold more potent than the *S*-isomer. The decreased activity of the *S*-isomer might be explained by steric compression resulting from the α-methyl group eclipsing the indole 5-hydrogen to achieve optimal binding of the carboxyl group with the catalytic calcium.

The indole-3-glyoxamides with a sulfur-linked acidic functionality are an isolated example where 5-substitution is preferred over 4-substitution. The 4-thioacetic acid compound, **15** (0.145 μM), was less potent than the 5-thiobutanoic acid derivative **17** (0.049 μM) in the chromogenic assay. Both were much less potent than **6m**.

Replacing the oxygen linker of the oxyacetic acid of **6m** with a nitrogen (**27**) caused a large decrease in activity in the chromogenic assay (1.6 μM). To test whether this loss of activity was due to the basic nitrogen, an acetyl group was added (**31a** and **31b**), but these compounds showed even poorer activity, possibly due to steric considerations. Compounds with the 4-acidic substituent appended via an all-carbon chain (**39** and **40**) were also less active than the oxyacetic acid compounds.

Compound **6m** was cocrystallized with hnps-PLA_2 and was examined by X-ray crystallography.[15] The X-ray crystal structure of this complex revealed several interactions between **6m** and the enzyme active site. The carboxyl group of the 4-substituent and the carboxamide carbonyl of the 3-glyoxamide both function as ligands for the calcium in the active site. The carboxamide

Table 2. Inhibition of Selected PLA$_2$'s

compd	IC$_{50}$ (μM) human nonpancreatic PLA$_2$	human pancreatic PLA$_2$	porcine pancreatic PLA$_2$
6c	0.011 ± 0.004	0.761	0.015
6d	0.006 ± 0.001	0.364	0.097
6e	0.009 ± 0.001	0.57	0.007
6f	0.043 ± 0.003	1.09	
6i	0.009 ± 0.004	1.2	
6l	0.008 ± 0.003	0.78	
6m	0.009 ± 0.001	0.228	0.048
6o	0.004 ± 0.001	0.062	
6p	0.007 ± 0.002	0.390	0.003
39	46	>100	
40	0.145 ± 0.006	>100	

hydrogen bonds to His 48. The ketone carbonyl of the glyoxamide appears to interact with Phe 106 of the enzyme. The indole itself fits well into the space normally occupied by the substrate. The sum of all these observable interactions between the inhibitor and the enzyme accounts for the exceptional potency of these indole-3-glyoxamide derivatives as inhibitors of hnps-PLA$_2$.

As shown in Table 1, the hydrolytic activity of hnps-PLA$_2$ in the *in vitro* assays is inhibited by the more active compounds at mole fractions in the 10^{-6} range. This level of potency is at the stoichiometric limit of the chromogenic assay and approaches the stoichiometric limit of the DOC/PC assay. These compounds displayed potent inhibition against hnps-PLA$_2$ challenge in the tissue-based assay, with K_B values below 100 nM, while selectivity in the control tissues challenged with arachidonic acid remained high. This indicates that inhibition of the hnps-PLA$_2$-induced contractile response is a consequence of direct inhibition of the enzyme rather than inhibition at some point subsequent to the action of the PLA$_2$.

Table 2 compares IC$_{50}$ values generated for the indole-3-glyoxamides as inhibitors of human nonpancreatic secretory PLA$_2$ relative to their inhibition of pancreatic secretory PLA$_2$ enzymes. The indole-3-glyoxamide derivatives show increased potency against the pancreatic enzymes as compared to the indole-3-acetamides, but still exhibit selectivity for human nonpancreatic secretory PLA$_2$.

On the basis of consideration of the combination of chemical, physical, and pharmacological characteristics, LY315920 (**6m**) has been chosen for clinical evaluation as an inhibitor of hnps-PLA$_2$.

Summary

The application of structure-based drug design methodology to a screening hit has resulted in the identification of clinical candidate LY315920. This inhibitor is 6500-fold more potent than the lead compound, achieving near stoichiometric inhibition of hnps-PLA$_2$ through optimized tight-binding interactions at the enzyme's catalytic site.

Experimental Section

Melting points were obtained on a Thomas-Hoover Mel Temp apparatus 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. Compounds **1a** and **1b**, 5-methoxy-1*H*-indole and 4-methoxy-1*H*-indole, were commercially available, as was 2-methylindoline (**32**). Syntheses of 4-methoxy-2-methyl-1*H*-indole (**1c**), 2-ethyl-4-methoxy-1*H*-indole (**1d**), 4-methoxy-2-propyl-1*H*-indole (**1e**), 2-cyclopropyl-4-methoxy-1*H*-indole (**1f**), and 2-ethyl-5-methoxy-1*H*-indole (**1g**) are described in the first paper of this series, as are compounds **2b**, **2m**, and **2p**. Compounds **3ag**, **16**, **18**, and **24** are described in the preceding paper.

5-Methoxy-1-(phenylmethyl)-1*H*-indole (2a). A solution of 940 mg (6.0 mmol) of 5-methoxy-1*H*-indole (**1a**) in 10 mL of DMF was stirred with 255 mg of NaH (60% in mineral oil; 6.4 mmol) for 5 min and then with 800 mg (6.3 mmol) of benzyl chloride for 1 h. The solution was 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 5% EtOAc/hexane, to give **2a**: 1.21 g (yield 85%); mp 64−67 °C; MS (FD) 237 (M$^+$). Anal. ($C_{16}H_{15}NO$) C, H, N.

The following compounds were prepared from **1** by the above procedure (utilizing the appropriate alkyl or acyl halide) and purified by the method indicated.

4-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole (2c) (chromatography on silica gel, 20% EtOAc/hexane): yield 84%; mp 96−116 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.32−6.92 (m, 7H), 6.85 (d, 1H), 6.53 (d, 1H), 5.29 (s, 2H), 3.96 (s, 3H), 2.36 (s, 3H); MS (FD$^+$) 251 (M$^+$). Anal. ($C_{17}H_{17}NO$) C, H, N.

1-([1,1′-Biphenyl]-2-ylmethyl)-4-methoxy-2-methyl-1*H*-indole (2d) (chromatography on silica gel, 16% EtOAc/hexane): yield 80%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.56−6.96 (m, 10H), 6.73 (d, 1H), 6.56−6.40 (m, 2H), 5.16 (s, 2H), 3.95 (s, 3H), 2.23 (s, 3H); MS (FD$^+$) 327 (M$^+$). Anal. ($C_{23}H_{21}NO$) C; H: calcd, 6.46; found, 5.66; N: calcd, 4.28; found, 3.83.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-methoxy-2-methyl-1*H*-indole (2e) (chromatography on silica gel, 20% EtOAc/hexane): yield 76%; mp 127−131 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.66−7.00 (m, 9H), 6.89 (d, 2H), 6.53 (d, 1H), 6.45 (br s, 1H), 5.35 (s, 2H), 3.98 (s, 3H), 2.39 (s, 3H); MS (FD$^+$) 327 (M$^+$). Anal. ($C_{23}H_{21}NO$) H, N; C: calcd, 84.37; found, 83.30.

1-([1,1′-Biphenyl]-4-ylmethyl)-4-methoxy-2-methyl-1*H*-indole (2f) (chromatography on silica gel, 20% EtOAc/hexane): yield 80%; mp 118−123 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.70−7.00 (m, 10H), 6.89 (d, 1H), 6.55 (d, 1H), 6.45 (br s, 1H), 5.32 (s, 2H), 3.96 (s, 3H), 2.39 (s, 3H); MS (FD$^+$) 327 (M$^+$). Anal. ($C_{23}H_{21}NO$) C, H, N.

1-[(4-Fluorophenyl)methyl]-4-methoxy-2-methyl-1*H*-indole (2g) (chromatography on silica gel, 20% EtOAc/hexane): yield 82%; mp 104−108 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.21−6.86 (m, 5H), 6.82 (d, 1H), 6.52 (d, 1H), 6.42 (s, 1H), 5.23 (s, 2H), 3.94 (s, 3H), 2.33 (s, 3H); MS (FD$^+$) 269 (M$^+$). Anal. ($C_{17}H_{16}FNO$) H, N; C: calcd, 75.82; found, 73.82.

1-[(2,6-Dichlorophenyl)methyl]-4-methoxy-2-methyl-1*H*-indole (2h) (chromatography on silica gel, 20% EtOAc/hexane): yield 84%; mp 154−157 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.41−7.17 (m, 3H), 6.95 (t, 1H), 6.73 (d, 1H), 6.48 (d, 1H), 6.37 (br s, 1H), 5.50 (s, 2H), 3.92 (s, 3H), 2.39 (s, 3H); MS (FD$^+$) 319 (M − 1, 100), 321 (M + 1, 75). Anal. ($C_{17}H_{15}Cl_2NO$) H, N; C: calcd, 63.77; found, 67.16.

4-Methoxy-2-methyl-1-[(1-naphthyl)methyl]-1*H*-indole (2i) (chromatography on silica gel, 20% EtOAc/hexane): yield 97%; oil; ^{1}H NMR ($CDCl_3$) ∂ 8.21−7.16 (m, 6H), 7.02 (t, 1H), 6.79 (d, 1H), 6.59−6.47 (m, 2H), 6.37 (d, 1H), 5.75 (s, 2H), 4.00 (s, 3H), 2.34 (s, 3H); MS (FD$^+$) 301 (M$^+$). Anal. ($C_{21}H_{19}NO$) C, H, N.

1-[(2-Chlorophenyl)methyl]-4-methoxy-2-methyl-1*H*-indole (2j) (chromatography on silica gel, 20% EtOAc/hexane): yield 85%; mp 150−157 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.42 (d, 1H), 7.18 (br t, 1H), 7.13−6.98 (m, 2H), 6.80 (d, 1H), 6.56 (d, 1H), 6.48 (s, 1H), 6.27 (d, 2H), 5.33 (s, 2H), 3.96 (s, 3H), 2.32 (s, 3H). Anal. ($C_{17}H_{16}ClNO$) C, H, N.

4-Methoxy-2-methyl-1-[(2-methylphenyl)methyl]-1*H*-indole (2k) (chromatography on silica gel, 20% EtOAc/hexane): yield 62%; mp 126−146 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.26−6.94 (m, 4H), 6.75 (d, 1H), 6.53 (d, 1H), 6.48 (br s, 1H), 6.25 (d, 1H), 5.21 (s, 2H), 3.96 (s, 3H), 2.41 (s, 3H), 2.30 (s, 3H); MS (FD$^+$) 265 (M$^+$). Anal. ($C_{18}H_{19}NO$) H; C: calcd, 81.47; found, 77.56; N: calcd, 5.28; found, 4.37.

4-Methoxy-2-methyl-1-*n*-octyl-1*H*-indole (2l) (chromatography on silica gel, 20% EtOAc/hexane): yield 76%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.07 (t, 1H), 6.90 (d, 1H), 6.49 (d, 1H), 6.33 (s,

1H), 4.02 (t, 2H), 3.92 (s, 3H), 2.41 (s, 3H), 1.82−0.84 (m, 15H); MS (FD^+) 273 (M^+). Anal. ($C_{18}H_{27}NO$) C, H, N.

1-([1,1′-Biphenyl]-2-ylmethyl)-2-ethyl-4-methoxy-1*H*-indole (2n) (chromatography on silica gel, 20% EtOAc/hexane): yield 37%; oil; MS (FD^+) 273 (M^+).

2-Ethyl-4-methoxy-1-[(2-[phenylmethyl]phenyl)methyl]-1*H*-indole (2o) (chromatography on silica gel, 20%EtOAc/hexane): yield 68%; oil; ^1H NMR ($CDCl_3$) ∂ 7.45−6.93 (m, 9H), 6.52 (dd, 2H), 6.43 (br s, 1H), 6.22 (d, 1H), 5.21 (s, 2H), 4.16 (s, 3H), 3.98 (s, 2H), 2.39 (q, 2H), 1.18 (t, 3H); MS (FD) 355 (M^+). Anal. ($C_{25}H_{25}NO$) C, H, N.

1-Benzoyl-2-ethyl-4-methoxy-1*H*-indole (2q) (chromatography on silica gel, 20% EtOAc/hexane): yield 43%; oil; ^1H NMR ($CDCl_3$) ∂ 7.41 (d, 2H), 7.31−7.08 (m, 3H), 6.93 (t, 1H), 6.66−6.51 (m, 2H), 6.50 (d, 1H), 3.95 (s, 3H), 2.84 (q, 2H), 1.29 (t, 3H).

1-([1,1′-Biphenyl]-2-ylmethyl)-4-methoxy-2-propyl-1*H*-indole (2r) (chromatography on silica gel, 20% EtOAc/hexane): yield 65%; oil; ^1H NMR ($CDCl_3$) ∂ 7.57−7.10 (m, 8H), 7.02 (t, 1H), 6.75 (d, 1H), 6.50 (dd, 2H), 6.42 (s, 1H), 5.16 (s, 2H), 3.96 (s, 3H), 2.49 (t, 2H), 1.74−1.58 (m, 2H), 0.93 (t, 3H); MS (FD^+) 355 (M^+).

2-Cyclopropyl-4-methoxy-1-(phenylmethyl)-1*H*-indole (2s) (chromatography on silica gel, 20% EtOAc/hexane): yield 45%; oil; ^1H NMR ($CDCl_3$) ∂ 7.42−7.00 (m, 6H), 6.92 (d, 1H), 6.60 (d, 1H), 6.40 (s, 1H), 5.54 (s, 2H), 4.04 (s, 3H), 1.90−1.79 (m, 1H), 1.00−0.89 (m, 2H), 0.82−0.70 (m, 2H); MS (FD) 277 (M^+).

1-([1,1′-Biphenyl]-2-ylmethyl)-2-cyclopropyl-4-methoxy-1*H*-indole (2t) (chromatography on silica gel, 20% EtOAc/hexane): yield 52%; MS (FD) 353 (M^+).

2-Ethyl-4-hydroxy-1-(phenylmethyl)-1*H*-indole (3m). To a solution of 3.1 g (11.7 mmol) of **2m** in 40 mL of CH_2Cl_2 was added 47 mL of a 1 M solution of BBr_3 in CH_2Cl_2. The mixture was stirred for 4 h, and the solvent was evaporated at reduced pressure. The residue was dissolved in EtOAc/water, and the organic phase was separated, washed with brine, dried over $MgSO_4$, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with 20% EtOAc/hexane, to give **3m**: 1.58 g (yield 54%); mp 86−90 °C: ^1H NMR ($CDCl_3$) ∂ 7.41−6.94 (m, 6H), 6.85 (d, 1H), 6.53 (d, 1H), 6.41 (s, 1H), 5.33 (s, 2H), 4.98 (s, 1H), 2.71 (q, 2H) 1.35 (t, 3H); MS (FD^+) 251 (M^+). Anal ($C_{17}H_{17}NO$) C, H, N.

The following compounds were prepared utilizing the above procedure.

5-Hydroxy-1-(phenylmethyl)-1*H*-indole (3a) (chromatography on silica gel, gradient, 20−100% Et_2O/hexane): yield 41%; ^1H NMR($CDCl_3$) ∂ 7.45−7.25(m, 4H), 7.25−7.05(m, 4H), 6.85(dd, 1H), 6.55(d, 1H), 5.65(br s, 1H), 5.25(s, 2H).

4-Hydroxy-1-(phenylmethyl)-1*H*-indole (3b) (crude product): yield 100%.

4-Hydroxy-2-methyl-1-(phenylmethyl)-1*H*-indole (3c) (chromatography on silica gel, 20% EtOAc/hexane): yield 49%; mp 125−127 °C; ^1H NMR ($CDCl_3$) ∂ 7.45−6.94 (m, 6H), 6.83 (d, 1H), 6.52 (d, 1H), 6.39 (s, 1H), 5.29 (s, 2H), 4.97 (s, 1H), 2.38 (s, 3H); MS (FD) 237 (M^+). Anal. ($C_{16}H_{15}NO$) C, H, N.

1-([1,1′-Biphenyl]-2-ylmethyl)-4-hydroxy-2-methyl-1*H*-indole (3d) (chromatography on silica gel, 20% EtOAc/hexane): yield 55%; oil; ^1H NMR ($CDCl_3$) ∂ 7.60−7.15 (m, 8H), 6.94 (t, 1H), 6.72 (d, 1H), 6.55−6.45 (m, 2H), 6.34 (s, 1H), 5.16 (s, 2H), 4.99 (s, 1H), 2.25 (s, 3H); MS (FD) 313 (M^+). Anal. ($C_{22}H_{19}NO$) C, H, N.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-hydroxy-2-methyl-1*H*-indole (3e) (chromatography on silica gel, 20% EtOAc/hexane): yield 87%; oil; ^1H NMR ($CDCl_3$) ∂ 7.66−6.82 (m, 11H), 6.52 (d, 1H), 6.39 (s, 1H), 5.33 (s, 2H), 5.00 (s, 1H), 2.40 (s, 3H); MS (FD^+) 313 (M^+).

1-([1,1′-Biphenyl]-4-ylmethyl)-4-hydroxy-2-methyl-1*H*-indole (3f) (chromatography on silica gel, 20% EtOAc/hexane): yield 77%; oil; ^1H NMR ($CDCl_3$) ∂ 7.65−6.97 (m, 10H), 6.86 (d, 1H), 6.52 (d, 1H), 6.39 (br s, 1H), 5.32 (s, 2H), 4.90 (br s, 1H), 2.41 (s, 3H); MS (FD^+) 313 (M^+).

1-[(4-Fluorophenyl)methyl]-4-hydroxy-2-methyl-1*H*-indole (3g) (chromatography on silica gel, 20% EtOAc/hexane): yield 84%; oil; ^1H NMR ($CDCl_3$) ∂ 7.08−6.90 (m, 5H), 6.82 (d, 1H), 6.52 (d, 1H), 6.38 (s, 1H), 5.25 (s, 2H), 4.95 (s, 1H), 2.36 (s, 3H); MS (FD^+) 255 (M^+).

1-[(2,6-Dichlorophenyl)methyl]-4-hydroxy-2-methyl-1*H*-indole (3h) (chromatography on silica gel, 20% EtOAc/hexane): yield 83%; oil; ^1H NMR ($CDCl_3$) ∂ 7.41−7.19 (m, 3H), 6.89 (t, 1H), 6.71 (d, 1H), 6.47 (d, 1H), 6.31 (br s, 1H), 5.49 (s, 2H), 4.82 (br s, 1H), 2.40 (s, 3H); MS (FD^+) 305 (M − 1, 100), 307 (M + 1, 90). Anal. ($C_{16}H_{13}Cl_2NO$) C, H, N.

4-Hydroxy-2-methyl-1-[(1-naphthyl)methyl]-1*H*-indole (3i) (chromatography on silica gel, 20% EtOAc/hexane): yield 71%; oil; ^1H NMR ($CDCl_3$) ∂ 8.14 (d, 1H), 7.94 (d, 1H), 7.75 (d, 1H), 7.72−7.21 (m, 3H), 6.96 (t, 1H), 6.76 (d, 1H), 6.55 (d, 1H), 6.47 (s, 1H), 6.37 (d, 1H), 5.75 (s, 2H), 4.94 (s, 1H), 2.35 (s, 3H); MS (FD^+) 287 (M^+).

1-[(2-Chlorophenyl)methyl]-4-hydroxy-2-methyl-1*H*-indole (3j) (chromatography on silica gel, 20% EtOAc/hexane): yield 55%; oil; ^1H NMR ($CDCl_3$) ∂ 7.43 (d, 1H), 7.21 (t, 1H), 7.12−7.00 (m, 1H), 6.98 (t, 1H), 6.77 (d, 1H), 6.55 (d, 1H), 6.42 (s, 1H), 6.30 (d, 1H), 5.33 (s, 2H), 4.89 (br s, 1H), 2.33 (s, 3H); MS (FD) 271 (M − 1, 100), 273 (M + 1, 33). Anal. ($C_{16}H_{14}ClNO$) C, H, N.

4-Hydroxy-2-methyl-1-[(2-methylphenyl)methyl]-1*H*-indole (3k) (chromatography on silica gel, 20% EtOAc/hexane): yield 43%; mp 156−166 °C; ^1H NMR ($CDCl_3$) ∂ 7.41−6.90 (m, 4H), 6.74 (d, 1H), 6.52 (d, 1H), 6.40 (s, 1H), 6.28 (d, 1H), 5.20 (s, 2H), 4.88 (s, 1H), 2.41 (s, 3H), 2.32 (s, 3H); MS (FD) 251 (M^+). Anal. ($C_{17}H_{17}NO$) H, N; C: calcd, 81.24; found, 80.61.

4-Hydroxy-2-methyl-1-*n*-octyl-1*H*-indole (3l) (chromatography on silica gel, 20% EtOAc/hexane): yield 59%; oil; ^1H NMR ($CDCl_3$) ∂ 7.04−6.93 (m, 1H), 6.88 (d, 1H), 6.48 (d, 1H), 6.25 (br s, 1H), 4.80 (br s, 1H), 4.02 (t, 2H), 2.41 (s, 3H), 1.74 (br t, 2H), 1.67−1.22 (m, 10H), 0.87 (t, 3H); MS (FD) 259 (M^+). Anal. ($C_{17}H_{25}NO$) C, H, N.

1-([1,1′-Biphenyl]-2-ylmethyl)-2-ethyl-4-hydroxy-1*H*-indole (3n) (chromatography on silica gel, 20% EtOAc/hexane): yield 69%; oil; ^1H NMR ($CDCl_3$) ∂ 7.70−7.20 (m, 8H), 7.08 (t, 1H), 6.84 (d, 1H), 6.64 (t, 2H), 6.49 (s, 1H), 5.29 (s, 2H), 4.99 (s, 1H), 2.66 (q, 2H), 1.39 (t, 3H); MS (FD) 327 (M^+).

2-Ethyl-4-hydroxy-1-[[2-(phenylmethyl)phenyl]methyl]-1*H*-indole (3o) (chromatography on silica gel, 20% EtOAc/hexane, then 50% EtOAc/hexane): yield 38%; oil; ^1H NMR ($CDCl_3$) ∂ 7.41−7.00 (m, 8H), 6.89 (t, 1H), 6.50 (t, 2H), 6.37 (br s, 1H), 6.23 (d, 1H), 5.11 (s, 2H), 4.88 (br s, 1H), 4.17 (s, 2H), 2.39 (q, 2H), 1.21 (t, 3H); MS (FD) 341 (M^+).

1-[(3-Chlorophenyl)methyl]-2-ethyl-4-hydroxy-1*H*-indole (3p) (chromatography on silica gel, EtOAc, then 5% MeOH/EtOAc): yield 40%; oil; ^1H NMR ($CDCl_3$) ∂ 7.27−6.94 (m, 4H), 6.80 (d, 2H), 6.53 (d, 1H), 6.42 (s, 1H), 5.25 (s, 2H), 5.00 (s, 1H), 2.67 (q, 2H), 1.34 (t, 3H); MS (FD^+) 285 (M − 1, 100), 287 (M + 1, 30).

1-Benzoyl-2-ethyl-4-hydroxy-1*H*-indole (3q) (chromatography on silica gel, 20% EtOAc/hexane, then 50% EtOAc/hexane): yield 52%; mp 91−110 °C; ^1H NMR ($CDCl_3$) ∂ 8.11 (d, 1H), 7.73 (d, 1H), 7.68−7.58 (m, 1H), 7.49 (t, 3H), 6.85 (t, 1H), 6.60−6.44 (m, 3H), 2.85 (q, 2H), 1.26 (t, 3H); MS (FD) 265 (M^+). Anal. ($C_{17}H_{15}NO_2$) H; C: calcd, 76.96; found, 74.04; N: calcd, 5.28; found, 4.45.

1-([1,1′-Biphenyl]-2-ylmethyl)-4-hydroxy-2-propyl-1*H*-indole (3r) (chromatography on silica gel, 20% EtOAc/hexane, then 50% EtOAc/hexane): yield 71%; oil; ^1H NMR ($CDCl_3$) ∂ 7.61−7.12 (m, 8H), 6.96 (t, 1H), 6.75 (d, 1H), 6.52 (dd, 2H), 6.38 (s, 1H), 5.18 (s, 2H), 4.90 (br s, 1H), 2.50 (t, 2H), 1.72−1.53 (m, 2H), 0.94 (t, 3H); MS (FD^+) 341 (M^+).

2-Cyclopropyl-4-hydroxy-1-(phenylmethyl)-1*H*-indole (3s) (chromatography on silica gel, 20% EtOAc/hexane): yield 52%; oil; ^1H NMR ($CDCl_3$) ∂ 7.34−6.90 (m, 6H), 6.80 (d, 1H), 6.47 (d, 1H), 6.22 (br s, 1H), 5.42 (s, 2H), 4.82 (br s, 1H), 1.82−1.77 (m, 1H), 0.90−0.82 (m, 2H), 0.74−0.66 (m, 2H); MS (FD) 263 (M^+).

1-([1,1′-Biphenyl]-2-ylmethyl)-2-cyclopropyl-4-hydroxy-1*H*-indole (3t) (chromatography on silica gel, 20% EtOAc/hexane): yield 29%; oil; ^1H NMR ($CDCl_3$) ∂ 7.52−7.08 (m, 6H), 6.91 (t, 1H), 6.67 (d, 1H), 6.52 (d, 1H), 6.45 (d, 2H), 6.17 (s, 1H), 5.30 (s, 2H), 4.79 (s, 1H), 1.70−1.49 (m, 1H), 0.80−0.66 (m, 2H), 0.62−0.52 (m, 2H); MS (FD) 263 (M^+).

2-[[2-Methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic Acid Methyl Ester (4c). A solution of 530 mg (2.2 mmol) of **3c** in 20 mL of DMF was stirred with 88 mg of NaH (60% in mineral oil; 2.2 mmol) for 40 min and then with 0.2 mL of methyl bromoacetate for 17 h. The solution was diluted with water and extracted with EtOAc. The organic phase was washed with water, dried over $MgSO_4$, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with 20%EtOAc/hexane, to give **4c**: 597 mg (yield 88%); mp 140−145 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.32−6.86 (m, 7H), 6.50 (s, 1H), 6.41 (d, 1H), 5.30 (s, 2H), 4.80 (s, 2H), 3.83 (s, 3H), 2.36 (s, 3H); MS (FD) 309 (M^+). Anal. ($C_{19}H_{19}NO_3$) C, H, N.

The following compounds were prepared by the procedure above (utilizing the appropriate ester alkyl halide) and purified by the indicated method.

4-[[1-(Phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid ethyl ester (4a) (chromatography on silica gel, gradient, 15−50% Et_2O/hexane): yield 40%; ^{1}H NMR ($CDCl_3$) ∂ 7.40−7.30 (m, 3H), 7.25−7.10 (m, 5H), 6.90 (dd, 1H), 6.55 (d, 1H), 5.25 (s, 2H), 4.15 (q, 2H), 4.10 (t, 2H), 3.70 (t, 2H), 2.15−195 (m, 2H), 1.20 (t, 3H).

2-[[1-(Phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid *tert*-butyl ester (4b) (chromatography on silica gel, gradient, 10−20% Et_2O/hexane): yield 12%.

2-[[1-([1,1′-Biphenyl]-2-ylmethyl)-2-methyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4d) (chromatography on silica gel, 20% EtOAc/hexane): yield 77%; mp 99−101 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.62−7.09 (m, 8H), 6.97 (t, 1H), 6.77 (d, 1H), 6.54−6.45 (m, 2H), 6.41 (d, 1H), 5.16 (s, 2H), 4.80 (s, 2H), 3.83 (s, 3H), 2.23 (s, 3H); MS (FD) 385 (M^+). Anal. ($C_{25}H_{23}NO_3$) C, H, N.

2-[[1-([1,1′-Biphenyl]-3-ylmethyl)-2-methyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4e) (chromatography on silica gel, 20% EtOAc/hexane): yield 79%; mp 99−102 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.57−6.84 (m, 11H), 6.53 (s, 1H), 6.44 (d, 1H), 5.35 (s, 2H), 4.82 (s, 2H), 3.82 (s, 3H), 2.40 (s, 3H); MS (FD) 385 (M^+). Anal. ($C_{25}H_{23}NO_3$) C, H, N.

2-[[1-([1,1′-Biphenyl]-4-ylmethyl)-2-methyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4f) (chromatography on silica gel, 20% EtOAc/hexane): yield 63%; mp 164−167 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.62−6.90 (m, 11H), 6.53 (s, 1H), 6.43 (d, 1H), 5.33 (s, 2H), 4.82 (s, 2H), 3.82 (s, 3H), 2.40 (s, 3H); MS (FD^+) 385 (M^+). Anal. ($C_{25}H_{23}NO_3$) H, N; C: calcd, 77.90; found, 78.83.

2-[[1-[(4-Fluorophenyl)methyl]-2-methyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4g) (chromatography on silica gel, 20% EtOAc/hexane): yield 81%; mp 92−98 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.02−6.82 (m, 6H), 6.50 (s, 1H), 6.42 (d, 1H), 5.25 (s, 2H), 4.81 (s, 2H), 3.82 (s, 3H), 2.34 (s, 3H); MS (FD^+) 327 (M^+). Anal. ($C_{19}H_{18}FNO_3$) N; C: calcd, 69.71; found, 70.83; H: calcd, 5.54; found, 6.00.

2-[[1-[(2,6-Dichlorophenyl)methyl]-2-methyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4h) (chromatography on silica gel, 20% EtOAc/hexane): yield 39%; mp 168−169 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.41−7.18 (m, 3H), 6.92 (t, 1H), 6.76 (d, 1H), 6.45 (s, 1H), 6.39 (d, 1H), 5.50 (s, 2H), 4.76 (s, 2H), 3.81 (s, 3H), 2.41 (s, 3H); MS (FD^+) 377 (M − 1, 100), 379 (M + 1, 70). Anal. ($C_{18}H_{17}Cl_2NO_3$) C, H, N.

2-[[2-Methyl-1-[(1-naphthyl)methyl]-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4i) (chromatography on silica gel, 20% EtOAc/hexane): yield 45%; mp 167−171 °C; ^{1}H NMR ($CDCl_3$) ∂ 8.11 (d, 1H), 7.92 (d, 1H), 7.74 (d, 1H), 7.68−7.54 (m, 2H), 7.23 (t, 1H), 6.95 (t, 1H), 6.81 (d, 1H), 6.59 (s, 1H), 6.44 (d, 1H), 6.36 (d, 1H), 5.76 (s, 2H), 4.82 (s, 2H), 3.85 (s, 3H), 2.35 (s, 3H); MS (FD^+) 359 (M^+). Anal. ($C_{23}H_{21}NO_3$) H, N; C: calcd, 76.86; found, 77.95.

2-[[1-[(2-Chlorophenyl)methyl]-2-methyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4j) (chromatography on silica gel, 20% EtOAc/hexane): yield 91%; mp 138−141 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.41 (d, 1H), 7.18 (t, 1H), 7.08−6.94 (m, 2H), 6.82 (d, 1H), 6.55 (s, 1H), 6.43 (d, 1H), 6.25 (d, 1H), 5.33 (s, 2H), 4.80 (s, 2H), 3.82 (s, 3H), 2.33 (s, 3H); MS (FD^+) 343 (M − 1, 100), 345 (M + 1, 60). Anal. ($C_{19}H_{18}ClNO_3$) C, H, N.

2-[[2-Methyl-1-[(2-methylphenyl)methyl]-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4k) (chromatography on silica gel, 20% EtOAc/hexane): yield 63%; mp 151−154 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.33−6.95 (m, 4H), 6.80 (d, 1H), 6.55 (s, 1H), 6.42 (d, 1H), 6.25 (d, 1H), 5.22 (s, 2H), 4.82 (s, 2H), 3.82 (s, 3H), 2.42 (s, 3H), 2.32 (s, 3H); MS (FD^+) 323 (M^+). Anal. ($C_{20}H_{21}NO_3$) C, H, N.

2-[(2-Methyl-1-*n*-octyl-1*H*-indol-4-yl)oxy]acetic acid methyl ester (4l) (chromatography on silica gel, 20% EtOAc/hexane): yield 82%; mp 66−68 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.07−6.92 (m, 2H), 6.41 (d, 2H), 4.77 (s, 2H), 4.02 (t, 2H), 3.81 (s, 3H), 2.41 (s, 3H), 1.74 (br t, 2H), 1.45−1.21 (m, 10H), 0.88 (t, 3H); MS (FD^+) 331 (M^+). Anal. ($C_{20}H_{29}NO_3$) H, N; C: calcd, 72.47; found, 73.36.

2-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4m) (chromatography on silica gel, 20% EtOAc/hexane): yield 69%; mp 89−92 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.30−6.85 (m, 7H), 6.53 (s, 1H), 6.42 (d, 1H), 5.30 (s, 2H), 4.81 (s, 2H), 3.82 (s, 3H), 2.67 (q, 2H), 1.33 (t, 3H); MS (FD^+) 323 (M^+). Anal. ($C_{20}H_{21}NO_3$) C, H, N.

2-[[1-([1,1′-Biphenyl]-2-ylmethyl)-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4n) (chromatography on silica gel, 20% EtOAc/hexane): yield 59%; ^{1}H NMR ($CDCl_3$) ∂ 7.74−7.23 (m, 9H), 7.11 (t, 1H), 6.91 (d, 1H), 6.64 (s, 1H), 6.53 (dd, 1H), 5.30 (s, 2H), 4.93 (s, 2H), 3.96 (s, 3H), 2.66 (q, 2H), 1.41 (t, 3H); MS (FD) 399 (M^+).

2-[[2-Ethyl-1-[[2-(phenylmethyl)phenyl]methyl]-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4o) (chromatography on silica gel, 20% EtOAc/hexane): yield 65%; mp 109−114 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.41−7.16 (m, 7H), 7.02 (t, 1H), 6.90 (t, 1H), 6.57 (d, 1H), 6.49 (s, 1H), 6.39 (d, 1H), 6.22 (d, 1H), 5.11 (s, 2H), 4.80 (s, 2H), 4.16 (s, 2H), 3.80 (s, 3H), 2.37 (q, 2H), 1.19 (t, 3H); MS (FD^+) 413 (M^+). Anal. ($C_{27}H_{27}NO_3$) H, N; C: calcd, 78.42; found, 80.14.

2-[[1-[(3-Chlorophenyl)methyl]-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4p) (chromatography on silica gel, 20% EtOAc/hexane): yield 65%; mp 85−90 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.25−6.75 (m, 6H), 6.56 (s, 1H), 6.43 (d, 1H), 5.27 (s, 2H), 4.83 (s, 2H), 3.83 (s, 3H), 2.66 (q, 2H), 1.35 (t, 3H); MS (FD^+) 357 (M − 1, 100), 359 (M + 1, 40). Anal. ($C_{20}H_{20}ClNO_3$) H; C: calcd, 67.13; found, 64.41; N: calcd, 3.91; found, 3.10.

2-[(1-Benzoyl-2-ethyl-1*H*-indol-4-yl)oxy]acetic acid *tert*-butyl ester (4q) (chromatography on silica gel, 20% EtOAc/hexane): yield 63%; oil; ^{1}H NMR ($CDCl_3$) ∂ 8.11 (d, 1H), 7.75−7.43 (m, 4H), 6.89 (t, 1H), 6.71 (s, 1H), 6.49 (dd, 1H), 4.75 (s, 2H), 2.83 (q, 2H), 1.49 (s, 3H), 1.28 (t, 3H); MS (FD^+) 379 (M^+). Anal. ($C_{23}H_{25}NO_4$) C, H, N.

2-[[1-([1,1′-Biphenyl]-2-ylmethyl)-2-propyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4r) (chromatography on silica gel, 20% EtOAc/hexane): yield 56%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.59−7.11 (m, 8H), 6.98 (t, 1H), 6.80 (d, 1H), 6.50 (s, 1H), 6.49 (d, 1H), 6.41 (d, 1H), 5.16 (s, 2H), 4.81 (s, 2H), 3.82 (s, 3H), 2.49 (t, 2H), 1.66 (q, 2H), 0.94 (t, 3H); MS (FD) 413 (M^+).

2-[[2-Cyclopropyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4s) (chromatography on silica gel, 20% EtOAc/hexane): yield 63%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.33−6.33 (m, 9H), 5.41 (s, 2H), 4.75 (s, 2H), 3.80 (s, 3H), 1.80−1.67 (m, 1H), 0.90−0.78 (m, 2H), 0.74−0.66 (m, 2H); MS (FD) 335 (M^+).

2-[[1-([1,1′-Biphenyl]-2-ylmethyl)-2-cyclopropyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (4t) (chromatography on silica gel, 20% EtOAc/hexane): yield 59%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.51−6.29 (m, 13H), 5.28 (s, 2H), 4.74 (s, 2H), 3.76 (s, 3H), 1.63−1.49 (m, 1H), 0.74−0.66 (m, 2H), 0.62−0.49 (m, 2H); MS (FD) 411 (M^+).

4-[[1-([1,1′-Biphenyl]-2-ylmethyl)-2-methyl-1*H*-indol-4-yl]oxy]butanoic acid ethyl ester (4v) (chromatography on silica gel, 20% EtOAc/hexane): yield 51%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.57−6.41 (m, 13H), 5.16 (s, 2H), 4.14 (q, 2H), 3.49 (t, 2H), 2.52 (t, 2H), 2.23 (s, 3H), 2.27−2.16 (m, 2H), 1.29 (t, 3H); MS (FD) 427 (M^+).

2-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]-2-methylpropionic acid methyl ester (4w) (chromatography on silica gel, 20% EtOAc/hexane): yield 49%; ^{1}H NMR ($CDCl_3$) ∂ 7.34−6.85 (m, 7H), 6.48 (s, 1H), 6.40 (d, 1H), 5.29 (s, 2H), 4.27 (q, 2H), 2.67 (q, 2H), 1.93 (s, 3H), 1.69 (s, 3H), 1.33 (t, 3H), 1.25 (t, 3H); MS (FD^+) 365 (M^+).

***dl*-2-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]-4-phenylbutanoic acid methyl ester ((dl)-4x)** (chromatog-

raphy on silica gel, 50% EtOAc/hexane): yield 86%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.45−6.80 (m, 12H), 6.53 (s, 1H), 6.34 (d, 1H), 5.27 (s, 2H), 4.88−4.74 (m, 1H), 4.23 (q, 2H), 3.10−2.82 (m, 2H), 2.67 (q, 2H), 2.49−2.25 (m, 2H), 1.33 (t, 3H), 1.25 (t, 3H); MS (FD) 441 (M^+). Anal. ($C_{29}H_{31}NO_3$) C, H, N.

***dl*-2-[[2-Methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]-propionic acid methyl ester ((dl)-4y)** (chromatography on silica gel, 20% EtOAc/hexane): yield 74%; ^{1}H NMR ($CDCl_3$) ∂ 7.37−6.84 (m, 7H), 6.50 (s, 1H), 6.41 (d, 1H), 5.26 (s, 2H), 4.94 (q, 1H), 3.75 (s, 3H), 2.34 (s, 3H), 1.71 (d, 3H); MS (FD^+) 323 (M^+).

***dl*-2-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic acid methyl ester ((dl)-4z)** (chromatography on silica gel, 20% EtOAc/hexane): yield 56%; ^{1}H NMR ($CDCl_3$) ∂ 7.35−6.84 (m, 7H), 6.57 (s, 1H), 6.40 (d, 1H), 5.30 (s, 2H), 4.95 (q, 1H), 3.78 (s, 3H), 2.69 (q, 2H), 1.74 (d, 3H), 1.34 (t, 3H); MS (FD^+) 337 (M^+).

2-[[5-Allyl-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]-acetic Acid Ethyl Ester (4u). A solution of 1.0 g (4 mmol) of **3m** in 10 mL of THF and 75 mL of DMF was stirred with 200 mg of NaH (60% in mineral oil; 5 mmol) for 10 min, and then with 0.4 mL (4.6 mmol) of allyl bromide for 2 h. The solution was 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 5−10% Et_2O/hexane to give 4-(allyloxy)-2-ethyl-1-(phenylmethyl)-1*H*-indole. This material was heated at reflux in 20 mL of *N*,*N*-dimethylaniline for 19 h, cooled, diluted with EtOAc, washed with 1 N HCl, H_2O, and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel, eluting with a gradient of 10−40% Et_2O/hexane to give 5-allyl-2-ethyl-4-hydroxy-1-(phenylmethyl)-1*H*-indole (**3u**), 1.0 g (yield 86%). This material (3.4 mmol) was dissolved in 60 mL of DMF and 10 mL of THF, 150 mg of NaH (60% in mineral oil; 3.7 mmol) was added, the mixture was stirred for 15 min, 0.4 mL (3.6 mmol) of ethyl bromoacetate was added, and stirring was continued for an additional 2.5 h. The solution was diluted with water and extracted with EtOAc. The organic phase 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 15−20% Et_2O/hexane, to give 780 mg (yield 61%) of **4u**: ^{1}H NMR ($CDCl_3$) ∂ 7.45−7.30 (m, 3H), 7.25−7.00 (m, 4H), 6.50 (s, 1H), 6.25−6.00 (m, 1H), 5.35 (s, 2H), 5.25−5.10 (m, 2H), 4.95 (s, 2H), 4.45 (q, 2H), 3.75 (d, 2H), 2.80 (q, 2H), 1.45 (t, 6H).

(*R*)-2-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic Acid Methyl Ester ((*R*)-4z). To a solution of 1.0 g (3 mmol) of **3m** in 75 mL of DMF was added 180 mg of NaH (60% in mineral oil; 4.4 mmol), the mixture was stirred for 5 min, and then 0.5 mL (4.7 mmol) of methyl (*S*)-(−)-2-chloropropionate was added. The solution was stirred for 1 h and then diluted with EtOAc and water. 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 1.36 g (yield 100%) of (*R*)-**4z**; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.20−7.10 (m, 3H), 6.95−6.80 (m, 3H), 6.75 (d, 1H), 6.50 (s, 1H), 6.35 (d, 1H), 5.15 (s, 2H), 4.95 (q, 1H), 3.70 (s, 3H), 2.60 (q, 2H), 1.65 (d, 3H), 1.25 (t, 3H).

(*S*)-2-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic Acid Methyl Ester ((*S*)-4z). Using reaction conditions identical to those above, **3m** was reacted with methyl (*R*)-(+)-2-chloropropionate to give a 90% yield of (*S*)-**4z**; oil; ^{1}H NMR data is identical to that given for (*R*)-**4z**.

(*R*)-2-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic Acid Methyl Ester ((*R*)-4z) (alternate preparation). A solution of 450 mg (1.0 mmol) of (*R*,*S*)-**9b** in 5 mL of THF and 5 mL of MeOH was added to a solution of 2 mmol of MeOMgBr (from MeOH and 3 M PhMgBr/Et_2O) in 25 mL of MeOH at 0−5 °C. The solution was stirred, cooled for 20 min, and then diluted with EtOAc and water. 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 15−20% Et_2O/hexane to give (*R*)-**4z**: 240 mg (yield 71%); oil; ^{1}H NMR data is identical to that given above for (*R*)-**4z**.

2-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetamide (4aa). A solution of 560 mg (1.73 mmol) of **4m**, 2 mL of hydrazine, and 10 mL of EtOH was refluxed for 1 h, cooled, diluted with water, and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated at reduced pressure to give 2-[[2-ethyl-1-(phenylmethyl)-**1*H*-**indol-4-yl]oxy]acetic acid hydrazide: 390 mg (yield 70%); mp 159−161 °C; ^{1}H NMR (DMSO-d_6) ∂ 9.34 (br s, 1H), 7.34−6.88 (m, 7H), 6.55 (s, 1H), 6.47 (d, 1H), 5.38 (s, 2H), 4.57 (s, 2H), 4.39 (d, 2H), 2.66 (q, 2H), 1.25 (t, 3H); MS (FD^+) 323 (M^+). A mixture of this material (1.2 mmol), ca. 0.5 g of Raney nickel catalyst, and 10 mL of EtOH was refluxed for 2 h and cooled, and the solution was decanted. The solids were washed with CH_2Cl_2 by decantation, and the combined organics were evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with EtOAc, to give **4aa**: 255 mg (yield 69%); mp 190−192 °C: ^{1}H NMR (DMSO-d_6) ∂ 7.49 (br s, 1H), 7.42 (br s, 1H), 7.33−6.87 (m, 7H), 6.52 (s, 1H), 6.42 (d, 1H), 5.34 (s, 2H), 4.48 (s, 2H), 2.63 (q, 2H), 1.24 (t, 3H); MS (FD^+) 308 (M^+). Anal. ($C_{19}H_{20}N_2O_2$) H, N; C: calcd, 74.01; found, 74.61.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-([1,1′-biphenyl]-3-ylmethyl)-2-methyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5e). A solution of 1.0 g (2.6 mmol) of **4e** in 15 mL of CH_2Cl_2 was stirred for 80 min with 0.23 mL (2.6 mmol) of oxalyl chloride. The solution was saturated with ammonia, evaporated at reduced pressure, and partitioned between EtOAc and water. 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 EtOAc, to give 791 mg of **5e**: yield 82%; mp 175−179 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.72 (br s, 1H), 7.62−7.34 (m, 9H), 7.22 (d, 1H), 7.08 (t, 1H), 6.93 (d, 1H), 6.59 (d, 1H), 5.59 (s, 2H), 4.77 (s, 2H), 3.71 (s, 3H), 2.57 (s, 3H); MS (FD^+) 456 (M^+). Anal. ($C_{27}H_{24}N_2O_5$) C, H, N.

The following compounds were prepared using the above procedure and the indicated purification method.

4-[[3-(2-Amino-1,2-dioxoethyl)-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid ethyl ester (5a) (crystallized from CH_2Cl_2/EtOH): yield 84%; mp 168−170 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.75 (s, 1H), 8.05 (br s, 1H), 7.70 (s, 2H), 7.45 (d, 1H), 7.35−7.15 (m, 5H), 6.85 (dd, 1H), 5.45 (s, 2H), 4.10−3.85 (m, 4H), 2.45 (t, 3H), 2.05−1.90 (m, 3H), 1.15 (t, 3H); MS (FD^+) 408 (M^+). Anal. ($C_{23}H_{24}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5b) (chromatography on silica gel, Et_2O): yield 41%; ^{1}H NMR ($CDCl_3$) ∂ 8.70 (s, 1H), 7.30 (br s, 1H), 7.20−7.10 (m, 3H), 7.05−6.95 (m, 3H), 6.80 (d, 1H), 6.55 (d, 1H), 5.85 (br s, 1H), 5.20 (s, 2H), 4.55 (s, 2H), 1.35 (s, 9H).

2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5c) (crude product filtered): yield 93%; mp 202−215 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.98 (br s, 1H), 7.71 (br s, 2H), 7.40−7.02 (m, 6H), 6.58 (d, 1H), 5.50 (s, 2H), 4.76 (s, 2H), 3.70 (s, 3H), 2.51 (s, 3H); MS (FD) 380 (M^+).

2-[[3-(2-Amino-1,2-dioxoethyl)-1-([1,1′-biphenyl]-2-ylmethyl)-2-methyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5d) (crude product filtered): yield 99%; mp 144−148 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.74 (br s, 1H), 7.63−7.21 (m, 9H), 7.05 (t, 1H), 6.92 (d, 1H), 6.57 (d, 1H), 6.42 (d, 1H), 5.38 (s, 2H), 4.77 (s, 2H), 3.72 (s, 3H), 2.55 (s, 3H); MS (FD^+) 443 (M^+).

2-[[3-(2-Amino-1,2-dioxoethyl)-1-([1,1′-biphenyl]-4-ylmethyl)-2-methyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5f) (crystallized from EtOAc): yield 94%; mp 215−217 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.73 (br s, 1H), 7.67−7.04 (m, 12H), 6.58 (d, 1H), 5.55 (s, 2H), 4.78 (s, 2H), 3.70 (s, 3H), 2.55 (s, 3H); MS (FD^+) 456 (M^+). Anal. ($C_{27}H_{24}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-[(4-fluorophenyl)methyl]-2-methyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5g) (chromatography on silica gel, EtOAc): yield 70%; mp 178−180 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.72 (br s, 1H), 7.39 (br s, 1H), 7.26−7.02 (m, 6H), 6.57 (d, 1H), 5.49 (s, 2H), 4.76 (s, 2H), 3.70 (s, 3H), 2.49 (s, 3H); MS (FD^+) 398 (M^+). Anal. ($C_{21}H_{19}N_2O_5$) H, N; C: calcd, 63.31; found, 62.31; residue 0.85%.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-[(2,6-dichlorophenyl)methyl]-2-methyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5h) (chromatography on silica gel, EtOAc): yield 88%; mp 200−202 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.68 (br s, 1H), 7.59−7.41 (m, 3H), 7.35 (br s, 1H), 6.97 (t, 1H), 6.79 (d, 1H), 6.51 (d, 1H), 5.67 (s, 2H), 4.73 (s, 2H), 3.68 (s, 3H), 2.50 (s, 3H); MS (FD$^+$) 448 (M − 1, 100), 450 (M + 1, 90). Anal. ($C_{21}H_{18}Cl_2N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-[(1-naphthyl)methyl]-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5i) (chromatography on silica gel, EtOAc): yield 95%; mp 188−190 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.34 (d, 1H), 8.04 (d, 1H), 7.86 (d, 1H), 7.79 (br s, 1H), 7.78−7.61 (m, 3H), 7.45 (br s, 1H), 7.36 (t, 1H), 7.16−7.04 (m, 2H), 6.66−6.60 (m, 2H), 6.28 (d, 1H), 6.05 (s, 2H), 4.84 (s, 2H), 3.76 (s, 3H), 2.53 (s, 3H); MS (FD$^+$) 430 (M$^+$). Anal. ($C_{25}H_{22}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-[(2-chlorophenyl)methyl]-2-methyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5j) (chromatography on silica gel, EtOAc): yield 71%; mp 198−200 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.44 (d, 1H), 7.36−7.06 (m, 3H), 6.86 (d, 1H), 6.63 (br s, 1H), 6.57 (d, 1H), 6.41 (d, 1H), 5.57 (br s, 1H), 5.40 (s, 2H), 4.78 (s, 2H), 3.80 (s, 3H), 2.55 (s, 3H); MS (FD$^+$) 414 (M − 1, 100), 416 (M + 1, 57). Anal. ($C_{21}H_{19}ClN_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-[(2-methylphenyl)methyl]-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5k) (chromatography on silica gel, EtOAc): yield 89%; mp 212−213 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.36−7.00 (m, 4H), 6.84 (d, 1H), 6.61 (br s, 1H), 6.58 (d, 1H), 6.38 (d, 1H), 5.49 (br s, 1H), 5.27 (s, 2H), 4.79 (s, 2H), 3.78 (s, 3H), 2.51 (s, 3H), 2.43 (s, 3H); MS (FD$^+$) 394 (M$^+$). Anal. ($C_{22}H_{22}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-*n*-octyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5l) (chromatography on silica gel, EtOAc): yield 77%; mp 143−144 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.14 (t, 1H), 6.98 (d, 1H), 6.57 (br s, 1H), 6.55 (d, 1H), 5.53 (br s, 1H), 4.74 (s, 2H), 4.07 (t, 2H), 3.75 (s, 3H), 2.59 (s, 3H), 1.77 (br t, 2H), 1.49−1.23 (m, 10H), 0.89 (t, 3H); MS (FD$^+$) 402 (M$^+$). Anal. ($C_{22}H_{30}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5m) (crystallized from EtOAc): yield 96%; mp 172−187 °C; ^{1}H NMR-(DMSO-d_6) ∂ 7.72(br s, 1H), 7.45−7.00(m, 8H), 6.57(d, 1H), 5.51(s, 2H), 4.76(s, 2H), 3.68(s, 3H), 2.90(q, 2H), 1.08(t, 3H); MS(FD$^+$) 394(M$^+$).

2-[[3-(2-Amino-1,2-dioxoethyl)-1-([1,1′-biphenyl]-2-ylmethyl)-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5n) (chromatography on silica gel, EtOAc): yield 92%; ^{1}H NMR (DMSO-d_6) ∂ 7.74 (br s, 1H), 7.66−7.19 (m, 9H), 7.07 (t, 1H), 6.96 (d, 1H), 6.57 (d, 1H), 6.49 (d, 1H), 5.37 (s, 2H), 4.76 (s, 2H), 3.71 (s, 3H), 2.70 (q, 2H), 0.92 (t, 3H); MS (FD) 470 (M$^+$).

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-[[2-(phenylmethyl)phenyl]methyl]-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5o) (crystallized from EtOAc): yield 59%; mp 161−163 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.43−6.98 (m, 10H), 6.55 (t, 2H), 6.38 (d, 1H), 5.45 (br s, 1H), 4.74 (s, 2H), 4.18 (s, 2H), 3.78 (s, 3H), 2.64 (q, 2H), 1.00 (t, 3H); MS (FD$^+$) 484 (M$^+$). Anal. ($C_{29}H_{28}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5p) (crystallized from EtOAc): yield 86%; mp 173−185 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.73 (br s, 1H), 7.45−6.56 (m, 8H), 5.55 (s, 2H), 4.77 (s, 2H), 3.72 (s, 3H), 2.90 (q, 2H), 1.08 (t, 3H); MS (FD$^+$) 428 (M − 1, 100), 430 (M + 1, 40).

2-[[3-(2-Amino-1,2-dioxoethyl)-1-benzoyl-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid *tert*-butyl ester (5q) (chromatography on silica gel, 50% EtOAc/hexane): yield 32%; mp 152−155 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.82 (d, 1H), 7.70 (t, 1H), 7.54 (t, 2H), 7.34−7.24 (m, 1H), 6.94 (t, 1H), 6.77 (br s, 1H), 6.52 (d, 1H), 6.42 (d, 1H), 5.49 (br s, 1H), 4.59 (s, 2H), 3.01 (q, 2H), 1.48 (s, 9H), 1.26 (t, 3H); MS (FD) 450 (M$^+$). Anal. ($C_{25}H_{26}N_2O_6$) H, N; C: calcd, 66.66; found, 69.84.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-([1,1′-biphenyl]-2-ylmethyl)-2-propyl-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5r) (chromatography on silica gel, EtOAc): yield 70%; foam; ^{1}H NMR ($CDCl_3$) ∂ 7.58−7.21 (m, 9H), 7.07 (t, 1H), 6.80 (d, 1H), 6.63 (d, 1H), 6.53 (d, 1H), 5.49 (br s, 1H), 5.21 (s, 2H), 4.74 (s, 2H), 3.79 (s, 3H), 2.74 (t, 2H), 1.47 (q, 2H), 0.89 (t, 3H); MS (FD) 484 (M$^+$).

2-[[3-(2-Amino-1,2-dioxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid methyl ester (5s) (crude product filtered): yield 73%; ^{1}H NMR (DMSO-d_6) ∂ 7.76 (br s, 1H), 7.47 (br s, 1H), 7.37−7.00 (m, 7H), 6.57−6.41 (m, 1H), 5.59 (s, 2H), 4.74 (s, 2H), 3.69 (s, 3H), 1.89−1.74 (m, 1H), 1.04−0.90 (m, 2H), 0.53−0.43 (m, 2H); MS (FD) 406 (M$^+$).

2-[[3-(2-Amino-1,2-dioxoethyl)-1-([1,1′-biphenyl]-2-ylmethyl)-2-cyclopropyl-1H-indol-4-yl]oxy]acetic acid methyl ester (5t) (chromatography on silica gel, EtOAc): yield 59%; ^{1}H NMR (DMSO-d_6) ∂ 7.75 (br s, 1H), 7.59−7.20 (m, 9H), 7.07 (t, 1H), 6.96 (d, 1H), 6.51 (d, 1H), 6.46 (d, 1H), 5.48 (s, 2H), 4.74 (s, 2H), 3.70 (s, 3H), 1.63−1.49 (m, 1H), 0.74−0.67 (m, 2H), 0.32−0.25 (m, 2H); MS (FD) 482 (M$^+$).

2-[[5-Allyl-3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid ethyl ester (5u) (chromatography on silica gel, gradient, 20−50% Et$_2$O/hexane): yield 73%; mp 149−151 °C; MS (FD$^+$) 448 (M$^+$); Anal. ($C_{26}H_{28}N_2O_5$) C, H, N.

4-[[3-(2-Amino-1,2-dioxoethyl)-1-([1,1′-biphenyl]-2-ylmethyl)-2-methyl-1*H*-indol-4-yl]oxy]butanoic acid ethyl ester (5v) (chromatography on silica gel, EtOAc): yield 71%; ^{1}H NMR ($CDCl_3$) ∂ 7.57−6.53 (m, 13H), 5.72 (br s, 1H), 5.18 (s, 2H), 4.20−4.07 (m, 4H), 2.57 (t, 2H), 2.39 (s, 3H), 2.25−2.10 (m, 2H), 1.29 (t, 3H); MS (FD) 498 (M$^+$).

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]-2-methylpropionic acid methyl ester (5w) (chromatography on silica gel, EtOAc): yield 48%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.38−6.97 (m, 6H), 6.82 (d, 2H), 6.36 (d, 1H), 5.53 (br s, 1H), 5.34 (s, 2H), 4.27−4.08 (m, 4H), 2.90 (q, 2H), 1.74 (s, 6H), 1.31−1.16 (m, 5H); MS (FD$^+$) 436 (M$^+$). Anal. ($C_{25}H_{28}N_2O_5$) H; C: calcd, 68.79; found, 67.97; N: calcd, 6.42; found, 5.99.

***dl*-2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]-4-phenylbutanoic acid methyl ester ((*dl*)-5x)** (crude product): yield 100%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.41−6.92 (m, 11H), 6.83 (d, 1H), 6.61 (br s, 1H), 6.44 (d, 1H), 5.55 (br s, 1H), 5.34 (s, 2H), 4.84−4.71 (m, 1H), 4.15 (q, 2H), 3.00−2.74 (m, 4H), 2.49−2.33 (m, 2H), 1.34−1.07 (m, 6H); MS (FD) 512 (M$^+$). Anal. ($C_{31}H_{32}N_2O_5$) H; C: calcd, 72.64; found, 70.15; N: calcd, 5.47; found, 6.27.

***(dl)*-2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic acid methyl ester ((*dl*)-5y)** (chromatography on silica gel, EtOAc): yield 90%; mp 175 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.79 (br s, 1H), 7.40 (br s, 1H), 7.38−7.00 (m, 7H), 6.42 (d, 1H), 5.49 (s, 2H), 4.70 (q, 1H), 3.63 (s, 3H), 2.46 (s, 3H), 1.58 (d, 3H); MS (FD$^+$) 394 (M$^+$). Anal. ($C_{22}H_{22}N_2O_5$) C, H, N.

***dl*-2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic acid methyl ester ((*dl*)-5z)** (chromatography on silica gel, EtOAc): yield 94%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.37−7.00 (m, 6H), 6.85 (d, 1H), 6.66 (br s, 1H), 6.48 (d, 1H), 5.49 (br s, 1H), 5.35 (s, 2H), 4.92 (q, 1H), 3.74 (s, 3H), 2.92 (q, 2H), 1.71 (d, 3H), 1.23 (t, 3H); MS (FD$^+$) 408 (M$^+$). Anal. ($C_{23}H_{24}N_2O_5$) C, H, N.

***(R)*-2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic acid methyl ester ((*R*)-5z)** (from oxazolidinone route) (crystallized from Et$_2$O/hexane): yield 61%; mp 153−155 °C; MS (FD) 408 (M$^+$); Anal. ($C_{23}H_{24}N_2O_5 \cdot 0.3Et_2O$) C, H, N.

***(R)*-2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic acid methyl ester ((*R*)-5z)** (from methyl chloropropionate route) (crystallized from Et$_2$O/hexane): yield 88%; mp 153−155 °C; MS (FD) 408 (M$^+$); optical rotation at 589 nm −13.3° (MeOH). Anal. ($C_{23}H_{24}N_2O_5$) C, H, N.

***(S)*-2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic acid methyl ester ((*S*)-5z)** (crystallized from Et$_2$O/hexane): yield 81%; mp 157−159 °C; MS (FD) 408 (M$^+$); optical rotation at 589 nm +13.9° (MeOH) Anal. ($C_{23}H_{24}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetamide (5aa) (crude product filtered): yield 70%; mp >230 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.07 (br s, 1H), 7.70 (br s, 1H), 7.51 (br s, 1H), 7.39 (br s, 1H), 7.36−

7.08 (m, 5H), 7.03 (d, 2H), 6.54 (dd, 1H), 5.55 (s, 2H), 4.47 (s, 2H), 2.94 (q, 2H), 1.08 (t, 3H); MS (FD^+) 394 (M^+). Anal. ($C_{21}H_{21}N_3O_4$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-5-propyl-1*H*-indol-4-yl]oxy]acetic Acid Ethyl Ester (5ab). A mixture of 380 mg (0.85 mmol) of **5u**, 0.2 g of 10% Pd/C, 50 mL of THF, and 50 mL of EtOH was stirred under 1 atm of H_2 for 6.5 h, filtered, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with Et_2O, to give **5ab**: 255 mg (yield 67%); mp 152−153 °C; ^1H NMR ($CDCl_3$) ∂ 7.20−7.05 (m, 3H), 6.95−6.80 (m, 3H), 6.75 (d, 1H), 6.65 (br s, 1H), 6.15 (br s, 1H), 5.15 (s, 1H), 4.40 (s, 2H), 4.05 (q, 2H), 2.80 (q, 2H), 2.55 (t, 2H), 1.75−1.55 (m, 2H), 1.05 (t, 6H), 0.85 (t, 3H); MS (FD^+) 420 (M^+). Anal. ($C_{26}H_{30}N_2O_5$) C, H, N.

4-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic Acid *tert*-Butyl Ester (5ac). A solution of 4.1 g (23.4 mmol) of 2-ethyl-5-methoxyindole (**1g**) in 200 mL of CH_2Cl_2 was stirred with 2.2 mL (25 mmol) of oxalyl chloride for 10 min and then poured into 500 mL of THF saturated with ammonia at 0−5 °C. The mixture was extracted with CH_2Cl_2/2-propanol (3:1). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated at reduced pressure to give 3.0 g (yield 52%) of 3-(2-amino-1,2-dioxoethyl)-2-ethyl-5-methoxy-1*H*-indole (**7**). This material (12.2 mmol) was dissolved in 25 mL of THF and 125 mL of DMSO and stirred with 520 mg of NaH (60% in mineral oil; 13 mmol) for 15 min, and then with 1.6 mL (13 mmol) of benzyl bromide for 45 min. The solution was diluted with water and extracted with EtOAc. The organic phase was washed with water, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 0−4% MeOH/CH_2Cl_2, to give 1.6 g (yield 40%) of 3-(2-amino-1,2-dioxoethyl)-2-ethyl-5-methoxy-1-(phenylmethyl)-1*H*-indole. A solution of 1.3 g (4.0 mmol) of this material in 100 mL of CH_2Cl_2 was stirred with 16 mL of 1 M BBr_3/CH_2Cl_2 for 1.5 h. The mixture was decomposed with ice/water and the organic layer 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 1−3% MeOH/CH_2Cl_2, to give 440 mg of 3-(2-amino-1,2-dioxoethyl)-2-ethyl-5-hydroxy-1-(phenylmethyl)-1*H*-indole. A solution of 355 mg (1.1 mmol) of this material in 10 mL of THF and 40 mL of DMF was stirred with 50 mg of NaH (60% in mineral oil; 1.2 mmol) for 10 min, and then with 290 mg (1.3 mmol) of *tert*-butyl 4-bromobutyrate for 5 h. The solution was 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 0−2% MeOH/CH_2Cl_2, to give **5ac**: 460 mg (yield 90%); mp 101−104 °C: ^1H NMR ($CDCl_3$) ∂ 7.65 (d, 1H), 7.30−7.20 (m, 3H), 7.05−6.95 (m, 4H), 6.75 (dd, 1H), 6.50 (br s, 1H), 5.25 (s, 2H), 4.00 (t, 2H), 3.05 (q, 2H), 2.40 (t, 2H), 2.10−1.95 (m, 2H), 1.45 (s, 9H), 1.15 (t, 3H); MS (FD^+) 464 (M^+). Anal. ($C_{27}H_{32}N_2O_5$) H, N; C: calcd, 69.81; found, 70.54.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-(phenylsulfonyl)-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid *tert*-Butyl Ester (5ad). A solution of 148 mg (0.33 mmol) of **5q**, 2 mL of 1 N NaOH, and 9 mL of MeOH was stirred at room temperature for 2 min and then diluted with EtOAc and water. The organic phase was washed with brine, dried over $MgSO_4$, evaporated at reduced pressure, and then crystallized from MeOH to give 91 mg (yield 80%) of **8**. This material (82 mg, 0.24 mmol) was dissolved in 5 mL of DMF, treated with 10 mg (0.24 mmol) of 60% NaH/mineral oil, and stirred for 1.5 h. Benzenesulfonyl chloride (0.3 mL, 0.24 mmol) was added, and the solution was stirred for 20 h. The solution was diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 50% EtOAc/hexane and then 66% EtOAc/hexane, to give 35 mg (yield 30%) of **5ad**: ^1H NMR ($CDCl_3$) ∂ 7.88−7.80 (m, 3H), 7.58 (t, 1H), 7.48 (t, 2H), 7.23 (t, 1H), 6.80 (br s, 1H), 6.58 (d, 1H), 5.72 (br s, 1H), 4.51 (s, 2H), 3.09 (q, 2H), 1.44 (s, 9H), 1.35 (t, 3H); MS (FD^+) 486 (M^+).

2-[[3-(2-Amino-1,2-dioxoethyl)-1-([1,1′-biphenyl]-3-ylmethyl)-2-methyl-1*H*-indol-4-yl]oxy]acetic Acid (6e). A mixture of 956 mg (2.1 mmol) of **5b**, 10 mL of 1 N NaOH, and 30 mL of MeOH was refluxed for 40 min, cooled, concentrated, and stirred with EtOAc and water. Filtration afforded the sodium salt of **6e**: 403 mg (yield 41%); mp >250 °C; ^1H NMR (DMSO-d_6) ∂ 8.47 (br s, 1H), 7.64−7.32 (m, 8H), 7.28 (br s, 1H), 7.07 (d, 1H), 7.01 (t, 1H), 6.90 (d, 1H), 6.48 (d, 1H), 5.56 (s, 2H), 4.16 (s, 2H), 2.52 (s, 3H); MS (FAB) 465.2 (M + Na + 1)$^+$. Anal. ($C_{26}H_{21}N_2O_5Na$) C, H, N. The filtrate was acidified and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, concentrated at reduced pressure, and filtered to give **6e**: 346 mg (yield 37%); mp 236−238 °C: ^1H NMR (DMSO-d_6) ∂ 12.88 (br s, 1H), 7.77 (br s, 1H), 7.64−7.32 (m, 9H), 7.22 (d, 1H), 7.09 (t, 1H), 6.93 (d, 1H), 6.56 (d, 1H), 5.59 (s, 2H), 4.67 (s, 2H), 2.58 (s, 3H); MS (FD) 443 (M^+). Anal. ($C_{26}H_{22}N_2O_5$) C, H, N.

The following compounds were prepared using the above procedure.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid (6c): yield 69%; mp 218−220 °C; ^1H NMR (DMSO-d_6) ∂ 12.88 (br s, 1H), 7.75 (br s, 1H), 7.43 (br s, 1H), 7.34−7.07 (m, 7H), 6.55 (d, 1H), 5.50 (s, 2H), 4.66 (s, 2H), 2.51 (s, 3H); MS (FD^+) 366 (M^+). Anal. ($C_{20}H_{18}N_2O_5$) H; C: calcd, 65.57; found, 63.31; N: calcd, 7.65; found, 6.91.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-[(1,1′-biphenyl)-2-ylmethyl]-2-methyl-1*H*-indol-4-yl]oxy]acetic acid (6d) (sodium salt): yield 69%; mp >255 °C; ^1H NMR (DMSO-d_6) ∂ 8.33 (br s, 1H), 7.66−7.21 (m, 9H), 6.97 (t, 1H), 6.76 (d, 1H), 6.46 (d, 1H), 6.40 (d, 1H), 5.33 (s, 2H), 4.16 (s, 2H), 2.32 (s, 3H); MS (FAB) 465.2 (M + Na + 1)$^+$. Anal. ($C_{26}H_{21}N_2O_5Na$) C, H, N.

6d: yield 15%; mp 228−231 °C; ^1H NMR (DMSO-d_6) ∂ 7.80 (br s, 1H), 7.72−7.25 (m, 9H), 7.07 (t, 1H), 6.93 (d, 1H), 6.57 (d, 1H), 6.43 (d, 1H), 5.39 (s, 2H), 4.68 (s, 2H), 2.38 (s, 3H); MS (FD^+) 442 (M^+). Anal. ($C_{26}H_{22}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-([1,1′-biphenyl]-4-ylmethyl)-2-methyl-1*H*-indol-4-yl]oxy]acetic acid (6f) (sodium salt): yield 74%; mp >250 °C; ^1H NMR (DMSO-d_6) ∂ 8.40 (br s, 1H), 7.66−7.32 (m, 7H), 7.28 (br s, 1H), 7.14 (d, 1H), 7.08−6.98 (m, 2H), 6.48 (dd, 1H), 5.52 (s, 2H), 4.17 (s, 2H), 2.47 (s, 3H); MS (FAB) 465.2 (M + Na + 1)$^+$. Anal. ($C_{26}H_{21}N_2O_5Na$) C, H, N.

6f: yield 4%; mp 228−232 °C; ^1H NMR (DMSO-d_6) ∂ 12.90 (br s, 1H), 7.78 (br s, 1H), 7.66−7.06 (m, 12H), 6.56 (d, 1H), 5.56 (s, 2H), 4.67 (s, 2H), 2.56 (s, 3H); MS (FD) 443 (M^+). Anal. ($C_{26}H_{22}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-[(4-fluorophenyl)methyl]-2-methyl-1*H*-indol-4-yl]oxy]acetic acid (6g): yield 81%; mp 244−247 °C; ^1H NMR (DMSO-d_6) ∂ 12.88 (br s, 1H), 7.75 (br s, 1H), 7.43 (br s, 1H), 7.20−7.04 (m, 6H), 6.55 (d, 1H), 5.50 (s, 2H), 4.66 (s, 2H), 2.49 (s, 3H); MS (FD) 384 (M^+). Anal. ($C_{20}H_{17}FN_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-[(2,6-dichlorophenyl)methyl]-2-methyl-1*H*-indol-4-yl]oxy]acetic acid (6h): yield 86%; mp 236−239 °C; ^1H NMR (DMSO-d_6) ∂ 12.90 (br s, 1H), 7.74 (br s, 1H), 7.60−7.40 (m, 4H), 7.00 (t, 1H), 6.81 (d, 1H), 6.51 (d, 1H), 5.72 (s, 2H), 4.65 (s, 2H), 2.50 (s, 3H); MS (FD^+) 434 (M − 1, 100), 436 (M + 1, 70). Anal. ($C_{20}H_{16}Cl_2N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-[(1-naphthyl)methyl]-1*H*-indol-4-yl]oxy]acetic acid (6i): yield 75%; mp 233−235 °C; ^1H NMR (DMSO-d_6) ∂ 12.92 (br s, 1H), 8.32 (d, 1H), 8.02 (d, 1H), 7.85 (d, 1H), 7.80 (br s, 1H), 7.74-7.60 (m, 2H), 7.48 (br s, 1H), 7.32 (t, 1H), 7.02 (d, 2H), 6.57 (t, 1H), 6.25 (d, 1H), 6.00 (s, 2H), 4.69 (s, 2H), 2.46 (s, 3H); MS (FD^+) 416 (M^+). Anal. ($C_{24}H_{20}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-[(2-chlorophenyl)methyl]-2-methyl-1*H*-indol-4-yl]oxy]acetic acid (6j): yield 79%; mp 223−226 °C; ^1H NMR (DMSO-d_6) ∂ 12.90 (br s, 1H), 7.77 (br s, 1H), 7.56 (d, 1H), 7.45 (br s, 1H), 7.32 (t, 1H), 7.21 (t, 1H), 7.10−7.00 (m, 2H), 6.56 (d, 1H), 6.32 (d, 1H), 5.54 (s, 2H), 4.66 (s, 2H), 2.46 (s, 3H); MS (FD^+) 400 (M − 1, 100), 402 (M + 1, 35). Anal. ($C_{20}H_{17}ClN_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-[(2-methylphenyl)methyl]-1*H*-indol-4-yl]oxy]acetic acid (6k): yield 57%;

mp 235−238 °C; ^{1}H NMR (DMSO-d_6) ∂ 12.90 (br s, 1H), 7.77 (br s, 1H), 7.45 (br s, 1H), 7.25 (d, 1H), 7.15 (t, 1H), 7.10−6.97 (m, 3H), 6.56 (dd, 1H), 6.06 (d, 1H), 5.45 (s, 2H), 4.68 (s, 2H), 2.44 (s, 6H); MS (FD$^+$) 380 (M$^+$). Anal. ($C_{21}H_{20}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-*n*-octyl-1*H*-indol-4-yl]oxy]acetic acid (6l): yield 82%; mp 195−196 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.74 (br s, 1H), 7.41 (br s, 1H), 7.22−7.08 (m, 2H), 6.56 (d, 1H), 4.66 (s, 2H), 4.18 (t, 2H), 2.57 (s, 3H), 1.75−1.62 (m, 2H), 1,41−1.18 (m, 10H), 0.84 (t, 3H); MS (FD$^+$) 388 (M$^+$). Anal. ($C_{21}H_{28}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid (6m): yield 74%; mp 230−234 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.80 (br s, 1H), 7.43 (br s, 1H), 7.38−7.00 (m, 7H), 6.55 (dd, 1H), 5.52 (s, 2H), 4.67 (s, 2H), 2.91 (q, 2H), 1.09 (t, 3H); MS (FD) 380 (M$^+$). Anal. ($C_{21}H_{20}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-([1,1′-biphenyl]-2-ylmethyl)-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid (6n): yield 59%; mp 211−214 °C; ^{1}H NMR (DMSO-d_6) ∂ 12.90 (br s, 1H), 7.74 (br s, 1H), 7.58−7.46 (m, 5H), 7.41 (br s, 1H), 7.36−7.20 (m, 3H), 7.05 (t, 1H), 6.93 (d, 1H), 6.52 (dd, 1H), 5.37 (s, 2H), 4.65 (s, 2H), 2.71 (q, 2H), 0.93 (t, 3H); MS (FD) 456 (M$^+$). Anal. ($C_{27}H_{24}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-[(2-(phenylmethyl)phenyl]methyl]-1*H*-indol-4-yl]oxy]acetic acid (6o): yield 86%; mp 245−246 °C; ^{1}H NMR (DMSO-d_6) ∂ 12.92 (br s, 1H), 7.75 (br s, 1H), 7.46−7.20 (m, 8H), 7.07 (t, 1H), 6.98 (t, 1H), 6.67 (d, 1H), 6.52 (d, 1H), 6.04 (d, 1H), 5.37 (s, 2H), 4.67 (s, 2H), 4.24 (s, 2H), 2.60 (q, 2H), 0.90 (t, 3H); MS (FD$^+$) 470 (M$^+$). Anal. ($C_{28}H_{26}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-[(3-chlorophenyl)methyl]-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid (6p) (sodium salt): yield 61%; mp >250 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.51 (br s, 1H), 7.37−7.30 (m, 2H), 7.27 (br s, 1H), 7.14 (s, 1H), 7.05−6.85 (m, 3H), 6.48 (d, 1H), 5.51 (s, 2H), 4.14 (s, 2H), 4.84 (q, 2H), 1.06 (t, 3H); MS (FAB) 437.1 (M + Na)$^+$. Anal. ($C_{21}H_{18}ClN_2O_5Na$) Calcd. C, 57.74; H, 4.15; N, 6.41. Found: C, 58.36; H, 4.61; N, 5.57.

6p: yield 14%; mp 210−213 °C; ^{1}H NMR (DMSO-d_6) ∂ 12.90 (br s, 1H), 7.77 (br s, 1H), 7.44 (br s, 1H), 7.36−7.32 (m, 2H), 7.26 (s, 1H), 7.09 (d, 2H), 6.94−6.87 (m, 1H), 6.56 (t, 1H), 5.55 (s, 2H), 4.69 (s, 2H), 2.90 (q, 2H), 1.67 (t, 3H); MS (FD$^+$) 414 (M − 1, 100), 416 (M + 1, 30). Anal. ($C_{21}H_{19}ClN_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-benzoyl-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid (6q): yield 63%; mp 194−196 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.97 (br s, 1H), 7.86−7.61 (m, 6H), 7.01 (t, 1H), 6.64 (d, 1H), 6.34 (d, 1H), 4.70 (s, 2H), 2.82 (q, 2H), 1.17 (t, 3H); MS (FD$^+$) 394 (M$^+$). Anal. ($C_{21}H_{18}N_2O_6$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-([1,1′-biphenyl]-2-ylmethyl)-2-propyl-1*H*-indol-4-yl]oxy]acetic acid (6r): yield 88%; foam; ^{1}H NMR (DMSO-d_6) ∂ 12.87 (br s, 1H), 7.74 (br s, 1H), 7.60−7.45 (m, 4H), 7.41 (br s, 1H), 7.36−7.20 (m, 4H), 7.07 (t, 1H), 6.96 (d, 1H), 6.52 (t, 2H), 5.38 (s, 2H), 4.65 (s, 2H), 2.65 (br t, 2H), 1.32 (br q, 2H), 0.77 (t, 3H); MS (FD$^+$) 470 (M$^+$). Anal. ($C_{28}H_{26}N_2O_5$) H; C: calcd, 71.47; found, 69.58; N: calcd, 5.95; found, 5.53.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-cyclopropyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid (6s): yield 80%; mp 246−249 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.81 (br s, 1H), 7.51 (br s, 1H), 7.39−7.02 (m, 7H), 6.59−6.48 (m, 1H), 5.59 (s, 2H), 4.65 (s, 2H), 1.90−1.75 (m, 1H), 1.08−0.90 (m, 2H), 0.51−0.43 (m, 2H); MS (FD) 392 (M$^+$). Anal. ($C_{22}H_{20}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-([1,1′-biphenyl]-2-ylmethyl)-2-cyclopropyl-1*H*-indol-4-yl]oxy]acetic acid (6t): yield 62%; mp 172−174 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.76 (br s, 1H), 7.59−7.19 (m, 9H), 7.07 (t, 1H), 6.96 (d, 1H), 6.48 (t, 2H), 5.49 (s, 2H), 4.65 (s, 2H), 1.59−1.49 (m, 1H), 0.75−0.66 (m, 2H), 0.33−0.25 (m, 2H); MS (FD) 468 (M$^+$). Anal. ($C_{28}H_{24}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-5-allyl-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetic acid (6u): yield 90%; mp 165 °C; MS (FD$^+$) 420 (M$^+$). Anal. ($C_{24}H_{24}N_2O_5$) C, H; N: calcd, 6.66; found 6.12.

4-[[3-(2-Amino-1,2-dioxoethyl)-1-([1,1′-biphenyl]-2-ylmethyl)-2-methyl-1*H*-indol-4-yl]oxy]butanoic acid (6v): yield 28%; mp 205−208 °C; ^{1}H NMR (DMSO-d_6) ∂ 12.08 (br s, 1H), 7.77 (br s, 1H), 7.60−7.20 (m, 9H), 7.04 (t, 1H), 6.85 (d, 1H), 6.64 (d, 1H), 6.40 (d, 1H), 5.34 (s, 2H), 4.04 (t, 2H), 2.41 (t, 2H), 2.32 (s, 3H), 2.06−1.95 (m, 2H); MS (FD) 468 (M$^+$). Anal. ($C_{28}H_{26}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]-2-methylpropionic acid (6w): yield 13%; mp 114−116 °C; ^{1}H NMR (DMSO-d_6) ∂ 12.87 (br s, 1H), 7.86 (br s, 1H), 7.56 (br s, 1H), 7.36−6.96 (m, 7H), 7.32 (dd, 1H), 5.50 (s, 2H), 2.82 (q, 2H), 1.61 (s, 6H), 1.07 (t, 3H); MS (FD$^+$) 408 (M$^+$). Anal. ($C_{23}H_{24}N_2O_5$) C, H, N.

***dl*-2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]-4-phenylbutanoic acid (6x)**: yield 51%; mp 180−182 °C; ^{1}H NMR (DMSO-d_6) ∂ 12.70 (br s, 1H), 8.04 (br s, 1H), 7.64 (br s, 1H), 7.37−7.00 (m, 7H), 6.40 (d, 1H), 5.53 (s, 2H), 4.65 (dd, 1H), 3.96−3.78 (m, 4H), 2.40−2.36 (m, 1H), 2.20−2.04 (m, 1H), 1.10 (t, 3H); MS (FD) 484 (M$^+$). Anal. ($C_{29}H_{28}N_2O_5$) C, H, N.

***dl*-2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic acid ((*dl*)-6y)**: yield 50%; mp 201−204 °C; ^{1}H NMR (DMSO-d_6) ∂ 12.72 (br s, 1H), 7.89 (br s, 1H), 7.53 (br s, 1H), 7.36−7.00 (m, 7H), 6.44 (d, 1H), 5.50 (s, 2H), 4.84 (q, 1H), 2.48 (s, 3H), 1.37 (d, 3H); MS (FD) 380 (M$^+$). Anal. ($C_{21}H_{20}N_2O_5$) H, N; C: calcd, 66.31; found, 65.63.

***dl*-2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic acid ((*dl*)-6z)**: yield 56%; mp 185−187 °C; ^{1}H NMR (DMSO-d_6) ∂ 12.73 (br s, 1H), 7.90 (br s, 1H), 7.52 (br s, 1H), 7.38−7.00 (m, 7H), 6.48−6.40 (m, 1H), 5.51 (s, 2H), 4.84 (q, 1H), 2.96−2.80 (m, 2H), 1.58 (d, 3H), 1.08 (t, 3H); MS (FD$^+$) 394 (M$^+$). Anal. ($C_{22}H_{22}N_2O_5$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-5-propyl-1*H*-indol-4-yl]oxy]acetic acid (6ab): yield 56%; mp 138 °C; MS (FD$^+$) 422 (M$^+$). Anal. ($C_{24}H_{26}N_2O_5 \cdot 1.2\ H_2O$) C, H, N.

4-[[3-(2-Amino-1,2-dioxoethyl)-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic Acid (6a). A solution of 450 mg (1.1 mmol) of compound **5a** in 50 mL of THF and 50 mL of 5 N HCl was stirred for 16h. and then 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 2%MeOH/CH_2Cl_2, to give recovered **5a**, 110 mg, and then eluting with EtOAc to give **6a**: 190 mg (yield 46%); mp 193−195 °C: ^{1}H NMR (DMSO-d_6) ∂ 12.05 (br s, 1H), 8.80 (s, 1H), 8.05 (br s, 1H), 7.70 (d, 1H), 7.40 (d, 1H), 7.30-7.15 (m, 5H), 6.85 (dd, 1H), 5.70 (s, 1H), 5.45 (s, 2H), 3.95 (t, 2H), 2.35 (t, 2H), 1.95−1.85 (m, 2H); MS (FD$^+$) 380 (M$^+$). Anal. ($C_{21}H_{20}N_2O_5$) H; C: calcd, 66.31; found, 60.82; N: calcd, 7.36; found, 6.64.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]acetic Acid (6b). A solution of 180 mg (0.44 mmol) of **5b** in 30 mL of CH_2Cl_2 and 5 mL of TFA was stirred for 1 h and evaporated at reduced pressure, and the residue was crystallized with EtOH/Et_2O to give **6b**: 155 mg (yield 100); mp 225−227 °C; MS (FD) 352 (M$^+$). Anal. ($C_{19}H_{16}N_2O_5$) C, H, N.

The following compounds were prepared utilizing the above procedure.

4-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]oxy]butanoic acid (6ac): yield 64%; mp 173−175 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.15 (s, 1H), 7.75 (s, 1H), 7.50 (d, 1H), 7.35 (d, 1H), 7.35−7.15 (m, 3H), 7.05−6.90 (m, 2H), 6.80 (dd, 1H), 5.45 (s, 2H), 3.95 (t, 2H), 3.00 (q, 2H), 2.35 (t, 2H), 2.05−1.85 (m, 2H), 1.05 (t, 3H); MS (FD$^+$) 408 (M$^+$). Anal. ($C_{23}H_{24}N_2O_5 \cdot 0.3H_2O$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-1-(phenylsulfonyl)-2-ethyl-1*H*-indol-4-yl]oxy]acetic acid (6ad): yield 40%; mp 202−204 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.98 (d, 3H), 7.82−7.64 (m, 5H), 7.28 (t, 1H), 6.75 (d, 1H), 4.66 (s, 2H), 3.04 (q, 2H), 1.26 (t, 3H); MS (FD$^+$) 430 (M$^+$). Anal. ($C_{20}H_{18}N_2O_7S$) H, N; C: calcd, 55.81; found, 56.96.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1*H*-indol-4-yl]-oxy]acetic acid (6ae): yield 58%; mp 244−246 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.76 (br s, 1H), 7.40 (br s, 1H), 7.09−6.98 (m, 2H), 6.49 (dd, 1H), 4.64 (s, 2H), 2.89 (q, 2H), 1.26 (t, 3H); MS (FD$^+$) 290 (M$^+$). Anal. ($C_{14}H_{14}N_2O_5$) C, H, N.

Preparation of (S)-*N*-((S)-2-bromopropionyl)-4-(phenylmethyl)-2-oxazolidinone (A) and (S)-*N*-((R)-2-bromopropionyl)-4-(phenylmethyl)-2-oxazolidinone (B). To 1.8 g (10.2 mmol) of (*S*)-(−)-4-benzyl-2-oxazolidine in 150 mL of THF at −75 °C was added 6.4 mL of *n*-butyllithium (1.6 M in hexane; 1.2 mmol) and then 1.1 mL (10.5 mmol) of 2-bromopropionyl bromide. The solution was stirred for 20 min, diluted with EtOAc, and washed with an aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 15−50% Et_2O/hexane to give 1.6 g (yield 50%) each of **A** and **B**.

(*S*)-*N*-[(*R*)-2-[[2-Methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionyl]-4-(phenylmethyl)-2-oxazolidinone ((*R,S*)-9a). To a solution of 455 mg (2 mmol) of **3c** in 70 mL of DMF was added 90 mg of NaH (60% in mineral oil; 2.2 mmol). The mixture was stirred for 5 min, and then 0.5 mL (4.7 mmol) of **A** dissolved in 15 mL of THF was added. The solution was stirred for 1 h and then diluted with EtOAc and water. 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 1.3 g (yield 100) of (*R,S*)-**9a**.

The following compounds were prepared by the procedure above: (*S,S*)-**9a** from **3c** and **B**; (*R,S*)-**9b** from **3m** and **A**; and (*S,S*)-**9b** from **3m** and **B**.

(*S*)-*N*-[(*S*)-2-[[2-Methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionyl]-4-(phenylmethyl)-2-oxazolidinone ((*S,S*)-9a) (chromatography on silica gel, gradient, 20−50% Et_2O/hexane): yield 34%.

(*S*)-N-[(*R*)-2-[(2-Ethyl-1-(phenylmethyl)-1*H*-indol-4-yl)oxy]propionyl]-4-(phenylmethyl)-2-oxazolidinone ((*R,S*)-9b) (chromatography on silica gel, gradient, 20−50% Et_2O/hexane): yield 89%; foam; ^1H NMR($CDCl_3$) ∂ 7.45−7.10 (m, 8H), 7.05−6.85 (m, 3H), 6.80 (d, 1H), 6.65 (s, 1H), 6.20 (d, 1H), 6.15 (q, 1H), 5.25 (s, 2H), 4.75−4.55 (m, 1H), 4.10 (q, 2H), 3.15 (dd, 1H), 2.75 (dd, 1H), 3.65 (q, 2H), 1.85 (d, 3H), 1.30 (t, 3H); MS (FD^+) 482 (M^+); optical rotation at 589 nm +16.6° (MeOH). Anal. ($C_{30}H_{30}N_2O_4$) C, H, N.

(*S*)-*N*-[(*S*)-2-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionyl]-4-(phenylmethyl)-2-oxazolidinone ((*S,S*)-9b) (chromatography on silica gel, gradient, 20−50% Et_2O/hexane): yield 89%; foam; ^1H NMR identical to that given for (*R,S*)-**9b**; MS (FD^+) 482 (M^+); optical rotation at 589 nm +63.2° (MeOH). Anal. ($C_{30}H_{30}N_2O_4$) C, H, N.

(*S*)-2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic Acid ((*S*)-6z). To a solution of 480 mg (1.0 mmol) of (*S,S*)-**9b** in 15 mL of THF was added a solution of 4 mmol of $LiOCH_2Ph$ (from *n*-BuLi and $PhCH_2OH$) in 70 mL of THF at −5 °C. The mixture was stirred with cooling for 2.5 h and then diluted with EtOAc/water. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated at reduced pressure to give 365 mg (yield 90%) of (*S*)-2-[[2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic acid benzyl ester: ^1H NMR ($CDCl_3$) ∂ 7.40 (s, 1H), 7.35−7.20 (m, 8H), 7.05−6.95 (m, 2H), 6.90 (d, 1H), 6.60 (s, 1H), 6.45 (d, 1H), 5.30 (s, 2H), 5.25 (s, 2H), 5.05 (q, 1H), 2.70 (q, 2H), 1.80 (d, 3H), 1.35 (t, 3H). This material (0.9 mmol) in 30 mL of CH_2Cl_2 was stirred for 30 min with 0.12 mL (1.4 mmol) of oxalyl chloride. The solution was washed with brine, dried (Na_2SO_4), and evaporated at reduced pressure to give the indole-3-glyoxamide derivative, 380 mg (yield 87%), as an oil: ^1H NMR ($CDCl_3$) ∂ 7.35−7.15 (m, 8H), 7.05−6.90 (m, 3H), 6.80 (d, 1H), 6.70 (br d, 2H), 6.40 (d, 1H), 5.30 (s, 2H), 5.15 (s, 2H), 2.90 (m, 2H), 1.70 (d, 3H), 1.15 (t, 3H). This material (0.79 mmol), 0.2 g of 10% Pd/C, and 50 mL of EtOH were stirred under 1 atm of H_2 for 2.5 h, filtered, and evaporated at reduced pressure to give (*S*)-**6z**: 200 mg (yield 65%); foam: MS (FD^+) 394 (M^+); optical rotation at 589 nm +49.5° (MeOH). Anal. ($C_{22}H_{22}N_2O_5$) H, N; C: calcd, 66.99; found, 63.23.

The following compounds were prepared utilizing the above procedure.

(*R*)-2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic acid ((*R*)-6y): yield 81%; mp 196−198 °C; MS (FD) 380 (M^+); optical rotation at 589 nm −65.8° (MeOH, cloudy). Anal. ($C_{21}H_{20}N_2O_5 \cdot 0.3H_2O$) C, H, N.

(*S*)-2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]propionic acid ((*S*)-6y): yield 38%; foam; MS (FD^+) 380 (M^+); optical rotation at 589 nm +31.3° (MeOH, cloudy). Anal. ($C_{21}H_{20}N_2O_5 \cdot 1.3H_2O$) C, H, N.

4-[[(Dimethylaminothio)carbonyl]oxy]-2-ethyl-1-(phenylmethyl)-1*H*-indole (10). A solution of 1.0 g (4 mmol) of **3m** in 20 mL of DMF was stirred with 180 mg of NaH (60% in mineral oil; 4.5 mmol) for 30 min and then with 556 mg (4.5 mmol) of dimethylthiocarbonyl chloride for 17 h. The solution was 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 33% EtOAc/hexane, to give **10**: 1.08 g (yield 80%); mp 127−130 °C: ^1H NMR (DMSO-d_6) ∂ 7.32−6.95 (m, 7H), 6.68 (d, 1H), 6.14 (s, 1H), 5.42 (s, 2H), 3.40 (d, 6H), 2.68 (q, 2H), 1.22 (t, 3H); MS (FD) 339 (M^+). Anal. ($C_{20}H_{22}N_2OS$) H, N; C: calcd, 70.97; found, 71.89.

4-[[(Dimethylamino)carbonyl]thio]-2-ethyl-1-(phenylmethyl)-1*H*-indole (11). A mixture of 1.07 g (3.17 mmol) of **10** and 25 mL of diphenyl ether was refluxed for 24 h, cooled, and chromatographed on silica gel, eluting with a gradient of 20% EtOAc/hexane and then 50% EtOAc/hexane, to give **11**: 864 mg (yield 81%); mp 111−113 °C; ^1H NMR ($CDCl_3$) ∂ 7.31−6.93 (m, 8H), 6.44 (s, 1H), 5.31 (s, 2H), 3.21 (br s, 3H), 3.06 (br s, 3H), 2.69 (q, 2H), 1.34 (t, 3H); MS (FD) 338 (M^+). Anal. ($C_{20}H_{22}N_2OS$) C, H, N.

2-Ethyl-4-mercapto-1-(phenylmethyl)-1*H*-indole (12). A mixture of 850 mg (2.5 mmol) of **11**, 30 mL of EtOH, and 10 mL of 5 N NaOH was refluxed for 3 h, cooled, 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 20% EtOAc/hexane, to give **12**: 323 mg (yield 48%); oil: ^1H NMR ($CDCl_3$) ∂ 7.33−6.90 (m, 8H), 6.39 (s, 1H), 5.30 (s, 2H), 3.53 (s, 1H), 2.69 (q, 2H), 1.34 (t, 3H); MS (FD^+) 267 (M^+). Anal. ($C_{17}H_{17}NS$) C, H, N.

2-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]thio]acetic Acid *tert*-Butyl Ester (13). A solution of 439 mg (1.64 mmol) of **12** in 10 mL of DMF was saturated with nitrogen, 66 mg of NaH (60% in mineral oil; 1.64 mmol) was added, the solution was stirred for 20 min, 0.26 mL (1.64 mmol) of *tert*-butyl bromoacetate was added, and the mixture was stirred an additional 1 h. The solution was diluted with water and 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 20% EtOAc/hexane, to give **13**: 476 mg (yield 76%); oil: ^1H NMR ($CDCl_3$) ∂ 7.33−6.92 (m, 8H), 6.53 (s, 1H), 5.31 (s, 2H), 3.66 (s, 2H), 2.66 (q, 2H), 1.34 (s, 9H), 1.32 (t, 3H); MS (FD) 382 (M^+). Anal. ($C_{23}H_{27}NO_2S$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]thio]acetic Acid *tert*-Butyl Ester (14). To a solution of 443 mg (1.16 mmol) of **13** in 10 mL of CH_2Cl_2 was added 0.17 mL (1.9 mmol) of oxalyl chloride. The solution was stirred for 1 h, and then ammonia gas was bubbled into the solution for 10 min. The solvent was evaporated at reduced pressure, and the residue was diluted with EtOAc and water. 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 20% EtOAc/hexane and then 50% EtOAc/hexane, to give **14**: 477 mg (yield 91%): ^1H NMR ($CDCl_3$) ∂ 7.36−7.00 (m, 9H), 5.57 (br s, 1H), 5.38 (s, 2H), 3.50 (s, 2H), 2.86 (q, 2H), 1.27 (s, 9H), 1.21 (t, 3H); MS (FD) 452 (M^+). Anal. ($C_{25}H_{28}N_2O_4S$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]thio]acetic Acid (15). To a solution of 454 mg (1.0 mmol) of **14** in 15 mL of CH_2Cl_2 was added 2 mL of trifluoroacetic acid. This mixture was stirred for 1.5 h, the solvent was evaporated at reduced pressure, and the residue was diluted with EtOAc and water. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated at reduced pressure. The solid residue was stirred with CH_2Cl_2/Et_2O, filtered, and dried to give **15**: 322 mg (yield 81%); mp 210−213 °C: ^1H NMR ($CDCl_3$) ∂ 12.60 (br s, 1H), 8.03 (br s, 1H), 7.68 (br s, 1H), 7.40−7.12 (m, 6H), 7.03 (d, 2H), 5.53 (s, 2H), 3.64 (s, 2H), 2.82 (q, 2H), 1.07 (t, 3H); MS (FD) 396 (M^+). Anal. ($C_{21}H_{20}N_2O_4S$) C, H, N.

4-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-5-yl]thio]butanoic Acid (17). A solution of 240 mg (0.53 mmol) of **16** in 20 mL of THF, 60 mL of EtOH, and 5 mL of 2 N NaOH was stirred for 2.5 h, acidified with 1 N HCl, and extracted with EtOAc. The organic solution was washed with brine, dried over Na_2SO_4, and evaporated at reduced pressure. The residue was crystallized from CH_2Cl_2/Et_2O to give **17**: 135 mg (yield 58%); mp 135−138 °C; MS (FD^+) 424 (M^+). Anal. ($C_{23}H_{24}N_2O_4S\cdot0.5H_2O$) C, H, N, S.

4-Amino-2-ethyl-1-(phenylmethyl)-1*H*-indole (19). To a solution of 1.77 g (6.32 mmol) of **18** in 50 mL of EtOH was added 175 mg of 5% Pt/C. The mixture was hydrogenated for 2 h at an initial pressure of 60 psi of hydrogen. The catalyst was filtered, and the solvent was evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with 20% EtOAc/hexane, to give **19**: 1.16 g (yield 73%); ^1H NMR ($CDCl_3$) ∂ 7.35−6.90 (m, 6H), 6.70 (d, 1H), 6.41 (d, 1H), 6.27 (s, 1H), 5.26 (s, 2H), 4.00 (br s, 2H), 2.66 (q, 2H), 1.31 (t, 3H); MS (FD) 250 (M^+). Anal. ($C_{17}H_{18}N_2$) C, H, N.

2-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]amino]acetic Acid Methyl Ester (20a). A mixture of 500 mg (2 mmol) of **19**, 840 mg (10 mmol) of $NaHCO_3$, 5 mL of DMF, and 0.2 mL (2.1 mmol) of methyl bromoacetate was stirred for 16 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 20% EtOAc/hexane, to give **20a**: 416 mg (yield 65%); oil; ^1H NMR ($CDCl_3$) ∂ 7.41−6.90 (m, 6H), 6.70 (d, 1H), 6.33 (s, 1H), 6.19 (d, 1H), 5.26 (s, 2H), 4.71 (br s, 2H), 4.10 (s, 2H), 3.82 (s, 3H), 2.66 (q, 2H), 1.33 (t, 3H); MS (FD^+) 322 (M^+). Anal. ($C_{20}H_{22}N_2O_2$) C, H, N.

3-[[2-Ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]amino]propionic Acid Methyl Ester (20b). A mixture of 500 mg (2 mmol) of **19**, 1.5 mL (16.5 mmol) of methyl acrylate, and 5 mL of MeOH was stirred for 72 h and then evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with 20% EtOAc/hexane to separate **19** (317 mg; 63% recovered starting material) from **20b**: 186 mg (yield 28%); oil: ^1H NMR ($CDCl_3$) ∂ 7.37−6.91 (m, 6H), 6.66 (d, 1H), 6.32 (d, 1H), 6.24 (s, 1H), 5.25 (s, 2H), 3.70 (s, 3H), 3.63 (t, 2H), 2.74 (t, 2H), 2.66 (q, 2H), 1.31 (t, 3H); MS (FD^+) 336 (M^+). Anal. ($C_{21}H_{24}N_2O_2$) H, N; C: calcd,74.97; found, 72.31.

***N*-[(Methoxycarbonyl)methyl]-2-[[2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]amino]acetic Acid Methyl Ester (21).** A mixture of 119 mg (0.48 mmol) of **19**, 201 mg (2.4 mmol) of $NaHCO_3$, 5 mL of DMF, and 0.11 mL (1.2 mmol) of methyl bromoacetate was stirred for 72 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 20% EtOAc/hexane, to give **21**: 124 mg (yield 66%); oil; ^1H NMR ($CDCl_3$) ∂ 7.31−7.02 (m, 6H), 6.82 (d, 1H), 6.47 (d, 1H), 6.26 (s, 1H), 5.26 (s, 2H), 4.40 (s, 4H), 3.77 (s, 6H), 2.66 (q, 2H), 1.31 (t, 3H); MS (FD) 394 (M^+).

2,3-Dioxo-7-ethyl-1-[(methoxycarbonyl)methyl]-6-(phenylmethyl)benzo[1,2-*b*:3′,4′-*b*′]dipyrrole (22). To a solution of 410 mg (1.27 mmol) of **20a** in 10 mL of CH_2Cl_2 was added 0.11 mL (1.27 mmol) of oxalyl chloride. The solution was stirred for 2.5 h, ammonia gas was bubbled into the solution for 15 min, and then the reaction mixture was stirred an additional 15 min. The solvent was evaporated at reduced pressure, and the residue was diluted with EtOAc and water. 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 20% EtOAc/hexane, to give **22**: 161 mg (yield 32%): ^1H NMR ($CDCl_3$) ∂ 7.39 (d, 1H), 7.30 (t, 1H), 6.96 (dd, 1H), 6.83 (d, 1H), 6.25 (s, 1H), 5.27 (s, 2H), 4.80 (s, 2H), 3.80 (s, 3H), 2.66 (q, 2H), 1.32 (t, 3H); MS (FD^+) 376 (M^+). Anal. ($C_{22}H_{20}N_2O_4$) C, H, N.

***N*-[(Methoxycarbonyl)methyl]-2-[[7-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]amino]-acetic Acid Methyl Ester (23).** Using reaction conditions identical to those above, **21** was reacted with oxalyl chloride and then ammonia to give a mixture of **22** and **23**, which were separated by chromatography on silica gel, eluting with 20% EtOAc/hexane, then 50% EtOAc/hexane, and then EtOAc. ^1H NMRdata of compound **22** is identical to that given above. Compound **23** was obtained in 43% yield: ^1H NMR ($CDCl_3$) ∂ 7.69 (d, 1H), 7.18−7.11 (m, 3H), 6.63 (dd, 2H), 6.56 (br s, 1H), 6.34 (s, 1H), 6.31 (d, 1H), 5.70 (s, 1H), 5.46 (s, 2H), 4.45 (s, 4H), 3.80 (s, 6H), 2.74 (q, 2H), 1.34 (t, 3H); MS (FD^+) 465 (M^+).

4-Amino-3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indole (25). A mixture of 6.0 g (17.1 mmol) of **24**, 1.0 g of 5% Pd/$BaSO_4$, 70 mL of THF, and 70 mL of EtOH was shaken under hydrogen at an initial pressure of 60 psi for 4 h, filtered, and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with 50% EtOAc/hexane to separate a mixture of 4-amino-2-ethyl-α-oxy-1-(phenylmethyl)-1*H*-indole-3-acetamide; 1.28 g (yield 23%), and **25**, 1.66 g (yield 30%): ^1H NMR ($CDCl_3$) ∂ 7.33−7.25 (m, 3H), 7.00 (t, 3H), 6.66 (br s, 1H), 6.56 (d, 1H), 6.48 (d, 1H), 5.72 (br s, 1H), 5.33 (s, 2H), 5.21 (br s, 2H), 2.96 (q, 2H), 1.24 (t, 3H); MS (FD^+) 321 (M^+). Anal. ($C_{19}H_{19}N_3O_2$) H; C: calcd, 71.01; found, 68.50; N: calcd, 13.08; found, 11.88.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]amino]acetic Acid Methyl Ester (26). A mixture of 250 mg (0.78 mmol) of **25**, 327 mg (3.9 mmol) of $NaHCO_3$, 0.07 mL (0.78 mmol) of methyl bromoacetate, and 4 mL of DMF was heated at 60 °C for 1 h, stirred for an additional 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 solid residue was stirred with EtOAc, filtered, and dried to give **26**: 185 mg (yield 60%); oil; ^1H NMR ($CDCl_3$) ∂ 7.56 (br t, 1H), 7.33−7.25 (m, 2H), 7.08 (t, 1H), 7.00 (dd, 2H), 6.62 (br s, 1H), 6.55 (d, 1H), 6.23 (d, 1H), 5.60 (br s, 1H), 5.33 (s, 2H), 4.06 (d, 2H), 3.80 (s, 3H), 2.97 (q, 2H), 1.23 (t, 3H); MS (FD^+) 393 (M^+). Anal. ($C_{22}H_{23}N_3O_4$) C, H, N.

2-[[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]amino]acetic acid (27). A solution of 190 mg (0.48 mmol) of **26** and 5 mL of 1 N NaOH in 15 mL of MeOH was heated at reflux for 20 min, stirred an additional 1 h, diluted with water, acidified with 1 N HCl, and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated at reduced pressure. The residue was crystallized from MeOH to give 96 mg (yield 53%) of **27**; ^1H NMR (DMSO-d_6) ∂ 8.25 (br s, 1H), 7.79 (br s, 1H), 7.35−6.94 (m, 6H), 6.63 (d, 1H), 6.52 (d, 1H), 5.49 (s, 2H), 3.93 (s, 2H), 3.00 (q, 2H), 1.11 (t, 3H); MS (FAB) 380.2 (M^+). Anal. ($C_{21}H_{21}N_3O_4$) C, H, N.

***N*-(2-Amino-1,2-dioxoethyl)-2-[[3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]amino]acetic Acid Methyl Ester (28).** To a solution of 140 mg (0.36 mmol) of **26** in 5 mL of CH_2Cl_2 was added 0.03 mL (0.36 mmol) of oxalyl chloride. The solution was stirred for 19 h, ammonia gas was bubbled into the solution for 15 min, and then the reaction mixture was stirred for an additional 1 h. The solvent was evaporated at reduced pressure, and the residue was chromatographed on silica gel, eluting with EtOAc, to give **28**: 61 mg (yield 38%); ^1H NMR ($CDCl_3$) ∂ 7.49−6.96 (m, 10H), 6.20 (br s, 1H), 5.59 (br s, 1H), 5.40 (s, 2H), 4.89 (d, 1H), 3.78 (d, 1H), 3.70 (s, 3H), 3.08−2.86 (m, 2H), 1.33−1.19 (m, 3H); MS (FD^+) 464 (M^+).

***N*-Acetyl-2-[[2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]-amino]acetic Acid Methyl Ester (29a).** A solution of 137 mg (0.43 mmol) of **20a** and 0.5 mL of acetic anhydride in 10 mL of CH_2Cl_2 was stirred for 1 h. The solvent was evaporated at reduced pressure, and the residue was diluted with EtOAc/water. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with 50% EtOAc/hexane, to give **29a**: 130 mg (yield 83%); MS (FD^+) 364 (M^+).

***N*-Acetyl-3-[[2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]-amino]propionic Acid Methyl Ester (29b).** Using reaction conditions identical to those above, **20b** was reacted with acetic anhydride to give a 92% yield of **29b**: ^1H NMR ($CDCl_3$) ∂ 7.37−6.84 (m, 8H), 6.24 (s, 1H), 5.32 (s, 2H), 4.33−4.23 (m, 1H), 4.03−3.90 (m, 1H), 3.58 (s, 3H), 2.75−2.63 (m, 4H), 1.84 (s, 3H), 1.33 (t, 3H); MS (FD^+) 378 (M^+).

***N*-Acetyl-2-[[3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]amino]acetic Acid Methyl Ester (30a).** To a solution of 130 mg (0.36 mmol) of **29a** in 2 mL of CH_2Cl_2 was added 0.16 mL (1.8 mmol) of oxalyl chloride. The solution was stirred for 4 h, and ammonia gas was bubbled

into the solution for 30 min. The solvent was evaporated, and the residue was diluted with EtOAc and water. 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 50% EtOAc/hexane, to give **30a**: 90 mg (yield 57%); foam; ^{1}H NMR ($CDCl_3$) ∂ 7.43−7.16 (m, 6H), 7.05 (d, 2H), 6.73 (br s, 1H), 5.57 (br s, 1H), 5.40 (s, 2H), 4.90 (d, 1H), 3.72 (s, 3H), 2.93 (q, 2H), 1.98 (s, 3H), 1.25 (t, 3H); MS (FD^+) 435 (M^+).

***N*-Acetyl-3-[[3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]amino]propionic Acid Methyl Ester (30b).** Using reaction conditions identical to those above, **29b** was reacted with oxalyl chloride and then ammonia to give a 27% yield of **30b**: ^{1}H NMR ($CDCl_3$) ∂ 7.39−7.14 (m, 5H), 7.07 (d, 2H), 6.96 (d, 1H), 6.80 (br s, 1H), 5.75 (br s, 1H), 5.40 (s, 2H), 4.59−4.49 (m, 1H), 3.56 (s, 3H), 3.24−3.12 (m, 1H), 3.07−2.86 (m, 2H), 2.71−2.59 (m, 1H), 2.48−2.34 (m, 1H), 2.00 (s, 3H), 1.25 (t, 3H); MS (FD^+) 449 (M^+).

***N*-Acetyl-2-[[3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]amino]acetic Acid (31a).** A solution of 85 mg (0.2 mmol) of **30a** and 1 mL of 1 N NaOH in 5 mL of MeOH was stirred for 1.5 h, diluted with water, acidified with 1 N HCl, and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated at reduced pressure. The residue was dissolved in MeOH, and insoluble material was filtered off. The filtrate contained 34 mg (yield 40%) of **31a**: ^{1}H NMR ($CDCl_3$) ∂ 7.48−6.82 (m, 10H), 5.40 (s, 2H), 4.89 (d, 1H), 3.80 (d, 1H), 2.94 (q, 2H), 1.96 (s, 3H), 1.23 (t, 3H); MS (FD^+) 421 (M^+). Anal. ($C_{23}H_{23}N_3O_5$) H; C: calcd, 65.49; found 64.66; N: calcd, 9.97; found, 9.19.

***N*-Acetyl-3-[[3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]amino]propionic Acid (31b).** Using reaction conditions identical to those above, **30b** was hydrolyzed to give a 73% yield of **31b**: ^{1}H NMR ($CDCl_3$) ∂ 7.36−7.12 (m, 6H), 7.06 (d, 2H), 6.98 (d, 1H), 6.44 (br s, 1H), 5.39 (s, 2H), 4.51−4.47 (m, 1H), 3.25−3.15 (m, 1H), 3.02−2.85 (m, 2H), 2.74−2.59 (m, 1H), 2.49−2.34 (m, 1H), 1.98 (s, 3H), 1.23 (t, 3H); MS (FD^+) 435 (M^+). Anal. ($C_{24}H_{25}N_3O_5$) H, N; C: calcd, 66.19; found, 61.01.

4-Formyl-2-methyl-1-(phenylmethyl)indoline (34a). To 150 mL of H_2SO_4 cooled in ice/water was added in portions 30 mL (0.23 mol) of 2-methylindoline, **32**, followed by 37.4 g (0.12 mol) of Ag_2SO_4. The cooling bath was removed, and the mixture was stirred to give a complete solution, cooled in ice/water, and treated dropwise with 20 mL (0.21 mol) of bromine at a temperature below 15 °C. After being left to stand at room temperature overnight, it was poured on ice, made basic with NaOH, and extracted with EtOAc. The organic phase was washed with brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel, eluting with a gradient of 20−50% Et_2O/hexane to give 32 g of a mixture of **32**, 4-bromo-2-methylindoline, and 6-bromo-2-methylindoline. This mixture was stirred with 50 g of K_2CO_3, 25 mL of benzyl bromide, and 200 mL of DMF, heated at 85 °C for 5 h, then cooled, diluted with water, and extracted with EtOAc. The organic phase 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 5−10% Et_2O/hexane to give 42.7 g of a mixture of 4-bromo-2-methyl-1-(phenylmethyl)indoline (**33a**) and 6-bromo-2-methyl-1-(phenylmethyl)indoline (**33b**). This mixture (0.14 mol) was dissolved in 500 mL of THF, cooled to −75 °C, and treated slowly with 100 mL of *n*-butyllithium (1.6 M in hexane; 0.16 mol) and then with 14 mL (0.18 mol) of DMF by rapid dropwise addition. The cooling bath was removed and the solution stirred for 2 h, diluted with water, and extracted with EtOAc. The organic phase 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 5−15% Et_2O/hexane to give 4-formyl-2-methyl-1-(phenylmethyl)indoline (**34a**) [1.33 g (yield 4%); oil; ^{1}H NMR ($CDCl_3$) ∂ 10.10 (s, 1H), 7.40−7.20 (m, 5H), 7.15 (t, 1H), 7.10 (d, 1H), 6.50 (d, 1H), 4.45 (d, 1H), 4.25 (d, 1H), 3.95−3.8 (m, 1H), 3.75−3.65 (m, 1H), 3.05−2.95 (m, 1H), 1.35 (d, 3H)] and 6-formyl-2-methyl-1-(phenylmethyl)indoline (**34b**): 16.6 g, 47%; oil; ^{1}H NMR ($CDCl_3$) ∂ 9.85 (s, 1H), 7.40−7.20 (m, 5H), 7.20−7.10 (m, 2H), 6.85 (s, 1H), 4.45 (d, 1H), 4.25 (d, 1H), 3.90−3.75 (m, 1H), 3.30−3.20 (m, 1H), 2.75−2.65 (m, 1H), 1.35 (d, 3H).

3-[2-Methyl-1-(phenylmethyl)indolin-4-yl]acrylic Acid Methyl Ester (35). A solution of 1.3 g (5.3 mmol) of **34a** and 2.0 g (6 mmol) of methyl (triphenylphosphoranylidene)acetate in 100 mL of THF was refluxed for 19h, cooled, diluted with EtOAc, washed with water, 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 2−10% Et_2O/hexane to give **35**: 1.1 g (yield 69%); oil; ^{1}H NMR ($CDCl_3$) ∂ 7.75 (d, 1H), 7.40−7.25 (m, 5H), 7.05 (t, 1H), 6.90 (d, 1H), 6.40 (d, 1H), 6.35 (d, 1H), 4.45 (d, 1H), 4.25 (d, 1H), 3.85 (s, 3H), 3.85−3.75 (m, 1H), 3.45−3.35 (m, 1H), 2.85−2.75 (m, 1H), 1.35 (d, 3H).

3-[2-Methyl-1-(phenylmethyl)-1*H*-indol-4-yl]acrylic Acid Methyl Ester (36). A solution of 465 mg (1.5 mmol) of **35** and 410 mg (1.8 mmol) of dichlorodicyanoquinone in 50 mL of dioxane was heated at 85 °C for 15 min, cooled, poured into aqueous $NaHCO_3$, 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 15−20% Et_2O/hexane to give the indole **36**: 320 mg (yield 69%); oil; ^{1}H NMR ($CDCl_3$) ∂ 8.20 (d, 1H), 7.35 (d, 1H), 7.30−7.15 (m, 4H), 7.10 (d, 1H), 7.00 (d, 2H), 6.70 (s, 1H), 6.65 (d, 1H), 5.25 (s, 2H), 3.85 (s, 3H), 2.40 (s, 3H).

3-[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]acrylic Acid Methyl Ester (37). A solution of 350 mg (1.1 mmol) of **36** in 50 mL of CH_2Cl_2 was stirred with 0.11 mL (1.2 mmol) of oxalyl chloride for 45 min, 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 Et_2O and then EtOAc, to give **37** which crystallized when mixed with $CDCl_3$: 325 mg (yield 73%); mp 181−183 °C: MS (FD) 377 $(M + 1)^+$. Anal. ($C_{22}H_{20}N_2O_4 \cdot 0.2\ CDCl_3$) C, H, N.

3-[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]propionic Acid Methyl Ester (38). A mixture of 170 mg (0.56 mmol) of **36**, 0.2 g of 10% Pd/C, 25 mL of THF, and 25 mL of MeOH was stirred under 1 atm of H_2 for 2.5 h, filtered, and evaporated at reduced pressure. The residue was dissolved in 30 mL of CH_2Cl_2, stirred with 0.1 mL of oxalyl chloride for 1 h, saturated with ammonia, washed with brine, dried (Na_2SO_4), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with Et_2O and then EtOAc, to give **38**: 185 mg (yield 88%); mp 147−149 °C; MS (FD) 379 $(M + 1)^+$. Anal. ($C_{22}H_{22}N_2O_4$) C, H, N.

3-[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]acrylic Acid (39). A solution of 300 mg (0.8 mmol) of **37** and 4 mL of 2 N NaOH in 10 mL of THF and 30 mL of EtOH was stirred for 15.5 h, acidified with 1 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 $CDCl_3$ to give **39**: 135 mg (yield 46%): MS (FD^+) 362 (M^+). Anal. ($C_{21}H_{18}N_2O_4 \cdot 0.35\ CDCl_3$) C, H, N.

3-[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1*H*-indol-4-yl]propionic Acid (40). Using reaction conditions identical to those above, **38** was hydrolyzed to give a 60% yield of **40**: MS (FD^+) 364 (M^+). Anal. ($C_{21}H_{20}N_2O_4 \cdot 0.2\ CDCl_3$) C, H; N: calcd, 7.21; found, 6.72.

DOC/PC Phospholipase A_2 Inhibition Assay. Aliquots of 10 μL of test compound solutions in DMSO were added to 20 μL (10 ng) of enzyme in 25 mM Tris·HCl (pH 8) with 0.25 mg/mL BSA and 150 μL of assay buffer containing 50mM Tris (pH 8), 0.2 M NaCl, 2 mM $CaCl_2$, and 1 mg/mL fatty acid free BSA (Sigma, no. A7030). To each tube was added 20 μL of a freshly prepared, iced 10× concentrated stock solution of the PC and bile salt, which had been sonicated and concocted such that the final 200 μL reaction volume would contain 3 mM DOC/1 mM total PC and approximately 100 000 cpm of [^{14}C]-PC. To prepare the lipid substrate, aliquots of labeled PC (1-palmitoyl-2[^{14}C]-oleoylphosphatidyl choline: Amersham, no. CFA656) and 100 mM stock cold PC (Sigma, no. P3017) in chloroform, and 100 mM DOC (sodium salt of deoxycholic acid: Sigma, no. D6750) in ethanol were mixed, dried under

a N_2 stream, and then reconstituted in 10 mM Tris with 0.2 mM NaCl, before sonicating for 10 min. The assay tubes were incubated for 1 h in a 40 °C water bath. The reaction was stopped with 1.5 mL of Doles 2-propanol/heptane/0.5 M H_2SO_4 at 40:10:1 (v/v) with 1 mg/mL palmitic acid. The mixtures were then heated for 1 min at 60 °C before 1 mL of H_2O and 1.25 mL of heptane were added and mixed thoroughly. After the two phases were allowed to separate, the upper phase was transferred to 1 mL of heptane containing 150 mg of dried silica (100−200 mesh) and mixed again before centrifugation for 5 min at 1500*g*. The supernatant was removed for scintillation counting of the liberated [^{14}C]oleic acid. The degree of inhibition was compared to diluent controls, and the inhibitory concentrations were calculated.

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