Indole Inhibitors of Human Nonpancreatic Secretory Phospholipase A_2. 1. Indole-3-acetamides

Robert D. Dillard, Nicholas J. Bach,* Susan E. Draheim, Dennis R. Berry, Donald G. Carlson, Nickolay Y. Chirgadze, David K. Clawson, Lawrence W. Hartley, Lea M. Johnson, Noel D. Jones, Emma R. McKinney, Edward D. Mihelich, Jennifer L. Olkowski, Richard W. Schevitz, Amy C. Smith, David W. Snyder, Cynthia D. Sommers, and Jean-Pierre Wery

Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285

Received July 5, 1996[⊗]

Phospholipases (PLAs) produce rate-limiting precursors in the biosynthesis of various types of biologically active lipids involved in inflammatory processes. Increased levels of human nonpancreatic secretory phospholipase A_2 (hnps-PLA_2) have been detected in several pathological conditions. An inhibitor of this enzyme could have therapeutic utility. A broad screening program was carried out to identify chemical structures which could inhibit hnps-PLA_2. One of the lead compounds generated by the screening program was 5-methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid (**13a**). We describe the syntheses, structure−activity relationships, and pharmacological activities of a series of indole-3-acetamides and related compounds derived from this lead. This SAR was undertaken with the aid of X-ray crystal structures of complexes between the inhibitors and hnps-PLA_2 which were of great value in directing the SAR.

Introduction

Human nonpancreatic secretory phospholipase A_2 (hnps-PLA_2) has been isolated from human synovial fluid as well as other human cells and identified[1] to be a 14 kDa stable protein whose properties have been well characterized. This enzyme contains the site characteristic of phospholipases which is capable of hydrolyzing the *sn*-2 position of certain cellular phospholipids, liberating arachidonic acid and leading to the biosynthesis of eicosanoid products (prostaglandins, thromboxanes, leukotrienes). The exact physiological role of this enzyme is not known; however, high levels of enzyme have been observed in the synovial fluid of arthritic joints[2] and in the serum of patients with severe acute pancreatitis,[3] septic shock,[4] and multiple injuries.[5] A potent and selective inhibitor of hnps-PLA_2 would be a useful pharmacological tool for investigating its biological role in these diseases and other diseases where high levels of eicosanoids are thought to have a role.[6] Such an inhibitor would have the potential of being developed as a useful drug in treating diseases where elevated levels of the enzyme are found.

A program was initiated to find novel structures that were inhibitors of hnps-PLA_2 and could be investigated chemically in structure−activity relationship (SAR) studies. Initially, the inhibition of hnps-PLA_2 activity was determined by measuring the release of ^{14}C oleate from [^{14}C]oleate-labeled autoclaved *Escherichia coli* membranes.[7] This system was easily automated, used very small amounts of enzyme, and was extremely sensitive. The "hit" rate (compounds with IC_{50}'s less than 50 μM) was quite high, and it was necessary to develop a secondary test where the hits could be further evaluated to verify that activity was true inhibition at the enzyme active site and not a nonspecific perturbation of the enyzme or its substrate.

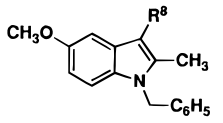
Using recombinant DNA methods,[8] a large quantity of hnps-PLA_2 was supplied for this program. This ready availability of the enzyme allowed for the development of a secondary *in vitro* assay employing lung pleural tissue as the "natural substrate" for hnps-PLA_2. In this tissue assay system,[9] guinea pig pleural lung strips were challenged with hnps-PLA_2, resulting in a contractile response which could be quantitated. Any of the above hits that inhibited the response were potential hnps-PLA_2 inhibitors. However, this was only an indirect measure of hnps-PLA_2 inhibitory activity since the contractile response is mediated by the catalytic release of arachidonic acid and the subsequent formation of eicosanoids. Cyclooxygenase or lipoxygenase inhibitors, which act downstream to PLA_2 in the arachidonic acid cascade, would also suppress the contractile response although they are not hnps-PLA_2 inhibitors. To eliminate these false positives, tissues were challenged in a separate experiment with exogenously administered arachidonic acid, in the presence and absence of drug, and inhibition of the contractile response was measured. The presence of arachidonic acid circumvents the requirement for its PLA_2-mediated release, and any agent that demonstrated suppression of the arachidonic acid-induced response, as would a cyclooxygenase inhibitor, such as indomethacin, could be ruled out as a specific inhibitor of hnps-PLA_2 and was of less interest.

Using this tissue assay system, most of the hits from the *E. coli* assay were eliminated in that they did not inhibit the contractile response induced by hnps-PLA_2. The contraction was inhibited by 5-methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid (**13a**), identifying this compound as one of the first viable inhibitors. This indole-3-acetic acid derivative blocked the effect of hnps-PLA_2, giving an apparent K_B of 2.89 ± 0.86 μM. At higher drug concentrations, it also antagonized the effects of arachidonic acid; however, concentration response comparisons indicated a component that most likely reflected the blocking of hnps-PLA_2. A large number of related indole-3-acetic acids were made and evaluated as hnps-PLA_2 inhibitors using the *E. coli* substrate system, but none of these were much more

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1996.

S0022-2623(96)00485-2 CCC: $12.00

Table 1. Inhibitory Activity of 3-Substituted 1*H*-Indoles



		chromogenic assay	
compd	R^8	IC_{50} (μM)	mole fraction[a]
13a	CH_2CO_2H	13.6 ± 4.2	1.1×10^{-2}
9an	$CH_2CO_2CH_3$	115.8 ($n = 1$)	9.4×10^{-2}
17c	CH_2CONH_2	0.84 ± 0.17	6.8×10^{-4}
20b	$COCONH_2$	1.23 ± 0.17	1.0×10^{-3}
21b	$CH(OH)CONH_2$	20.06 ($n = 1$)	1.6×10^{-2}
10f	$CH_2CONHNH_2$	0.86 ± 0.09	7.0×10^{-4}
24	$CH_2CH_2CONH_2$	28.1 ± 6.7	2.3×10^{-2}
25	CH_2CSNH_2	74.1 ($n = 1$)	6.0×10^{-2}
27	CH_2CN	b	
28a	CH_2CN_4H[c]	84.7 ($n = 1$)	6.9×10^{-2}
28b	CH_2CNHNH_2	64.7 ± 7.1	5.3×10^{-2}
29a	$CH_2CONHCH_3$	141.8 ($n = 1$)	1.2×10^{-1}
29b	$CH_2CONHOCH_3$	40 ± 8	3.3×10^{-2}

[a] Mole fraction is the IC_{50} concentration value divided by the total lipid concentration, 1230 μM. [b] 47% inhibition at 45 μg/mL (highest dose tested), [c] CN_4H = 5-(1*H*-tetrazoyl).

potent than the original lead compound **13a**, and all showed considerable inhibition of the arachidonic acid-induced contractile response.

The availability of large quantites of recombinant hnps-PLA_2 aided the resolution of the X-ray crystal structure of the enzyme.[10] The crystallization of the enzyme complexed with **13a** was also accomplished and recently reported by Schevitz et al.[11a,b] The 3-dimensional structure was solved and the compound was in fact located in the active site. These X-ray crystallography studies and pH dependency studies suggested that the carboxylic acid functionality should be replaced with an amide functionality. The syntheses and biological evalution of a series of 1*H*-indole-3-acetamides and related acetic acid hydrazides are the topic of this publication.

Although the hnps-PLA_2 assay using *E. coli* membranes as substrate was indeed able to identify inhibitors, it was far too sensitive to other factors and gave many erroneous results. Other assay systems were investigated, and the system that used the synthetic substrate 1,2-bis(heptanoylthio)-1,2-dideoxy-*rac*-glycero-3-phosphorylcholine described by Reynolds et al.[12] was selected. In this test, hnps-PLA_2 hydrolyzes the *sn*-2 thioester to liberate a free thio that reacts with the thio-sensitive 5,5-dithiobis(2-nitrobenzoic acid) to give the chromogenic agent, 5-thio-2-nitrobenzoic acid. This was measured spectrophotometrically at 405 nM and allowed for easy automation of the system. The enzyme is not nearly as efficient in hydrolyzing the synthetic substrate as for the *E. coli* membranes, and much larger quantities of hnps-PLA_2 have to be used in the test. When this system was used in the broad screening, very few hits were obtained; however, practically all of the hits were corroborated very well by the secondary guinea pig lung tissue test.

This chromogenic test system was used to evaluate all of the newly synthesized amides and related compounds as hnps-PLA_2 inhibitors, and selected compounds were further evaluated in the guinea pig lung tissue test. Compounds showing interesting activities in both of these systems were candidates for enzyme crystallization studies in order to obtain further 3-dimensional information to facilitate future drug design.

Chemistry

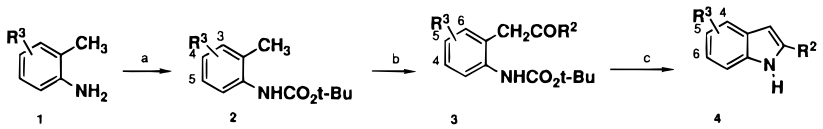
The indole-3-acetamides and related compounds were synthesized by known chemical processes. The general synthetic route involved an intermediary indole unsubstituted in the 1- and 3-positions. Some of these indoles (**4**) were commerically available, and others were made by reported methods (see the Experimental Section). Indoles **4**, with a 2-alkyl group and a 4-, 5-, or 6-methoxy substituent, were synthesized using substituted 2-methylanilines **1** as starting materials (see Scheme 1). This conversion was accomplished by procedures described by Clark et al.[13] in which treatment of 2-methyl-*N*-BOC-anilines **2** with 2 equiv of *sec*-butyllithium afforded the stabilized dianions which were acylated by *N*-methyl-*N*-methoxyamides to produce ketones **3**. These ketones could be cyclized to *N*-BOC-indoles with dilute trifluoroacetic acid in dichloromethane and then hydrolyzed to indoles **4** with aqueous base or cyclized and deprotected by trifluoroacetic acid to indoles **4**. To obtain 2-ethyl-6-isopropropyl-5-methoxy-1*H*-indole (**4e**), the 5-isopropropyl-4-methoxy-2-methylaniline precursor was prepared in two steps from aminothymol.[14] The aminothymol was first reacted with di-*tert*-butyl dicarbonate, and then the hydroxy intermediate, **2d,** was treated with sodium hydride and methyl iodide to give **2e**. Similarly, to obtain 2-ethyl-6-methyl-5-methoxy-1*H*-indole (**4f**), the 2,5-dimethyl-4-methoxyaniline precursor, **2g**, was prepared from **2f**.

The 2-chloroindole **4n** (Scheme 2) was obtained by reacting 5-methoxy-1*H*-indole with formaldehyde and dimethylamine to give 1-[(dimethylamino)methyl]-5-methoxy-1*H*-indole (**8**), and then the lithium salt[15] was treated with benzenesulfonyl chloride and the *ortho*-directing (dimethylamino)methyl group was hydrolyzed with aqueous hydrochloric acid.

An acetic acid ester group was introduced into the indole 3-positon by reacting the zinc salt of **4** with 2-bromoalkanoic acid esters[16] to give the indole acetic acid esters **5** (Scheme 2). The use of zinc salts of indoles is the preferred method for producing 3-alkylation or acylation without complication by reaction at the 1-position. When the indole-3-acetic acids were available, such as **6a**, their methyl esters could be obtained by treatment with methanol and acid. In some cases, 4-substituted phenylhydrazines (**7**) were converted by the classical Fischer-indole synthesis[17] to give **5** directly.

The indole-3-acetic acid esters were alkylated on the indole nitrogen by forming the sodium salt with sodium hydride or the potassium salt with potassium *tert*-butoxide and treating with an arylmethyl halide to give **9** (Scheme 3). Following the N-alkylation, the 5-bromo substituent of **9g** could be replaced by phenyl to give **9h** using the palladium(0)-catalyzed coupling of arylboronic acids and aryl halides as described by Miyura et al.[18] Catalytic hydrogenation of **9c** gave the 5-hydroxyindole, **9ai**. Similarly, the 1-[(3-hydroxyphenyl)methyl]indole-3-acetic acid ester (**9al**) and the 1-[(3-aminophenyl)methyl]indole-3-acetic acid ester (**9ak**) were obtained by catalytic hydrogenation of their intermediate benzyl ether and nitro derivatives, respectively. The 5-carboxyindole-3-acetic acid ester **9aj** was obtained after basic hydrolysis of the diester of **9ah** on

Scheme 1. Preparation of 2-Alkylindoles[a]



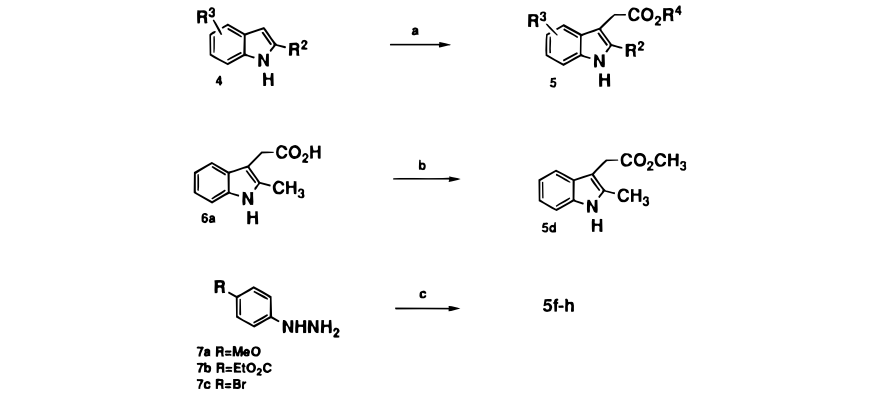
compound	R^3
1a, 2a	3-MeO
1b, 2b	4-MeO
1c, 2c	5-MeO
1d, 2d	4-HO; 5-i-Pr
2e	4-MeO; 5-i-Pr
1f, 2f	4-HO; 5-Me
2g	4-MeO; 5-Me

compound	R^2	R^3
3a	CH_3	6-MeO
3b	CH_3	4-MeO
3c	CH_3CH_2	6-MeO
3d	CH_3CH_2	5-MeO
3e	CH_3CH_2	5-MeO; 4-i-Pr
3f	CH_3CH_2	5-MeO; 4-Me
3g	$CH_3CH_2CH_2$	6-MeO
3h	$CH_3CH_2CH_2$	5-MeO
3i	cyclopropyl	6-MeO
3j	cyclopropyl	5-MeO

compound	R^2	R^3
4a	CH_3	4-MeO
4b	CH_3	6-MeO
4c	CH_3CH_2	4-MeO
4d	CH_3CH_2	5-MeO
4e	CH_3CH_2	5-MeO; 6-i-Pr
4f	CH_3CH_2	5-MeO; 6-Me
4g	$CH_3CH_2CH_2$	4-MeO
4h	$CH_3CH_2CH_2$	5-MeO
4i	cyclopropyl	4-MeO
4j	cyclopropyl	5-MeO

[a] Reagents: (a) $(t\text{-}BuO_2C)_2O$, THF, heat; (b) 2 equiv of *s*-BuLi, $R_2CON(OMe)Me$, THF, −40 °C → room temperature; (c) CF_3CO_2H or (1) CF_3CO_2H, CH_2Cl_2, (2) NaOH, EtOH, H_2O, heat; (d) NaH, CH_3I, THF.

Scheme 2. Preparation of Indole-3-acetic Acid Esters[a]



compound	R^2	R^3	R^4
4k, 5a	H	5-MeO	CH_3CH_2
4l, 5b	H	5-MeO; 6-Cl	CH_3
4m, 5c	H	5-$C_6H_5CH_2O$	CH_3CH_2
5d	CH_3	H	CH_3
4a, 5e	CH_3	4-MeO	CH_3CH_2
5f	CH_3	5-MeO	CH_3CH_2
5g	CH_3	5-EtO_2C	CH_3CH_2
5h	CH_3	5-Br	CH_3CH_2
4d, 5i	CH_3CH_2	5-MeO	CH_3
4h, 5j	$CH_3CH_2CH_2$	5-MeO	CH_3
4j, 5k	cyclopropyl	5-MeO	CH_3
4n, 5l	Cl	5-MeO	CH_3

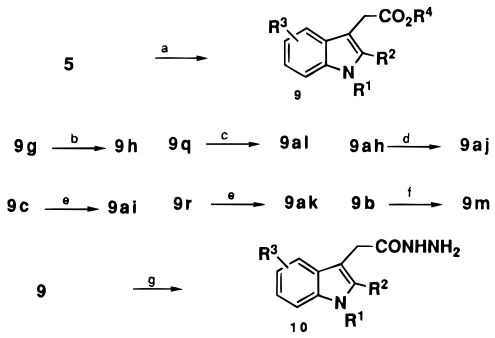
[a] Reagents: (a) (1) *n*-BuLi, $ZnCl_2$, THF, 0 °C, (2) $BrCH_2CO_2R_4$, toluene, room temperature; (b) CH_3SO_3H, CH_3OH; (c) $HO_2CCH_2CH_2COCH_3$, HCl, EtOH, heat; (d) HCHO, H_2O, THF, Me_2NH, heat; (e) (1) *s*-BuLi, benzenesulfonyl chloride, THF, −50 °C, (2) HCl, H_2O.

attempted crystallization of the resulting dicarboxylic acid from methanol.

A bromine atom was introduced into the 2-position of **9b** with *N*-bromosuccinimide to give **9m** (Scheme 3). Similarly, **9ao** was reacted with *N*-bromosuccinimide to give the 2-bromoindole **9aq** (Scheme 4). When **9ao** was reacted with sulfuryl chloride and boron trifluoride etherate, or with methylsulfenyl chloride, the 2-chloro- and 2-(methylthio)indoles **9ap** and **9ar** were obtained, respectively. The chlorination reaction gave a poor yield of the 2-chloroindole (the preferred route to the 2-chloro compounds is that of Scheme 2). The methylthio group of **9ar** was readily oxidized to methylsulfinyl with *m*-chloroperbenzoic acid to give **9as**.

The 1-phenylindole-3-acetic acid ester **9am** was obtained by indolization of the diphenylhydrazone, **11**, with phosphorous trichloride[19] (Scheme 4). This indolization procedure, developed by Baccolini et al., is quite distinct in mechanism from the Fischer process. The phosphorous trichloride-induced reaction tolerates

Scheme 3. Preparation of 1-Substituted Indole-3-acetic Acid Esters and Hydrazides[a]



compound	R^1	R^2	R^3	R^4
9a, 10a	$C_6H_5CH_2$	H	5-MeO	CH_3CH_2
9b	$C_6H_5CH_2$	H	5-MeO; 6-Cl	CH_3
9c	$C_6H_5CH_2$	H	5-$C_6H_5CH_2O$	CH_3CH_2
9d, 10d	$C_6H_5CH_2$	CH_3	H	CH_3
9e, 10e	$C_6H_5CH_2$	CH_3	4-MeO	CH_3CH_2
9f, 10f	$C_6H_5CH_2$	CH_3	5-MeO	CH_3CH_2
9g, 10g	$C_6H_5CH_2$	CH_3	5-Br	CH_3CH_2
9h, 10h	$C_6H_5CH_2$	CH_3	5-C_6H_5	CH_3CH_2
9i, 10i	$C_6H_5CH_2$	CH_3CH_2	5-MeO	CH_3
9j, 10j	$C_6H_5CH_2$	$CH_3CH_2CH_2$	5-MeO	CH_3
9k, 10k	$C_6H_5CH_2$	cyclopropyl	5-MeO	CH_3
9l	$C_6H_5CH_2$	Cl	5-MeO	CH_3
9m	$C_6H_5CH_2$	Br	5-MeO; 6-Cl	CH_3
9n, 10n	$C_6H_5CHCH_3$	CH_3	5-MeO	CH_3CH_2
9o, 10o	$C_6H_5CHC_6H_5$	CH_3	5-MeO	CH_3CH_2
9p, 10p	3-$MeOC_6H_4CH_2$	CH_3	5-MeO	CH_3CH_2
9q, 10q	3-$C_6H_5CH_2OC_6H_4CH_2$	CH_3	5-MeO	CH_3CH_2
9r, 10r	3-$O_2NC_6H_4CH_2$	CH_3	5-MeO	CH_3CH_2
9s, 10s	2-$ClC_6H_4CH_2$	CH_3	5-MeO	CH_3CH_2
9t, 10t	3-$ClC_6H_4CH_2$	CH_3	4-MeO	CH_3CH_2
9u, 10u	3-$ClC_6H_4CH_2$	CH_3	5-MeO	CH_3CH_2
9v, 10v	3-$ClC_6H_4CH_2$	CH_3CH_2	5-MeO	CH_3
9w, 10w	4-$ClC_6H_4CH_2$	CH_3	5-MeO	CH_3CH_2
9x, 10x	2,5-$Cl_2C_6H_3CH_2$	CH_3	5-MeO	CH_3CH_2
9y, 10y	2,6-$Cl_2C_6H_3CH_2$	CH_3	5-MeO	CH_3CH_2
9z, 10z	2-(C_6H_5)$C_6H_4CH_2$	CH_3	4-MeO	CH_3CH_2
9aa, 10aa	2-(C_6H_5)$C_6H_4CH_2$	CH_3	5-MeO	CH_3CH_2
9ab, 10ab	2-(C_6H_5)$C_6H_4CH_2$	CH_3CH_2	5-MeO	CH_3
9ac, 10ac	3-(C_6H_5)$C_6H_4CH_2$	CH_3	5-MeO	CH_3CH_2
9ad, 10ad	2-pyridylCH_2	CH_3	5-MeO	CH_3CH_2
9ae	cyclohexylCH_2	CH_3	5-MeO	CH_3CH_2
9af, 10af	$CH_3(CH_2)_9$	CH_3	5-MeO	CH_3CH_2
9ag, 10ag	$C_6H_5(CH_2)_3$	CH_3	5-MeO	CH_3CH_2
9ah	3-$ClC_6H_4CH_2$	CH_3	5-EtO_2C	CH_3CH_2
9ai	$C_6H_5CH_2$	H	5-HO	CH_3CH_2
9aj, 10aj	3-$ClC_6H_4CH_2$	CH_3	5-HO_2C	CH_3
9ak, 10ak	3-$H_2NC_6H_4CH_2$	CH_3	5-MeO	CH_3CH_2
9al, 10al	3-$HOC_6H_4CH_2$	CH_3	5-MeO	CH_3CH_2

[a] Reagents: (a) NaH or *t*-BuOK, arylmethyl halide, DMF; (b) $[(C_6H_5)_3P]_4Pd(0)$, phenylboronic acid, Na_2CO_3, H_2O, benzene, EtOH, heat; (c) H_2, $Pd/BaSO_4$, EtOH; (d) (1) NaOH, EtOH, H_2O, heat, (2) HCl, H_2O; (e) H_2, Pd/C, EtOH; (f) NBS, CCl_4; (g) hydrazine, EtOH, heat.

a variety of functional groups and is particularly effective for the preparation of 1-substituted indoles from N-substituted hydrazine precursors.

Indole-3-acetic acid esters such as **9an** were prepared from the precursor indole-3-acetic acid by heating with methanesulfonic acid in methanol.

To obtain indoles where the α-carbon atom of the acetic acid ester group was substituted (**15a**−**c**) (Scheme 5), the zinc salts of the appropriate starting indoles were treated with α-bromoalkanoic acid esters, and the resulting indoles were N-alkylated by the reaction sequences previously described.

The 1-(arylmethyl)indole-3-acetic acid esters **9** and **15** of Schemes 3−5 were readily converted to the corresponding 1-(arylmethyl)indole-3-acetic acid hydrazides (**10**, **16**) by heating with hydrazine in ethanol. These hydrazides served, not only as intermediates, but as interesting compounds for evaluating as PLA_2 inhibitors.

Heating the hydrazides with Raney nickel in ethanol gave the corresponding 1-(arylmethyl)indole-3-acetamides **17** (Scheme 6). Amides **17m**−**o** were obtained by reacting the corresponding precursor esters with methylchloroaluminum amide[20] since the presence of halogen and sulfur would have complicated the approach involving reductive cleavage of the hydrazides to produce the amides. Amides unsubstituted at the 2-position could be treated with methanesulfenyl chloride to give the 2-methylthio deriative, such as **17p**. Treatment of indole-3-acetic acids with methyl chloroformate and triethylamine, followed by reaction of the intermediate mixed anhydride with ammonia, offered another route to the indole-3-acetamides, such as **17q**. This sequence, followed by acylation of the indole sodium salt, was utilized in the preparation of the 1-benzoylindole **17t**.

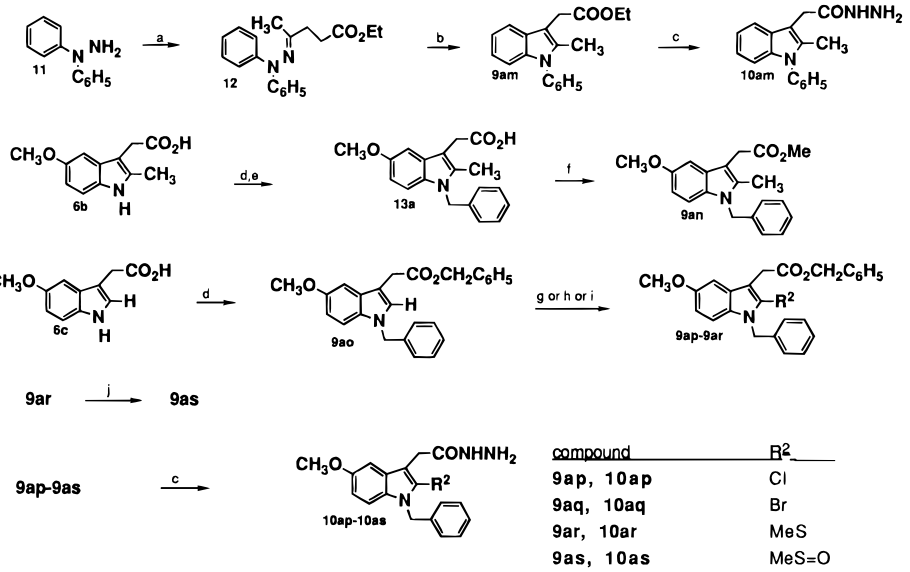
Additional 1-(arylmethyl)indole-3-acetamides were made by the route shown in Scheme 7. Indoles **4** were first alkylated on nitrogen with the arylmethyl group to give **19**, and these were reacted with oxalyl chloride and then ammonia to give the α-oxoacetamides[21] **20**. Stepwise reduction first with sodium borohydride and then with triethylsilane/trifluoroacetic acid[22] gave the amides **17u**−**z**. The 5-aminoindole **17aa** was obtained by catalytic hydrogenation of the corresponding nitro compound **17w**.

The higher homolog, indole-3-propionamide **24** (Scheme 8), was made by methods previously described for the indole-3-acetamide series, derived from a Fischer-indole product. The indole-3-thioacetamide **25** was made by heating the acetamide **17c** with Lawesson's reagent[23] in toluene. The analogous amidine compound **28b** was obtained by treating 5-methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetonitrile (**27**) with methylchloroaluminum amide[24] in toluene. When the same intermediate (**27**) was treated with triethylammonium azide in DMF, the 3-(tetrazoylmethyl)indole **28a** was obtained. The *N*-methyl- and *N*-methoxyamides **29a**,**b** were formed by treatment of **13a** with methyl chloroformate and the appriopriate substituted amine.

Pharmacology

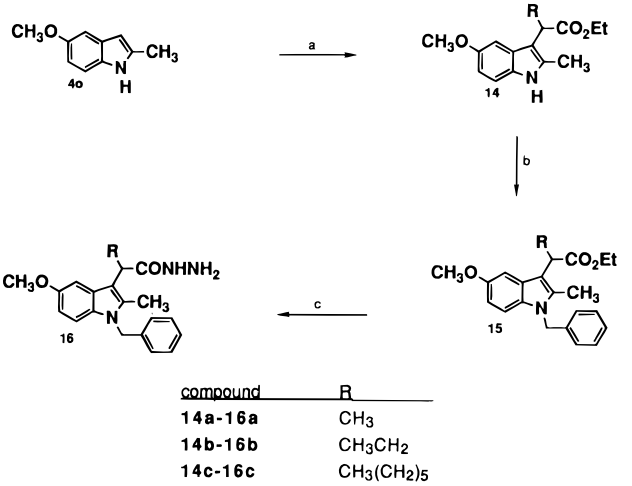
The initial screening program utilized the hnps-PLA_2-induced release of [^{14}C]oleate from *E. coli* membranes to identify and evaluate inhibitors of recombinant human secreted phospholipase A_2. This *E. coli* assay was later replaced with a chromogenic assay system utilizing a synthetic substrate, 1,2-bis(heptanoylthio)-1,2-dideoxy-*rac*-glycero-3-phosphorylcholine. A general description of the method has been published.[12] The assay has been adapted for high-volume screening using 96-well microtiter plates. All compounds were tested in triplicate. Typically, compounds were tested at a final concentration of 5 μg/mL. Lack of color development evidenced inhibition. Compounds initially found to be active were reassayed to confirm their activity, and if they were sufficiently active, IC_{50} values were determined.

Scheme 4. Alternate Preparation of 1-Substituted Indole-3-acetic Acid Esters and Hydrazides[a]



[a] Reagents: (a) $EtO_2CCH_2CH_2COCH_3$, benzene, heat; (b) PCl_3, dichloroethane, heat; (c) hydrazine, EtOH, heat; (d) NaH, benzyl bromide, DMF; (e) (1) NaOH, H_2O, EtOH, (2) HCl, H_2O; (f) $MeSO_3H$, MeOH, heat; (g) SO_2Cl_2, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (h) NBS, CCl_4; (i) MeSCl, CH_2Cl_2; (j) *m*-chloroperbenzoic acid, CH_2Cl_2.

Scheme 5. Preparation of α-Alkylindole-3-acetic Acid Hydrazides[a]



[a] Reagents: (a) (1) *n*-BuLi, $ZnCl_2$, THF, 0 °C; (2) $BrCHRCO_2Et$, toluene, room temperature; (b) NaH, benzyl halide, DMF; (c) hydrazine, EtOH, heat.

A guinea pig lung tissue bath assay was developed to serve as the secondary *in vitro* assay to evaluate inhibitors of hnps-PLA$_2$. The rationale for establishing this assay was based on the knowledge that hnps-PLA$_2$ requires mM calcium to become catalytically active, and this requirement can be met by its secretion from a cell into the external environment. Challenging isolated guinea pig lung pleural strips with hnps-PLA$_2$, with mM concentrations of calcium in the bath fluid, would be analogous to the cellular secretion of the protein into the tissue environment. This tissue preparation is sensitive to the contractile effects of eicosanoids which are formed from the arachidonic acid released via the catalytic action of hnps-PLA$_2$ on the tissues.

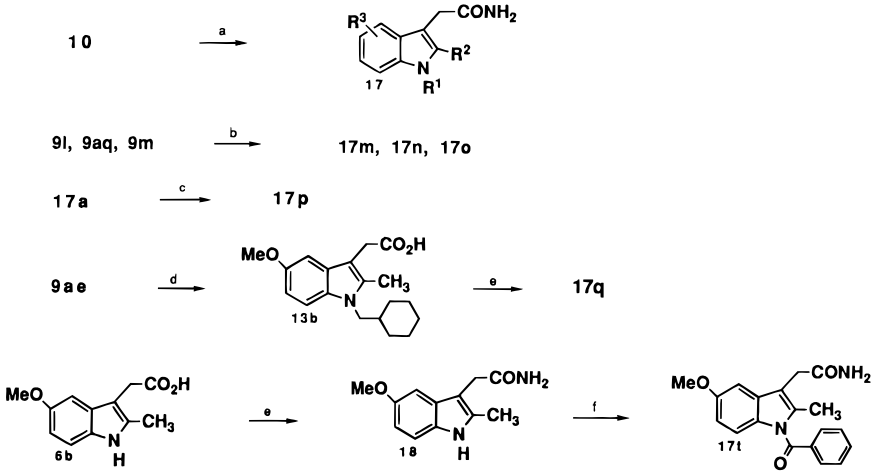
Table 2. Inhibitory Activity of 1*H*-Indole-3-acetic Acid Hydrazides

	chromogenic assay		contraction of GP lung tissue	
compd	IC_{50} (μM) ($n = 3$)	mole fraction	PLA_2-induced apparent K_B (μM) ($n = 4$)	AA-induced ED_{50} (μM) ($n = 4$)
10a	4.9 ± 1.2	4.0×10^{-3}	5.64 ± 0.79	>10
10d	2.36 ± 0.60	1.9×10^{-3}		
10e	0.55 ± 0.27	4.5×10^{-4}		
10f	0.85 ± 0.14	6.9×10^{-4}	1.57 ± 0.23	>30
10g	1.02 ± 0.43	8.3×10^{-4}		
10h	0.86 ± 0.20	7.0×10^{-4}		
10i	0.42 ± 0.16	3.4×10^{-4}	2.04 ± 0.25	>30
10j	70.5 ± 2.2	5.7×10^{-2}	27.13 ± 7.04	>30
10k	0.39 ± 0.13	3.2×10^{-4}		
10n	5.32 ± 1.36	4.3×10^{-3}		
10o	40.2 ± 2.7	3.3×10^{-2}		
10p	2.12 ± 0.27	1.7×10^{-3}		
10q	0.61 ± 0.17	5.0×10^{-4}	3.86 ± 0.35	>30
10r	15.22 ± 0.55	1.2×10^{-2}		
10s	1.71 ± 0.18	1.4×10^{-3}		
10t	0.23 ± 0.09	1.9×10^{-4}		
10u	1.36 ± 0.34	1.1×10^{-3}	1.13 ± 0.25	>30
10w	9.28 ± 1.55	7.5×10^{-3}		
10x	9.39 ± 1.56	7.6×10^{-3}		
10y	0.64 ± 0.13	5.2×10^{-4}		
10aa	0.26 ± 0.06	2.1×10^{-4}	>10	>10
10ab	2.35 ($n = 1$)	1.9×10^{-3}	30.10 ± 4.71	>30
10ac	0.94 ± 0.27	7.6×10^{-4}	22.62 ± 5.43	
10ad	27.18 ± 6.06	2.2×10^{-2}		
10af	9.43 ± 2.35	7.7×10^{-3}		
10ag	16.7 ± 2.2	1.4×10^{-2}		
10aj	0.36 ± 0.02	2.9×10^{-4}	1.39 ± 0.21	>30
10ak	4.32 ± 0.60	3.5×10^{-3}		
10al	3.0 ± 0.93	2.4×10^{-3}	5.96 ± 0.91	>30
10am	38.2 ± 0.70	3.1×10^{-2}		
10ap	0.39 ± 0.03	3.2×10^{-4}	0.85 ± 0.26	9.37 ± 2.03
10aq	0.43 ± 0.02	3.5×10^{-4}	0.76 ± 0.18	7.32 ± 1.75
10ar	0.62 ± 0.10	5.0×10^{-4}		
10as	46.0 ± 18.0	3.7×10^{-2}		
16a	32.64 ($n = 1$)	2.7×10^{-2}		
16b	24.2 ± 7.4	2.0×10^{-2}		
16c	101.2 ($n = 1$)	8.2×10^{-2}		

Discussion

An assay measuring the hnps-PLA$_2$-induced release of [^{14}C]oleate from [^{14}C]oleate-labeled *E. coli* membranes was used to screen a wide variety of chemical structures for their ability to inhibit the action of this enzyme. This screening effort identified 5-methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid (**13a**) as a potential inhibitor of hnps-PLA$_2$. This hit was verified by the

Scheme 6. Preparation of Indole-3-acetamides[a]



compound	R^1	R^2	R^3
17a	$C_6H_5CH_2$	H	5-MeO
17b	$C_6H_5CH_2$	CH_3	4-MeO
17c	$C_6H_5CH_2$	CH_3	5-MeO
17d	$C_6H_5CH_2$	CH_3CH_2	5-MeO
17e	$C_6H_5CH_2$	$CH_3CH_2CH_2$	5-MeO
17f	$C_6H_5CH_2$	cyclopropyl	5-MeO
17g	3-$ClC_6H_4CH_2$	CH_3	4-MeO
17h	3-$ClC_6H_4CH_2$	CH_3	5-MeO
17i	3-$ClC_6H_4CH_2$	CH_3CH_2	5-MeO
17j	2-(C_6H_5)$C_6H_4CH_2$	CH_3	4-MeO
17k	2-(C_6H_5)$C_6H_4CH_2$	CH_3	5-MeO
17l	$C_6H_5(CH_2)_3$	CH_3	5-MeO
17m	$C_6H_5CH_2$	Cl	5-MeO
17n	$C_6H_5CH_2$	Br	5-MeO
17o	$C_6H_5CH_2$	Br	5-MeO; 6-Cl
17p	$C_6H_5CH_2$	CH_3S	5-MeO
17q	cyclohexylCH_2	CH_3	5-MeO
17r	2-pyridylCH_2	CH_3	5-MeO
17s	$CH_3(CH_2)_9$	CH_3	5-MeO

[a] Reagents: (a) Raney Ni, EtOH, heat; (b) $MeClAlNH_2$, benzene/toluene; (c) CH_3SCl, CH_2Cl_2; (d) (1) NaOH, EtOH, H_2O, (2) HCl, H_2O; (e) (1) MeO_2CCl, Et_3N, EtOAc, (2) ammonia; (f) NaH, C_6H_5COCl, DMF.

secondary guinea pig lung pleural strip tissue assay system, and a SAR for this lead compound was undertaken to optimize its inhibitory activity.

The preparation of numerous indole-3-acetic acid derivatives with various substituents at other positions of the indole nucleus produced only moderate changes in activity. X-ray crystallographic studies of the crystalline complex between **13a** and hnps-PLA_2 showed that the indole was located in the active site of the enzyme. However, no active site calcium could be seen in the structure, and the Asp 49, which normally provides two of the seven ligands for calcium, was protonated and formed a bifurcated hydrogen bond to both oxygen atoms of the carboxyl of **13a**. A comparison of this structure with that from a mutant porcine enzyme and an amide substrate analogue[27] (ASA) led to the supposition that replacing the 3-acetic acid substituent with a 3-acetamide could enhance activity by mimicking some of the interactions observed with the ASA.

At this time the *E. coli* assay, which had produced a number of hits not verified by the tissue assay, was replaced by a chromogenic assay utilizing a thioPC substrate.[12] All of the newly synthesized substituted indoles were evaluated in the chromogenic assay, and selected compounds were further evaluated in the tissue assay. The tissue assay was used to verify the chromogenic assay results and to demonstrate that the inhibitors were free of cyclooxygenase and lipoxygenase inhibiting activity.

The acetamide **17c**, which differs from the lead compound **13a** only by replacement of the 3-acetic acid with a 3-acetamide, was synthesized and proved to be a more potent inhibitor than **13a**. The IC_{50} of **17c** in the chromogenic assay showed a 20-fold improvement over that of **13a**. An X-ray crystal structure obtained for the complex between **17c** and hnps-PLA_2 showed the amide carbonyl interacting with the calcium in the active site and the amide NH binding to the active site His 48.

When the 1-benzyl group of **17c** was replaced with large alkyl groups or was substituted at the 2- or 3-positions of the phenyl ring, activity was retained or improved. Substitution at the 4-position of the phenyl ring caused a loss of activity, as could be expected from the X-ray structure of the enzyme complex with **17c**, which shows this position directed into the main chain of the enzyme.

The indole 2-methyl substituent could be replaced by halo, methylthio, ethyl, or cyclopropyl to give more potent inhibitors, while 2-H or other 2-alkyl-substituted compounds lost effectiveness. These changes in activity that were seen with variation of the 2-substituent could also be anticipated from the X-ray structure of the

Table 3. Inhibitory Activity of 1*H*-Indole-3-acetamides

	chromogenic assay		contraction of GP lung tissue	
			PLA$_2$-induced	AA-induced
compd	IC$_{50}$ (μM) ($n = 3$)	mole fraction	apparent K_B (μM) ($n = 4$)	ED$_{50}$ (μM) ($n = 4$)
17a	3.7 ± 2.0	3.0×10^{-3}		
17b	2.36 ± 0.15	1.9×10^{-3}		
17c	0.84 ± 0.17	6.8×10^{-4}	3.43 ± 0.88	>30
17d	0.26 ± 0.11	2.1×10^{-4}	5.91 ± 0.97	>30
17e	38.1 ± 1.9	3.1×10^{-2}		
17f	0.336 ± 0.023	2.7×10^{-4}		
17g	1.38 ± 0.42	1.1×10^{-3}		
17h	0.91 ± 0.19	7.4×10^{-4}		
17l	11.13 (n=1)	9.0×10^{-3}		
17m	0.25 ± 0.03	2.0×10^{-4}		
17n	0.23 ± 0.04	1.9×10^{-4}		
17o	0.12 ± 0.02	9.8×10^{-5}		
17p	0.45 ± 0.01	3.7×10^{-4}	7.93 ± 3.52	
17q	2.05 ± 0.66	1.7×10^{-3}	22.54 ± 3.91	25.65 ± 5.75
17r	21.36 ± 6.07	1.7×10^{-2}		
17s	9.47 ± 4.86	7.7×10^{-3}		
17t	7.21 ± 0.70	5.9×10^{-3}		
17v	1.23 ± 0.23	1.0×10^{-3}		
17w	1.51 ± 0.45	1.2×10^{-3}		
17x	1.18 ± 0.39	9.6×10^{-4}		
17aa	1.61 ± 0.32	1.3×10^{-3}	1.98 ± 0.35	14.50 ± 3.00
20c	1.77 ± 0.15	1.4×10^{-3}		
20e	0.55 ± 0.24	4.5×10^{-4}		
20f	37.8 ± 6.0	3.1×10^{-2}		
20i	2.56 ± 0.55	2.1×10^{-3}		
21c	120.9 ± 7.0	9.8×10^{-2}		
21e	53.0 ± 2.7	4.3×10^{-2}		

enzyme complex with **17c**, since there is little room between the methyl group and the cavity wall. The 2-ethyl group of **17d** fills this space, providing a 3-fold increase in potency. The 2-propyl group of **17e** is too large, and this results in almost a 50-fold loss in activity.

Replacing the 5-methoxy group with various alkoxy, alkyl, aryl, halo, and carboxyl functionalites produced only moderate changes in activity. No significant change in activity was observed when the various 5-substituents were moved to the 4- or 6-positions of the indole.

Substitution on the nitrogen of the acetamide caused a large loss of activity with the exception of the 3-acetohydrazides which usually equaled the activity of the 3-acetamides. Alkyl substitution of the α-carbon of the 3-acetohydrazide resulted in decreased activity (**16a**−**c**). The use of thioamide, amidine, tetrazole, nitrile, or carboxylic acid groups in place of the carboxamide gave derivatives with little or no ability to inhibit the enzyme, as did lengthening the side chain as in the 3-propionamide compound **24**.

The α-oxo-3-acetamide intermediates (3-glyoxamides) of the alternate indole-3-acetamide synthesis (Scheme 7) which were tested in the chromogenic assay showed some interesting activity which was further explored and is detailed in the third paper of this series.

Summary

These studies provided compounds that were tighter binding inhibitors of hnps-PLA$_2$ than the screening hit **13a** and approximately 100-fold more potent. In order to make further improvements to the series, it was necessary to introduce an additional functional group to the indole structure whose purpose was to coordinate to the catalytic calcium.[11] The SAR describing these activities is presented in the following papers.

Experimental Section

Melting points were obtained on a Thomas-Hoover Mel Temp and are uncorrected. The NMR data were recorded on a QE300 instrument. Mass spectral data were obtained on a VG Analytical 70-SE instrument. The following indoles were commercially available: 5-methoxy-1*H*-indole (**4k**), 5-(benzyloxy)-1*H*-indole (**4m**), 5-methoxy-2-methyl-1*H*-indole (**4o**), 4-methoxy-1*H*-indole (**4p**), 2-methyl-1*H*-indole-3-acetic acid (**6a**), 5-methoxy-2-methyl-1*H*-indole-3-acetic acid (**6b**), and 5-methoxy-1*H*-indole-3-acetic acid (**6c**). The following compounds were made by the reported syntheses: 6-chloro-5-methoxy-1*H*-indole (**4l**),[28] 2-methyl-5-nitro-1*H*-indole (**4q**),[29] and 2-ethyl-4-nitro-1*H*-indole (**4r**).[30]

***N*-(*tert*-Butoxycarbonyl)-3-methoxy-2-methylaniline (2a).** A solution of 3-methoxy-2-methylaniline (**1a**) (13.7 g, 100 mmol) and 25 g (115 mmol) of di-*tert*-butyl dicarbonate in 125 mL of THF was heated slowly to reflux, and reflux was maintained for 2 h. After cooling, the reaction mixture was concentrated at reduced pressure and the residue dissolved in EtOAc. The EtOAc solution was washed with a 1 N citric acid solution, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was crystallized from hexane to give 17.25 g (yield 73%) of **2a**: mp 80−82 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.52 (br s, 1H), 7.08 (t, 1H), 6.92 (d, 1H), 6.75 (d, 1H), 3.76 (s, 3H), 2.00 (s, 3H), 1.46 (s, 9H); MS (FD) 237 (M^+). Anal. ($C_{13}H_{19}NO_3$) H, N; C: calcd, 65.80; found, 63.32.

Using this procedure, the following were synthesized from 4- and 5-methoxy-2-methylanilines (**1b** and **1c**), respectively.

***N*-(*tert*-Butoxycarbonyl)-4-methoxy-2-methylaniline (2b)** (crystallization, hexane): yield 73%; mp 80−82 °C; MS (FD^+) 237 (M^+). Anal. ($C_{13}H_{19}NO_3$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-5-methoxy-2-methylaniline (2c)** (crude product): yield 80%; mp 76−80 °C; MS (FD^+) 237 (M^+). Anal. ($C_{13}H_{19}NO_3$) C, H, N.

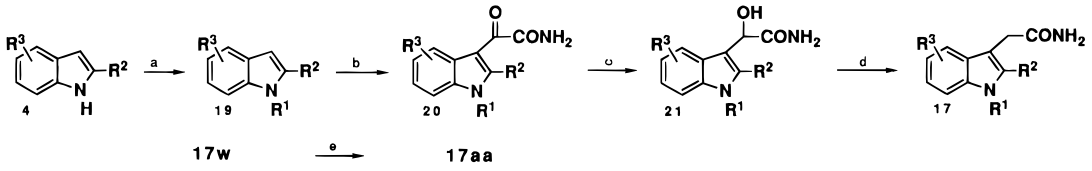
***N*-(*tert*-Butoxycarbonyl-5)-isopropyl-4-methoxy-2-methylaniline (2e).** A solution of 34.5 g (210 mmol) of aminothymol[14] (**1d**) and 45.8 g (210 mmol) of di-*tert*-butyl dicarbonate in 400 mL of THF was stirred for 4 h. The solvent was evaporated at reduced pressure, and the residue was crystallized from 20% EtOAc/hexane to give 53.8 g (yield 97%) of **2d**: mp 154−156 °C; ^{1}H NMR (DMSO-d_6) ∂ 9.00 (s, 1H), 8.18 (br s, 1H), 6.88 (s, 1H), 6.55 (s, 1H), 3.16−3.04 (m, 1H), 2.30 (s, 3H), 1.40 (s, 9H), 1.12 (d, 6H). To 27 g (100 mmol) of this material in 200 mL of DMF was added a suspension of 4 g (100 mmol) of 60% NaH/mineral oil (previously washed with hexanes), and the mixture was stirred for 1 h. Iodomethane (6.2 mL, 100 mmol) was added, the reaction mixture was stirred 17 h, water was added, and the product was extracted with EtOAc, washed with brine, and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed on silica gel, eluting with 20% EtOAc/hexane to give 20.6 g (yield 74%) of **2e**: mp 95−103 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.32 (br s, 1H), 7.00 (s, 1H), 6.75 (s, 1H), 3.75 (s, 3H), 3.25−3.08 (m, 1H), 2.13 (s, 3H), 1.46 (s, 9H), 1.13 (d, 6H); MS (FD^+) 279 (M^+). Anal. ($C_{16}H_{25}NO_3$) H, N; C: calcd, 68.79; found, 69.40.

Using the above procedure, **1f** was converted to **2g**.

***N*-(*tert*-Butoxycarbonyl)-2,5-dimethyl-4-methoxyaniline (2g)** (chromatography on silica gel, 10% EtOAc/hexane): yield 84%; mp 110−113 °C; MS (FD) 251 (M^+). Anal. ($C_{14}H_{21}NO_3$) C, H, N.

1-[2-[(*tert*-Butoxycarbonyl)amino]-4-methoxyphenyl]-2-propanone (3b). A solution of 1.3 M *sec*-butyllithium/cyclohexane (106 mL, 138 mmol) was added slowly to 16.4 g (69 mmol) of **2c** in 200 mL of THF while the temperature was kept below −40 °C with a dry ice/ethanol bath. After 0.25 h, 7.1 g (69 mmol) of *N*-methoxy-*N*-methylacetamide in an equal volume of THF was added dropwise. The reaction mixture was stirred for 1 h, the cooling bath was removed, and the mixture was stirred an additional 1 h. It was then poured into a mixture of 500 mL of Et_2O and 500 mL of 1 N HCl. The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated at reduced pressure to give after chromatography on silica gel, eluting with 33% EtOAc/hexane, 13.8 g (72% yield) of the title compound: ^{1}H NMR ($CDCl_3$) ∂ 7.75 (br s, 1H), 7.32 (d, 1H), 6.84 (d, 1H), 6.25 (s, 1H), 3.88 (s,

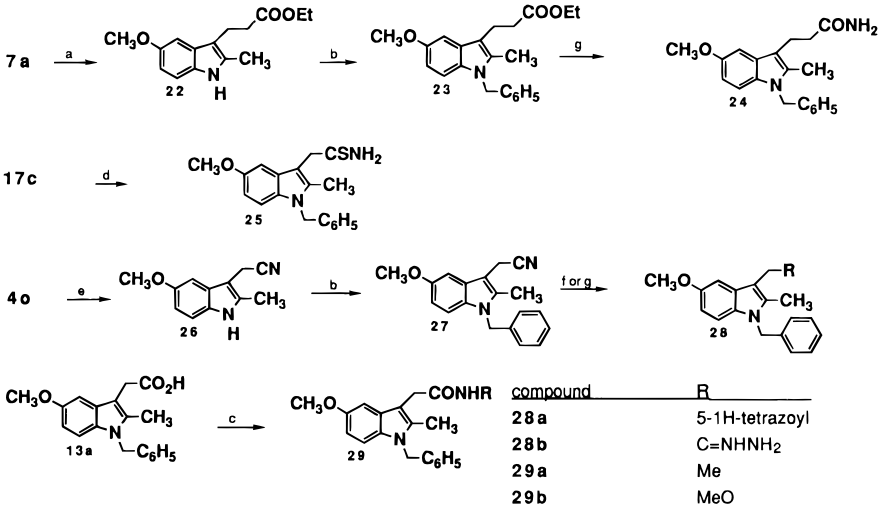
Scheme 7. Alternate Preparation of Indole-3-acetamides[a]



compound	R^1	R^2	R^3
19a-21a, 17u	$C_6H_5CH_2$	H	4-MeO
19b-21b	$C_6H_5CH_2$	CH_3	5-MeO
19c-21c, 17v	$C_6H_5CH_2$	CH_3	6-MeO
19d-21d, 17w	$C_6H_5CH_2$	CH_3	5-O_2N
19e-21e, 17x	$C_6H_5CH_2$	CH_3CH_2	4-MeO
19f-20f	$C_6H_5CH_2$	CH_3CH_2	4-O_2N
19g-21g, 17y	$C_6H_5CH_2$	CH_3CH_2	5-MeO; 6-i-Pr
19h-21h, 17z	3-Cl$C_6H_4CH_2$	CH_3CH_2	4-MeO
19i-20i	$C_6H_5CH_2$	CH_3CH_2	5-MeO
19j	$C_6H_5CH_2$	CH_3CH_2	5-MeO; 6-Me
17aa	$C_6H_5CH_2$	CH_3	5-H_2N

[a] Reagents: (a) NaH, arylmethyl halide, DMF; (b) (1) oxalyl chloride, CH_2Cl_2, (2) ammonia; (c) $NaBH_4$, EtOH; (d) Et_3SiH, TFA; (e) H_2, Pd/C, EtOH.

Scheme 8. Preparation of Other 3-Substituted Indoles[a]



compound	R
28a	5-1H-tetrazoyl
28b	C=$NHNH_2$
29a	Me
29b	MeO

[a] Reagents: (a) $EtO_2C(CH_2)_3COCH_3$, HCl, EtOH, heat; (b) *t*-BuOK, benzyl chloride, DMF; (c) (1) MeO_2CCl, Et_3N, THF, (2) RNH_2; (d) Lawesson's reagent, toluene, heat; (e) (1) *n*-BuLi, $ZnCl_2$, THF, 0 °C, (2) $BrCH_2CN$, toluene; (f) $Et_3N{\cdot}HCl$, NaN_3, DMF, 95−125 °C; (g) $MeClAlNH_2$, toluene, heat.

3H), 2.54 (s, 3H), 1.69 (s, 9H); MS (FD$^+$) 279 (M^+). Anal. ($C_{15}H_{21}N_2O_4$) H, N; C: calcd, 64.50; found, 63.80.

Using this procedure, the following conversions were made using the appropriate *N*-methoxy-*N*-methylamide: **2b** to **3d**, **3h** and **3j**; **2e** to **3e**.

1-[2-[(*tert*-Butoxycarbonyl)amino]-5-methoxyphenyl]-2-butanone (3d) (chromatography on silica gel, 5% EtOAc/toluene): yield 74%; mp 80−81 °C; MS (FD$^+$) 293 (M^+). Anal. ($C_{16}H_{23}NO_4$) C, H, N.

1-[2-[(*tert*-Butoxycarbonyl)amino]-4-isopropyl-5-methoxyphenyl]-2-butanone (3e) (crude product): yield 90%; oil; ^{1}H NMR (DMSO-d_6) ∂ 10.55 (br s, 1H), 8.35 (br s, 1H), 7.05 (s, 1H), 6.75 (s, 1H), 3.75 (s, 3H), 3.35 (s, 2H), 3.25−3.05 (m, 1H), 2.45 (q, 2H), 1.40 (s, 9H), 1.10 (d, 6H); MS (FD) 335 (M^+). Anal. ($C_{19}H_{29}NO_4$) H; C: calcd, 68.03; found, 69.99; N: calcd, 4.18; found, 5.09.

1-[2-[(*tert*-Butoxycarbonyl)amino]-5-methoxyphenyl]-2-pentanone (3h) (chromatography on silica gel, 5% EtOAc/toluene): yield 73%; mp 77−78 °C; MS (FD) 307 (M^+). Anal. ($C_{17}H_{25}NO_4$) C, H, N.

[2-[(*tert*-Butoxycarbonyl)amino]-5-methoxyphenyl]methyl cyclopropyl ketone (3j) (crystallization, hexane): yield 77%; mp 96−97 °C; MS (FD$^+$) 305 (M^+). Anal. ($C_{17}H_{23}NO_4$) C, H, N.

4-Methoxy-2-methyl-1*H*-indole (4a). A solution of 43 g (0.18 mol) of **2a** in 280 mL of THF was treated with 1.3 M *sec*-butyllithium/cyclohexane (280 mL, 0.36 mol) and then 18.5 g (0.18 mol) of *N*-methoxy-*N*-methylacetamide as described for **3b** to give a mixture of 1-[2-[(*tert*-butoxycarbonyl)amino]-6-methoxyphenyl]-2-propanone (**3a**) and starting anilide, **2a** (NMR analysis). This mixture was dissolved in 100 mL of CH_2Cl_2 and 40 mL of trifluoroacetic acid, stirred for a total of 26 h, washed with water, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was chromatographed on silica gel, eluting with 20% EtOAc/hexane to give on crystallization from CH_2Cl_2/hexane, 13.9 g (yield 48%, 2 steps) of **4a**: mp 80−86 °C; MS (FD) 161 (M^+). Anal. ($C_{10}H_{11}NO$) C, H, N.

2-Ethyl-4-methoxy-1*H*-indole (4c). Using the procedure described for **4a**, **2a** was converted to crude 1-[2-[(*tert*-butoxycarbonyl)amino]-6-methoxyphenyl]-2-butanone (**3c**), which was reacted with trifluoroacetic acid to give **4c** in 48% overall yield (chromatography on silica gel, 20% EtOAc/hexane): oil; ^{1}H NMR ($CDCl_3$) ∂ 7.90 (br s, 1H), 7.05 (t, 1H), 6.95 (d, 1H), 6.53 (d, 1H), 6.36 (s, 1H), 3.97 (s, 3H), 2.78 (q, 2H), 1.34 (t, 3H); MS (FD) 175 (M^+). Anal. ($C_{11}H_{13}NO$) H; C: calcd,75.40; found, 74.41; N: calcd, 7.99; found, 4.97.

2-Ethyl-5-methoxy-6-methyl-1*H*-indole (4f). To a solution of 27.3 g (109 mmol) of **2g** in 400 mL of THF at −60 °C was slowly added 168 mL (218 mmol) of a 1.3 M solution of *s*-BuLi in cyclohexane. Following the addition, the cooling bath was removed until the temperature reached 0 °C, the bath was then replaced, and 12.8 g (109 mmol) of *N*-methoxy-

N-methylpropionamide was added at −60 °C. The cooling bath was removed, and the reaction mixture was stirred for 16 h and then poured into Et_2O/water. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure to give 24.3 g (yield 73%) of 1-[2-[(*tert*-butoxycarbonyl)amino]-5-methoxy-4-methylphenyl]-2-butanone (**3f**). The crude product was stirred with 20 mL of trifluoroacetic acid in 400 mL of CH_2Cl_2 for 5 h, diluted with water, and neutralized with $NaHCO_3$. The CH_2Cl_2 layer was washed with brine, dried ($MgSO_4$), evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 10% EtOAc/hexane to give 8.21 g (28.4 mmol, yield 36%) of 1-(*tert*-butoxycarbonyl)-2-ethyl-5-methoxy-6-methyl-1*H*-indole as an oil. Anal. ($C_{17}H_{23}NO_3$) C, H, N. A solution of this indole and 20 mL of 5 N NaOH in 100 mL of EtOH was heated at reflux for 18 h. The solution was diluted with water, extracted with EtOAc, washed with brine, dried ($MgSO_4$), evaporated at reduced pressure, and then chromatographed on silica gel, eluting with 10% EtOAc/hexane to give 3.6 g (yield 67%) of **4f** as an oil: MS (FD$^+$) 189 (M$^+$). Anal. ($C_{12}H_{15}NO$) C, H, N.

Using this procedure, **2a** was converted to **4g** and **4i**.

4-Methoxy-2-propyl-1*H*-indole (4g) (chromatography on silica gel, 20% EtOAc/hexane): yield 36%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.89 (br s, 1H), 7.05 (t, 1H), 6.94 (d, 1H), 6.51 (d, 1H), 6.34 (s, 1H), 3.95 (s, 3H), 2.72 (t, 2H), 1.74 (q, 2H), 1.00 (t, 3H). Anal. ($C_{12}H_{15}NO\cdot 0.2EtOAc$) C, H, N.

2-Cyclopropyl-4-methoxy-1*H*-indole (4i) (chromatography on silica gel, 5% EtOAc/toluene): yield 24%; oil; MS (FD$^+$) 187 (M$^+$). Anal. ($C_{12}H_{13}NO\cdot 0.3EtOAc$) C, H, N.

6-Methoxy-2-methyl-1*H*-indole (4b). A solution of 13.7 g (49 mmol) of **3b** and 20 mL of trifluoroacetic acid in 250 mL of CH_2Cl_2 was stirred for 72 h and washed with water. After the solution was dried over $MgSO_4$ and concentrated, the residue was chromatographed on silica gel, eluting with 20% EtOAc/hexane to give 4.8 g (61% yield) of **4b**: ^{1}H NMR ($CDCl_3$) ∂ 7.70 (br s, 1H), 7.37 (d, 1H), 6.84−6.72 (m, 2H), 6.13 (br s, 1H), 3.83 (s, 3H), 2.43 (s, 3H).

Using a similar procedure, the following conversions were made: **3d**−**e**,**h**,**j** to **4d**−**e**,**h**,**j**, respectively.

2-Ethyl-5-methoxy-1*H*-indole (4d) (chromatography silica gel, 20% EtOAc/hexane): yield 58%; mp 49−50 °C; MS (FD$^+$) 175 (M$^+$). Anal. ($C_{11}H_{13}NO$) C, H, N.

2-Ethyl-6-isopropyl-5-methoxy-1*H*-indole (4e) (chromatography on silica gel, 20% EtOAc/hexane): yield 62%; mp 65−72 °C: MS (FD$^+$) 217 (M$^+$). Anal. ($C_{14}H_{19}NO$) C, H, N.

5-Methoxy-2-propyl-1*H*-indole (4h) (crystallization, hexane): yield 58%; mp 49−50 °C; MS (FD$^+$) 189 (M$^+$). Anal. ($C_{12}H_{15}NO$) C, H, N.

2-Cyclopropyl-5-methoxy-1*H*-indole (4j) (chromatography on silica gel, gradient, toluene−20% EtOAc/hexane): yield 49%; oil; ^{1}H NMR (DMSO-d_6) ∂ 10.65 (br s, 1H), 7.17 (d, 1H), 6.88 (d, 1H), 6.59 (dd, 1H), 5.98 (s, 1H), 3.72 (s, 3H), 2.04−1.96 (m, 1H), 0.96−0.90 (m, 2H), 0.79−0.70 (m, 2H); MS (FD$^+$) 187 (M$^+$). Anal. ($C_{12}H_{13}NO$) H, N; C: calcd, 76.98; found, 74.46.

5-Methoxy-1*H*-indole-3-acetic Acid Ethyl Ester (5a). To a cooled solution of 29.44 g (0.2 mol) of 5-methoxy-1*H*-indole (**4k**) in 400 mL of THF was added 125 mL (0.02 mol) of a 1.6 M solution of *n*-butyllithum in hexane, while the temperature was kept below 10 °C with an ice/ethanol bath. After 0.25 h, 200 mL (0.2 mol) of a 1 M solution of $ZnCl_2$ in Et_2O was added. The cooling bath was removed, and the mixture was stirred for 2 h and then concentrated at reduced pressure to a give a wax which was dissolved in 400 mL of toluene. To this solution was added 22.2 mL (0.2 mol) of ethyl 2-bromoacetate, and the mixture was stirred for 24 h and poured into 1 L of 1 N HCl and 1 L of EtOAc. The organic layer was washed twice with water, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with 5% EtOAc/toluene to give 20 g (43%) of **5a**, as an oil: MS (FD) 233 (M$^+$). Anal. ($C_{13}H_{15}NO_3$) C, H, N.

Using the preceding method, the following conversions were made using the appropriate 2-bromoacetic acid esters: **4l** to **5b**; **4m** to **5c**; **4a** to **5e**; **4d** to **5i**; **4h** to **5j**; and **4j** to **5k**.

6-Chloro-5-methoxy-1*H*-indole-3-acetic acid methyl ester (5b) (chromatography on silica gel gradient, 5−10% EtOAc/toluene): yield 64%; oil; MS (FD) 253 (M − 1, 100), 255 (M + 1, 40). Anal. ($C_{12}H_{12}ClNO_3$) C, H, N.

5-(Benzyloxy)-1*H*-indole-3-acetic acid ethyl ester (5c) (chromatography on silica gel, gradient, toluene−5% EtOAc/toluene): yield 27%; mp 57−59 °C; ^{1}H NMR (DMSO-d_6) ∂ 10.80 (br s, 1H), 7.50−7.21 (m, 7H), 7.11 (d, 1H), 6.83 (dd, 1H), 5.08 (s, 2H), 4.08 (q, 2H), 3.67 (s, 2H), 1.71 (t, 3H); MS (FD$^+$) 309 (M$^+$). Anal. ($C_{19}H_{19}NO_3$) C, H; N: calcd, 5.43; found, 4.50.

4-Methoxy-2-methyl-1*H*-indole-3-acetic acid ethyl ester (5e) (chromatography on silica gel, 20% EtOAc/hexane): yield 53%; mp 117−121 °C; MS (FD) 247 (M$^+$). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

2-Ethyl-5-methoxy-1*H*-indole-3-acetic acid methyl ester (5i) (chromatography on silica gel, gradient, toluene−10% EtOAc/toluene); yield 59%; oil; MS (FD) 247 (M$^+$). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

5-Methoxy-2-propyl-1*H*-indole-3-acetic acid methyl ester (5j) (chromatography on silica gel, 20% EtOAc/hexane): yield 66%; oil; MS (FD$^+$) 261 (M$^+$). Anal. ($C_{15}H_{19}NO_3$) C, H, N.

2-Cyclopropyl-5-methoxy-1*H*-indole-3-acetic acid methyl ester (5k) (chromatography on silica gel, gradient, 5−15% EtOAc/toluene): yield 61%; oil; ^{1}H NMR (DMSO-d_6) ∂ 10.35 (br s, 1H), 7.11 (d, 1H), 6.88 (d, 1H), 6.65 (dd, 1H), 3.75 (s, 3H), 3.61 (s, 2H), 2.13−1.9 (m, 1H), 0.98−0.92 (m, 2H), 0.86−0.77 (m, 2H); MS (FD$^+$) 259 (M$^+$). Anal. ($C_{15}H_{17}NO_3\cdot 0.9H_2O$) C, H, N.

2-Methyl-1*H*-indole-3-acetic Acid Methyl Ester (5d). A mixture of 25 g (0.32 mol) of 2-methyl-1*H*-indole-3-acetic acid (**6a**) and 10 mL of methanesulfonic acid in 200 mL of MeOH was stirred for 24 h, poured into water, and extracted with EtOAc. The EtOAc solution was washed with a $NaHCO_3$ soution and water and dried ($MgSO_4$). The solvent was evaporated at reduced pressure to give 26.62 g (yield 97%) of **5d**: MS (FD$^+$) 203 (M$^+$). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

5-Methoxy-2-methyl-1*H*-indole-3-acetic Acid Ethyl Ester (5f). Dry hydrogen chloride was bubbled into a solution of 27.95 g (0.16 mol) of (4-methoxyphenyl)hydrazine hydrochloride (**7a**) and 19.72 g (0.17 mol) of levulinic acid in 500 mL of EtOH for 0.5 h while cooling with an ice/water bath. The bath was removed, the reaction mixture was slowly heated to reflux, and reflux was maintained for 20 h. After cooling, the mixture was poured into water and extracted with EtOAc. The EtOAc solution was washed with a $NaHCO_3$ solution and dried over Na_2SO_4. After the solvent was removed at reduced pressure, the residue was chromatographed on silica gel, eluting with 5% EtOAc/toluene to give 14.2 g (36% yield) of the title compound: mp 38−40 °C; MS (FD$^+$) 247 (M$^+$). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

The two following compounds were made by the above procedure from (4-carbethoxyphenyl)hydrazine (**7b**) and (4-bromophenyl)hydrazine hydrochloride (**7c**), respectively.

5-(Ethoxycarbonyl)-2-methyl-1*H*-indole-3-acetic acid ethyl ester (5g) (chromatography on silica gel, gradient, toluene−20% EtOAc/toluene): yield 8%; mp 74−76 °C; MS (FD) 289 (M$^+$). Anal. ($C_{16}H_{19}NO_4$) C, H, N.

5-Bromo-2-methyl-1*H*-indole-3-acetic acid ethyl ester (5h) (chromatography on silica gel, 5% EtOAc/toluene): yield 83%; mp 65−68 °C; ^{1}H NMR (DMSO-d_6) ∂ 11.10 (br s, 1H), 7.56 (s, 1H), 7.25 (d, 1H), 7.11 (d, 1H), 4.06 (q, 2H), 3.65 (s, 2H), 2.34 (s, 3H), 1.17 (t, 3H); MS (FD$^+$) 295 (M − 1), 297 (M + 1). Anal. ($C_{13}H_{14}BrNO_2$) H, N; C: calcd, 52.72; found, 53.99.

1-[(Dimethylamino)methyl]-5-methoxy-1*H*-indole (8). A 37% aqueous solution of formaldehyde (11 g, 0.176 mol) was added dropwise to 10 g (0.068 mol) of 5-methoxy-1*H*-indole (**4k**) and 17 mL (0.176 mol) of 40% aqueous dimethylamine in 100 mL of THF and the mixture heated to maintain reflux for 3 h. After cooling, water was added and the mixture extracted with EtOAc. The EtOAc solution was washed twice with water, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of CH_2Cl_2−2% MeOH/CH_2Cl_2, to give 6.26 g (45% yield) of **8** as an oil: MS (FD$^+$) 204 (M$^+$). Anal. ($C_{12}H_{16}N_2O$) C, H, N.

2-Chloro-5-methoxy-1*H*-indole-3-acetic Acid Methyl Ester (5l). Using a dry ice/ethanol bath for cooling, 20 mL

(0.026 mol) of 1.3 M *sec*-butyllithium/cyclohexane was added to 5.1 g (0.025 mol) of **8** in 100 mL of THF, while the temperature was kept below −50 °C. The cooling bath was removed and the temperature allowed to reach 0 °C. The bath was then replaced. At −60 °C, 3.32 mL (0.026 mol) of benzenesulfonyl chloride in 10 mL of THF was added, the mixture stirred, 0.3 h, the bath removed, and the temperature allowed to reach 20 °C over 1 h. To this mixture were added 100 mL of 1 N HCl and 50 mL of EtOAc, and the mixture was stirred for 20 h. After the solution was made basic with 5 N NaOH, the EtOAc layer was separated, washed with water, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica, eluting with toluene to give 1.37 g (29% yield) of crude 2-chloro-5-methoxy-1*H*-indole (**4n**). To this material (7.55 mmol) in 30 mL of THF was added 4.7 mL (7.55 mmol) of 1.6 M *n*-butyllithium/hexane, while the temperature was kept below 10 °C with an ethanol/ice bath. After 0.25 h, 7.55 mL (7.55 mmol) of 1 M $ZnCl_2$/Et_2O was added, the mixture stirred for 2 h and concentrated at reduced pressure, and 40 mL of toluene added followed by 0.72 mL (7.55 mmol) of methyl 2-bromoacetate. The mixture was stirred for 16 h, warmed at 76 °C for 4 h, and cooled, and 50 mL of 1 N HCl and 40 mL of EtOAc were added. After 0.5 h, the organic layer was separated, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of toluene−20% EtOAc/toluene to give 0.79 g (41% yield) of **5l** as an oil: ^{1}H NMR (DMSO-d_6) ∂ 11.60 (br s, 1H), 7.21 (d,1H), 6.98 (d, 1H), 6.77 (dd, 1H), 3.75 (s, 3H), 3.71 (s, 2H), 3.63 (s, 3H); MS (FD^+) 253 (M − 1, 100), 255 (M + 1, 34). Anal. ($C_{12}H_{12}ClNO_3$) C, H; N: calcd, 5.52; found, 4.99.

5-Methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic Acid Ethyl Ester (9a). Potassium *tert*-butoxide (1.51 g, 13.5 mmol) was added to 3.15 g (13.5 mmol) of **5a** in 50 mL of DMF, the mixture was stirred for 0.25 h, 1.55 mL (13.5 mmol) of benzyl chloride was added, and the mixture was stirred for 72 h. After being diluted with water, the mixture was extracted with EtOAc, and the EtOAc solution was washed four times with water and dried over Na_2SO_4. The solvent was removed at reduced pressure and the residue chromatographed on silica gel, eluting with a gradient of toluene−5% EtOAc/toluene, to give 1.76 g (66% yield) of **9a** as an oil: ^{1}H NMR (DMSO-d_6) ∂ 7.42−7.13 (m, 7H), 7.00 (d, 1H), 6.77 (dd, 1H), 5.35 (s, 2H), 4.08 (q, 2H), 3.77 (s, 3H), 3.71 (s, 2H), 1.19 (t, 3H); MS (FD^+) 323 (M^+). Anal. ($C_{20}H_{21}NO_3$) H, N; C: calcd, 74.28; found, 75.53.

Using the preceding chemical method, the following conversions were made using the appropriately substituted alkyl halides: **5c** to **9c**; **5d** to **9d**; **5f** to **9f**, **9ae**, and **9af**; **5g** to **9ah**; **5i** to **9i**.

5-(Benzyloxy)-1-(phenylmethyl)-1*H*-indole-3-acetic acid ethyl ester (9c) (chromatography on silica gel, gradient, toluene−10% EtOAc/toluene): yield 83%; mp 107−109 °C; MS (FD^+) 399.5 (M^+). Anal. ($C_{20}H_{21}NO_3$) C, H, N.

2-Methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid methyl ester (9d) (chromatography on silica gel, gradient, toluene−5% EtOAc/toluene): yield 68%; mp 71−73 °C; MS (FD^+) 293 (M^+). Anal. ($C_{19}H_{19}NO_2$) C, H, N.

5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid ethyl ester (9f) (chromatography on silica gel, gradient, toluene−10% EtOAc/toluene): yield 68%; mp 63−64 °C; MS (FD^+) 338 (M^+). Anal. ($C_{21}H_{23}NO_3$) C, H, N.

1-(Cyclohexylmethyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid ethyl ester (9ae) (chromatography on silica gel, gradient, toluene−5% EtOAc/toluene): yield 48%; oil; MS (FD^+) 343 (M^+). Anal. ($C_{21}H_{29}NO_3$) C, H, N.

1-Decyl-5-methoxy-2-methyl-1*H*-indole-3-acetic acid ethyl ester (9af) (chromatography on silica gel, gradient, toluene−5% EtOAc/toluene): yield 56%; mp 40−42 °C; MS (FD) 387 (M^+). Anal. ($C_{24}H_{37}NO_3$) C, H, N.

1-[(3-Chlorophenyl)methyl]-5-(ethoxycarbonyl)-2-methyl-1*H*-indole-3-acetic acid ethyl ester (9ah) (chromatography on silica gel, gradient, toluene−20% EtOAc/toluene): yield 34%; mp 100−102 °C; MS (FD^+) 413.5 (M − 1, 100), 415.5 (M + 1, 36). Anal. ($C_{23}H_{24}ClNO_4$) C, H, N.

2-Ethyl-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic acid methyl ester (9i) (chromatography on silica gel, gradient, toluene−10% EtOAc/toluene): yield 44%; oil; MS (FD^+) 337 (M^+). Anal. ($C_{21}H_{23}NO_3$) C, H, N.

4-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic Acid Ethyl Ester (9e). A suspension of 1.2 g (30 mmol) of 60% NaH/mineral oil was washed with hexane and placed in 50 mL of DMF. With ice-bath cooling, 7.4 g (30 mmol) of **5e** was added, the mixture was stirred 1 h, 3.6 mL (30 mmol) of benzyl bromide was then added, and stirring was maintained for 1.5 h. The mixture was diluted with water and extracted with EtOAc, and the EtOAc solution was washed with water and brine and dried ($MgSO_4$). The solution was concentrated at reduced pressure, and the product was chromatographed on silica gel, eluting with 25% EtOAc/hexane, and crystallized from MeOH/hexane to give 6.16 g (61% yield) of **9e**: mp 75−80 °C; MS (FD) 337 (M^+). Anal. ($C_{21}H_{23}NO_3$) C, H, N.

Using the above procedure, the following conversions were made using the appropriately substituted alkyl halides: **5b** to **9b**; **5e** to **9t** and **9z**; **5h** to **9g**; **5j** to **9j**; **5k** to **9k**; **5f** to **9n**−**s**, **9u**, **9w**−**y**, **9aa**, **9ac**, **9ad**, and **9ag**; **5i** to **9v** and **9ab**.

6-Chloro-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic acid methyl ester (9b) (chromatography on silica gel, gradient, 20−50% Et_2O/hexane): yield 67%; mp 64−66 °C; MS (FD^+) 343 (M − 1, 100), 345 (M + 1, 37). Anal. ($C_{19}H_{18}ClNO_3$) C, H, N, Cl.

5-Bromo-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid ethyl ester (9g) (chromatography on silica gel, 33% EtOAc/hexane): yield 42%; mp 83−84 °C; MS (FD^+) 385 (M − 1) 387 (M + 1). Anal. ($C_{20}H_{20}BrNO_2$) C, H, N.

5-Methoxy-1-(phenylmethyl)-2-propyl-1*H*-**indole-3-acetic acid methyl ester (9j)** (chromatography on silica gel, 25% EtOAc/hexane): yield 71%; oil; MS (FD) 352 (M^+). Anal. ($C_{21}H_{25}N_3O_2$) C, H, N.

2-Cyclopropyl-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic acid methyl ester (9k) (chromatography on silica gel, gradient, 5−15% EtOAc/toluene): yield 40%; oil; MS (FD^+) 349 (M^+). Anal. ($C_{22}H_{23}NO_3$) C, H, N.

2-Chloro-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic acid methyl ester (9l) (chromatography on silica gel, gradient, 5−15% Et_2O/hexane): yield 79%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.35−7.25 (m, 4H), 7.15−7.05 (m, 4H), 6.85 (dd, 1H), 5.35 (s, 2H), 3.85 (s, 3H), 3.80 (s, 2H), 3.75 (s, 3H).

5-Methoxy-2-methyl-1-(1-phenylethyl)-1*H*-indole-3-acetic acid ethyl ester (9n) (chromatography on silica gel, 25% EtOAc/hexane): yield 22%; oil; MS (FD^+) 337 (M^+). Anal. ($C_{22}H_{25}NO_3$) C, H, N.

1-(Diphenylmethyl)-5-methoxy-2-methyl-1*H*-**indole-3-acetic acid ethyl ester (9o)** (chromatography on silica gel, 25% EtOAc/hexane): yield 54%; oil; MS (FD^+) 413 (M^+). Anal. ($C_{27}H_{27}NO_3$) C, H, N.

5-Methoxy-1-[(3-methoxyphenyl)methyl]-2-methyl-1*H*-indole-3-acetic acid ethyl ester (9p) (chromatography on silica gel, 20% EtOAc/hexane, crystallization, MeOH): yield 58%; mp 88−90 °C; MS (FD^+) 367 (M^+). Anal. ($C_{22}H_{25}NO_4$) C, H, N.

1-[[3-(Benzyloxy)phenyl]methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic acid ethyl ester (9q) (chromatography on silica gel, 20% EtOAc/hexane, crystallization, MeOH): yield 42%; mp 60−70 °C. Anal. ($C_{28}H_{29}NO_4$) C, H, N.

5-Methoxy-2-methyl-1-[(3-nitrophenyl)methyl]-1*H*-indole-3-acetic acid ethyl ester (9r) (chromatography on silica gel, 25% EtOAc/hexane, crystallization, MeOH): yield 8%; mp 105−106 °C; MS (FD^+) 382 (M^+). Anal. ($C_{21}H_{22}N_2O_5$) C, H, N.

1-[(2-Chlorophenyl)methyl]-5-methoxy-2-methyl-1*H*-**indole-3-acetic acid ethyl ester (9s)** (chromatography on silica gel, 30% EtOAc/hexane, crystallization, MeOH): yield 56%; mp 74−77 °C; MS (FD) 371 (M − 1, 100), 373 (M + 1, 40). Anal. ($C_{21}H_{22}ClNO_3$) C, H, N.

1-[(3-Chlorophenyl)methyl]-4-methoxy-2-methyl-1*H*-indole-3-acetic acid ethyl ester (9t) (chromatography on silica gel, 20% EtOAc/hexane): yield 70%; mp 113−115 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.30−6.72 (m, 6H), 6.49 (d, 1H), 5.24 (s, 2H), 4.16 (q, 2H), 3.92 (s, 2H), 3.89 (s, 3H), 2.24 (s, 3H), 1.24

(t, 3H); MS (FD$^+$) 371 (M − 1, 100), 373 (M + 1, 36). Anal. ($C_{21}H_{22}ClNO_3$) H, N; C: calcd, 67.83; found, 70.39.

1-[(3-Chlorophenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic acid ethyl ester (9u) (chromatography on silica gel, 20% EtOAc/hexane): yield 70%; mp 113−115 °C; MS (FD$^+$) 371 (M − 1, 100), 373 (M + 1, 60). Anal. ($C_{21}H_{22}ClNO_3$) C, H, N.

1-[(3-Chlorophenyl)methyl]-2-ethyl-5-methoxy-1*H*-indole-3-acetic acid methyl ester (9v) (chromatography on silica gel, 25% EtOAc/hexane): yield 75%; oil; MS (FD$^+$) 371 (M − 1, 100), 373 (M + 1, 38). Anal. ($C_{22}H_{24}ClNO_3$) C, H, N.

1-[(4-Chlorophenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic acid ethyl ester (9w) (chromatography on silica gel, 30% EtOAc/hexane, crystallization, MeOH): yield 47%; mp 98−100 °C; MS (FD$^+$) 371 (M − 1, 100), 373 (M + 1, 43). Anal. ($C_{21}H_{22}ClNO_3$) C, H, N.

1-[(2,5-Dichlorophenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic acid ethyl ester (9x) (chromatography on silica gel, 20% EtOAc/hexane, crystallization, MeOH): yield 29%; mp 146−148 °C; MS (FD$^+$) 405 (M − 1, 100), 407 (M + 1, 75). Anal. ($C_{21}H_{21}Cl_2NO_3$) C, H, N.

1-[(2,6-Dichlorophenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic acid ethyl ester (9y) (chromatography on silica gel, 20% EtOAc/hexane): yield 68%; mp 131−131 °C; MS (FD$^+$) 405 (M − 1, 100), 407 (M + 1, 70). Anal. ($C_{21}H_{21}Cl_2NO_3$) C, H, N.

1-([1,1′-Biphenyl]-2-ylmethyl)-4-methoxy-2-methyl-1*H*-indole-3-acetic acid ethyl ester (9z) (chromatography on silica gel, 20% EtOAc/hexane): yield 71%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.64−7.08 (m, 8H), 7.95 (t, 1H), 6.74 (d, 1H), 6.53−6.41 (m, 2H), 5.16 (s, 2H), 4.1 (q, 2H), 3.90 (s, 2H), 3.88 (s, 3H), 2.15 (s, 3H), 1.25 (t, 3H).

1-([1,1′-Biphenyl]-2-ylmethyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid ethyl ester (9aa) (chromatography on silica gel, 25% EtOAc/hexane): yield 69%; oil; MS (FD$^+$) 413 (M$^+$). Anal. ($C_{27}H_{27}NO_3$) C, H, N.

1-([1,1′-Biphenyl]-2-ylmethyl)-2-ethyl-5-methoxy-1*H*-indole-3-acetic acid methyl ester (9ab) (chromatography on silica gel, 20% EtOAc/hexane): yield 44%; oil; MS (FD$^+$) 413 (M$^+$). Anal. ($C_{27}H_{27}NO_3$) C, H, N.

1-([1,1′-Biphenyl]-3-ylmethyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid ethyl ester (9ac) (chromatography on silica gel, 33% EtOAc/hexane): yield 62%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.54−7.26 (m, 8H), 7.15 (d, 1H), 7.08 (d, 1H), 6.88 (d, 1H), 6.79 (dd, 1H), 5.35 (s, 2H), 4.13 (q, 2H), 3.88 (s, 3H), 3.71 (s, 2H), 2.38 (s, 3H), 1.24 (t, 3H); MS (FD$^+$) 413.5 (M$^+$). Anal. ($C_{27}H_{27}NO_3$) H, N; C: calcd, 78.42; found, 80.59.

5-Methoxy-2-methyl-1-(2-pyridylmethyl)-1*H*-indole-3-acetic acid ethyl ester (9ad) (chromatography on silica gel, 50% EtOAc/hexane): yield 75%; oil; MS (FD) 338 (M$^+$). Anal. ($C_{20}H_{22}N_2O_3$) C, H, N.

5-Methoxy-2-methyl-1-(3-phenylpropyl)-1*H*-indole-3-acetic acid ethyl ester (9ag) (chromatography on silica gel, 25% EtOAc/hexane): yield 58%; oil; MS (FD$^+$) 365 (M$^+$). Anal. ($C_{23}H_{27}NO_3$) C, H, N.

2-Methyl-5-phenyl-1-(phenylmethyl)-1*H*-indole-3-acetic Acid Ethyl Ester (9h). To 25 mL of EtOH were added 266 mg (0.7 mmol) of **9g**, 194 mg (0.168 mmol) of Pd[P(Ph)$_3$]$_4$, and 3.2 mL of a 2 M Na_2CO_3 solution. To this solution was added 196 mg (1.6 mmol) of phenylboronic acid in 5 mL of EtOH and the resulting mixture heated to maintain reflux for 16 h. After cooling, the mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with water and a saturated NaCl solution, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was chromatographed on silica gel, eluting with 25% EtOAc/hexane, and then recrystallized twice from MeOH to give 95 mg (35% yield) of **9h**: mp 115−117 °C; MS (FD$^+$) 383 (M$^+$). Anal. ($C_{26}H_{25}NO_2$) C, H, N.

2-Bromo-6-chloro-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic Acid Methyl Ester (9m). A mixture of 1.0 g (3.0 mmol) of **9b** and 600 mg (3.3 mmol) of NBS in 100 mL of CCl_4 was stirred for 30 h. The mixture was washed with an aqueous $Na_2S_2O_3$ solution, washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica gel, eluted with a gradient of 20% Et_2O/hexane−Et_2O, to give 1.0 g (79% yield) of the title compound that melted at 133−134 °C after crystallization from CH_2Cl_2/Et_2O: ^{1}H NMR ($CDCl_3$) ∂ 7.35−7.20 (m, 4H), 7.15−700 (m, 3H), 5.25 (s, 2H), 3.90 (s, 3H), 3.75 (s, 2H), 3.70 (s, 3H); MS (FD) 421 (M − 1, 80%), 423 (M + 1, 100%). Anal. ($C_{19}H_{17}BrClNO_3$) H, N; C: calcd, 53.99; found, 54.70; Br: calcd, 18.90; found, 16.04; Cl: calcd, 8.40; found, 9.97.

5-Hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetic Acid Ethyl Ester (9ai). A solution of **9c** (8.1 g, 20.3 mmol) in 150 mL of EtOH and 25 mL THF was hydrogenated with 3 g of 10% Pd/C catalyst at approximately 40 psi of hydrogen. The catalyst was filtered, and the filtrate was concentrated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 30−50% Et_2O/hexane to give 5.7 g (yield 90%) of **9ai**: ^{1}H NMR ($CDCl_3$) ∂ 7.40−7.30 (m, 3H), 7.25−7.10 (m, 5H), 6.80 (dd, 1H), 6.00 (s, 1H), 5.25 (s, 2H), 4.25 (q, 2H), 3.75 (s, 3H), 1.30 (t, 3H).

1-[(3-Hydroxyphenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic Acid Ethyl Ester (9al). A solution of 357 mg (0.8 mmol) of **9q** in 30 mL of 1:1 THF/EtOH was hydrogenated at 60 psi of hydrogen for 16 h using 90 mg of Pd/$BaSO_4$. The catalyst was filtered and the filtrate concentrated at reduced pressure. The residue was dissolved in EtOAc and washed with water and saturated NaCl solution. After drying over $MgSO_4$, the product was chromatographed on silica gel, eluting with 50% EtOAc/hexane, and then EtOAc to give, after crystallization from MeOH, 100 mg (35% yield) of **9al**: mp 114−116 °C; MS (FD$^+$) 353 (M$^+$). Anal. ($C_{21}H_{23}NO_4$) C, H, N.

1-[(3-Aminophenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic Acid Ethyl Ester (9ak). A solution of 500 mg (1.3 mmol) of **9r** in 50 mL of EtOH was hydrogenated for 16 h at room temperature using 0.1 g of 5% Pd/C and 60 psi of hydrogen. The catalyst was filtered and the filtrate concentrated at reduced pressure. The residue was chromatographed on silica gel, eluting with 25% EtOAc/hexane to give 234 mg (51% yield) of **9ak** as an oil: MS (FD$^+$) 352 (M$^+$). Anal. ($C_{21}H_{24}N_2O_3$) C, H, N.

5-Carboxy-1-[(3-chlorophenyl)methyl]-2-methyl-1*H*-indole-3-acetic Acid Methyl Ester (9aj). A solution of 0.27 g (0.65 mmol) of **9ah** and 2 mL of 5 N NaOH in 40 mL of EtOH was heated to maintain reflux for 4 h. After cooling, the mixture was diluted with water and extracted with EtOAc. The EtOAc solution which contained some precipitate was concentrated at reduced pressure, and the residue (containing a dicarboxylic acid) was crystallized from MeOH to give 100 mg (43% yield) of **9aj**: mp 216−217 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.15 (s, 1H), 7.71 (d, 1H), 7.45 (d, 1H), 7.38−7.29 (m, 2H), 7.04 (s, 1H), 6.94 (d, 1H), 5.50 (s, 2H), 3.84 (s, 2H), 3.65 (s, 3H), 2.32 (s, 3H); MS (FD) 371 (M$^+$). Anal. ($C_{20}H_{18}ClNO_4$) C, H; N: calcd, 3.77; found, 3.10.

2-Methyl-1-phenyl-1*H*-indoleacetic Acid Ethyl Ester (9am). Diphenylhydrazine hydrochloride (**11**, 4.6 g, 21 mmol) and 3 mL of ethyl levulinate in 250 mL of benzene was heated at reflux with a water separator for 48 h, cooled, washed with water, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica gel, eluting with 30% Et_2O/hexane to give 4.5 g of the hydrazone intermediate, **12**. A mixture of 2 g (6.45 mmol) of **12** and 3 mL of phosphorous trichloride in 125 mL of 1,2-dichloroethane was heated to maintain reflux for 17 h, cooled, and stirred with a mixture of ice and concentrated ammonia. The organic layer was separated and washed with brine, dried (Na_2SO_4), and evaporated at reduced pressure. The residue was chromatographed on silica gel, eluting with 10% Et_2O/hexane to give 0.98 g (52% yield) of **9am** as an oil: ^{1}H NMR ($CDCl_3$) ∂ 7.75 (d, 1H), 7.65−7.45 (m, 3H), 7.40 (d, 2H), 7.25 −7.15 (m, 3H), 4.25 (q, 2H), 3.85 (s, 2H), 2.35 (s, 3H), 1.15 (t, 3H).

5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic Acid (13a). A solution of 438 mg (2.0 mmol) of 5-methoxy-2-methyl-1*H*-indole-3-acetic acid (**6b**) in 5 mL of THF and 25 mL of DMSO was treated with 160 mg (4.0 mmol) of NaH (60% in mineral oil) and then with 0.3 mL of benzyl bromide for 16 h. The solution which contained 5-methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid benzyl ester was diluted with 2 N NaOH, stirred for 6 h, and washed with Et_2O. The

aqueous solution was acidified with 5 N HCl, extracted with brine, dried (Na_2SO_4), and evaporated at reduced pressure to give, after crystallization from EtOH, 540 mg (yield 87%) of **13a**: mp 173−174 °C; MS (FD^+) 309 (M^+). Anal. ($C_{19}H_{19}NO_3$) C, H, N.

5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic Acid Methyl Ester (9an). A solution of 0.2 g of **13a** in 50 mL of MeOH and 1 mL of methanesulfonic acid was refluxed for 3 h, diluted with water, and extracted with EtOAc. The organic phase was washed with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated at reduced pressure to give 100 mg (yield 48%) of **9an** as an oil which solidified on standing, mp 72−75 °C. Anal. ($C_{20}H_{21}NO_3$) C, H, N.

2-Chloro-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic Acid Phenylmethyl Ester (9ap). A solution of 2.0 g (10 mmol) of 5-methoxy-1*H*-indole-3-acetic acid (**6c**) in 100 mL of DMF was treated in portions with 1.0 g (25 mmol) of 60% NaH/mineral oil, and after 10 min, 3 mL of benzyl bromide was added. After 22 h, the mixture was diluted with water and extracted with EtOAc, and the EtOAc solution was washed with water and saturated NaCl solution and dried over Na_2SO_4. After the mixture was concentrated at reduced pressure, the residue was chromatographed on silica gel, eluting with CH_2Cl_2, to give 3.7 g (96% yield) of 5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic acid phenylmethyl ester (**9ao**) as an oil: ^1H NMR ($CDCl_3$) ∂ 7.35−7.15 (m, 9H), 7.10−7.00 (m, 4H), 6.75 (dd, 1H), 5.15 (s, 2H), 5.10 (s, 2H), 3.75 (s, 3H), 3.70 (s, 2H). While cooling at −5 °C, 0.6 mL (4.9 mmol) of boron trifluoride etherate was added to 770 mg (2 mmol) of **9ao** in 100 mL of CH_2Cl_2, followed by 0.24 mL (3 mmol) of SO_2Cl_2. After 10 min, an aqueous $NaHCO_3$ solution was added, and the CH_2Cl_2 layer was separated, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica gel, eluting with a gradient of 15% Et_2O/hexane−Et_2O, to give 100 mg (12% yield) of **9ap**: ^1H NMR ($CDCl_3$) ∂ 7.35−7.15 (m, 8H), 7.05−6.95 (m, 3H), 6.90 (d, 1H), 6.70 (dd, 1H), 5.25 (s, 2H), 5.10 (s, 2H), 3.75 (s, 3H), 3.70 (s, 2H).

2-Bromo-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic Acid Phenylmethyl Ester (9aq). With stirring, 450 mg (2.5 mmol) of *N*-bromosuccinimide was added to 910 mg (2.4 mmol) of **9ao** in 75 mL of CCl_4. After 15 min, the reaction mixture was washed with an aqueous $Na_2S_2O_3$ solution, water, and a saturated NaCl solution and dried over Na_2SO_4. After the mixture was concentrated at reduced pressure, the residue was chromatographed on silica gel, eluting with CH_2Cl_2, and crystallized from Et_2O/hexane to give 420 mg (69% yield) of **9aq**: mp 89−90 °C; MS (FD) 463 (M − 1), 465 (M + 1). Anal. ($C_{25}H_{22}BrNO_3$) C, H, N.

5-Methoxy-2-(methylthio)-1-(phenylmethyl)-1*H*-indole-3-acetic Acid Phenylmethyl Ester (9ar). A solution of 1.0 mL (11 mmol) of dimethyl disulfide in 25 mL of CH_2Cl_2 was cooled to −25 °C, 0.8 mL (10 mmol) of SO_2Cl_2 was added, the cooling bath was removed, and the mixture was stirred and let warm to room temperature. Three milliliters of this solution was added to 770 mg (2 mmol) of **9ao** in 100 mL of CH_2Cl_2. After 0.5 h, the reaction mixture was washed with an aqueous Na_2CO_3 solution and a saturated NaCl solution and dried over Na_2SO_4. After the mixture was concentrated at reduced pressure, the residue was chromatographed on silica gel, eluted with a gradient of 20−30% Et_2O/hexane, and crystallized from Et_2O/hexane to give 600 mg (70% yield) of **9ar**: mp 89−90 °C: MS (FD^+) 431 (M^+). Anal. ($C_{26}H_{25}NO_3S$) C, H, N, S.

5-Methoxy-2-(methylsulfinyl)-1-(phenylmethyl)-1*H*-indole-3-acetic Acid Phenylmethyl Ester (9as). To a solution of 460 mg (1 mmol) of **9ar** in 50 mL of CH_2Cl_2 was added 200 mg (1.0 mmol) of *m*-chloroperbenzoic acid (80−85% pure), and the mixture was stirred for 0.75 h. The reaction mixture was washed with a Na_2CO_3 solution, dried (Na_2SO_4), and concentrated at reduced pressure to give a residue that was chromatographed on silica gel, eluted with CH_2Cl_2 and then Et_2O, and crystallized from EtOH to give 424 mg (95% yield) of **9as** as a solid: MS (FD) 447 (M^+). Anal. ($C_{26}H_{25}NO_4S$) C, H, N, S.

5-Methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic Acid Hydrazide (10a). A solution of 1.4 g (4.33 mmol) of **9a** and 10 mL of hydrazine in 75 mL of EtOH was heated to maintain reflux for 16 h. On cooling of the reaction mixture, a precipitate formed that was filtered to give 1.33 g (93% yield) of **10a**: mp 143−144 °C; MS (FD^+) 309 (M^+). Anal. ($C_{18}H_{19}N_3O_2$) C, H, N.

Using this procedure, **9d**,**f**,**i**,**af**,**ap**−**as** were converted to **10d**,**f**,**i**,**af**,**ap**−**as**, respectively.

2-Methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid hydrazide (10d) (crystallization, MeOH): yield 60%; mp 140−143 °C; MS (FD^+) 293 (M^+). Anal. ($C_{18}H_{19}N_3O$) C, H, N.

5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid hydrazide (10f) (trituration with Et_2O): yield 96%; mp 161−162 °C; MS (FD) 323 (M^+). Anal. ($C_{19}H_{21}N_3O_2 \cdot 0.8H_2O$) C, H, N.

2-Ethyl-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic acid hydrazide (10i) (crystallized from reaction mixture): yield 77%; mp 138−140 °C; MS (FD^+) 337 (M^+). Anal. ($C_{20}H_{23}N_3O_2$) C, H, N.

1-Decyl-5-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10af) (crystallization, MeOH): yield 32%; mp 129−131 °C; MS (FD^+) 373 (M^+). Anal. ($C_{22}H_{35}N_3O_2$) C, H, N.

2-Chloro-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic acid hydrazide (10ap) (trituration with Et_2O): yield 100%; mp 186−187 °C; ^1H NMR (DMSO-d_6) ∂ 9.25 (br s, 1H), 7.40−7.10 (m, 7H), 6.90 (dd, 1H), 5.35 (s, 2H), 4.20 (br s, 2H), 3.70 (s, 3H), 3.45 (s, 2H); MS (FD) 343 (M − 1, 100%), 345 (M + 1, 60%). Anal. ($C_{18}H_{18}ClN_3O_2$) H, Cl; C: calcd, 62.88; found, 62.31; N: calcd, 12.22; found, 11.30.

2-Bromo-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic acid hydrazide (10aq) (chromatography on silica gel, Et_2O, then EtOAc): yield 71%; mp 178−180 °C; ^1H NMR (DMSO-d_6) ∂ 9.30 (br s, 1H), 7.40−7.05 (m, 7H), 6.80 (dd, 1H), 5.45 (s, 2H), 4.30 (br s, 2H) 3.80 (s, 3H), 3.55 (s, 2H); MS (FD^+) 387 (M − 1), 389 (M + 1). Anal. ($C_{18}H_{18}BrN_3O_2$) H, N; C: calcd, 55.68; found, 54.02; Br: calcd, 20.58; found, 23.17.

5-Methoxy-2-(methylthio)-1-(phenylmethyl)-1*H*-indole-3-acetic acid hydrazide (10ar) (crude product): yield 100%; mp 181−182 °C; MS (FD) 355 (M^+). Anal. ($C_{19}H_{21}N_3O_2S$) C, H, N, S.

5-Methoxy-2-(methylsulfinyl)-1-(phenylmethyl)-1*H*-indole-3-acetic acid hydrazide (10as) (crystallization, EtOAc): yield 85%; mp 172−174 °C; MS (FD) 371 (M^+). Anal. ($C_{19}H_{21}N_3O_3S$) C, H, N, S.

4-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid hydrazide (10e). A solution of 2.8 g (8.3 mmol) of **9e** and 10 mL of hydrazine in 40 mL of EtOH was heated to maintain reflux for 16 h, diluted with water, and extracted with EtOAc. The EtOAc solution was washed with brine, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was crystallized from MeOH to give 2.0 g (75% yield) of **10e**: mp 145−147 °C; MS (FD) 323 (M^+). Anal. ($C_{19}H_{21}N_3O_2$) C, H, N.

Using the above procedure, **9g**,**h**,**j**−**k**,**o**−**z**,**aa**−**ad**,**ag**,**aj**−**am** were converted to **10g**,**h**,**j**−**k**,**o**−**z**,**aa**−**ad**,**ag**,**aj**−**am**, respectively.

5-Bromo-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid hydrazide (10g) (crystallization, MeOH): yield 43%; mp 181−182 °C; MS (FD^+) 371 (M − 1), 373 (M + 1). Anal. ($C_{18}H_{18}BrN_3O$) C, H, N.

2-Methyl-5-phenyl-1-(phenylmethyl)-1*H*-indole-3-acetic acid hydrazide (10h) (crystallization, MeOH): yield 35%; mp 154−156 °C; MS (FD^+) 369 (M^+). Anal. ($C_{24}H_{23}N_3O$) C, H, N.

5-Methoxy-1-(phenylmethyl)-2-propyl-1*H*-indole-3-acetic acid hydrazide (10j) (crystallization, MeOH): yield 74%; mp 140−141 °C; MS (FD^+) 351 (M^+). Anal. ($C_{21}H_{25}N_3O_2$) C, H, N.

2-Cyclopropyl-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetic acid hydrazide (10k) (crystallization, EtOH): yield 74%; mp 173−174 °C; MS (FD^+) 349 (M^+). Anal. ($C_{21}H_{23}N_3O_2$) C, H, N.

5-Methoxy-2-methyl-1-(1-phenylethyl)-1*H*-indole-3-acetic acid hydrazide (10n) (chromatography on silica gel, EtOAc): yield 59%; foam; MS (FD^+) 337 (M^+). Anal. ($C_{20}H_{23}N_3O_2$) C, H, N.

1-(Diphenylmethyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10o) (chromatography on silica gel, 5% MeOH/EtOAc): yield 28%; foam; ^{1}H NMR ($CDCl_3$) ∂ 7.45−6.80 (m, 12H), 6.58 (s, 1H), 3.84 (s, 3H), 3.71 (s, 2H), 2.26 (s, 3H); MS (FD$^+$) 399 (M$^+$). Anal. ($C_{25}H_{25}N_3O_2$) H; C: calcd, 75.16; found, 77.25; N: calcd, 10.52; found, 8.89.

5-Methoxy-1-[(3-methoxyphenyl)methyl]-2-methyl-1*H*-indole-3-acetic acid hydrazide (10p) (crystallization, MeOH): yield 62%; mp 161−163 °C. Anal. ($C_{20}H_{23}N_3O_3$) C, H, N.

1-[[3-(Benzyloxy)phenyl]methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10q) (crystallization, MeOH): yield 51%; mp 130−132 °C; MS (FD$^+$) 353 (M$^+$). Anal. ($C_{26}H_{27}N_3O_3$) C, H, N.

5-Methoxy-2-methyl-1-[(3-nitrophenyl)methyl]-1*H*-indole-3-acetic acid hydrazide (10r) (crystallization, MeOH): yield 38%; mp 177−179 °C; ^{1}H NMR ($CDCl_3$) ∂ 8.14 (d, 1H), 7.91 (s, 1H), 7.47 (t, 1H), 7.33−6.74 (m, 5H), 5.39 (s, 2H), 3.86 (s, 3H), 3.73 (s, 2H), 2.3 (s, 3H); MS (FD) 368 (M$^+$). Anal. ($C_{19}H_{20}N_4O_4$) H, N; C: calcd, 61.95; found, 62.53.

1-[(2-Chlorophenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10s) (crystallization, MeOH): yield 53%; mp 99−100.5 °C; MS (FD) 357 (M − 1, 100), 359 (M + 1, 49). Anal. ($C_{19}H_{20}ClN_3O_2$) C, H, N.

1-[(3-Chlorophenyl)methyl]-4-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10t) (crystallization, MeOH): yield 98%; mp 160−162 °C; MS (FD$^+$) 357 (M − 1, 100), 359 (M + 1, 36). Anal. ($C_{19}H_{20}ClN_3O_2$) C, H, N.

1-[(3-Chlorophenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10u) (crystallization, EtOAc): yield 98%; mp 160−162 °C; MS (FD) 357 (M − 1, 100), 359 (M + 1, 43). Anal. ($C_{19}H_{20}ClN_3O_2$) C, H, N.

1-[(3-Chlorophenyl)methyl]-2-ethyl-5-methoxy-1*H*-indole-3-acetic acid hydrazide (10v) (crystallization, MeOH): yield 62%; mp 115−117 °C. Anal. ($C_{20}H_{22}ClN_3O_2$) C, H, N.

1-[(4-Chlorophenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10w) (crystallization, MeOH): yield 78%; mp 177−180 °C; MS (FD) 357 (M − 1, 100), 359 (M + 1, 33). Anal. ($C_{19}H_{20}ClN_3O_2$) C, H, N.

1-[(2,5-Dichlorophenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10x) (crystallization, MeOH): yield 64%; mp 168−170 °C; MS (FD$^+$) 391 (M − 1, 100), 393 (M + 1, 66). Anal. ($C_{19}H_{19}Cl_2N_3O_2$) C, H, N.

1-[(2,6-Dichlorophenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10y) (crystallization, MeOH): yield 61%; mp 194−196 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.45−7.20 (m, 3H), 6.50−6.40 (m, 2H), 6.38 (d, 1H), 6.21 (dd, 1H), 5.50 (s, 2H), 3.84 (s, 3H), 3.67 (s, 2H), 2.3 (s, 3H); MS (FD$^+$) 391 (M − 1, 100), 393 (M + 1, 64). Anal. ($C_{19}H_{19}Cl_2N_3O_2$) H, N; C: calcd, 58.17; found, 58.65.

1-([1,1′-Biphenyl]-2-ylmethyl)-4-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10z) (chromatography on silica gel, EtOAc, then 10% MeOH/EtOAc): yield 56%; mp 148−150 °C; MS (FD$^+$) 399 (M$^+$). Anal. ($C_{25}H_{25}N_3O_2$) C, H, N.

1-([1,1′-Biphenyl]-2-ylmethyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10aa) (chromatography on silica gel, EtOAc): yield 28%: wax; MS (FD$^+$) 399 (M$^+$). Anal. ($C_{25}H_{25}N_3O_2$) C, H, N.

1-([1,1′-Biphenyl]-2-ylmethyl)-2-ethyl-5-methoxy-1*H*-indole-3-acetic acid hydrazide (10ab) (crystallization, MeOH): yield 49%; mp 67−73 °C; MS (FD$^+$) 413 (M$^+$). Anal. ($C_{26}H_{27}N_3O_2$) C, H, N.

1-([1,1′-Biphenyl]-3-ylmethyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10ac) (crystallization, MeOH): yield 66%; mp 159−160 °C; MS (FD$^+$) 399 (M$^+$). Anal. ($C_{25}H_{25}N_3O_2$) C, H, N.

5-Methoxy-2-methyl-1-(2-pyridylmethyl)-1*H*-indole-3-acetic acid hydrazide (10ad) (crystallization, MeOH): yield 67%; mp 147−148 °C; MS (FD$^+$) 324 (M$^+$). Anal. ($C_{18}H_{20}N_4O_2$) C, H, N.

5-Methoxy-2-methyl-1-(3-phenylpropyl)-1*H*-indole-3-acetic acid hydrazide (10ag) (crystallization, MeOH): yield 31%; mp 133−135 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.41−6.7 (m, 9H), 4.24 (t, 2H), 3.83 (s, 3H), 3.66 (s, 2H), 2.70 (t, 3H), 2.54 (br s, 2H), 2.28 (s, 3H), 2.16−2.00 (m, 2H); MS (FD) 336 (M$^+$). Anal. ($C_{21}H_{25}N_3O_2$) H, N; C: calcd, 74.97; found, 73.81.

5-Carboxy-1-[(3-chlorophenyl)methyl]-2-methyl-1*H*-indole-3-acetic acid hydrazide (10aj) (crystallization, EtOH): yield 10%; mp 216−217 °C; MS (FD) 371 (M − 1, 100), 373 (M + 1, 50). Anal. ($C_{19}H_{18}ClN_3O_3$) C, H, N.

1-[(3-Aminophenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10ak) (crystallization, MeOH): yield 40%; mp 154−156 °C; MS (FD) 338 (M$^+$). Anal. ($C_{19}H_{22}N_4O_2$) C, H, N.

1-[(3-Hydroxyphenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetic acid hydrazide (10al) (crystallization, MeOH): yield 47%; mp 201−203 °C; MS (FD$^+$) 339 (M$^+$). Anal. ($C_{19}H_{21}N_3O_3$) C, H, N.

2-Methyl-1-phenyl-1*H*-indoleacetic acid hydrazide (10am) (crystallization, MeOH): yield 73%; mp 113−115 °C; MS (FD$^+$) 279 (M$^+$). Anal. ($C_{17}H_{17}N_3O$) C, H, N.

Using the procedure described for **5a**, the following indolealkanoic acid esters (**14**) were made by reacting 5-methoxy-2-methyl-1*H*-indole (**4o**) with methyl 2-bromopropanoate, ethyl 2-bromobutyrate, and ethyl 2-bromooctanoate, respectively.

2-(5-Methoxy-2-methyl-1*H*-indol-3-yl)propanoic acid methyl ester (14a) (chromatography on silica gel, 10% EtOAc/hexane): yield 59%; oil; MS (FD$^+$) 247 (M$^+$). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

2-(5-Methoxy-2-methyl-1*H*-indol-3-yl)butanoic acid ethyl ester (14b) (chromatography on silica gel, gradient, toluene−10% EtOAc/toluene): yield 56%; oil; MS (FD$^+$) 275 (M$^+$). Anal. ($C_{16}H_{21}NO_3$) C, H, N.

2-(5-Methoxy-2-methyl-1*H*-indol-3-yl)octanoic acid ethyl ester (14c) (additional 6 h at 80 °C, chromatography on silica gel, gradient, toluene−10% EtOAc/toluene): yield 34%; oil; MS (FD$^+$) 331 (M$^+$). Anal. ($C_{20}H_{29}NO_3$) C, H, N.

Using the procedure described for **9e**, the following indoles, **15a**−**c**, were prepared by reacting **14a**−**c** with benzyl bromide.

2-[5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indol-3-yl]propanoic acid methyl ester (15a) (chromatography on silica gel, gradient, toluene−10% EtOAc/toluene): yield 61%; oil; MS (FD) 338 (M$^+$). Anal. ($C_{21}H_{23}NO_3$) C, H, N.

2-[5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indol-3-yl]butanoic acid ethyl ester (15b) (chromatography on silica gel, 25% EtOAc/hexane): yield 79%; oil; MS (FD$^+$) 365 (M$^+$). Anal. ($C_{23}H_{27}NO_3$) C, H, N.

2-[5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indol-3-yl]octanoic acid ethyl ester (15c) (chromatography on silica gel, 25% EtOAc/hexane): yield 86%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.35−7.20 (m, 4H), 7.08 (d, 1H), 6.94 (d, 2H), 6.75 (dd, 1H), 5.27 (s, 2H), 4.20-4.00 (m, 2H), 3.88 (s, 3H), 3.79 (t, 1H), 2.34 (s, 3H), 2.30−2.15 (m, 1H), 2.05−1.90 (m, 1H), 1.40−1.15 (m, 11H), 0.84 (t, 3H); MS (FD$^+$) 421 (M$^+$). Anal. ($C_{27}H_{35}NO_3$) C, N; H: calcd, 8.37; found, 7.49.

Using the procedure for **10e**, the following conversions of esters to acid hydrazides were made, **15a**−**c** to **16a**−**c**.

2-[5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indol-3-yl]propanoic acid hydrazide (16a) (chromatography on silica gel, gradient, CH_2Cl_2−10% MeOH/CH_2Cl_2): yield 40%; wax; MS (FD) 323 (M$^+$). Anal. ($C_{19}H_{21}N_3O_2$) C, H, N.

2-[5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indol-3-yl]butanoic acid hydrazide (16b) (chromatography on silica gel, 50% EtOAc/hexane, then EtOAc): yield 35%; oil; MS (FD) 337 (M$^+$). Anal. ($C_{20}H_{23}N_3O_2$) C, H, N.

2-[5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indol-3-yl]octanoic acid hydrazide (16c) (chromatography on silica gel, 50% EtOAc/hexane, then EtOAc): yield 56%; oil; MS (FD) 393 (M$^+$). Anal. ($C_{24}H_{31}N_3O_2$) C, H, N.

5-Methoxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (17a). One gram of Raney nickel was added to 790 mg (2.4 mmol) of **10a** in 120 mL of EtOH and the mixture heated at reflux for 2 h. After the catalyst was filtered off, the filtrate was concentrated at reduced pressure and the residue triturated with Et_2O to give 675 mg (89% yield) of **17a**: mp 156−158 °C; MS (FD$^+$) 294 (M$^+$). Anal. ($C_{18}H_{18}N_2O_2\cdot 0.8H_2O$) C, H, N.

Using the above method, the following acetic acid hydrazides were converted to acetamides: **10e**,**f**,**i**,**j**,**k**,**t**,**u**,**v**,**z**,**aa**,**ag**,**ad**,**af** to **17b**−**l**,**17r**−**s**, respectively:

4-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (17b) (chromatography on silica gel, 5% MeOH/EtOAc): yield 79%; mp 145−146 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.34−7.21 (m, 3H), 7.04 (t, 1H), 6.96 (d, 2H), 6.88 (d, 1H), 6.54 (d, 1H), 6.11 (br s, 1H), 5.29 (s, 2H), 5.19 (br s, 1H), 3.95 (s, 3H), 3.88 (s, 2H), 2.34 (s, 3H); MS (FD) 308 (M^+). Anal. ($C_{19}H_{20}N_2O_2$) H, N; C: calcd, 74.08; found, 75.09.

5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (17c) (filtered through silica gel, EtOAc, crystallization, CH_2Cl_2/MeOH): yield 25%; mp 130−131 °C; MS (FD^+) 308 (M^+). Anal. ($C_{19}H_{20}N_2O_2$) C, H, N.

2-Ethyl-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (17d) (chromatography on silica gel, 50% EtOAc/hexane, EtOAc, and then 5% MeOH/EtOAc, crystallization, MeOH): yield 21%; mp 161−166 °C; MS (FD^+) 322 (M^+). Anal. ($C_{20}H_{22}N_2O_2$) C, H, N.

5-Methoxy-1-(phenylmethyl)-2-propyl-1*H*-indole-3-acetamide (17e) (chromatography on silica gel, EtOAc, crystallization, MeOH): yield 36%; mp 154−156 °C. Anal. ($C_{21}H_{24}N_2O_2$) C, H, N.

2-Cyclopropyl-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (17f) (crystallization, EtOH/water): yield 49%; mp 156−158 °C; MS (FD^+) 334 (M^+). Anal. ($C_{21}H_{22}N_2O_2$) C, H, N.

1-[(3-Chlorophenyl)methyl]-4-methoxy-2-methyl-1*H*-indole-3-acetamide (17g) (chromatography on silica gel, EtOAc): yield 77%; mp 171−173 °C; MS (FD^+) 342 (M^+). Anal. ($C_{19}H_{19}ClN_2O_2$) C, H, N.

1-[(3-Chlorophenyl)methyl]-5-methoxy-2-methyl-1*H*-indole-3-acetamide (17h) (chromatography on silica gel, EtOAc): yield 77%; mp 171−173 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.34−6.76 (m, 7H), 5.63 (br s, 1H), 5.36−5.20 (m, 3H), 3.85 (s, 3H), 3.70 (s, 2H), 2.32 (s, 3H).

1-[(3-Chlorophenyl)methyl]-2-ethyl-5-methoxy-1*H*-indole-3-acetamide (17i) (chromatography on silica gel, EtOAc): yield 74%; foam; MS (FD^+) 357 (M^+). Anal. ($C_{19}H_{20}ClN_3O_2$) C, H, N.

1-([1,1′-Biphenyl]-2-ylmethyl)-4-methoxy-2-methyl-1*H*-indole-3-acetamide (17j) (crude product): yield 71%; mp 173−175 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.62−7.08 (m, 8H), 7.04 (t, 1H), 6.78 (d, 1H), 6.5 (d, 1H), 6.48 (d, 1H), 6.07 (br s, 1H), 5.17 (s, 3H), 3.96 (s, 3H), 3.82 (s, 2H), 2.20 (s, 3H); MS (FD^+) 384 (M^+). Anal. ($C_{25}H_{24}N_2O_2$) H, N; C: calcd, 78.10; found, 78.94.

1-([1,1′-Biphenyl]-2-ylmethyl)-5-methoxy-2-methyl-1*H*-indole-3-acetamide (17k) (chromatography on silica gel, EtOAc): yield 67%; ^{1}H NMR ($CDCl_3$) ∂ 7.74−6.74 (m, 11H), 6.46 (d, 1H), 5.59 (br s, 1H), 5.31 (br s, 1H), 5.17 (s, 2H), 3.86 (s, 3H), 3.67 (s, 2H), 2.18 (s, 3H); MS (FD) 384 (M^+).

5-Methoxy-2-methyl-1-(3-phenylpropyl)-1*H*-indole-3-acetamide (17l) (chromatography on silica gel, EtOAc, crystallization, MeOH): yield 25%; mp 129−132 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.45−6.70 (m, 8H), 5.59 (br s, 1H), 5.25 (br s, 1H), 4.07 (t, 2H), 3.84 (s, 3H), 3.65 (s, 2H), 2.70 (t, 2H), 2.33 (s, 3H), 2.20−2.0 (m, 2H); MS (FD) 336 (M^+). Anal. ($C_{21}H_{24}N_2O_2$) H, N; C: calcd, 74.97; found, 73.81.

5-Methoxy-2-methyl-1-(2-pyridylmethyl)-1*H*-indole-3-acetamide (17r) (chromatography on silica gel, EtOAc, then 5% MeOH/EtOAc): yield 28%; semisolid material; MS (FD^+) 309 (M^+). Anal. ($C_{18}H_{19}N_3O_2$) C, H, N.

1-Decyl-5-methoxy-2-methyl-1*H*-indole-3-acetamide (17s) (crystallization, EtOAc): yield 32%; mp 97−99 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.25 (d, 1H), 7.20 (br s, 1H), 7.04 (d, 1H), 6.77 (br s, 1H), 6.66 (dd, 1H), 4.04 (t, 2H), 3.80 (s, 3H), 3.42 (s, 2H), 2.34 (s, 3H), 1.70−1.50 (m, 2H), 1.35−1.17 (m, 14H), 0.88 (t, 3H); MS (FD^+) 358 (M^+). Anal. ($C_{22}H_{34}N_2O_2$) H, N; C: calcd, 73.70; found, 76.80.

2-Chloro-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (17m). There was added 5 mL of 0.67 M methylchloroaluminum amide in benzene to 344 mg (1 mmol) of **9l** in 20 mL of benzene, the mixture was heated to maintain reflux for 2 h, an additional 5 mL of aluminum reagent was added, and heating was continued for 1.5 h. After being cooled with an ice bath, the mixture was decomposed with 1 N HCl and extracted with EtOAc, and the EtOAc solution was washed with saturated NaCl, dried (Na_2SO_4), and concentrated at reduced pressure. Chromatography of the residue on silica gel, eluted with a gradient of CH_2Cl_2−2% MeOH/CH_2Cl_2, gave 50 mg of starting material (**9l**) and 165 mg (50% yield) of **17m**: mp 166−168 °C; MS (FD^+) 328 (M − 1, 100), 330 (M + 1, 36). Anal. ($C_{18}H_{17}ClN_2O_2$) C, H, N, Cl.

Using the above procedure, **9aq** and **9m** were converted to **17n** and **17o**, respectively.

2-Bromo-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (17n) (heated an additional 20 h, chromatography on silica gel, gradient, CH_2Cl_2−2% MeOH/CH_2Cl_2): yield 100; mp 172−174 °C; MS (FD^+) 372 (M − 1), 374 (M + 1). Anal. ($C_{18}H_{17}BrN_2O_2$) C, H, N, Br.

2-Bromo-6-chloro-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (17o) (crystallization, EtOH/CH_2Cl_2): yield 65%; mp 205 °C dec; ^{1}H NMR (DMSO-d_6) ∂ 7.60 (s, 1H), 7.40 (br s, 1H), 7.30−7.20 (m, 4H), 7.00 (d, 2H), 6.90 (br s, 1H), 5.40 (s, 2H), 3.80 (s, 3H), 3.50 (s, 2H); MS (FD) 406 (M − 1, 75), 408 (M + 1, 100). Anal. ($C_{18}H_{16}BrClN_2O_2$) H, N, Br; C: calcd, 53.03; found, 53.72; Cl: calcd, 8.70; found, 9.36.

5-Methoxy-2-(methylthio)-1-(phenylmethyl)-1*H*-indole-3-acetamide (17p). Surfuryl chloride (0.8 mL, 10 mmol) was added to an ice bath cooled solution of 1.0 mL of dimethyl disulfide in 25 mL of CH_2Cl_2, the cooling bath was removed, and the mixture was allowed to warm to room temperature. Three milliliters of this solution (containing methanesulfenyl chloride) was added to 320 mg (1.1 mmol) of **17a** in 100 mL of CH_2Cl_2, the mixture was stirred for 0.33 h, a saturated $NaHCO_3$ solution was added, the mixture was stirred well, and the CH_2Cl_2 solution was separated, washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed on silica gel, eluted with a gradient of 40% EtOAc/hexane−EtOAc, to give 115 mg (31% yield) of **17p**: mp 195−197 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.40 (br s, 1H), 7.25−7.15 (m, 4H), 7.05 (d, 1H), 6.95 (d, 2H), 6.90 (br s, 1H), 6.75 (dd, 1H), 3.70 (s, 3H), 3.60 (s, 2H), 2.10 (s, 3H); MS (FD) 340 (M^+). Anal. ($C_{19}H_{20}N_2O_2S$) H, N; C: calcd, 67.03; found, 66.57; S: calcd, 9.42; found, 9.88.

1-(Cyclohexylmethyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic Acid (13b). A solution of 3.1 g (9.0 mmol) of **9ae** and 5 mL of 5 N NaOH in 50 mL of EtOH was heated to maintain reflux for 3 h, diluted with water, and made acidic with 5 N HCl solution. The mixture was extracted with EtOAc, and the EtOAc solution was dried over Na_2SO_4 and concentrated at reduced pressure. The residue was crystallized from toluene to give 2.1 g (74% yield) of **13b**, melting at 173−175 °C after crystallization from toluene: MS (FD) 315 (M^+). Anal. ($C_{19}H_{25}NO_3$) C, H, N.

1-(Cyclohexylmethyl)-5-methoxy-2-methyl-1*H*-indole-3-acetamide (17q). A solution of 0.63 g (2.0 mmol) of **13b** in 25 mL of THF was cooled with an ice/water bath and 0.56 mL (4.0 mmol) of triethylamine was added followed by 0.163 mL (2.1 mmol) of methyl chloroformate. After 0.5 h, gaseous NH_3 was bubbled into the reaction mixture for 0.5 h, the cooling bath removed, and the mixture stirred for 2 h. It was then poured into water and extracted with EtOAc, and the EtOAc solution was washed with a Na_2CO_3 solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue gave 0.3 g (48% yield) of **17q**: mp 125−126 °C; MS (FD^+) 314 (M^+). Anal. ($C_{19}H_{26}N_2O_2$) C, H, N.

5-Methoxy-2-methyl-1*H*-indole-3-acetamide (18). To a solution of **6b** (307 mg, 1.4 mmol) in 20 mL THF at 0 °C were added 0.4 mL (2.8 mmol) of triethylamine and 0.17 mL (1.75 mmol) of ethyl chloroformate. The mixture was stirred for 30 min, ammonia gas was added for 30 min, and the mixture was stirred an additional 3 h. Water was added, and the mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), concentrated at reduced pressure, and then crystallized from CH_2Cl_2/MeOH to give 220 mg (yield 72%) of **18**: mp 102−120 °C; MS (FD^+) 218 (M^+). Anal. ($C_{12}H_{14}N_2O_2$) C, H, N.

1-Benzoyl-5-methoxy-2-methyl-1*H*-indole-3-acetamide (17t). To a suspension of 35 mg (0.87 mmol) of 60% NaH/minerial oil (previously washed with hexane) in 5 mL of DMF was added 190 mg (0.87 mmol) of **18**. After 1 h, 0.1 mL (0.87 mmol) of benzoyl chloride was added. After 4 h, the mixture was diluted with water, extracted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated at reduced

pressure. The residue was stirred with EtOAc, and **17t** was filtered off and dried to give 77 mg (27% yield): mp 209−214 °C; MS (FD$^+$) 322 (M$^+$). Anal. ($C_{19}H_{18}N_2O_3$) C, H, N.

4-Methoxy-1-(phenylmethyl)-1*H*-indole (19a). 4-Methoxy-1*H*-indole (**4p**) (1.5 g, 10 mmol) was dissolved in 20 mL of DMF, and 400 mg (10 mmol) of 60% NaH/minerial oil was added. After 1 h, 1.2 mL (10 mmol) of benzyl bromide was added. After 3.5 h, the mixture was diluted with water and extracted twice with EtOAc. The combined EtOAc was washed with brine, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with 20% EtOAc/hexane to give 1.77 g (75% yield) of **19a**: MS (FD) 237 (M$^+$). Anal. ($C_{16}H_{15}NO$) C, H, N.

Using the procedure above, the following conversions were made: **4o** to **19b**; **4b** to **19c**; 2-methyl-5-nitro-1*H*-indole (**4q**) to **19d**; **4c** to **19e** and **19h** (alkylated with 3-chlorobenzyl bromide); 2-ethyl-4-nitro-1*H*-indole (**4r**) to **19f**; **4e** to **19g**; **4d** to **19i**; and **4f** to **19j**.

5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole (19b) (chromatography on silica gel, 25% EtOH/hexane, crystallization, MeOH/CH_2Cl_2): yield 45%; mp 113−115 °C; MS (FD$^+$) 251 (M$^+$). Anal. ($C_{17}H_{17}NO$) C, H, N.

6-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole (19c) (crude product): yield 63%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.35−7.17 (m, 4H), 7.00 (d, 2H), 6.75 (d, 1H), 6.67 (s, 1H), 5.25 (s, 2H), 3.77 (s, 3H), 2.34 (s, 3H); MS (FD$^+$) 251 (M$^+$). Anal. ($C_{17}H_{17}NO$) H; C: calcd, 81.24; found, 80.52; N: calcd, 5.57; found, 4.78.

2-Methyl-5-nitro-1-(phenylmethyl)-1*H*-indole (19d) (crystallization, EtOAc): yield 75%; mp 150−152 °C; MS (FD$^+$) 266 (M$^+$). Anal. ($C_{16}H_{14}N_2O_2$) C, H, N.

2-Ethyl-4-methoxy-1-(phenylmethyl)-1*H*-indole (19e) (chromatography on silica gel, gradient, 5−10% Et_2O/hexane): yield 90%; oil; MS (FD$^+$) 265 (M$^+$). Anal. ($C_{18}H_{19}NO$) C, H, N.

2-Ethyl-4-nitro-1-(phenylmethyl)-1*H*-indole (19f) (chromatography on silica gel, gradient, 25−50% EtOAc/hexane): yield 84%; oil; MS (FD) 281 (M$^+$). Anal. ($C_{17}H_{16}N_2O_2$) C, H, N.

2-Ethyl-6-isopropyl-5-methoxy-1-(phenylmethyl)-1*H*-indole (19g) (chromatography on silica gel, 20% EtOAc/hexane): yield 47%; oil; ^{1}H NMR (DMSO-d_6) ∂ 7.34−6.76 (m, 7H), 6.17 (s, 1H), 5.36 (s, 2H), 3.77 (s, 3H), 3.35−3.15 (m, 1H), 2.78−2.60 (m, 2H), 1.30−1.00 (m, 9H); MS (FD$^+$) 307 (M$^+$). Anal. ($C_{21}H_{25}NO$) H; C: calcd, 82.04; found, 80.95; N: calcd, 4.56; found, 4.11.

1-[(3-Chlorophenyl)methyl]-2-ethyl-4-methoxy-1*H*-indole (19h) (chromatography on silica gel, gradient, 20−40% CH_2Cl_2/hexane): yield 51%; oil; MS (FD) 299 (M − 1, 100), 301 (M + 1, 37). Anal. ($C_{18}H_{18}ClNO$) C, H, N, Cl.

2-Ethyl-5-methoxy-1-(phenylmethyl)-1*H*-indole (19i) (chromatography on silica gel, 20% EtOAc/hexane): yield 49%; oil; MS (FD$^+$) 265 (M$^+$). Anal. ($C_{18}H_{19}NO$) C, H, N.

2-Ethyl-5-methoxy-6-methyl-1-(phenylmethyl)-1*H*-indole (19j) (chromatography on silica gel, 10% EtOAc/hexane): yield 57%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.49−6.90 (m, 7H), 6.26 (s, 1H), 5.25 (s, 2H), 3.87 (s, 3H), 2.65 (q, 2H), 2.27 (s, 3H), 1.29 (t, 3H); MS (FD$^+$) 279 (M$^+$). Anal. ($C_{19}H_{21}NO$) H, N; C: calcd, 81.68; found, 83.01.

4-Methoxy-α-oxo-1-(phenylmethyl)-1*H*-indole-3-acetamide (20a). Oxalyl chloride (0.63 mL, 7.2 mmol) was added to 1.7 g (7.2 mmol) of **19a** in 20 mL of CH_2Cl_2, and the mixture was stirred for 1 h and concentrated at reduced pressure. The residue was redissolved in 25 mL of CH_2Cl_2, anhydrous ammonia bubbled in for 0.25 h, and the mixture concentrated. The residue was stirred with EtOAc and the insoluble material filtered to give a mixture of 1.42 g of **20a** and ammonium chloride: ^{1}H NMR (DMSO-d_6) ∂ 8.48 (s, 1H), 8.05−708 (m, 9H), 6.72 (d, 1H), 5.50 (s, 2H), 3.80 (s, 3H); MS (FD) 308 (M$^+$). Anal. ($C_{18}H_{16}N_2O_3 \cdot 1.8NH_4Cl$) C, H, N.

Using the above procedure, the following conversions were made: **19b**−**h** to **20b**−**h**.

5-Methoxy-2-methyl-α-oxo-1-(phenylmethyl)-1*H*-indole-3-acetamide (20b) (chromatography on silica gel, EtOAc, crystallization, MeOH): yield 23%; mp 205−207 °C; MS (FD$^+$) 322 (M$^+$). Anal. ($C_{19}H_{18}N_2O_3$) C, H, N.

6-Methoxy-2-methyl-1-α-oxo-1-(phenylmethyl)-1*H*-indole-3-acetamide (20c) (crystallization, EtOAc): yield 34%; mp 230−234 °C; ^{1}H NMR (DMSO-d_6) ∂ 8.20 (br s, 1H), 7.95 (d, 1H), 7.75 (br s, 1H), 7.40−7.20 (m, 3H), 7.17 (d, 1H), 7.04 (d, 2H), 6.88 (dd, 1H), 5.55 (s, 2H), 3.75 (s, 3H), 2.61 (s, 3H); MS (FD) 322 (M$^+$). Anal. ($C_{19}H_{18}N_2O_3$) H, N; C: calcd, 70.79; found, 70.11.

2-Methyl-5-nitro-α-oxo-1-(phenylmethyl)-1*H*-indole-3-acetamide (20d) (crystallization, MeOH): yield 67%; mp 204−206 °C; MS (FD$^+$) 337 (M$^+$). Anal. ($C_{18}H_{15}N_3O_4$) C, H, N.

2-Ethyl-4-methoxy-α-oxo-1-(phenylmethyl)-1*H*-indole-3-acetamide (20e) (crude product washed with H_2O/EtOAc and Et_2O): yield 36%; mp 193−199 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.98 (br s, 1H), 7.80−6.90 (m, 8H), 6.67 (d, 1H), 5.52 (s, 2H), 3.77 (s, 3H), 2.89 (q, 2H), 1.06 (t, 3H); MS (FD$^+$) 336 (M$^+$). Anal. ($C_{20}H_{20}N_2O_3$) H; C: calcd, 71.41; found, 66.22; N: calcd, 8.33; found, 10.42.

2-Ethyl-4-nitro-α-oxo-1-(phenylmethyl)-1*H*-indole-3-acetamide (20f) (chromatography on silica gel, 20% EtOAc/hexane): yield 75%; mp 207−208 °C; MS (FD$^+$) 351 (M$^+$). Anal. ($C_{19}H_{17}N_3O_4$) C, H, N.

2-Ethyl-6-isopropyl-5-methoxy-α-oxo-1-(phenylmethyl)-1*H*-indole-3-acetamide (20g) (chromatography on silica gel, 50% EtOAc/hexane): yield 58%, wax; MS (FD) 378 (M$^+$). Anal. ($C_{23}H_{26}N_2O_3$) C, H, N.

1-[(3-Chlorophenyl)methyl]-2-ethyl-4-methoxy-α-oxo-1*H*-indole-3-acetamide (20h) (chromatography-50% EtOAc/hexane, then EtOAc, crystallization, MeOH): yield 75%; mp 186−189 °C; MS (FD) 370 (M − 1, 100), 372 (M + 1, 25). Anal. ($C_{20}H_{19}ClN_2O_3$) C, H, N.

2-Ethyl-5-methoxy-α-oxo-1-(phenylmethyl)-1*H*-indole (20i) (chromatography on silica gel, gradient, CH_2Cl_2−4% MeOH/CH_2Cl_2): yield 18%; MS (FD$^+$) 336 (M$^+$). Anal. ($C_{20}H_{20}N_2O_3 \cdot 0.8MeOH$) C, H, N.

4-Methoxy-α-hydroxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (21a). A mixture of 1.4 g (4.5 mmol) of **20a** and 213 mg (5.6 mmol) of $NaBH_4$ and 50 mL of EtOH was stirred for 20 h, 213 mg (5.6 mmol) of $NaBH_4$ was added, and the mixture was stirred for an additional 20 h, filtered, and evaporated at reduced pressure. The residue was stirred with EtOAc and water, and the insoluble material was filtered to give 600 mg (43%) of **23a**: mp 179−182 °C; MS (FD) 310 (M$^+$). Anal. ($C_{18}H_{18}N_2O_3$) C, H, N.

Using the above procedure, the following were converted: **20b**−**e**,**g**,**h** to **21b**−**e**,**gm**,**h**.

α-Hydroxy-5-methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (21b) (crystallization, MeOH): yield 83%; solid; ^{1}H NMR ($CDCl_3$) ∂ 7.37−6.70 (m, 9H), 6.08 (br s, 1H), 5.62 (br s, 1H), 5.39 (s, 1H), 5.26 (s, 2H), 3.83 (s, 3H), 2.40 (s, 3H); MS (FD$^+$) 324 (M$^+$). Anal. ($C_{18}H_{20}N_2O_3$) C, calcd 70.35, found 68.75; H, calcd 6.21, found 5.55; N, calcd 8.64, found 8.14.

α-Hydroxy-6-methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (21c) (washed with EtOAc): yield 63%; mp 196−198 °C; MS (FD) 324 (M$^+$). Anal. ($C_{19}H_{20}N_2O_3$) C, H, N.

α-Hydroxy-2-methyl-5-nitro-1-(phenylmethyl)-1*H*-indole-3-acetamide (21d) (crude product): yield 100%; mp 120−124 °C; MS (FD$^+$) 339 (M$^+$). Anal. ($C_{18}H_{17}N_3O_4$) C, H, N.

2-Ethyl-α-hydroxy-4-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (21e) (crude product washed with Et_2O): yield 88%; mp 160−162 °C; MS (FD$^+$) 339 (M$^+$). Anal. ($C_{20}H_{22}N_2O_3$) C, H, N.

2-Ethyl-α-hydroxy-6-isopropyl-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (21g) (triturated with Et_2O/hexane): yield 91%; mp 155−157 °C; MS (FD$^+$) 380 (M$^+$). Anal. ($C_{23}H_{28}N_2O_3$) C, H, N.

1-[(3-Chlorophenyl)methyl]-2-ethyl-α-hydroxy-4-methoxy-1*H*-indole (21h) (crystallization, MeOH): yield 39%; mp 134−136 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.34−6.84 (m, 8H), 6.55 (d, 1H), 5.54 (d, 1H), 5.40 (s, 2H), 5.33 (d, 1H), 3.85 (s, 3H), 2.86−2.64 (m, 2H), 1.03 (t, 3H); MS (FD) 372 (M$^+$). Anal. ($C_{20}H_{21}ClN_2O_3$) H; C: calcd, 64.43; found, 65.61; N: calcd, 7.51; found, 11.24.

4-Methoxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (17u). A solution of 600 mg (1.9 mmol) of **21a** and 0.32 mL (2 mmol) of triethylsilane in 5 mL of trifluoroacetic acid was stirred for 16 h and concentrated under reduced pressure. The residue was dissolved in EtOAc and water, and the EtOAc was separated, washed with brine, and dried ($MgSO_4$). The residue was chromatographed on silica gel, eluted first with 50% EtOAc/hexane and then EtOAc, to give, after crystallization from MeOH, 262 mg (47% yield) of **17u**: mp 184−187 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.34−6.96 (m, 9H), 6.77 (br s, 1H), 6.47 (t, 1H), 5.31 (s, 2H), 3.81 (s, 3H), 3.60 (s, 2H); MS (FD) 294 (M^+). Anal. ($C_{18}H_{18}N_2O_2$) C, calcd 73.45, found 77.20; H, calcd 6.16, found 6.80; N, calcd 9.52, found 9.13.

By the above procedure, additional acetamides were prepared from α-hydroxyacetamides: **21c** to **17v**, **21d** to **17w**, **21e** to **17x**, **21g** to **17y**, and **21h** to **17z**:

6-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (17v) (chromatography on silica gel, 33% EtOAc/hexane, crystallization, CH_2Cl_2/MeOH): yield 24%; mp 136−139 °C; MS (FD^+) 308 (M^+). Anal. ($C_{19}H_{20}N_2O_2$) C, H, N.

2-Methyl-5-nitro-1-(phenylmethyl)-1*H*-indole-3-acetamide (17w) (chromatography on silica gel, EtOAc, crystallization, MeOH/CH_2Cl_2): yield 52%; mp 189−192 °C; MS (FD^+) 323 (M^+). Anal. ($C_{18}H_{17}N_3O_3$) C, H, N.

2-Ethyl-4-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (17x) (chromatography on silica gel, 50% EtOAc/hexane, then EtOAc): yield 62%; mp 152−154 °C; MS (FD^+) 322 (M^+). Anal. ($C_{20}H_{22}N_2O_2$) C, H, N.

2-Ethyl-6-isopropyl-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (17y) (triturated with Et_2O/MeOH): yield 76%; mp 153−155 °C; MS (FD^+) 364 (M^+). Anal. ($C_{23}H_{28}N_2O_2$) C, H, N.

1-[(3-Chlorophenyl)methyl]-2-ethyl-4-methoxy-1*H*-indole-3-acetamide (17z) (chromatography on silica gel, EtOAc): yield 48%; oil; ^{1}H NMR ($CDCl_3$) ∂ 7.35−6.74 (m, 6H), 6.58 (d, 1H), 6.25 (br s, 1H), 5.71 (br s, 1H), 5.29 (s, 2H), 3.97 (s, 3H), 3.86 (s, 2H), 2.75 (q, 2H), 1.13 (t, 3H); MS (FD^+) 364 (M^+).

5-Amino-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (17aa). A solution of 205 mg (0.634 mmol) of **17w** in 30 mL of 2:1 THF/EtOH was hydrogenated at 60 psi of hydrogen for 4 h using 0.1 g of Pd/C as catalyst. The catalyst was filtered and the filtrate concentrated at reduced pressure. The residue was chromatographed on silica gel, eluting with EtOAc and then 5% MeOH/EtOAc to give 52 mg (28% yield) of **17aa**: mp 175−178 °C; MS (FD) 293 (M^+). Anal. ($C_{18}H_{19}N_3O$) C, H, N.

3-[2-Methyl-5-methoxy-1-(phenylmethyl)-1*H*-indol-3-yl]propanoic Acid Ethyl Ester (23). A solution 3.2 g (12.3 mmol) of 3-(2-methyl-5-methoxy-1*H*-indol-3-yl)propanoic acid ethyl ester (**22**, crude product from **7a** and 5-oxohexanoic acid ethyl ester as described for **5f**) in 40 mL of DMF was treated with 1.37 g (12.3 mmol) of potassium *tert*-butoxide for 0.5 h and then with 1.41 mL (12.3 mmol) of benzyl chloride for 24 h, poured into 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 toluene−10% EtOAc/toluene to give 1.66 g (yield 39%) of **23**: mp 53−54 °C; MS (FD^+) 351 (M^+). Anal. ($C_{22}H_{25}NO_3$) C, H, N.

3-[2-Methyl-5-methoxy-1-(phenylmethyl)-1*H*-indol-3-yl]propionamide (24). A solution of 800 mg (2.3 mmol) of **23** and 2 mL of hydrazine in 20 mL of EtOH was refluxed for 18 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 764 mg (yield 93%) of the intermediate propanoic acid hydrazide as a solid. This material and 0.3 g of Raney nickel catalyst (W-4) in 25 mL of EtOH were refluxed for 2.5 h. The solution was decanted and evaporated at reduced pressure and the residue chromatographed on silica gel, eluting with EtOAc, to give 715 mg (yield 97%) of **24**: mp 151−153 °C; MS (FD^+) 322 (M^+). Anal. ($C_{20}H_{22}N_2O_2$) C, H, N.

5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-thioacetamide (25). A mixture of 100 mg (0.32 mmol) of **17c** and 85 mg (0.2 mmol) of Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide] in 20 mL of toluene was refluxed 1 h, 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 CH_2Cl_2, to give **25**: 12 mg (yield 10%); ^{1}H NMR ($CDCl_3$) ∂ 7.35−7.25 (m, 3H), 7.15 (d, 1H), 7.05 (d, 1H), 6.95 (d, 2H), 6.85 (dd, 1), 5.23 (s, 2H), 3.90 (s, 3H), 3.7 (s, 2H), 2.35 (s, 3H).

5-Methoxy-2-methyl-1*H*-indole-3-acetonitrile (26). Using the procedure as described for **5a**, 6.45 g (40 mmol) of **4o**, 25 mL of 1.6 M *n*-BuLi/hexane (40 mmol), 40 mL of 1 M $ZnCl_2$/Et_2O (40 mmol), and 2.70 mL (40 mmol) of bromoacetonitrile were reacted to give after chromatography on silica gel, eluted with 5% EtOAc/toluene, 5.2 g (yield 65%) of **26**: mp 126−128 °C; MS (FD^+) 200 (M^+). Anal. ($C_{12}H_{12}N_2O$) C, H, N.

5-Methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetonitrile (27). Using the procedure described for **10a**, 2.0 g (10 mmol) of **26** was treated with 1.12 g (10 mmol) of *t*-BuOK and 1.15 mL (10 mmol) of benzyl chloride to give 2.0 g of **27** (chromatography on silica gel, 5% EtOAc/toluene): yield 69%; mp 126−128 °C; MS (FD^+) 290 (M^+). Anal. ($C_{19}H_{18}N_2O$) C, H, N.

5-Methoxy-2-methyl-1-(phenylmethyl)-3-[(1*H*-tetrazol-5-yl)methyl]-1*H*-indole (28a). A mixture of 2.0 g (6.9 mmol) of **27**, 4.8 g (35 mmol) of triethylamine hydrochloride, 2.3 g (30 mmol) of sodium azide, and 40 mL of DMF was heated at 95−105 °C for 20 h, cooled, concentrated at reduced pressure, acidified with 6 N HCl, and extracted with EtOAc. The organic phase was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by HPLC on an C-18 RP column, eluted with 2% MeOH/CH_2Cl_2 to give 1.4 g (yield 60%) of **28a**: solid; MS (FD^+) 333 (M^+). Anal. ($C_{19}H_{19}N_5O$) C, H, N.

3-(Amidinomethyl)-5-methoxy-2-methyl-1-(phenylmethyl)-1*H*-indole (28b). To a solution of 3 mmol of methylchloroaluminum amide[24] in 15 mL of toluene was added 290 mg (1.0 mmol) of **27**, and the resulting solution was refluxed for 16 h, cooled, diluted with EtOAc, washed with aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4, and evaporated at reduced pressure to give **28b**: 50 mg (yield 20%); ^{1}H NMR (DMSO-d_6) ∂ 9.00−8.60 (br s, 3H), 7.30−7.15 (m, 4H), 7.05 (s, 1H), 6.95 (d, 2H), 6.65 (d, 1H), 5.30 (s, 2H), 3.85 (s, 2H), 3.70 (s, 3H), 2.30 (s, 3H); MS (FD^+) 307 (M^+).

***N*,5-Dimethoxy-2-methyl-1-(phenylmethyl)-1*H*-indole-3-acetamide (29b).** A solution of 310 mg (1.0 mmol) of **13a** and 0.2 mL (1.4 mmol) of triethylamine in 50 mL of THF was cooled to −5 °C and treated with 0.1 mL (1.3 mmol) of methyl chloroformate for 10 min and then treated with a solution of methoxylamine prepared by stirring 250 mg (1.3 mmol) of methoxylamine hydrochloride and an excess of triethylamine in THF. The mixture was left overnight at room temperature, diluted 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 chromatographed on silica gel, eluting with a gradient of 50% Et_2O/hexane−Et_2O to give 45 mg of **29b** (yield 13%): mp 123−125 °C; ^{1}H NMR ($CDCl_3$) ∂ 8.40 (br s, 1H), 7.30−7.20 (m, 3H), 7.10 (d, 1H), 7.00−6.90 (m, 3H), 6.80 (dd, 1H), 5.25 (s, 2H), 3.80 (s, 3H), 3.65 (s, 3H), 2.30 (s, 3H); MS (FD) 338 (M^+). Anal. ($C_{20}H_{22}N_2O_3$) H; C: calcd, 70.99; found, 71.55; N: calcd, 8.28; found, 7.84.

Also prepared by this procedure from **13a** and methylamine was the following.

***N*,2-Dimethyl-5-methoxy-1-(phenylmethyl)-1*H*-indole-3-acetamide (29a)** (crystallization, Et_2O): yield 83%; mp 137−139 °C; ^{1}H NMR (DMSO-d_6) ∂ 7.70 (br s, 1H), 7.30−7.15 (m, 4H), 7.05 (d, 1H), 6.95 (d, 2H), 6.65 (dd, 1H), 5.30 (s, 2H), 3.75 (s, 3H), 3.45 (s, 2H), 2.55 (d, 3H), 2.25 (s, 3H); MS (FD^+) 322 (M^+). Anal. ($C_{20}H_{22}N_2O_2$) H, N; C: calcd, 74.51; found, 75.38.

(^{14}C)Oleate-Labeled *E. coli* Assay. A reaction mixture (total volume 250 μL) composed of 2.5×10^8 autoclaved *E. coli* labeled with [^{14}C]oleate[7] [a mix of labeled and unlabeled bacteria to provide approximately 10 000 counts per minute (cpm) of radioactivity], containing phospholipid, 40 mM of Tris-HCl, and 10 mM of $CaCl_2$, is incubated with enzyme (in

presence or absence of inhibitor) at 37 °C for 15 min, the reaction stopped by the addition of ice-cold 0.5% BSA, and the mixture promptly centrifuged at 10000*g* for 2 min at room temperature. The sedimented bacteria contain the undegraded phospholipids, and the albumin-complexed products of hydrolysis are in the supernatant. A measured sample of the supernatant is counted by liquid scintillation for quantification of hydrolysis.

Chromogenic Assay. The assay as described here has been adapted for high-volume screening using 96-well microtiter plates.

Reagents:

(A) Reaction Buffer: $CaCl_2 \cdot 2H_2O$, 1.47 g/L; KCl, 7.455 g/L; bovine serum albumin (fatty acid free), 1 g/L; Tris·HCl, 3.94 g/L; pH 7.5 (adjust with NaOH).

(B) Enzyme Buffer: 0.05 N $NaOAc \cdot 3H_2O$; 0.2 N NaCl; adjust pH to 4.5 with HOAc; DTNB, 5,5′-dithiobis(2-nitrobenzoic acid); racemic diheptanoylthiopc; racemic 1,2-bis(heptanoylthio)-1,2-dideoxy-*sn*-glycero-3-phosphorylcholine; TRITON X-100, prepared at 6.249 mg/mL in reaction buffer to equal 10 μM.

Reaction Mixture. A measured volume of racemic diheptanoylthio PC supplied in $CHCl_3$ at a concentration of 100 mg/mL is taken to dryness and redissolved in 10 mM Triton X-100 nonionic detergent aqueous solution. Reaction buffer is added to the solution, then DTNB to give the reaction mixture which contains 1 mM diheptanoylthio PC substrate, 0.29 mM Triton X-100 detergent, and 0.12 mM DTNB in a buffered aqueous solution at pH 7.5.

Assay procedure: (1) add 0.2 mL of reaction mixture to all wells; (2) add 10 μL of test compound (or solvent blank) to appropriate wells, mix 20 s; (3) add 50 ng of $sPLA_2$ (10 μL) to appropriate wells; (4) incubate plate at 40 °C for 30 min; (5) read absorbance of wells at 405 nm with an automatic plate reader.

Typically, the IC_{50} values were determined by diluting test compound serially 2-fold such that the final concentration in the reaction ranged from 45 to 0.35 μg/mL. More potent inhibitors required significantly greater dilution. In all cases, the percent inhibition measured at 405 nm generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions was determined. Each sample was titrated in triplicate, and result values were averaged for plotting and calculation of IC_{50} values. The IC_{50} values were determined by plotting log concentration versus inhibition values in the range from 10 to 90% inhibition.

Guinea Pig Lung Tissue Bath Assay. Male Hartley strain guinea pigs (500−700 g) were killed by cervical dislocation and their heart and lungs removed intact and placed in aerated (95% O_2:5% CO_2) Krebs' buffer. The composition of Krebs' buffer was (mM) as follows: NaCl, 118.2; KCl, 4.6; $CaCl_2 \cdot 2H_2O$, 2.5; $MgSO_4 \cdot 7H_2O$, 1.2; $NaHCO_3$, 24.8; KH_2PO_4, 1.0; and dextrose, 10.0. Dorsal pleural strips (4 × 1 × 25 mm) were dissected from intact parenchymal segments (8 × 4 × 25 mm) cut parallel to the outer edge of the lower lung lobes. Two adjacent pleural strips, obtained from a single lobe and representing a single tissue sample, were tied at either end and independently attached to a metal support rod. One rod was attached to a Grass force-displacement transducer (FT03C). Changes in isometric tension were displayed on a Modular Instruments monitor and thermal recorder. All tissues were placed in 10 mL jacketed tissue baths containing Krebs' buffer that was continuously aerated and maintained at 37 °C. Pleural strips from the opposite lobes of the lung were used for paired experiments. Preliminary data generated from tension/response curves demonstrated that resting tension of 800 mg was optimal. The tissues were allowed to equilibrate for 45 min as the bath fluid was changed periodically.

Initially tissues were challenged three times with KCl (40 mM) to test tissue viability and to obtain a consistent response. After the maximal response to KCl was recorded, the tissues were washed and allowed to return to baseline before the next challenge. Cumulative concentration−response curves were obtained from pleural strips by increasing the agonist concentration ($sPLA_2$ or arachidonic acid) in the tissue bath by half-$\log_{10}$ increments while the previous concentration remained in contact with the tissues.[25] Agonist concentration was increased after reaching the plateau of the contraction elicited by the preceding concentration. One concentration−response curve was obtained from each tissue. To minimize variability between tissues obtained from different animals, contractile responses were expressed as a percentage of the maximal response obtained with the final KCl challenge. When studying the effect of various drugs on the contractile effects of $sPLA_2$, the compounds and their respective vehicles were added to the tissues 30 min prior to starting the $sPLA_2$ concentration−response curves. This incubation period allowed for observation of any intrinsic contractile activity exhibited by the compounds, which was not a desirable characteristic.

Data from different experiments were pooled and presented as a percentage of the maximal KCl responses (mean ± SEM). To estimate the drug-induced rightward shifts in the concentration−response curves, the curves were analyzed simultaneously using statistical nonlinear modeling methods similiar to those described by Waud.[26] The model includes four parameters: the maximum tissue response which was assumed the same for each curve, the ED_{50} for the control curve, the steepness of the curves, and the pA_2 (apparent K_B), the concentration of antagonist that requires a 2-fold increase in agonist to achieve an equivalent response. The Schild slope was determined to be 1, using statistical nonlinear modeling methods similiar to those described by Waud.[26] The Schild slope equal to 1 indicates the model is consistent with the assumptions of a competitive antagonist; therefore the pA_2 or apparent K_B could be interpreted as the dissociation constant of the inhibitor.

To estimate the drug induced suppression of the maximal responses, $sPLA_2$ responses (10 μg/mL) were determined in the absence and presence of drug, and percent suppression was calculated for each pair of tissues.

Acknowledgment. We would like to acknowledge our colleagues at the Shionogi Research Laboratories, Osaka, Japan, who have collaborated with us during the course of this research project. We would also like to thank R. B. Hermann and R. E. Holmes for their SAR suggestions.

References

(1) (a) Kramer, R. M.; Johansen, B.; Hession, C.; Pepinsky, R. B. Characterization of a Secretable Phospholipase A_2 from Human Platelets. In *Advances in Prostoglandin, Thromboxane, and Leukotriene Research*, Samuelsson, B., Dahlen, S.-E., Fritsch, J., Hedqvist, P., Eds.; Raven Press: New York, 1990; Vol. 20, pp 79−86. (b) Stefanski, E.; Pruzanski, W.; Sternby, B.; Vadas, P. Purification of a soluble phospholipase A_2 from a synovial fluid in rheumatoid arthritis. *J. Biochem.* **1986**, *100*, 1297−1303. (c) Hara, S.; Kudo, I.; Matsuta, K.; Miyamoto, T.; Inoue, K. Amino acid composition and NH_2-terminal amino acid sequence of human phospholipase A_2 purified from rheumatoid synovial fluid. *J. Biochem.* **1988**, *104*, 326−328. (d) Kanda, A.; Ono, T.; Yoshida, N.; Tojo, H.; Okamoto, M. The primary structure of a membrane-associated phospholipase A_2 from human spleen. *Biochem. Biophys. Res. Commun.* **1989**, *163*, 42−48. (e) Seilhamer, J. J.; Plant, S.; Pruzanski, W.; Schilling, J.; Stefanski, E.; Vadas, P.; Johnson, L. K. Multiple forms of phospholipase A_2 in arthritic synovial fluid. *J. Biochem.* **1989**, *106*, 38−42.

(2) (a) Hara, S.; Kudo, I.; Chang, H. W.; Matsuta, K. Purification and characterization of extracellular phospholipase A_2 from human synovial fluid in rheumatoid arthritis. *J. Biochem.* **1989**, *105*, 395−399. (b) Lai, C.-Y.; Wada, K. Phospholipase A_2 from human synovial fluid: purification and structural homology to the placental enzyme. *Biochem. Biophys. Res. Commun.* **1988**, *157*, 488−493. (c) Bomalaski, J. S.; Lawton, P.; Browning, J. L. Human extracellular recombinant phospholipase A_2 induces an inflammatory response in rabbit joints. *J. Immunol.* **1991**, *146*, 3904−3910.

(3) Gronroos, J. M.; Nevalainen, T. J. Increased concentrations of synovial-type phospholipase A_2 in serum and pulmonary and renal complications in acute pancreatitis. *Digestion* **1992**, *52*, 232−236.

(4) (a) Green, J. A.; Smith, G. M.; Buchta, R.; Lee, R.; Ho, K. Y.; Rajkovic, I. A.; Scott, K. F. Circulating phospholipase A_2 activity associated with sepsis and septic shock is indistinguishable from that associated with rheumatoid arthritis. *Inflammation* **1991**, *15*, 355−367. (b) Santos, A. A.; et al. Are events after endotoxemia related to circulating phospholipase A_2? *Ann. Surg.* **1994**, *219*, 183−192. (c) Vadas, P.; Pruzanski, W. Induction of group II phospholipase A_2 expression and pathogenesis of the sepsis syndrome. *Circ. Shock* **1993**, *39*, 160−167.

(5) Uhl, W.; Buchler, M.; Nevalainen, T. J.; Deller, A.; Beger, H. G. Serum phospholipase A_2 in patients with multiple injuries. *J. Trauma* **1990**, *30*, 1285−1290.

(6) (a) Samuelsson, B.; Dahlen, S.-E.; Lindgren, J. A.; Rouzer, C. A.; Serhan, C. N. Leukotrienes and lipoxins: Structures, biosynthesis, and biological effects. *Science* **1987**, *237*, 1171−1176. (b)Nevalainen, T. J. Serum phospholipases A_2 in inflammatory diseases. *Clin. Chem.* **1993**, *39*, 2453−2459. (c) Pruzanski, W.; Vadas, P.; Browning, J. Secretory non-pancreatic group II phospholipase A_2: role in physiologic and inflammatory processes. *J. Lipid Med.* **1993**, *8*, 161−167.

(7) Elsbach, P.; Weiss, J. Utilization of Labeled *Escherichia coli* as Phospholipase Substrate. In *Methods in Enzymology*; Dennis, E. A., Ed.; Academic Press, Inc.: San Diego, 1991; Vol. 197, pp 24−31.

(8) Seilhamer, J. J.; Pruzanski, W.; Vadas, P.; Plant, S.; Miller, J. A.; Kloss, J.; Johnson, L. K. Cloning and recombinant expression of phospholipase A_2 present in rheumatoid arthritic synovial fluid. *J. Biol. Chem.* **1989**, *264*, 5335−5338.

(9) Snyder, D. W.; Sommers, C. D.; Bobbit, J. L.; Mihelich, E. D. Characterization of the contractile effects of human recombinant nonpancreatic secretory phospholipase A_2 (PLA_2) and other PLA_2s on guinea pig lung pleural strips. *J. Pharmacol. Exp. Ther.* **1993**, *266*, 1147−1155.

(10) Wery, J.-P.; Schevitz, R. W.; Clawson, D. K.; Bobbit, J. L.; Dow, E. R.; Gamboa, G.; Goodson, T. Jr.; Hermann, R. B.; Kramer, R. M.; McClure, D. B.; Mihelich, E. D.; Putnam, J. E.; Sharp, J. D.; Stark, D. H.; Tester, C.; Warrick, M. W.; Jones, N. D. Structure of recombinant human rheumatoid arthritic synovial fluid phospholipase A_2 at 2.2 Angstrom resolution. *Nature* **1991**, *352*, 79−82.

(11) (a) Schevitz, R. W.; Bach, N. J.; Carlson, D. G.; Chirgadze, N. Y.; Clawson, D. K.; Dillard, R. D.; Draheim, S. E.; Hartley, L. W.; Jones, N. D.; Mihelich, E. D.; Olkowski, J. L.; Snyder, D. W.; Sommers, C. D.; Wery, J.-P. Structure-based design of the first potent and selective inhibitor of human non-pancreatic secretory phospholipase A_2. *Nat. Struct. Biol.* **1995**, *2*, 458−465. (b) See the above reference for a complete description of this and other X-ray structures referred to in this publication.

(12) Reynolds, L. J.; Hughes, L. L.; Dennis, E. A. Analysis of human synovial fluid phospholipase A_2 on short chain phosphatidylcholine-mixed micelles: development of a spectrophotometric assay suitable for a microtiterplate reader. *Anal. Biochem.* **1992**, *204*, 190−197.

(13) Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippin, L. A.; Repke, D. B.; Souchet, M. Preparation of indoles and oxindoles from N-(*tert*-butoxycarbonyl)-2-alkylanilines. *Synthesis* **1991**, 871−878.

(14) Kremus, E.; Wakeman, N.; Hixon, R. M. Thymoquinone. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, pp 511−513.

(15) (a) Hlasta, D. J.; Bell, M. R. The directed lithiation of isogramine and subsequent reactions with electrophiles in the preparation of 2-substituted isogramine derivatives. *Heterocycles* **1989**, *29*, 849−852. (b) Katritzky, A. R.; Lue, P.; Chen, Y.-X. An alternative route to 2-substituted indoles via N-aminal-directed lithiation. *J. Org. Chem.* **1990**, *55*, 3688−3691.

(16) Ito, Y.; Sato, H.; Murakami, M. The first total synthesis of OPC-15161. *J. Org. Chem.* **1991**, *56*, 4864−4867.

(17) Robinson, B. *The Fischer Indole Synthesis*; John Wiley & Sons: New York, 1982.

(18) Miyaura, N.; Yanagi, T.; Suzuki, A. The palladium-catalyzed cross-coupling reaction of phenylboronic acid with haloarenes in the presence of bases. *Synth. Commun.* **1981**, *11*, 513−519.

(19) Baccolini, G.; Dalpozzo, R.; Todesco, P. E, Indolization by phosphorous trichloride of functionalized ketone arylhydrazones: Synthesis of pharmacologically interesting ketones. *J. Chem. Soc., Perkin. Trans. 1* **1988**, 971−973.

(20) Levin, J. I.; Turos, E.; Weinreb, S. M. An alternative procedure for the aluminum-mediated conversion of esters to amides. *Synth. Commun.* **1982**, *12*, 989−993.

(21) (a) Speeter, M. E.; Anthony, W. C. The action of oxalyl chloride on indoles: A new approach to tryptamines. *J. Am. Chem. Soc.* **1954**, *76*, 6208−6210. (b)Domschke, D.; Furst, H. Notiz zur darstellung einiger [1-benzyl-2-methyl-5-methoxy-indolyl-(3)]-glyoxylsaureamide. *Ber.* **1961**, *94*, 2353−2355.

(22) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. Silane reductions in acidic media. II. Reductions of aryl aldehydes and ketones by trialkylsilanes in trifluoroacetic acid. A selective method for converting the carbonyl group to methylene. *J. Org. Chem.* **1973**, *38*, 2675−2681.

(23) Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. Thiation with 2, 4-bis-(4-methoxyphenyl)-1, 3, 2, 4-dithiadiphosphetane 2, 4-disulfide: N-methylthiapyrrolidone. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 372−375.

(24) Garigipati, R. S. An efficient conversion of nitriles to amidines. *Tetrahedron Lett.* **1990**, *31*, 1969−1972.

(25) van Rossum, J. M. Cumulative dose-response curves. II. Technique for the making of dose-response curves in isolated organs and the evaluation of drug parameters. *Arch. Int. Pharmacodyn. Ther.* **1963**, *143*, 299−330.

(26) Waud, D. R. Analysis of Dose-Response Relationships. In *Advances in General and Cellular Pharmacology*; Narahashi, T., Bianchi, C. P., Eds.; Plenum Press; New York, 1976; Vol. 1, pp 145−178.

(27) Thunnissen, M. M. G. M.; Eiso A. B.; Kalk, K. H.; Drenth, J.; Dijkstra, B. W.; Kuipers, O. P.; Dijkman, R.; de Hass, G. H.; Verheij, H. M. X-ray structure of phospholipase A_2 complexed with a substrate-derived inhibitor. *Nature* **1990**, *347*, 689−691.

(28) Flaugh, M. E.; Crowell, T. A.; Clemens, J. A.; Sawyer, B. D. Synthesis and evaluation of the antiovulatory activity of a variety of melatonin analogues. *J. Med. Chem.* **1979**, *22*, 63−69.

(29) Noland, W. F.; Smith, L. R.; Johnson, D. C. Nitration of indoles. II. The mononitration of methylindoles. *J. Org. Chem.* **1963**, *28*, 2262−2266.

(30) Bergman, J.; Sand, P. Synthesis of indoles *via* ring closure of 2-alkylnitroaniline derivatives. *Tetrahedron* **1990**, *46*, 6085−6112.

JM960485V