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(54) Title: INHIBITORS OF HIV REVERSE TRANSCRIPTASE

(57) Abstract

Novel indole compounds inhibit HIV reverse transcriptase, and are useful in the prevention or treatment of infection by HIV and the treatment of AIDS, either as compounds, pharmaceutically acceptable salts, pharmaceutical composition ingredients, whether or not in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. Methods of treating AIDS and methods of preventing or treating infection by HIV are also described.

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TITLE OF THE INVENTION
INHIBITORS OF HIV REVERSE TRANSCRIPTASE

This application is a continuation-in-part of co-pending application U.S. Serial No. 07/866,765 filed April 9, 1992, which itself is a continuation-in-part of application U.S. Serial No. 07/832,260 filed February 7, 1992 and now abandoned, which itself was a continuation-in-part of application U.S. Serial No. 07/756,013, filed September 6, 1991, now abandoned.

The present invention is concerned with compounds which inhibit the reverse transcriptase encoded by human immunodeficiency virus (HIV) or pharmaceutically acceptable salts thereof and are of value in the prevention of infection by HIV, the treatment of infection by HIV and the treatment of the resulting acquired immune deficiency syndrome (AIDS). It also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds and other agents for the treatment of AIDS and viral infection by HIV.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is reverse transcription of the RNA genome by a virally encoded reverse transcriptase to generate DNA copies of HIV sequences, a required step in viral replication. It is known that some compounds are reverse transcriptase inhibitors and are effective agents in the treatment of AIDS and similar diseases, e.g., azidothymidine or AZT.

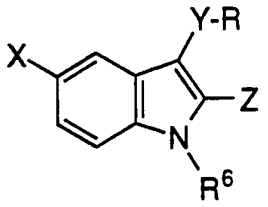
Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the

pol sequence encodes reverse transcriptase, an endonuclease and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature 329, 351 (1987)].

The compounds of this invention are inhibitors of HIV reverse transcriptase. Furthermore, the compounds of the present invention do not require bioactivation to be effective.

BRIEF DESCRIPTION OF THE INVENTION

Novel compounds of formula A:

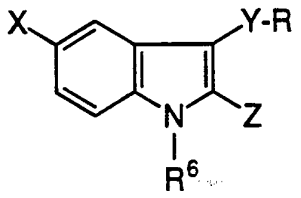


A

as herein defined, are disclosed. These compounds are useful in the inhibition of HIV reverse transcriptase, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS and/or ARC, either as compounds, pharmaceutically acceptable salts (when appropriate), pharmaceutical composition ingredients, whether or not in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. Methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV are also disclosed.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

This invention is concerned with the compounds of formula A described below, combinations thereof, or pharmaceutically acceptable salts or esters thereof, in the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by HIV and in the treatment of the resulting acquired immune deficiency syndrome (AIDS). The compounds of this invention include those with structural formula A:



A

wherein

X is -H, -Cl, -F, -Br, -NO_2, -CN, -OR^2, -NR^2R^2, -$NHSO_2$-C_{1-3}alkyl, or -NHCO-C_{1-3}alkyl;

Y is -$S(O)_n$- or -O-, wherein n is zero, 1 or 2;

R is

1) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
   a) -C_{1-5}alkyl,
   b) -C_{1-5}alkoxy,
   c) -OH, or
   d) aryl, unsubstituted or substituted with one or more of:
      i) -C_{1-5}alkyl,
      ii) -C_{1-5}alkoxy,
      iii) -OH,
      iv) halogen, or
      v) -NR^2R^2,
2) aryl, unsubstituted or substituted with one or more of:
   a) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
      i) -OH or
      ii) -C_{1-5}alkoxy,
   b) -C_{1-5}alkoxy,
   c) -OH,
   d) halogen, or
   e) -NR^2R^2,
3) heterocycle, unsubstituted or substituted with one or more of:

a) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
   i) -OH or
   ii) -C_{1-5}alkoxy,
b) -C_{1-5}alkoxy,
c) -OH,
d) halogen, or
e) -NR^2R^2, or

4) -NR^2R^3, provided that Y is -$S(O)_n$-;

Z is

1) $-\overset{\overset{W}{\|}}{C}-NR^2R^3$,

wherein W is O, S, -N-CN, or -N-OR^2,

2) -COR^{1a},

3) -$COOR^{1b}$,

4) -CR^2R^2-$S(O)_n$-R^{1a},

wherein n is defined above,

5) -$CR^2R^2NHR^4$,

6) -CR^2R^2-CO-R^5,

7) -C_{1-3}alkyl substituted with one or more of:
   a) aryl, unsubstituted or substituted with one or more of:
      i) -C_{1-5}alkyl,
      ii) -C_{1-5}alkoxy,
      iii) -OH,
      iv) halogen, or

v) $-NR^2R^2$, or

b) heterocycle, unsubstituted or substituted with one or more of:

i) $-C_{1-5}$alkyl,

ii) $-C_{1-5}$alkoxy,

iii) -OH,

iv) halogen, or

v) $-NR^2R^2$, or

8) -CN;

R^1 is

1) hydrogen,

2) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:

a) $-C_{1-5}$alkyl,

b) $-C_{1-5}$alkoxy,

c) -OH,

d) aryl, unsubstituted or substituted with one or more of:

i) $-C_{1-5}$alkyl,

ii) $-C_{1-5}$alkoxy,

iii) -OH,

iv) halogen, or

v) $-NR^2R^2$, or

e) heterocycle, unsubstituted or substituted with one or more of:

i) $-C_{1-5}$alkyl,

ii) $-C_{1-5}$alkoxy,

iii) -OH,

iv) halogen, or

v) $-NR^2R^2$, or

3) aryl, unsubstituted or substituted with one or more of:

a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:

i) -OH or
ii) -C_{1-5}alkoxy,

b) -C_{1-5}alkoxy,
c) -OH,
d) halogen,
e) -CN,
f) -NO_2, or
g) -NR^2R^2; or

4) heterocycle, unsubstituted or substituted with one or more of:
a) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
i) -OH or
ii) -C_{1-5}alkoxy,
b) -C_{1-5}alkoxy,
c) -OH,
d) halogen, or
g) -NR^2R^2;

R^{1a} is

1) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
a) -C_{1-5}alkyl,
b) -C_{1-5}alkoxy,
c) -OH,
d) aryl, unsubstituted or substituted with one or more of:
i) -C_{1-5}alkyl,
ii) -C_{1-5}alkoxy,
iii) -OH,
iv) halogen, or
v) -NR^2R^2, or
e) heterocycle, unsubstituted or substituted with one or more of:

i) -C_{1-5}alkyl,
ii) -C_{1-5}alkoxy,
iii) -OH,
iv) halogen, or
v) -NR^2R^2, or

2) aryl, unsubstituted or substituted with one or more of:
a) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
i) -OH or
ii) -C_{1-5}alkoxy,
b) -C_{1-5}alkoxy,
c) -OH,
d) halogen,
e) -CN,
f) -NO_2, or
g) -NR^2R^2;

3) heterocycle, unsubstituted or substituted with one or more of:
a) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
i) -OH or
ii) -C_{1-5}alkoxy,
b) -C_{1-5}alkoxy, or
c) -OH,
d) halogen, or
e) -NR^2R^2, or

4) C_{3-6}cycloalkyl;

R^{1b} is

1) -C_{1-5}alkyl substituted with one or more of:
a) -C_{1-5}alkoxy,
b) -OH,
c) aryl, unsubstituted or substituted with one or more of:

i) -C_{1-5}alkyl,
ii) -C_{1-5}alkoxy,
iii) -OH,
iv) halogen, or
v) -NR^2R^2, or

d) heterocycle, unsubstituted or substituted with one or more of:
i) -C_{1-5}alkyl,
ii) -C_{1-5}alkoxy,
iii) -OH,
iv) halogen, or
v) -NR^2R^2,

2) aryl, unsubstituted or substituted with one or more of:
a) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
i) -OH or
ii) -C_{1-5}alkoxy,
b) -C_{1-5}alkoxy,
c) -OH,
d) halogen,
e) -CN,
f) -NO_2, or
g) -NR^2R^2; or

3) heterocycle, unsubstituted or substituted with one or more of:
a) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
i) -OH or
ii) -C_{1-5}alkoxy,
b) -C_{1-5}alkoxy,
c) -OH,
d) halogen, or
e) -NR^2R^2;

R^2 is hydrogen or C_{1-3}alkyl;

R^3 is

1) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
   a) $-C_{1-5}$alkyl,
   b) $-C_{1-5}$alkoxy, unsubstituted or substituted with -OH,
   c) -OH,
   d) $-OC(O)R^7$;
   e) $-COOR^2$
   f) aryl, unsubstituted or substituted with one or more of:
      i) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of -OH,
      ii) $-C_{1-5}$alkoxy,
      iii) -OH,
      iv) halogen,
      v) $-NO_2$,
      vi) $-NR^2R^2$,
      vii) $-NHCO-C_{1-3}$alkyl, or
      viii) $-NHSO_2-C_{1-3}$alkyl,
   g) heterocycle, unsubstituted or substituted with one or more of:
      i) $-C_{1-5}$alkyl,
      ii) $-C_{1-5}$alkoxy,
      iii) -OH,
      iv) C_{1-3}alkyl-NR^2R^2,
      v) halogen,
      vi) oxo,
      vii) $-NO_2$,
      viii) $-NR2_R2$,
      ix) $-NHCO-C_{1-3}$alkyl, or
      x) $-NHSO_2-C_{1-3}$alkyl,
   h) $-NR^2R^2$,

i) -C_{3-6}cycloalkyl,

2) aryl, unsubstituted or substituted with one or more of:
   a) -C_{1-5}alkyl,
   b) -C_{1-5}alkoxy,
   c) -OH,
   d) halogen, or
   e) -NR^2R^2,

3) heterocycle, unsubstituted or substituted with one or more of:
   i) -C_{1-5}alkyl,
   ii) -C_{1-5}alkoxy,
   iii) -OH,
   iv) halogen, or
   v) -NR^2R^2,

4) -C_{1-5}alkoxy,
5) -OH,
6) -C_{3-6}cycloalkyl, or
7) hydrogen;

R^4 is
1) R^1 or
2) -COR^1;

R^5 is
1) R^1,
2) -C_{1-5}alkoxy,
3) -NHR^1, or
4) heterocycle, unsubstituted or substituted with one or more of:
   i) -C_{1-5}alkyl,
   ii) -C_{1-5}alkoxy,

iii) -OH,
iv) halogen, or
v) $-NR^2R^2$;

R^6 is

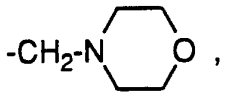
1) hydrogen,
2) $-COR^1$,
3) $-CONHR^1$;

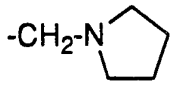
R^7 is

1) aryl, unsubstituted or substituted with one or more of -Cl, -Br, -OH, $-OCH_3$, or -CN, or
2) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of -OH or $-NR^2R^2$; and

with the proviso that when X is -H, Y is -S, R is unsubstituted phenyl and R^6 is -H,

Z is not $-CH_2$-SO-Ph, -COH,



, or 

;

or a pharmaceutically acceptable salt or ester thereof.

One embodiment of this invention encompasses compounds of Formula A further limited to:

X is -H, -Cl or -F;
Y is $-S(O)_n-$;
R is -Ph, -tolyl, 3-Cl-phenyl, 2-pyridyl or 2-thiazolyl;
R^6 is -H; and

Z is

$-\overset{\overset{W}{\|}}{C}-NR^2R^3$, $-COOR^{1b}$, $-COR^{1a}$,

$-CR^2R^2-S(O)_n-R^{1a}$ or

$-C_{1-3}$alkyl substituted with heterocycle.

One class of compounds within the first embodiment is further limited to compounds wherein

X is -H or -Cl;

Y is $-S(O)_n-$;

R is -Ph, -tolyl, 3-Cl-phenyl or 2-thiazolyl;

R^6 is -H; and

Z is

1) $-\overset{\overset{W}{\|}}{C}-NR^2R^3$,

wherein R^2 is -H and W is -O, -S or -NCN, or

2) $-CR^2R^2$-SO-aryl, wherein the aryl group is unsubstituted or substituted with one or more of C_{1-5}alkyl.

A sub-class of compounds within this class is further limited to compounds wherein

X is -Cl;

Y is $-S(O)_n-$;

n is 1 or 2;

R is -Ph, 3-Cl-phenyl or 2-thiazolyl;

R^6 is -H;

Z is

$-\overset{\overset{W}{\|}}{C}-NR^2R^3$,

wherein R^2 is -H, and W is -O, -S or -NCN; and

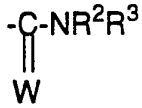
R^3 is

1) -C_{1-5}alkyl, unsubstituted or substituted with one or more of
   a) -C_{1-5}alkoxy, unsubstituted or substituted with -OH,
   b) -OH,
   c) -OC(O)R^7,
   d) aryl, unsubstituted or substituted with one or more of:
      i) -C_{1-5}alkyl, unsubstituted or substituted with one or more of -OH,
      ii) -C_{1-5}alkoxy,
      iii) -OH,
      iv) halogen, or
      v) -NR^2R^2,
   e) heterocycle, unsubstituted or substituted with one or more of:
      i) -C_{1-5}alkyl,
      ii) -C_{1-5}alkoxy,
      iii) -OH,
      iv) halogen, or
      v) -NR^2R^2, or
   f) C_{3-6}cycloalkyl,
2) heterocycle, unsubstituted or substituted with one or more of:
      i) -C_{1-5}alkyl,
      ii) -C_{1-5}alkoxy,
      iii) -OH,
      iv) halogen, or
      v) -NR^2R^2,
3) hydrogen, or
4) C_{3-6} cycloalkyl.

A second embodiment of this invention encompasses compounds of formula A wherein X is selected from the group consisting of:

1) $-NR^2R^2$,
2) $-NHSO_2-C_{1-3}alkyl$, and
3) $-NHCO-C_{1-3}alkyl$.

A third embodiment of this invention encompasses compounds of formula A wherein Z is



and R^3 is selected from the group consisting of:

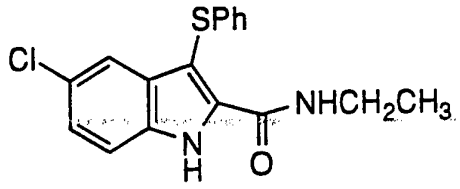
1) $C_{1-3}alkyl$ substituted with phenyl wherein phenyl is substituted with one or more of:
   a) $-NO_2$,
   b) $-NR^2R^2$,
   c) $-NHCO-C_{1-3}alkyl$ or
   d) $-NHSO_2-C_{1-3}alkyl$, and

2) $C_{1-3}alkyl$ substituted with heterocycle, wherein heterocycle is substituted with one or more of:
   a) halogen,
   b) oxo,
   c) $-NO_2$,
   d) $-NR^2R^2$,
   e) $-NHCO-C_{1-3}alkyl$, or
   f) $-NHSO_2-C_{1-3}alkyl$.

A fourth embodiment of this invention encompasses compounds of formula A wherein Y is $-S(O)_n-$ and R is $-NR^2R^3$.

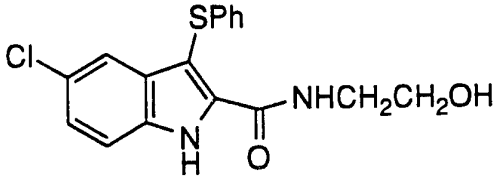
The most preferred compounds of this invention are compounds 1 through 39, shown below.

Compound 1:



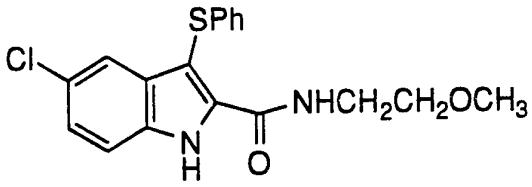
N-ethyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 2:



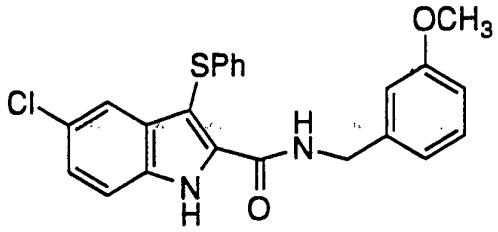
N-2-hydroxyethyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 3:



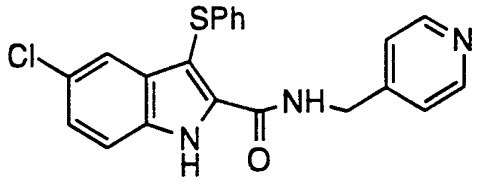
N-2-methoxyethyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 4:



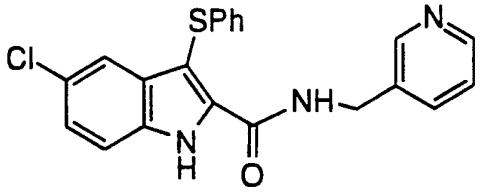
N-3-methoxybenzyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 5:



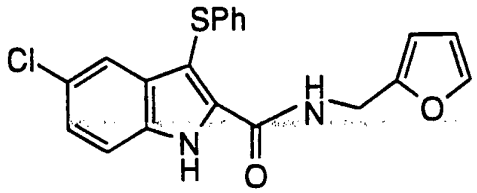
N-4-pyridylmethyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 6:



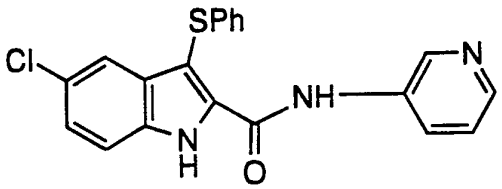
N-3-pyridylmethyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 7:



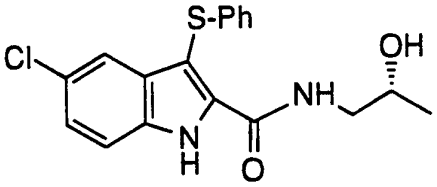
N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 8:



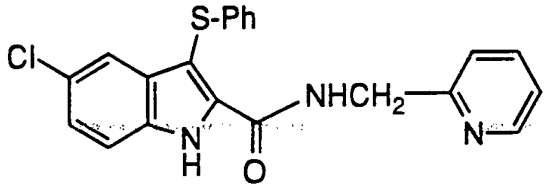
N-3-pyridyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 9:



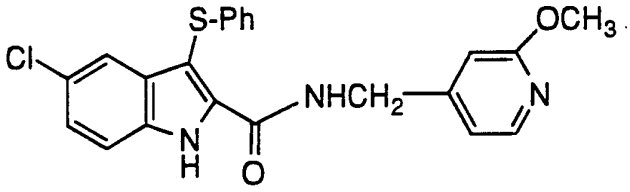
N-[1-(2(R)-hydroxypropyl)]-5-chloro-3-phenyl-thioindole-2-carboxamide

Compound 10:



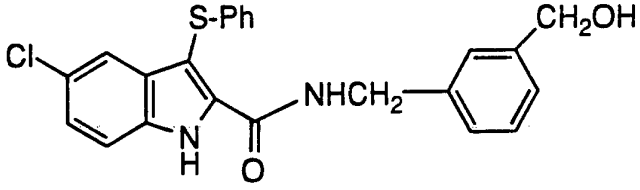
N-(2-pyridyl)methyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 11:



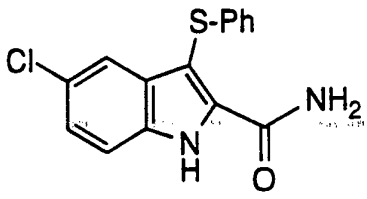
N-(3-methoxy-4-pyridyl)methyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 12:



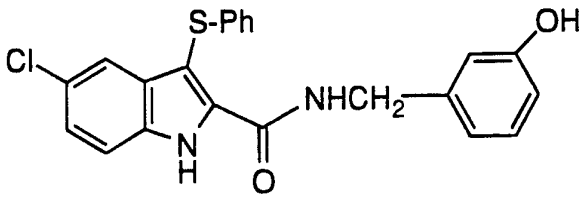
N-(3-hydroxymethyl)benzyl-5-chloro-3-phenylthioindole-2-carboxamide

Compound 13:



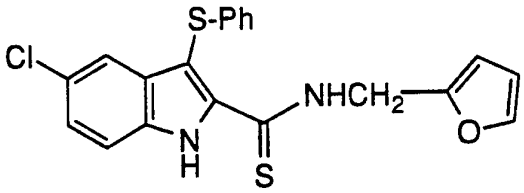
5-chloro-3-phenylthioindole-2-carboxamide

Compound 14:



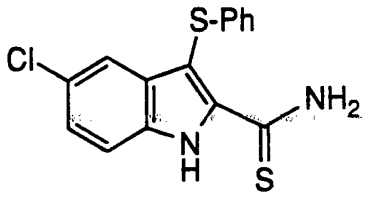
N-(3-hydroxybenzyl)-5-chloro-3-phenylthioindole-2-carboxamide

Compound 15:



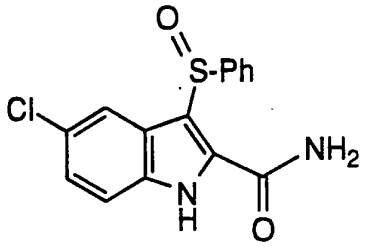
N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-thiocarboxamide

Compound 16:



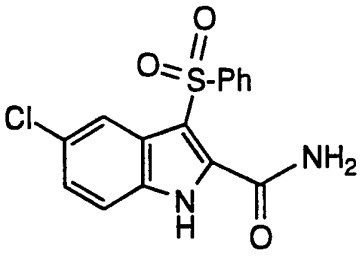
5-chloro-3-phenylthioindole-2-thiocarboxamide

Compound 17:



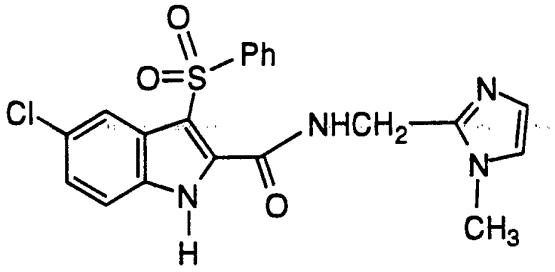
5-chloro-3-phenylsulfinylindole-2-carboxamide

Compound 18:



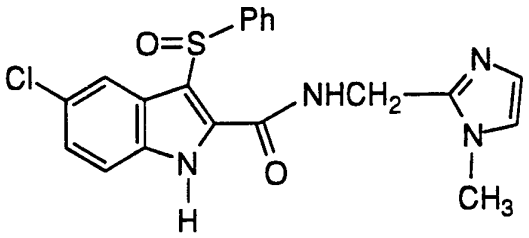
5-chloro-3-phenylsulfonylindole-2-carboxamide.

Compound 19:



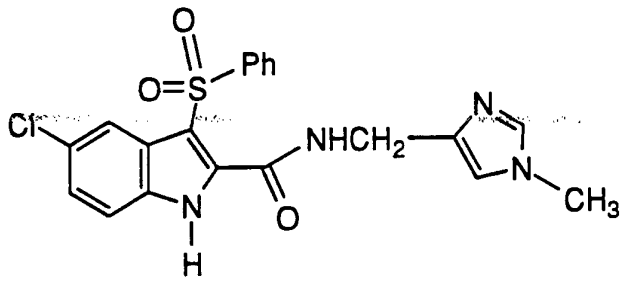
N-[(1-methylimidazol-2-yl)methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Compound 20:



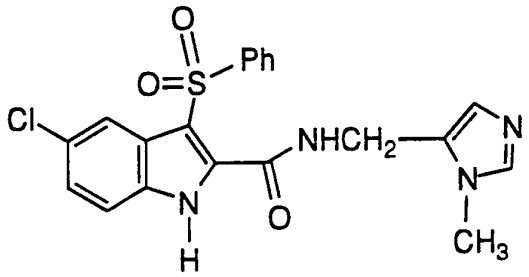
N-[(1-methylimidazol-2-yl)methyl]-3-phenylsulfinyl-5-chloroindole-2-carboxamide

Compound 21:



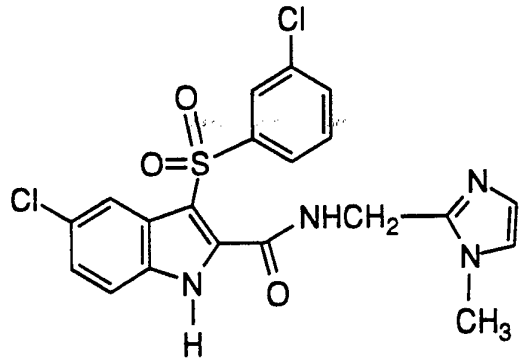
N-[(1-methylimidazol-4-yl)methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Compound 22:



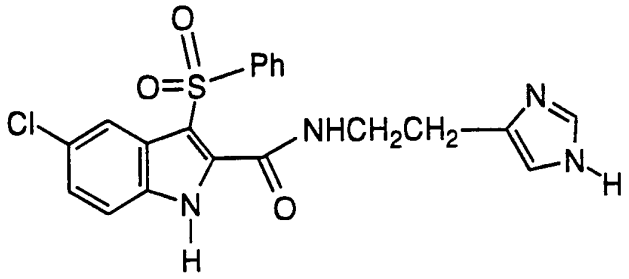
N-[(1-methylimidazol-5-yl)methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Compound 23:



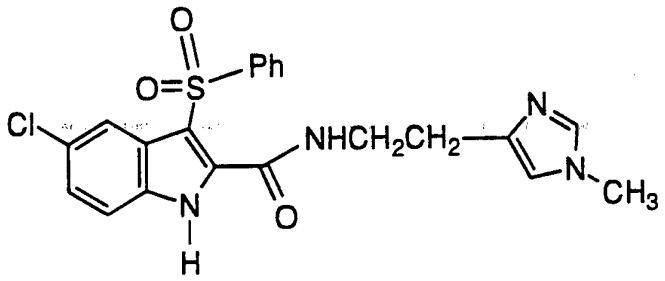
N-[(1-methylimidazol-2-yl)methyl]-3-(3-chlorophenyl-sulfonyl)-5-chloroindole-2-carboxamide

Compound 24:



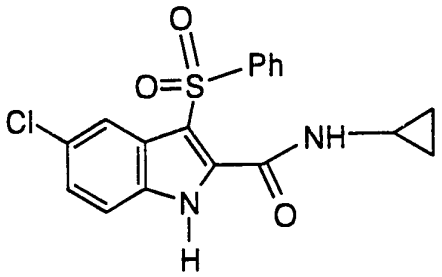
N-[2-(imidazol-4-yl)ethyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Compound 25:



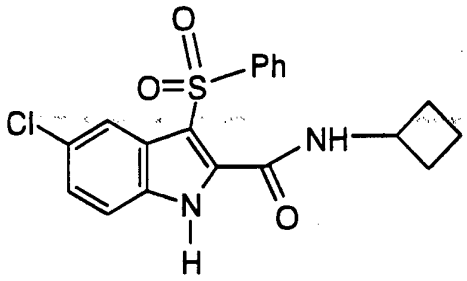
N-[2-(1-methylimidazol-4-yl)ethyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Compound 26:



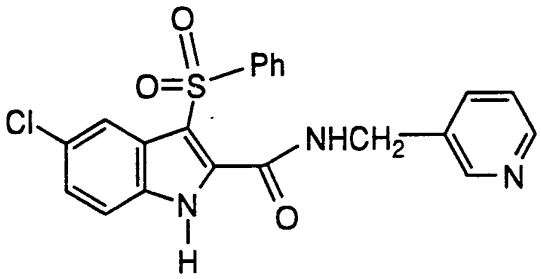
N-cyclopropyl-5-chloro-3-phenylsulfonylindole-2-carboxamide

Compound 27:



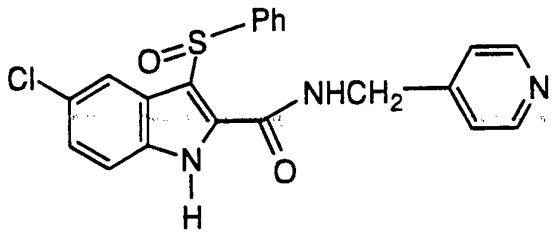
N-cyclobutyl-5-chloro-3-phenylsulfonylindole-2-carboxamide

Compound 28:



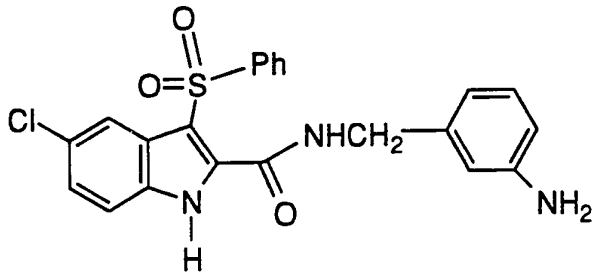
N-(3-pyridylmethyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Compound 29:



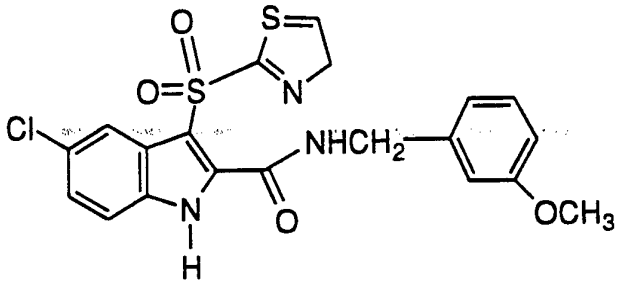
N-(4-pyridylmethyl)-5-chloro-3-phenylsulfinylindole-2-carboxamide

Compound 30:



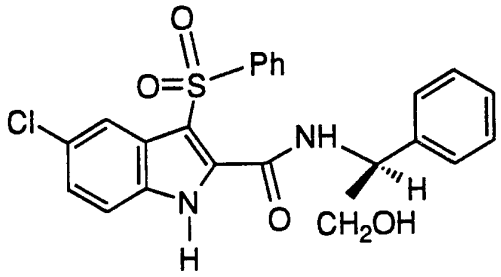
N-(3-aminobenzyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Compound 31:



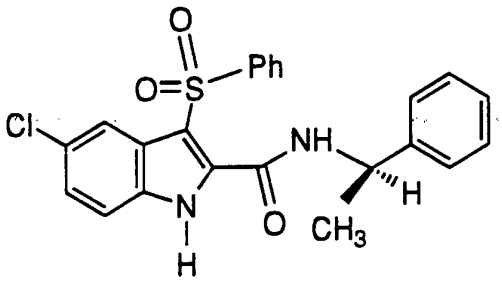
N-(3-methoxybenzyl)-5-chloro-3-(2-thiazolyl)sulfonyl-indole-2-carboxamide

Compound 32:



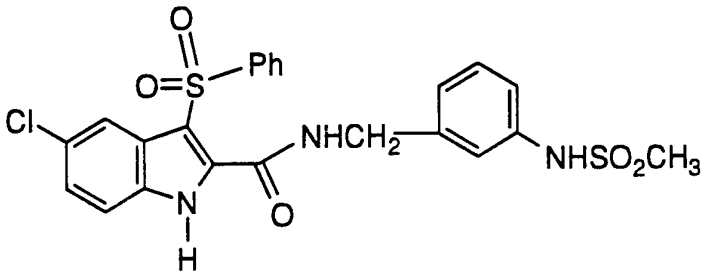
N-[(S)-1-phenyl-2-hydroxyethyl]-5-chloro-3-phenylsulfonylindole-2-carboxamide

Compound 33:



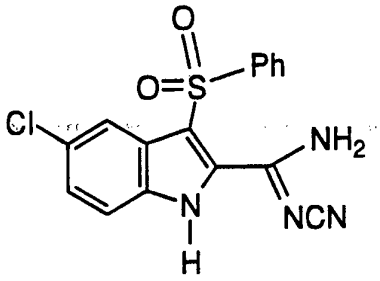
N-[(R)-1-phenylethyl]-5-chloro-3-phenylsulfonylindole-2-carboxamide

Compound 34:



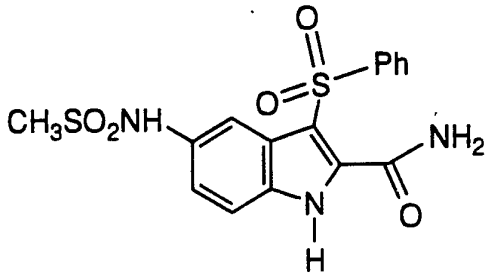
N-(3-methylsulfonylaminobenzyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Compound 35:



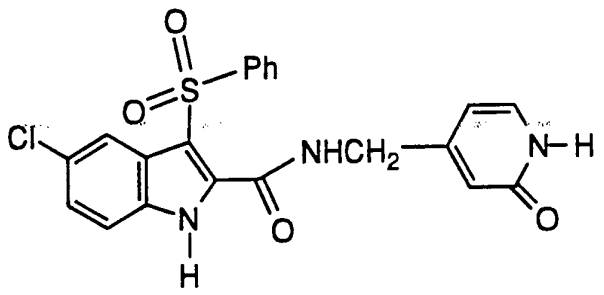
N-cyano-5-chloro-3-phenylsulfonylindole-2-carboximid-amide

Compound 36:



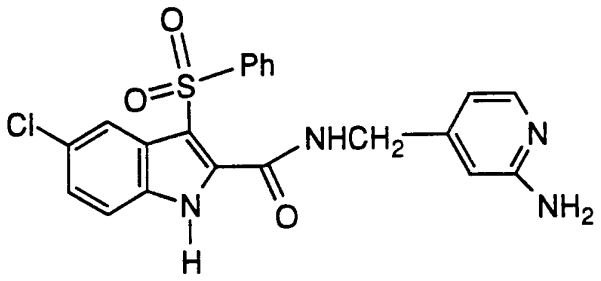
3-phenylsulfonyl-5-methylsulfonylaminoindole-2-carboxamide

Compound 37:



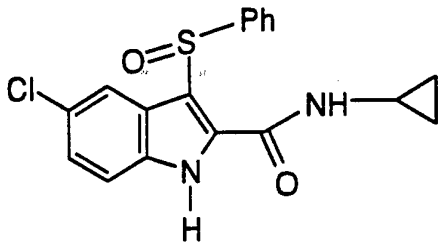
4-[(5-chloro-3-phenylsulfonylindole-2-carboxamido)-methyl]pyridin-2(1H)-one

Compound 38:



N-(2-amino-4-pyridylmethyl)-5-chloro-3-phenylsulfonyl-indole-2-carboxamide, and

Compound 39:



N-cyclopropyl-5-chloro-3-phenylsulfinylindole-2-carboxamide.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, individual diastereomers, or enantiomers, with all isomeric forms being included in the present invention.

When any variable (e.g., aryl, heterocycle, R^1, R^2, R^3, etc.) occurs more than one time in any constituent or in formula A of this invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Halogen" or "halo" as used herein, means fluoro, chloro, bromo and iodo.

As used herein, with exceptions as noted, "aryl" is intended to mean any stable monocyclic, bicyclic or tricyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, biphenyl.

The term heterocycle or heterocyclic, as used herein except where noted, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, benzofuranyl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl.

Further abbreviations that may appear in this application are as follows:

Me	methyl
Et	ethyl
Ph	phenyl
BuLi	butyllithium
n-Bu_3P	tri-n-butyl phosphine
LAH	lithium aluminum hydride
DMF	dimethylformamide
THF	tetrahydrofuran
Et_3N	tri-ethylamine
MMPP	monoperoxyphthalic acid, magnesium salt

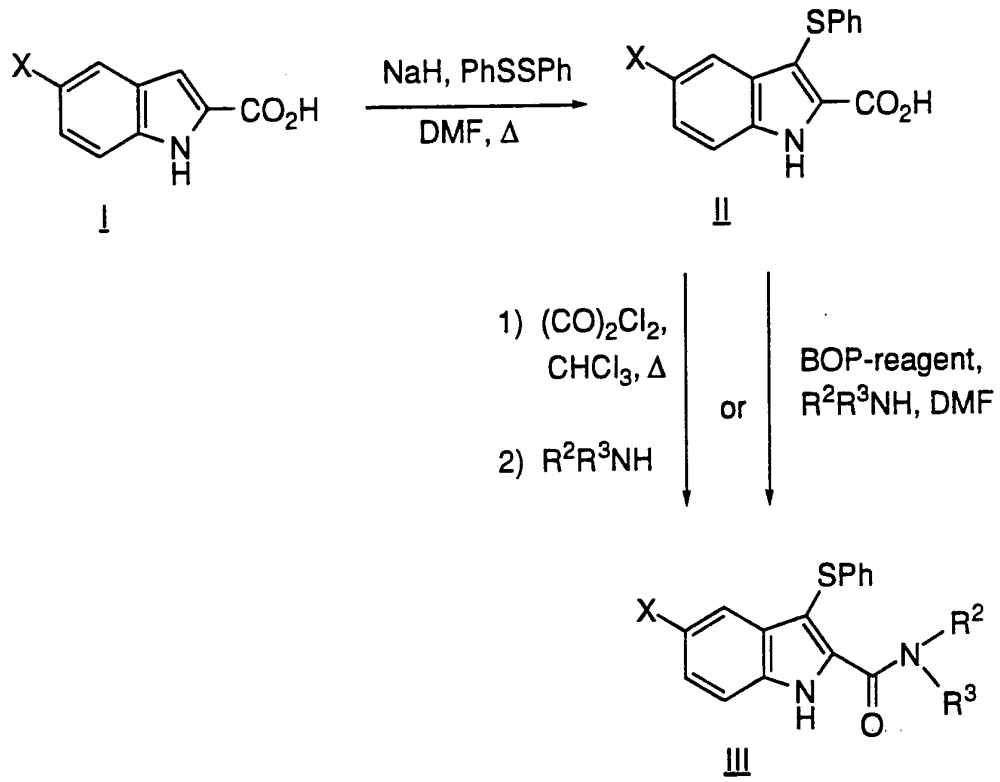
BOP-reagent	benzotriazol-1-yloxytris-(dimethyl-amino)phosphonium hexafluorophosphate
mp or m.p.	melting point

The pharmaceutically-acceptable salts of the novel compounds of this invention that are capable of salt formation (in the form of water- or oil- soluble or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts of these compounds, which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bissulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others. Esters are also encompassed by the present invention, and include those which would readily occur to the skilled artisan, for example, C_{1-4} alkyl esters.

Schemes I-VIII for preparing the novel compounds of this invention are presented below. Tables I - VII which follow the schemes illustrate the compounds that can be synthesized by Schemes I-VIII, but Schemes I - VIII are not limited by the compounds in the tables nor by any particular substituents employed in the schemes for illustrative purposes. The examples specifically illustrate the application of the following schemes to specific compounds.

Scheme I, below, is a general route for synthesizing, e.g., the compounds shown in Table I, infra. The substituent groups (e.g., X, R, R^1, etc.) employed in Scheme I correspond to the substituent groups as defined in Table I, but Scheme I is not limited by the defined substituents or compounds of Table I.

SCHEME I

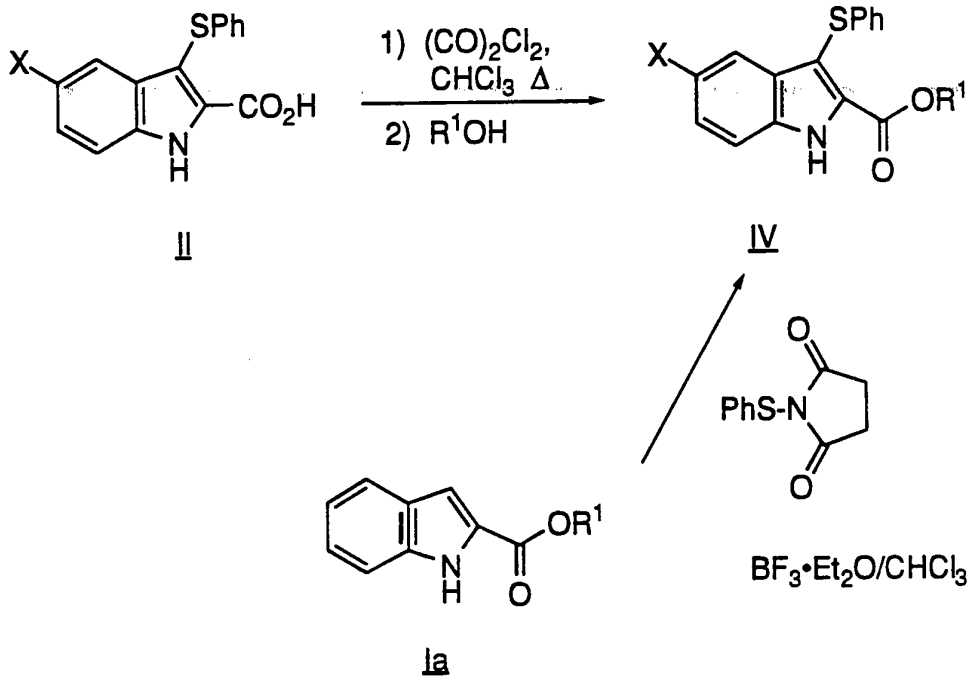


As shown in Scheme I, commercially available indole-2-carboxylic acid (or 5-chloro, 5-fluoro or 5-methoxyindole-2-carboxylic acid) I is treated with an excess of sodium hydride in dimethyl-formamide in the presence of an aryl disulfide such as phenyldisulfide at 0°C to 60°C, according to the general procedure described by Atkinson, et al., in Synthesis, p. 480-481 (1988). The resulting product II is reacted with oxalyl chloride in refluxing chloroform for about 30

minutes to 1 hour to produce the corresponding acid chloride which is then reacted with a primary or secondary amine in chloroform at 0°C to 20°C to give the amide III. Alternatively, amide III can be produced directly from II by treatment with BOP reagent (benzotriazol-1-yloxytris-(dimethylamino)-phosphonium hexafluorophosphate) in the presence of the desired primary or secondary amine and triethylamine, in a solvent such as dimethyl-formamide. Other carboxyl group activating reagents such as 1,1'-carbonyl-diimidazole can also be used for this step. Saponification of ethyl 5-chloro-3-benzylindole-2-carboxylate (prepared as described below) by methods familiar to those skilled in the art, yields 5-chloro-3-benzylindole-2-carboxylic acid, which can be converted to the desired amides in the manner described for the synthesis of amides III.

The compounds shown in Table II infra, are generally synthesized as in Scheme I, except R^1OH is used in place of R^2R^3NH, as depicted in Scheme II below. The substituent groups employed in Scheme II correspond to the substituent groups as defined in Table II, but Scheme II is not limited by the defined substituents or compounds of Table II.

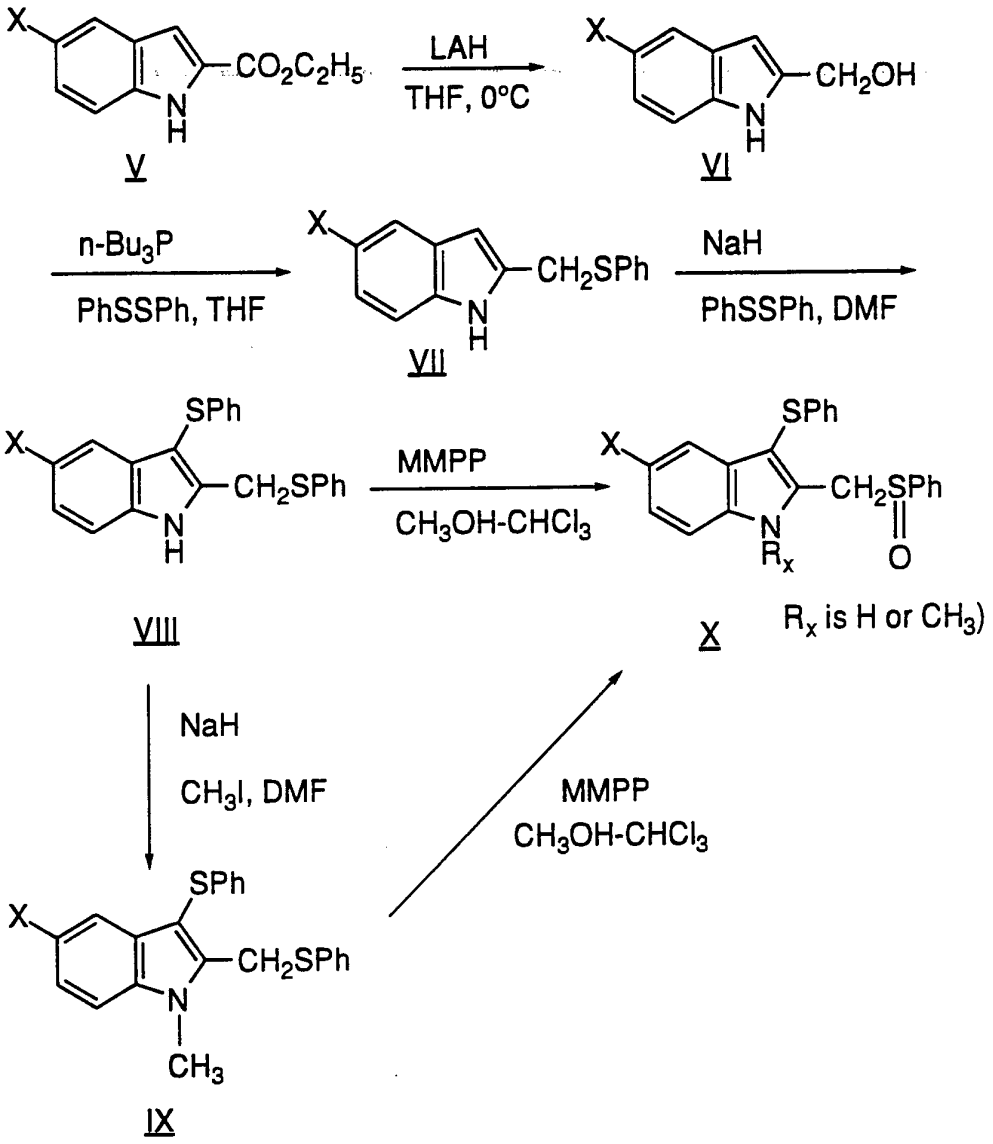
SCHEME II



As shown in Scheme II, 3-phenylthioindole-2-carboxylic acid II can be converted to the corresponding acid chloride with oxalyl chloride in refluxing chloroform, and reacted with an alcohol to give the ester IV. In an alternative procedure, Ia may be converted to IV by reaction with N-phenylthio-succinimide in chloroform at room temperature with a Lewis acid, such as boron trifluoride etherate, as catalyst (as shown in Scheme II). The compound ethyl 5-chloro-3-benzylindole-2-carboxylate was prepared according to the procedure described by Inaba, et al., in Chem. Pharm. Bull., 24, p. 1076-1082 (1976).

Scheme III, below, is a general route for synthesizing, e.g., the compounds shown in Table III, infra. The substituent groups employed in Scheme III correspond to the substituent groups as defined in Table III, but Scheme III is not limited by the defined substituents or compounds of Table III.

SCHEME III

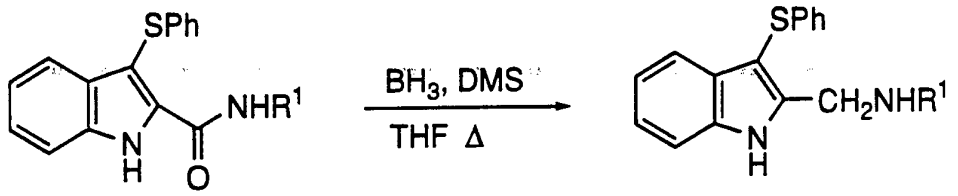


As shown in Scheme III, commercially available ethyl indole-2-carboxylate (compound V wherein X is -H) or ethyl 5-chloroindole-2-carboxylate (compound V wherein X is -Cl), was reduced to the primary alcohol VI with an excess of lithium aluminum hydride in tetrahydrofuran at 0°C. Compound VI was converted to the sulfide VII by treatment with an excess of tri-n-butylphosphine and an

aryldisulfide such as phenyl-disulfide in tetrahydrofuran at 0°C to 20°C for 6-24 hours. Reaction of sulfide VII with sodium hydride, an aryldisulfide such as phenyldisulfide, in dimethylformamide at 0°C to 20°C for 1 to 18 hours produces bis-sulfide VIII. Aryl disulfides which were not commercially available were obtained by oxidation of the commercially available aryl mercaptan with dimethyl sulfoxide and iodine, according to the procedure described by Orville G. Lowe in J. Org. Chem., 40, p. 2096-2098 (1975). Compound VIII can be N-alkylated, if desired, by methods familiar to those trained in the art, e.g., by treatment with sodium hydride in dimethylformamide at 0°C in the presence of an alkylating agent such as iodomethane, to give compound IX. Thereafter, compound VIII (or IX) is treated with one equivalent of peracid such as monoperoxyphthalic acid, magnesium salt (MMPP), or meta-chloroperoxy-benzoic acid in methanol or chloroform-methanol at 0°C for 30 minutes to 3 hours, to give predominately sulfoxide X.

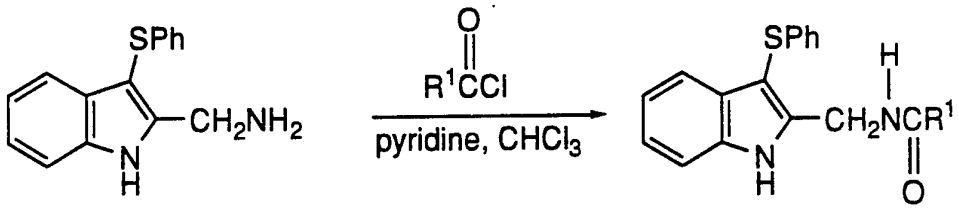
Schemes IV-A and IV-B , below, show a general route for synthesizing, e.g., the compounds shown in Tables IV-A and IV-B, infra. The substituent groups employed in Schemes IV-A and IV-B, respectively, correspond to the substituent groups as defined in Tables IV-A and IV-B, respectively, but Schemes IV-A and IV-B are not limited by the defined substituents or compounds of Tables IV-A and IV-B.

SCHEME IV-A



XI XII

SCHEME IV-B

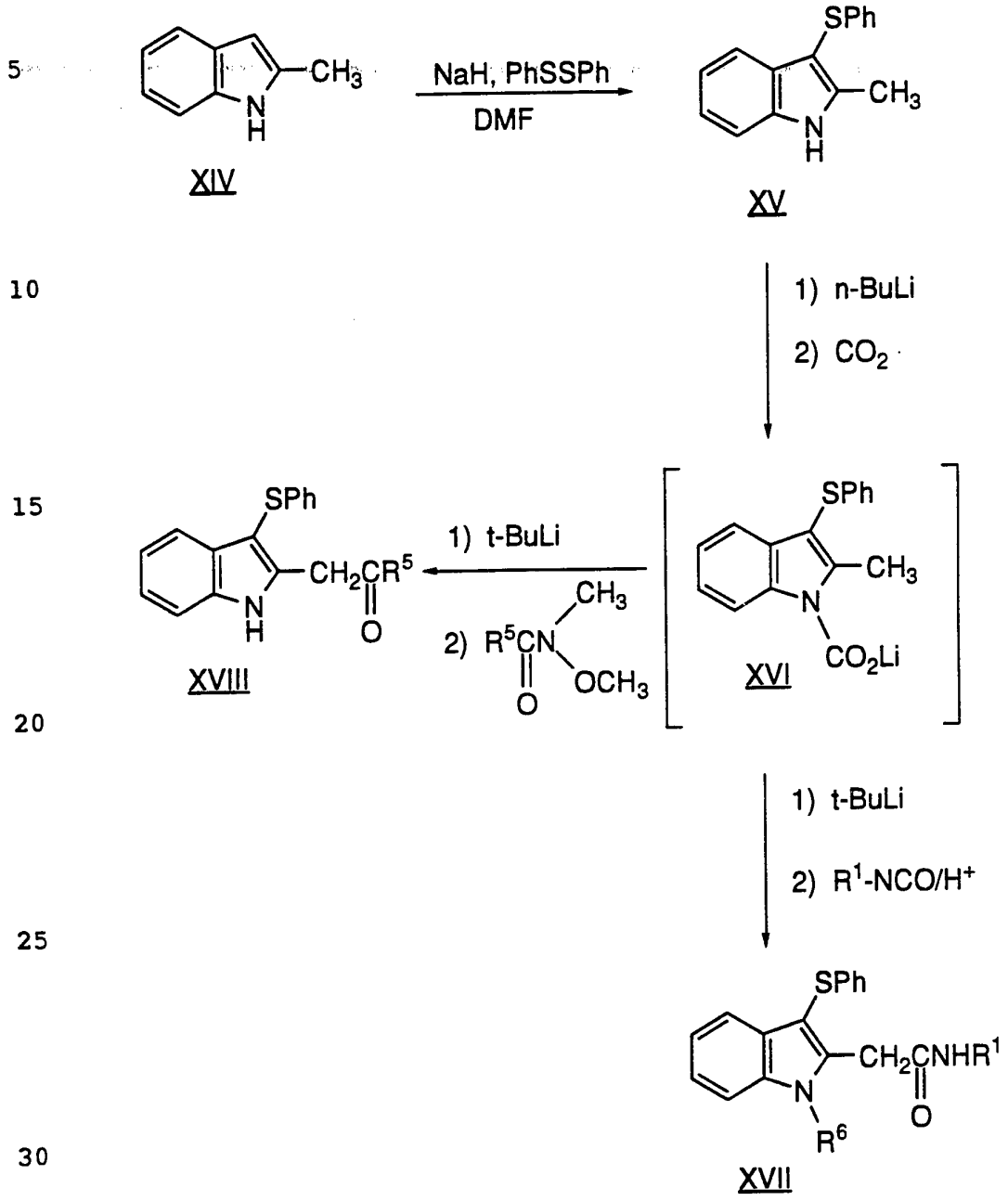


XII-A XIII

As shown in Scheme IV-A, 3-phenylthioindole-2-carboxamides XI can be reduced to primary or secondary amines XII by reaction with an excess of borane-dimethylsulfide complex in refluxing tetrahydrofuran for 6-24 hours. As shown in Scheme IV-B, the primary amine XII-A can be acylated with an acid chloride, such as benzoyl chloride, in chloroform in the presence of pyridine, to give the amide XIII.

Scheme V, below, is a general route for synthesizing, e.g., the compounds shown in Table V-A and Table V-B, infra. The substituent groups employed in Scheme V correspond to the substituent groups as defined in Tables V-A and V-B, but Scheme V is not limited by the defined substituents or compounds of Tables V-A and V-B.

SCHEME V

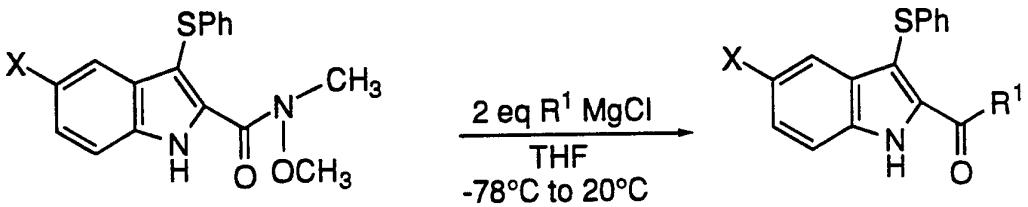


XIV XV XVI XVIII XVII

As shown in Scheme V, commercially available 2-methyl-indole XIV can be treated with sodium hydride in dimethylformamide in the presence of an aryldisulfide such as phenyldisulfide to give compound XV. Compound XV can be converted to the monoanion with n-butyl-lithium in tetrahydrofuran at -78°C, and then reacted with carbon dioxide to give carboxylate XVI. The dianion formed by the reaction of XVI with t-butyllithium could be reacted with an isocyanate, such as phenyliso-cyanate, to give a mixture of monoacylated product and diacylated product XVII (see Table V-B). Alternatively, the dianion formed by the reaction of XVI with t-butyllithium could be reacted with an N-methoxy-N-methyl amide such as N-methoxy-N-methyl-furan-2-carboxamide (prepared in a manner familiar to those skilled in the art, e.g., by the methods described in Scheme 1) to produce ketones XVIII. The methodology described above is essentially that used by A. J. Katritsky and K. Akutagawa to prepare 2-indoleacetic acids, and is published in J. Am. Chem. Soc., 108, 6808 (1986).

Scheme VI, below, is a general route for synthesizing, e.g., the compounds shown in Table VI, infra. The substituent groups employed in Scheme VI correspond to the substituent groups as defined in Table VI, but Scheme VI is not limited by the defined substituents or compounds of Table VI.

SCHEME VI



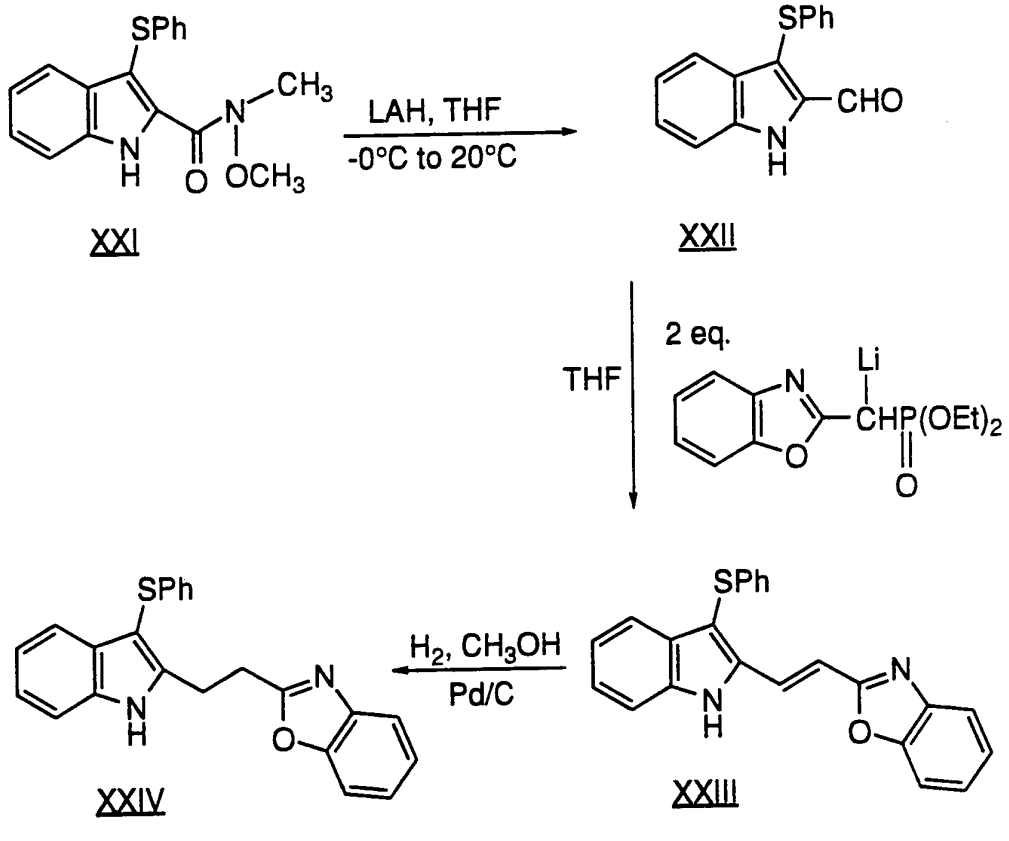
XIX XX

As shown in Scheme VI, N-methoxy-N-methyl-3-phenyl-thioindole-2-carboxamide XIX (or N-methoxy-N-methyl-5-chloro-3-phenylthioindole-2-carboxamide) (prepared as in Scheme 1) can be reacted with Grignard reagents (wherein R^1 is not hydrogen) such as

phenylmagnesium chloride, in tetrahyrodrofuran at -78°C to 20°C for 18-48 hours, or XIX can be reacted with other organometallic reagents well known in the art to one of ordinary skill, to produce ketones XX.

The compounds shown in Table VII infra, can generally be synthesized by those of ordinary skill in the art according to methods described in Schemes I through VI, with the exception of 2-(2-benzoxazol-2-ylethyl)-3-phenylthioindole (compound XXIV), the synthesis of which is described below in Scheme VII.

SCHEME VII



As shown in Scheme VII, N-methoxy-N-methyl-3-phenylthioindole-2-carboxamide XXI can be reduced to aldehyde XXII with lithium aluminum hydride in tetrahydrofuran at 0°C to 20°C for 2-4 hours. Aldehyde XXII could be reacted with the lithium salt of

[(benzoxal-2-yl)methyl]diethyl-phosphonate to produce olefin XXIII, which is then hydrogenated in the presence of 10% palladium on charcoal in methanol under one atmosphere of hydrogen to give compound XXIV.

The compound 5-chloro-2-cyano-3-phenylthioindole in Table VII can be prepared by dehydro-sulfurization of 5-chloro-3-phenyl-thioindole-2-thiocarboxamide with, e.g., $Hg(OAc)_2$.

Using methods well-known to those skilled in the art, compounds of formula A where Y is -SO- or $-SO_2-$ can be synthesized by treatment of compounds where Y is -S- with a suitable oxidizing agent such as, for example, meta-chloroperoxybenzoic acid (MCPBA), sodium periodate or hydrogen peroxide in an appropriate solvent such as MeOH, $CHCl_3$ or acetic acid, or potassium persulfate in a solvent such as $MeOH/H_2O$.

Alternative routes to amide derivatives of formula A where Y = -SO- or $-SO_2-$ are shown in Scheme VIII. Intermediate acid II can be oxidized (with for example meta-chloroperoxybenzoic acid (MCPBA) in $CHCl_3$) to the Y = -SO- or $-SO_2-$ acid derivative XXV which can then be converted to the corresponding amide derivatives XXVII employing the amide forming conditions indicated in Scheme I. In another useful sequence, intermediate ester IVa can be oxidized to the Y = -SO- or $-SO_2-$ ester intermediate XXVI which on reaction with ammonia or a primary amine with heating is converted to compounds of formula XXVII.

SCHEME VIII

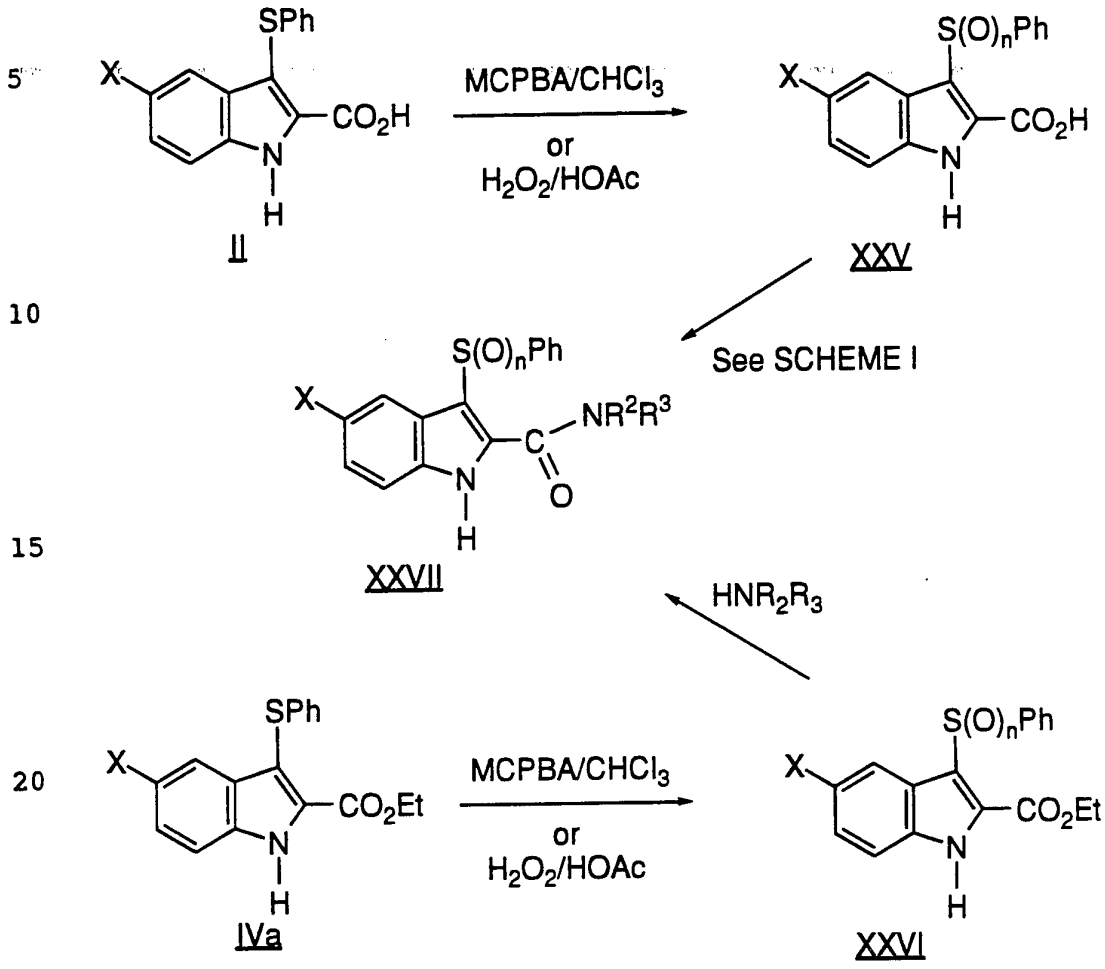
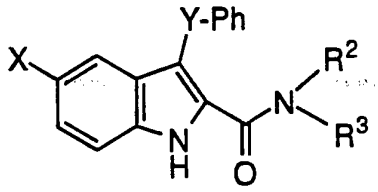

SPh
X
CO2H
N
H
II
MCPBA/CHCl3
or
H2O2/HOAc
S(O)nPh
X
CO2H
N
H
XXV
See SCHEME I
S(O)nPh
X
NR2R3
C
O
N
H
XXVII
HNR2R3
SPh
X
CO2Et
N
H
IVa
MCPBA/CHCl3
or
H2O2/HOAc
S(O)nPh
X
CO2Et
N
H
XXVI

TABLE I



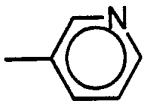
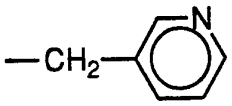
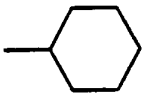
X	Y	R^2	R^3	m.p.
H	S	CH_3	CH_3	194-195°C
H	S	H	CH_2Ph	179-181°C
H	S	H	Ph	194-196°C
H	S	H	$n\text{-}C_4H_9$	161-163°C
H	S	H	CH_2CH_2Ph	147-149°C
Cl	S	CH_3	OCH_3	57-59°C
Cl	S	H		255-256°C
H	S	H	CH_3	197-199°C
Cl	S	H	nC_3H_7	210-212°C
Cl	S	H		240-241°C
Cl	S	H		255-256°C

TABLE I, Cont'd

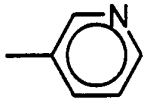
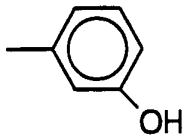
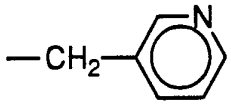
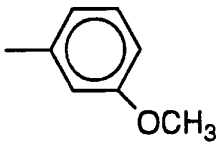
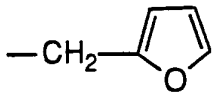
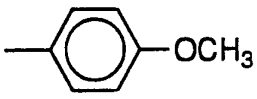
X	Y	R^2	R^3	m.p.
F	S	H		239-241°C
Cl	S	H		232-233°C
Cl	CH_2	H		243-244°C
Cl	S	H		221°C
Cl	S	H		214°C
Cl	S	H	$—CH_2CH_2CH_2OH$	215°C
Cl	S	H		229°C
Cl	S	H	CH_3	220-221°C

TABLE I, Cont'd

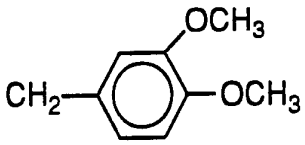
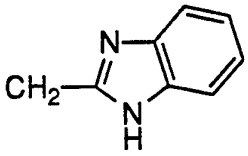
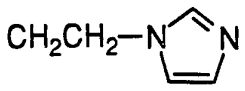
X	Y	R^2	R^3	m.p.
Cl	S	H	$CH_2CH_2CH_2OCH_3$	170-171°C
Cl	S	H		184°C
Cl	S	H		259-260°C (HCl salt)
Cl	S	H		256°C (HCl salt)
Cl	S	H	$CH(CH_3)_2$	193-194°C
Cl	S	CH_3	Ph	191-192°C
Cl	S	H	$CH_2CH_2CH_2N(CH_3)_2$	229-230°C (HCl salt)

TABLE I, Cont'd

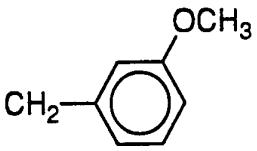
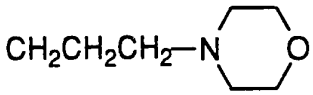
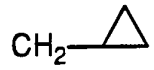
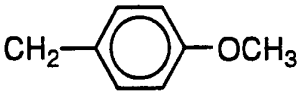
X	Y	R^2	R^3	m.p.
Cl	S	H	C_2H_5	210-211°C
Cl	S	H	Ph	245-246°C
Cl	S	H		172°C
Cl	S	H		162-164°C
Cl	S	H		219-219.5°C
Cl	S	H	CH_2Ph	222°C
Cl	S	H		198°C
Cl	S	H	$CH_2CH_2OCH_2CH_2OH$	161.5-162.5°C

TABLE I, Cont'd

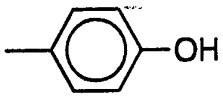
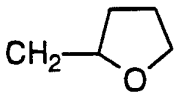
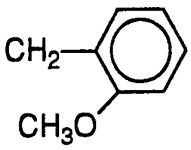
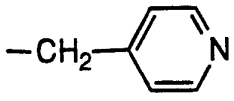
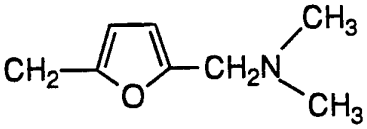
X	Y	R^2	R^3	m.p.
Cl	S	H		>300°C
Cl	S	H	$CH_2CH_2OCH_3$	216-217.5°C
Cl	S	H	$CH_2CH_2OC_2H_5$	165.5-167°C
Cl	S	H		182-183°C
Cl	S	H		201°C
Cl	S	H	CH_2CHCH_3 (OH)	205°C
Cl	S	H		228-229°C
Cl	S	H	CH_2CH_2OH	222-223.5°C
Cl	S	H		151-152°C

TABLE I, Cont'd

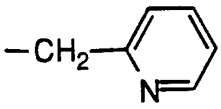
X	Y	R^2	R^3	m.p.
Cl	S	H	OCH_3	179-180°C
Cl	S	H	$-CH(CH_2OH)-CH_2CH_3$	153-154°C
Cl	S	H	$CH_2COC_2H_5$	215-215.2°C
Cl	S	H	$-CH(CH_3)-CH_2OCH_3$	168-169°C
Cl	S	H	$-CH_2-CH(OH)-CH_3$	202-203°C
Cl	S	H		209-210°C
Cl	S	H	$-CH_2CH_2CH_2-N$  $\cdot HCl$	188-189°C
Cl	S	H	$-CH_2-CH(OH)-CH_3$	201-206°C
Cl	S	H	$-CH(CH_2OH)-CH_2CH_3$	138-139°C

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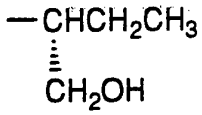
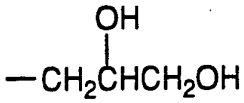
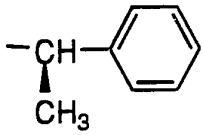
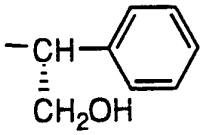
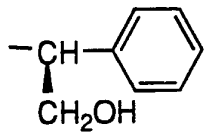
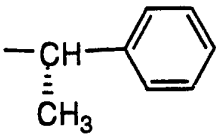
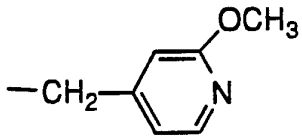
X	Y	R^2	R^3	m.p.
Cl	S	H		137.5-139°C
Cl	S	H		219-221°C
Cl	S	H		208-210°C
Cl	S	H		223-226°C
Cl	S	H		223-226°C
Cl	S	H		208-210°C
Cl	S	H		227-228°C

TABLE I, Cont'd

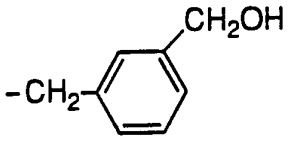
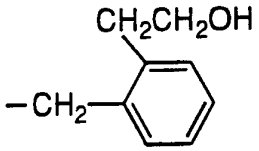
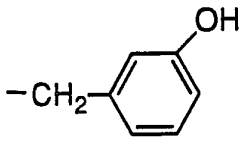
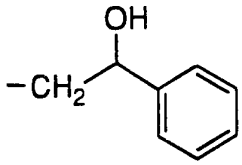
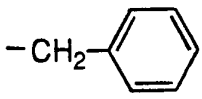
X	Y	R^2	R^3	m.p.
Cl	S	H		229-230°C
Cl	S	H		217-219°C
Cl	S	H		214-216°C
Cl	S	H		193-195.5°C
Cl	S	H	-H	213-215°C
Cl	SO_2	H	H	255-257°C
Cl	SO_2	H		249-251°C

TABLE I, Cont'd

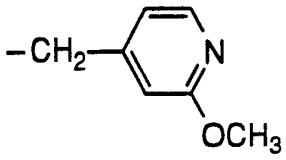
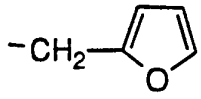
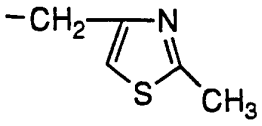
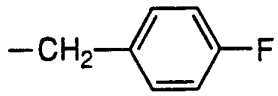
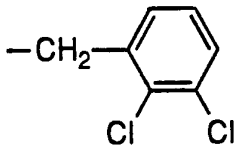
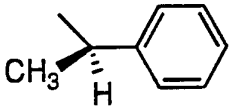
X	Y	R^2	R^3	m.p.
Cl	SO_2	H	$-CH_2CH_2OH$	198-200°C
Cl	SO_2	H		
Cl	SO_2	H		212-215°C
Cl	SO_2	H		211-215°C
Cl	SO_2	H		275-278°C
Cl	SO_2	H		265-270°C
Cl	SO_2	H		149°C

TABLE I, Cont'd

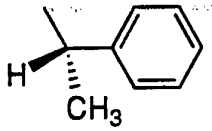
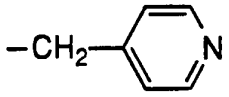
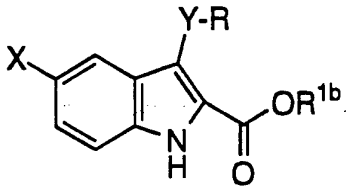
X	Y	R^2	R^3	m.p.
Cl	SO_2	H		175°C
Cl	SO_2	H		278-281°C

TABLE II



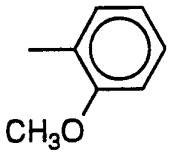
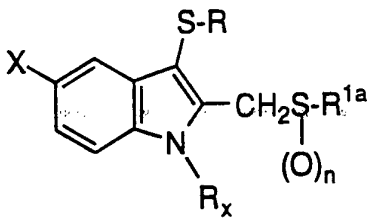
X	Y	R	R^{1b}	m.p.
H	S	Ph	CH_3	179-180°C
H	S		CH_3	195-197°C
OCH_3	S	Ph	CH_3	211-212°C
Cl	S	Ph	CH_3	193-196°C
Cl	S	Ph	CH_2Ph	154-155°C
Cl	S	Ph	C_2H_5	163-164°C
Cl	CH_2	Ph	C_2H_5	196-197°C
F	S	Ph	C_2H_5	149°C

TABLE III



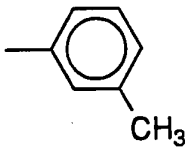
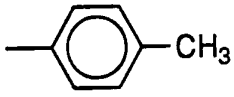
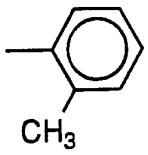
X	R	R^1	n	R_x	m.p.
H	Ph	Ph	1	H	71-74°C
H	Ph	Ph	0	H	---
H	Ph	Ph	2	H	168-169°C
H		Ph	1	H	166-167°C
H		Ph	1	H	164.5-166.5°C
OCH_3	Ph	Ph	1	H	70-80°C
H		Ph	1	H	171.5-172.5°C
H	Ph	Ph	0	CH_3	98-99°C

TABLE III, Cont'd

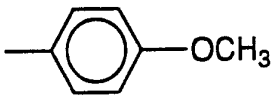
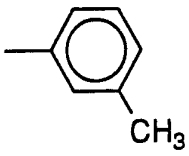
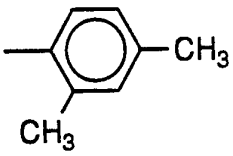
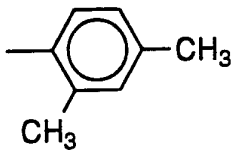
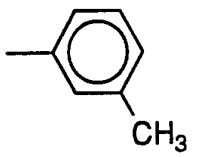
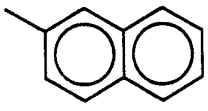
X	R	R^{1a}	n	R_x	m.p.
H	Ph	Ph	1	CH_3	177-178°C
H	Ph		1	H	---
H	Ph	CH_3	1	H	164-168°C
H	Ph		0	H	---
H	Ph		0	H	---
H	Ph		1	H	---
H	Ph		1	H	---
H	Ph		0	H	---

TABLE III, Cont'd

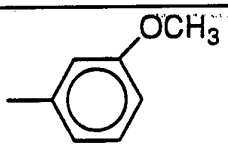
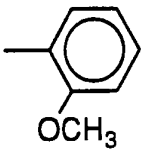
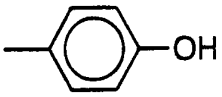
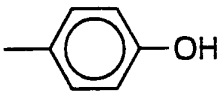
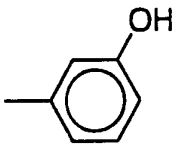
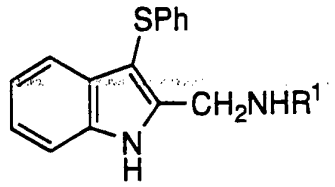
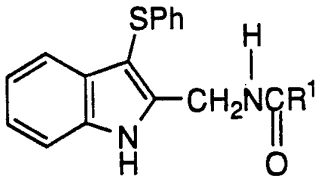
X	R	R^{1a}	n	R_x	m.p.
H	Ph		1	H	---
H	Ph		1	H	138-140°C
H	Ph		0	H	---
H	Ph		1	H	219-220°C
Cl	Ph	Ph	1	H	158-162°C
H	Ph		1	H	---

TABLE IV-A



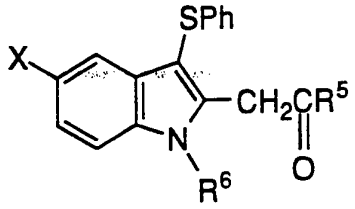
R^1	m.p.
$-CH_2Ph$	199-201°C
-Ph	167-170°C
$-n-C_4H_9$	177-179°C
-H	---

TABLE IV-B



R^1	m.p.
$-CH_3$	---
-Ph	64-65°C

TABLE V-A



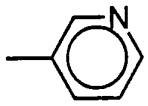
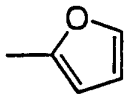
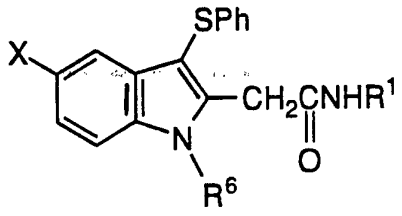
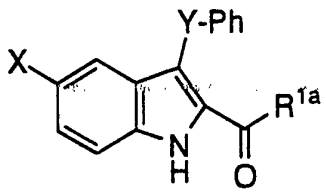
X	R^5	R^6	m.p.
H	$-CH_2Ph$	H	---
H	-Ph	H	154-155°C
H	$-CH_3$	H	101.5-103.5°C
H		H	87-90°C
H		H	127-129°C
Cl	$-OC_2H_5$	H	99-103°C

TABLE V-B



X	R^1	R^6	m.p.
H	-Ph	H	66-68°C
H	-Ph	-CNHPh (O)	123-125°C

TABLE VI



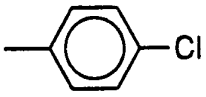
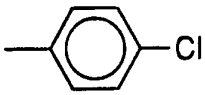
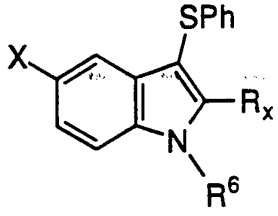
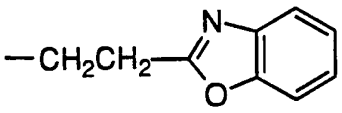
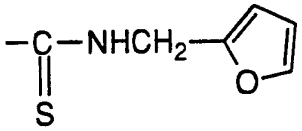
X	Y	R^{1a}	m.p.
Cl	S	-Ph	154-155°C
Cl	S	$-CH_2Ph$	219-220°C
H	S	-Ph	121.5-123.5°C
H	S		142-149°C
Cl	S	$-C_2H_5$	196-197°C
Cl	S		214-215°C
Cl	S	$-CH_3$	178°C
Cl	CH_2	$-C_2H_5$	203-205°C
Cl	CH_2	-Ph	161-163°C
Cl	SO_2	cyclopropy	224-226°C
Cl	SO_2	$-C_2H_5$	226-227°C
Cl	SO_2	$-CH_3$	184-187.5°C

TABLE VII



X	R_x	R^6	m.p.
H	$-CH_3$	H	128-130°C
H	$-CH_3$	$-\overset{\overset{O}{\|}}{C}NHPh$	157-159°C
H	$-CH_3$	$-\overset{\overset{O}{\|}}{C}Ph$	124-125°C
H	$-CH_2CH_2Ph$	H	117-120.5°C
H		H	92-193°C
Cl	-CN	H	172-174°C
Cl		H	143-144°C
Cl	$-\overset{\overset{S}{\|}}{C}-NH_2$	H	217° (decomp.)

The compounds of the present invention are useful in the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by the human immunodeficiency virus (HIV) and the treatment of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, organ transplant, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are also useful in the preparation and execution of screening for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HIV reverse transcriptase e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

For inhibition of HIV reverse transcriptase, the prevention or treatment of infection by HIV and the treatment of AIDS or ARC, the compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically-

effective amount of a compound of the present invention.

These pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets; nasal sprays; sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweetners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquidify and/or dissolve in the rectal cavity to release the drug.

The compounds of this invention can be administered orally to humans in a dosage range of 1 to 100 mg/kg body weight in divided doses. One preferred dosage range is 1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is 1 to 20 mg/kg body weight orally in divided doses. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The present invention is also directed to combinations of the HIV reverse transcriptase inhibitor compounds with one or more agents useful in the treatment of AIDS. The compounds of this invention can be administered in combination with other compounds that are HIV reverse transcriptase inhibitors, and/or with compounds that are HIV protease inhibitors. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, such as those in the following Table VIII.

When used in a combination treatment with compounds of the instant invention, dosage levels of HIV protease inhibitors of the order of 0.02 to 5.0 or 10.0 grams-per-day are useful in the treatment or prevention of the above-indicated conditions, with oral doses two-to-five time higher. For example, infection by HIV is effectively treated by the administration of from 10 to 50 milligrams of the HIV protease inhibitor per kilogram of body weight from one to three times per day. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity

of the particular condition, and the host undergoing therapy.

Dosages of HIV reverse transcriptase inhibitors, when used in a combination treatment with compounds of the instant invention, are comparable to those dosages specified above for the instant compounds.

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals is not limited by Table VIII but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

TABLE VIII

Drug Name	Manufacturer	Indication
ddI Dideoxyinosine	Bristol-Myers (New York, NY)	AIDS, ARC
Dideoxycytidine; ddC	Hoffman-La Roche (Nutley, NJ)	AIDS, ARC
Zidovudine; AZT	Burroughs Wellcome (Rsch. Triangle Park, NC)	AIDS, adv, ARC pediatric AIDS, Kaposi's sarcoma, asymptomatic HIV infection, less severe HIV disease, neurological involvement, in combination with other therapies.
L-697,661	Merck (Rahway, NJ)	AIDS, ARC, asymptomatic HIV positive, also in combination with AZT.

TABLE VIII (Cont'd)

Drug Name	Manufacturer	Indication
L-696,229	Merck (Rahway, NJ)	AIDS, ARC, asymptomatic HIV positive, also in combination with AZT.
L-735,524	Merck (Rahway, NJ)	AIDS, ARC, asymptomatic HIV positive, also in combination with AZT.
L-738,372	Merck (Rahway, NJ)	AIDS, ARC, asymptomatic HIV positive, also in combination with AZT.
L-738,872	Merck (Rahway, NJ)	AIDS, ARC, asymptomatic HIV positive, also in combination with AZT.

Compounds of Table VIII are the following: L-697,661 is 3-([(4,7-dichloro-1,3-benzoxazol-2-yl)-methyl]-amino)-5-ethyl-6-methyl-pyridin-2(1H)-one; L-696,229 is 3-[2-(1,3-benzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-pyridin-2(1H)-one; L-735,524 is an HIV protease inhibitor with the chemical name N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)piperazinyl))pentaneamide; L-738,372 is 6-chloro-4(S)-cyclopropyl-3,4-dihydro-4-((2-pyridyl)-ethynyl)-quinazolin-2(1H)-one; L-738,872 is N-tert-butyl-1-[2'-(R)-hydroxy-4'-phenyl-3'(S)-[3"(R)-[1'",1'"-dioxo-2'"(R)-methylethyl]tetrahydro-thienyloxycarbonylamino]-butyl]-4-[4'-(2"-chloro-6"-methyl)pyridyl-

methyl]-piperazine-2(S)-carboxamide.

REVERSE TRANSCRIPTASE ASSAY

The assay measures the incorporation of tritiated deoxyguanosine monophosphate by recombinant HIV reverse transcriptase (HIV RT_R) (or other RT) into acid-precipitable cDNA at the Km values of dGTP and poly r(C)•oligo d(G)12-18. The inhibitors of the present invention inhibit this incorporation.

Thirty µL of a reaction mixture containing equal volumes of: 500 mM Tris•HCl (pH 8.2), 300 mM $MgCl_2$, 1200 mM KCl, 10 mM DTT, 400 µg/mL poly r(c)•oligo d(G) [prepared by dissolving 1.5 mg (25 U) poly r(C)•oligo d(G) in 1.5 ml sterile distilled H_2O and diluting to 400 µg/ml], 0.1 µCi/µl [^{3}H] dGTP, 160 µM dGTP, was added to 10 µl sterile distilled H_2O, 2.5 µl of potential inhibitor and 10 µL of 5 nM purified HIV RT_R in tubes. The mixture was incubated at 37°C for 45 minutes.

After incubation is complete, the tubes were cooled in ice for 5 minutes. Ice-cold 13% TCA containing 10 mM $NaPP_i$ (200 µl) are added and the mixture incubated on ice for 30 minutes. The precipitated cDNA is removed by filtration using presoaked glass filters [TCA, $NaPP_i$]. The precipitate is then washed with 1N HCl, 10 mM $NaPP_i$.

The filter discs are then counted in a scintillation counter.

Under these conditions [dGTP] and poly r(C)•oligo d(G)12-18 each are approximately equal to the appropriate Km value. Approximately 5-6,000 cpm of [^{3}H] dGMP are incorporated into acid-precipitable material. The RT reaction is concentration- and time-dependent. DMSO (up to 5%) does not affect enzyme activity. Calculated IC_{50} values for the tested compounds of this invention vary from about 3 nM to more than 300 µM. The IC_{50} values of the most preferred compounds range from about 3 nM to about 35 nM.

INHIBITION OF VIRUS SPREAD

A. Preparation of HIV-infected MT-4 Cell Suspension

MT cells were infected at Day O at a concentration of 250,000 per ml with a 1:2000 dilution of HIV-1 strain IIIb stock (final 125 pg p24/ml; sufficient to yield ≤ 1% infected cells on day 1 and 25-100% on day 4). Cells were infected and grown in the following medium: RPMI 1640 (Whittaker BioProducts), 10% inactivated fetal bovine serum, 4 mM glutamine (Gibco Labs) and 1:100 Penicillin-Streptomycin (Gibco Labs).

The mixture was incubated overnight at 37°C in 5% CO_2 atmosphere.

B. Treatment with Inhibitors

Serial two-fold dilutions of compound were prepared in cell culture medium. At Day 1, aliquots of 125 µl of compound were added to equal volumes of HIV-infected MT-4 cells (50,000 per well) in a 96-well microtiter cell culture plate. Incubation was continued for 3 days at 37°C in 5% CO_2 atmosphere.

C. Measurement of Virus Spread

Using a multichannel pipettor, the settled cells were resuspended and a 125 µl harvested into a separate microtiter plate. After the settling of the cells, the plates were frozen for subsequent assay of the supernatant for HIV p24 antigen.

The concentration of HIV p24 antigen was measured by an enzyme immunoassay, described as follows. Aliquots of p24 antigen to be measured were added to microwells coated with a monoclonal antibody specific for HIV core antigen. The microwells were washed at this point, and at other appropriate steps that follow. Biotinylated HIV-specific antibody was then added, followed by conjugated streptavidin-horseradish peroxidase. A color reaction occurs from the added hydrogen peroxide and tetramethylbenzidine substrate. Color intensity is proportional to the concentration of HIV p24 antigen.

The cell culture inhibitory concentration (ClC_{95}) for each compound is defined as that concentration which inhibited by greater than 95% the spread of infection, as assessed by a greater than 95% reduction in p24 antigen production relative to untreated controls. The tested compounds of the present invention were found to have CIC_{95} values ranging from about 3 nM to about 400 nM for preferred species, and up to about 40 μM for others.

EXAMPLE 1

Preparation of N-(3-pyridylmethyl)-5-chloro-3-phenylthioindole-2-carboxamide

Step A: 5-Chloro-3-phenylthioindole-2-carboxylic acid

To a suspension of sodium hydride (3.0 g, 60% dispersion in oil, 0.076 mol) in dimethylformamide (125 mL) was added 5-chloroindole-2-carboxylic acid (5.0 g, 0.0255 mol) and phenyldisulfide (6.1 g, 0.028 mol). The reaction was heated under nitrogen at 50°C overnight. The reaction was cooled, and additional sodium hydride (1.8 g) and phenyldisulfide (3.6 g) were added and heating continued for 1 h. The reaction was cooled and the dimethylformamide distilled *in vacuo*. The residue was partitioned between ethyl acetate and water. The aqueous layer was separated and the pH adjusted to pH1 with 10% aqueous hydrochloric acid. The aqueous phase was extracted with ethyl acetate, and the ethyl acetate extract was washed with water and saturated brine, and dried over magnesium sulfate. The crude product was recrystallized from ethyl acetate in hexane to afford the title compound as an off-white solid.

Step B: N-(3-pyridylmethyl)-5-chloro-3-phenylthioindole-2-carboxamide

Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorphosphate (0.73 g, 1.6 mmol) was added to a solution of 5-chloro-3-phenylthio-indole-2-carboxylic acid (0.50 g, 1.6 mmol), 3-

aminomethylpyridine (0.35 g, 3.2 mmol) and triethylamine (0.50 mL, 3.2 mmol) in degassed dimethylformamide (25 mL). The reaction was stirred at room temperature overnight. The precipitated product was filtered and the filter cake washed well with water. The solid was triturated with 30% ethyl acetate in hexane, filtered and dried at 60°C *in vacuo* for 72 h. The title compound was obtained as an off-white solid, mp 240-241°C.

Analysis calculated for $C_{21}H_{16}ClN_3OS \cdot 0.25\ H_2O$:
C, 63.31; H, 4.17; N, 10.54
Found: C, 63.34; H, 4.06; N, 10.71

NMR (DMSO-d_6): δ 12.54 (1H, s), 8.91 (1H, t, J=6 Hz), 8.51 (1H, s), 8.42 (1H, d, J=5 Hz), 7.58 (2H, m), 7.45 (1H, m), 7.25 (4H, m), 7.15 (1H, t, J=7 Hz), 7.04 (2H, d, J=8 Hz), 4.58 (2H, d, J=6 Hz).

EXAMPLE 2

Preparation of Methyl 5-chloro-3-phenylthioindole-2-carboxylate

Oxalyl chloride (0.70 mL, 9.6 mmol) was added to a solution of 5-chloro-3-phenylthioindole-2-carboxylic acid (0.97 g, 3.2 mmol) in chloroform (50 mL) under nitrogen. The reaction was refluxed for 3 h, cooled and reduced to dryness *in vacuo*. The resulting solid was dissolved in chloroform and added to methanol at 0°C. The methanol was removed *in vacuo* and the crude product chromatographed on silica gel with 20% ethyl acetate in hexane. The title compound was obtained as a solid, mp 193-196°C.

Analysis calculated for $C_{16}H_{12}ClNO_2S$
C, 60.47; H, 3.81; N, 4.42
Found: C, 60.09; H, 3.50; N, 4.67

EXAMPLE 3

Preparation of Ethyl 5-chloro-3-benzylindole-2-carboxylate

The title compound was prepared according to the procedure described by Inaba, S., et al., Chem. Pharm. Bull., 24, 1076-1082 (1976). Recrystallization from benzene gave the title compound as

pale yellow needles, mp 196-197°C.
Analysis calculated for $C_{18}H_{16}ClNO_2$
C, 68.90; H, 5.13; N, 4.46
Found: C, 68.64; H, 5.10; N, 4.56

EXAMPLE 4

Preparation of 2-Phenylsulfinylmethyl-3-phenylthioindole

Step A: 2-Hydroxymethylindole

A suspension of lithium aluminum hydride (2.0 g, 0.20 mol) in tetrahydrofuran (100 mL) was cooled with stirring to 0°C under nitrogen. A solution of ethyl indole-2-carboxylate (10.0 g, 0.052 mol) in tetrahydrofuran was added dropwise, maintaining the reaction temperature between 0-5°C. After 1 h, the reaction was quenched with saturated sodium potassium tartrate solution. The reaction was filtered and the filter cake washed well with tetrahydrofuran. The tetrahydrofuran was evaporated *in vacuo* and the residue partitioned between ethyl acetate and water. The ethyl acetate solution was washed with water, saturated brine, dried over magnesium sulfate, filtered and freed of solvent. The title compound was obtained as a yellowish solid.
NMR ($CDCl_3$): δ 8.18 (1H, bs), 7.57 (1H, d, J=8 Hz), 7.35 (1H, d, J=8 Hz), 7.26 (1H, s), 7.18 (1H, dt, J=1, 8 Hz), 7.10 (1H, dt, J=1, 8 Hz), 6.41 (1H, bs), 4.84 (2H, s).

Step B: 2-Phenylthiomethylindole

2-Hydroxymethylindole (6.94 g, 0.047 mol) and phenyldisulfide (10.8 g, 0.049 mol) were dissolved in tetrahydrofuran (200 mL) and cooled to 0°C under nitrogen. Tri-n-butylphosphine (11.7 mL, 0.047 mol) was added and the reaction stirred for 1 h. Additional phenyldisulfide (1.5 g, 0.007) and tri-n-butylphosphine (5.1 mL, 0.20 mol) was added, and the reaction stirred at room temperature until complete. The tetrahydrofuran was removed *in vacuo* and the residue chromatographed on silica gel eluting with 5% ethyl acetate in hexane. The title compound was obtained as clear colorless plates, mp

100-101.5°C.
Analysis calculated for $C_{15}H_{13}NS$
C, 75.27, H, 5.47, N, 5.85
Found: C, 74.52, H, 5.39, N, 5.95

Step C: 3-Phenylthio-2-phenylthiomethylindole

A suspension of sodium hydride (0.37 g 60% dispersion in oil, 9.4 mmol) in dimethylformamide (50 mL) was cooled to 0°C. 2-Phenylthiomethylindole (1.5 g, 6.3 mmol) was added portionwise, and the reaction stirred at 0°C for 15 min. Phenyldisulfide (1.5 g, 6.9 mmol) was added and the reaction stirred at 20°C for 6 h. The reaction was quenched with water and extracted with ethyl acetate. The organic extract was washed with water, saturated brine and dried over magnesium sulfate. Filtration and evaporation of solvent left an oil which was purified by medium pressure chromatography on silica gel using 5% ethyl acetate in hexane. The title compound was obtained as an oil.
Analysis calculated for $C_{21}H_{17}NS_2 \cdot H_2O \cdot 0.15 \cdot C_4H_8O_2$
C, 68.50; H, 5.33; N 3.60
Found: C, 68.40; H, 4.65; N, 3.86

Step D: 2-Phenylsulfinylmethyl-3-phenylthioindole

A solution of 3-phenylthio-2-phenylthiomethylindole (0.750 g, 2.94 mmol) in methanol (100 mL) was cooled to 0°C with stirring. Monoperoxyphthalic acid magnesium salt (0.908 g, 80% peracid) in methanol (50 mL) was added slowly dropwise. After addition, the reaction was stirred an additional 30 min., then quenched with 10% aqueous sodium thiosulfate (2 mL). The methanol was removed *in vacuo*, and the residue partitioned between ethyl acetate and water. The organic phase was washed successively with water and saturated brine, then dried over magnesium sulfate. Filtration and concentration of the filtrate *in vacuo* gave an oil which was purified by chromatography on silica gel using 20-30% ethyl acetate in hexane. The title compound was obtained as a foam, mp 71-74°C.
Exact mass calculated for $C_{21}H_{17}NOS_2$: 364.082982.

Found: 364.084549.
NMR (DMSO-d_6) δ 11.82 (1H, s), 7.50 (6H, m), 7.23 (1H, d, J=8 Hz), 7.15 (3 H, m) 7.05 (2H, m) 6.90 2H, m), 4.43 (1H, d, J=13 Hz), 4.38 (1H, d, J=13 Hz).

EXAMPLE 5

Preparation of 2-Phenylcarboxamidomethyl-3-phenylthioindole

Step A: 3-Phenythioindole-2-carboxamide

The title compound was prepared from 3-phenylthioindole-2-carboxylic acid (prepared according to the procedure described by Atkinson, J.G. et al., Synthesis, p. 480-481 (1988), (4.01 g, 0.015 mol), ammonia (large excess), and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorphosphate (7.2 g, 0.016 mol) in dimethylformamide according to the general procedure described in Example 1 for the preparation of N-(3-pyridylmethyl)-5-chloro-3-phenylthio-2-carboxamide. The title compound was obtained as a pale yellow solid.

Step B: 2-Aminomethyl-3-phenylthioindole

A solution of 3-phenylthioindole-2-carboxamide (1.9 g, 7.1 mmol) in tetrahydrofuran was cooled under nitrogen to 0°C and treated with neat boranedimethylsulfide complex (7.1 mL, 0.070 mol). The reaction was refluxed for 7 h, cooled to 0°C and quenched with 10% aqueous hydrochloric acid. The solution was adjusted to pH 8 with 20% aqueous sodium hydroxide. The reaction was extracted with ethyl acetate and the organic extract washed with saturated brine, and dried over magnesium sulfate. The title compound was obtained as a pale yellow oil.

Step C: 2-Phenylcarboxamidomethyl-3-phenylthioindole

2-Aminomethyl-3-phenylthioindole (0.85 g, 3.3 mmol) was dissolved in chloroform (15 mL) and cooled under nitrogen to 0°C.

Pyridine (2.7 mL, 33 mmol) was added, followed by benzoyl chloride (1.1 mL, 10 mmol). The reaction was stirred at 20°C for 1 h and 10% aqueous hydrochloric acid added. The layers were separated and the organic phase washed successively with water, saturated sodium bicarbonate and saturated brine. The chloroform solution was dried over magnesium sulfate, filtered and evaporated to dryness. The resulting oil was chromatographed on silica gel with 5% ethyl acetate in methylene chloride. The title compound was obtained as a solid, mp 64-65°C.

Analysis calculated for $C_{22}H_{18}N_2OS.0.2\ H_2O$
C, 73.00; H, 5.08; N, 7.74
Found: C, 72.93; H, 5.02; N, 7.66

EXAMPLE 6

Preparation of 2-(N-Phenylacetamido)-3-phenyl-thioindole and 2-(N-Phenylacetamido)-1-(phenyl-carbamoyl)-3-phenylthioindole

2-Methyl-3-phenylthioindole (0.50 g, 2.1 mmol) (prepared according to the procedure described by Atkinson, J. G., et al., Synthesis, p. 480-481 (1988), was dissolved in dry tetrahydrofuran and cooled under nitrogen to -78°C. A solution of n-butyllithium in hexane (0.83 mL, 2.5 M) was added via syringe. Carbon dioxide was bubbled into the reaction mixture over a period of several minutes; unreacted carbon dioxide was removed by freezing the reaction at liquid nitrogen temperature under high vacuum and warming to -78°C. A solution of t-butyllithium in hexane was added (1.35 mL, 1.7 M) and the reaction stirred for 20 min. Phenylisocyanate (0.23 mL, 2.1 mmol) in tetrahydrofuran (1.5 mL) was added and the reaction stirred at 20°C overnight. The reaction was diluted with water and extracted with ethyl acetate. The organic phase was washed with saturated brine and dried over magnesium sulfate. Filtration and evaporation of solvent left an amber oil. The crude products were chromatographed on silica gel eluting successively with 15%, 20%, and 40% ether in hexane. 2-(N-Phenylacetamido)-3-phenylthioindole was isolated as a solid, mp 66-68°C.

Analysis calculated for $C_{22}H_{18}N_2OS$
C, 72.98; H, 5.01; N, 7.73
Found: C, 72.99; H, 4.87; N, 7.52

Later fractions contained 2-(N-phenylacetamido)-1-(phenylcarbamoyl)-3-phenylthioindole, mp 123-125°C.

Analysis calculated for $C_{29}H_{23}N_3O_2S$
C, 70.28, H, 4.67, N, 8.47
Found: C, 70.37, H, 4.61; N, 8.34

EXAMPLE 7

Preparation of 2-(2-Oxo-2-furan-3-yl)ethyl-3-phenylthioindole

Step A: N-Methoxy-N-methylfuran-3-carboxamide

The title compound was prepared from furan-3-carboxylic acid (3.4 g, 0.030 mol), N,O-dimethylhydroxylamine hydrochloride hydrochloride (2.9 g, 0.030 mol) triethylamine (8.3 mL, 0.060 mol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorphosphate (13.3 g, 0.030 mol) according to the general procedure described in Example 1 for N-(3-pyridylmethyl)-5-chloro-3-phenylthio-2-carboxamide.
NMR (DMSO-d6) δ 8.25 (1H, s), 7.75 (1H, s), 3.70 (3H, s), 3.22 (3H, s).

Step B: 2-(2-Oxo-2-furan-3-yl)ethyl-3-phenylthioindole

The title compound was prepared from N-methoxy-N-methylfuran-3-carboxamide (0.32 g, 2.1 mmol), and 2-methyl-3-phenylthioindole (0.50 g, 2.1 mmol) according to the general procedure described in Example 6 for the preparation of 2-(N-phenylacetamido)-3-phenyl-thioindole. The crude product was chromatographed on silica gel with chloroform. The title compound was obtained as a pale yellow solid, mp 127-129°C.

Analysis calculated for $C_{20}H_{15}NO_2S$
C, 72.05; H, 4.54; N, 4.20
Found: C, 72.08; H, 4.57; N, 4.24

EXAMPLE 8

Preparation of 2-Benzoyl-5-chloro-3-phenylthioindole

Step A: N-Methoxy-N-methyl-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared from 5-chloro-3-phenylthioindole-2-carboxylic acid (1.0 g, 3.30 mmol)) N,O-dimethylhydroxylamine hydrochloride (0.64 g, 6.6 mmol), triethylamine (1.0 mL, 7 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorphosphate (1.64 g, 3.6 mmol) in dimethylformamide according to the general procedure described in Example 1 for the preparation of N-(3-pyridylmethyl)-5-chloro-3-phenylthio-2-carboxamide.

Step B: 2-Benzoyl-5-chloro-3-phenylthioindole

N-Methoxy-N-methyl-5-chloro-3-phenylthioindole-2-carboxamide (0.24 g, 0.69 mmol) was dissolved in dry tetrahydrofuran (5 mL) and cooled to -78°C under nitrogen. A solution of phenylmagnesium chloride in tetrahydrofuran (0.81 mL, 2M) was added via syringe and the reaction warmed to 20°C overnight. Water and ethyl acetate were added to the reaction and then separated. The organic phase was washed with water, 5% aqueous hydrochloric acid, saturated sodium bicarbonate, saturated brine, and dried over magnesium sulfate. Filtration and evaporation of solvent gave the crude product which was chromatographed on silica gel with 10% ether in hexane. The title compound was obtained as a solid, mp 154-155°C.

Analysis calculated for $C_{21}H_{14}ClNOS$
C, 69.32; H, 3.88; N, 3.85
Found: C, 68.61; H, 3.83; N, 3.83

EXAMPLE 9

Preparation of 2-(2-Benzoxazol-2-ylethyl)-3-phenylthioindole

Step A: N-Methoxy-N-methyl-3-phenylthioindole-2-carboxamide

The title compound was prepared from 3-phenylthioindole-2-carboxylic acid (1.0 g, 3.7 mmol), N,O-dimethylhydroxylamine hydrochloride (0.54 g, 5.5 mmol), triethylamine (1.5 mL, 11 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorphosphate (1.64 g, 3.7 mmol) according to the procedure described in Example 1 for N-(3-pyridylmethyl)-5-chloro-3-phenylthio-2-carboxamide.

Step B: 3-Phenylthioindole-2-carboxaldehyde

N-Methoxy-N-methyl-3-phenylthioindole-2-carboxamide (1.57 g, 5.26 mmol) was dissolved in tetrahydrofuran (150 mL) and cooled to 0°C under nitrogen. A solution of lithium aluminum hydride in tetrahydrofuran (5.76 mL, 1M) was added slowly via syringe and the reaction stirred a total of 1.5 h. Ethyl acetate (30 mL) was added, followed by saturated sodium potassium tartrate solution. The layers were separated and the organic phase washed with saturated brine and dried over magnesium sulfate. Filtration and evaporation of solvent gave the title compound as a yellow solid.

Step C: trans-2-(2-Benzoxazol-2-ylethenyl)-3-phenylthioindole

n-Butyllithium in hexane (3.47 mL, 2.5 M) was added to a solution of [(benzoxal-2-yl)-methyl]diethylphosphonate (2.34 g, 8.68 mmol) in tetrahydrofuran (50 mL) at -78°C under nitrogen. The reaction was stirred for 20 min., and warmed to -20°C. A solution of 3-phenylthioindole-2-carboxaldehyde (1.10 g, 4.34 mmol) in tetrahydrofuran (30 mL) was added and the reaction stirred at 20°C overnight. Ethyl acetate and water were added and the layers separated. The organic layer was washed with saturated brine and dried over magnesium sulfate. The crude product was triturated with 1:1 hexane

ethyl acetate and collected by filtration. The title compound was obtained as a yellow solid, mp 260°C.

Analysis calculated for $C_{23}H_{16}N_2OS$
C, 72,32; H, 4.58; N, 7.33
Found: C, 72.41; H, 4.50; N, 7.44

Step D: 2-(2-Benzoxazol-2-ylethyl)-3-phenylthioindole

A solution of trans-2-(2-benzoxazol-2-ylethenyl)-3-phenylthioindole (0.420 g, 1.14 mmol) in 1:1 methanol/tetrahydrofuran (250 mL) was stirred under 1 atmosphere of hydrogen in the presence of 10% palladium on charcoal (100 mg). Additional catalyst was added as needed to drive the reaction to completion. The catalyst was removed by filtration, and the filtrate concentrated *in vacuo*. The resulting solid was triturated with 10% ethyl acetate in hexane and collected by filtration to afford the title compound, mp 192-193°C.

Analysis calculated for $C_{23}H_{18}N_2OS$
C, 72.80; H, 5.04; N, 7.38
Found: C, 72.78; H, 4.95; N, 7.45

EXAMPLE 10

Preparation of N-2-Furanylmethyl-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in Example 1, Step B, except substituting 2-aminomethylfuran for 3-aminomethylpyridine. The dimethylformamide was removed *in vacuo*, and the residue triturated with 1:1 ethyl acetate-hexane and filtered. Recrystallization from acetonitrile gave the title compound, mp 214°C.

Analysis calculated for $C_{20}H_{15}ClN_2O_2S$
C, 62.74; H, 3.95; N, 7.32
Found: C, 62.27; H, 3.88; N, 7.41

NMR (DMSO-d_6): δ 12.55 (1H, s), 8.72 (1H, t, J=6 Hz), 7.55 (1H, m), 7.54 (1H, d, J=8 Hz), 7.45 (1H, d, J=2 Hz), 7.15 (1H, tt, J=7, 1 Hz), 7.08 (1H, s), 7.06 (1H, d, J= 8 Hz), 6.35 (1H, m), 6.18 (1H, m), 4.56 (2H, d, J=6 Hz).

EXAMPLE 11

Preparation of N-3-Pyridyl-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in Example 1, Step B, except substituting 3-aminopyridine for 3-aminomethyl-pyridine. The dimethylformamide was removed *in vacuo*, and the residue triturated with 1:1 ethyl acetate-hexane and filtered. Chromatography on silica gel with 40% ethyl acetate in hexane gave the title compound, mp 255-256°C.

Analysis calculated for $C_{20}H_{15}ClN_3OS$
C, 63.24; H, 3.98; N, 10.74
Found: C, 62.59; H, 3.86; N, 11.06

NMR (DMSO-d_6): δ 12.72 (1H, s), 10.55 (1H, s), 8.85 (1H, d, J=3 Hz), 8.35 (1H, dd, J=5, 1 Hz), 8.14 (1H, dm, J_d=8 Hz), 7.60 (1H, d, J=9 Hz), 7.48 (1H, d, J=2 Hz), 7.40 (1H, dd, J=9, 2 Hz), 7.25 (2H, t, J=7 Hz), 7.16 (1H, m), 7.11 (2H, t, J=7 Hz).

EXAMPLE 12

Preparation of N-Ethyl-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in Example 1, Step B, except substituting ethylamine for 3-aminomethylpyridine. The dimethylformamide was removed *in vacuo*, and the residue triturated with 1:1 ethyl acetate-hexane and filtered. Recrystallization from 2% methanol in ethyl acetate gave the title compound, mp 210-211°C.

Analysis calculated for $C_{17}H_{15}ClN_2OS \cdot 0.5\ H_2O$
C, 60.08; H, 4.74; N, 8.24
Found: C, 60.00; H, 4.18; N, 8.52

NMR (DMSO-d_6): δ 12.49 (1H, s), 8.31(1H, t, J=6 Hz), 7.54 (1H, d, J=9 Hz), 7.43 (1H, d, J= 2 Hz), 7.27 (3H, m), 7.15 (1H, tt, J=7, 2 Hz), 7.07 (2H, m), 3.35(4H, m), 1.06 (3H, t, J=7 Hz).

EXAMPLE 13

Preparation of N-3-Methoxybenzyl-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in Example 1, Step B, except substituting 3-methoxybenzylamine for 3-amino-methylpyridine. The dimethyl-formamide was removed *in vacuo*, and the residue triturated with 1:1 ethyl acetate-hexane and filtered. Recrystallization from acetonitrile gave the title compound, mp 172°C.

Analysis calculated for $C_{23}H_{19}ClN_2O_2S \cdot 0.3\ H_2O$
C, 64.48; H, 4.61; N, 6.54
Found: C, 64.41; H, 4.38; N, 6.75

NMR (DMSO-d_6): δ 12.55 (1H, s), 8.80 (1H, m), 7.55 (1H, d, J=8 Hz), 7.44 (1H, s), 7.25 (3H, m), 7.15 (2H, m), 7.05 (2H, d, J=7 Hz), 6.80 (3H, m), 4.54 (2H, d, J=6 Hz).

EXAMPLE 14

Preparation of N-2-Methoxyethyl-5-chloro-3-phenyl-thioindole-2-carboxamide

The title compound was prepared according to the procedure described in Example 1, Step B, except substituting 2-methoxyethylamine for 3-amino-methylpyridine. The dimethyl-formamide was removed *in vacuo*, and the residue triturated with 1:1 ethyl acetate-hexane and filtered to give the title compound, mp 216-217°C.

Analysis calculated for $C_{18}H_{17}ClN_2O_2S$: 0.25 H_2O
C, 59.17; H, 4.83; N, 7.67
Found: C, 59.11; H, 4.75; N, 7.82

NMR (DMSO-d_6): δ 12.54 (1H, s), 8.44 (1H, t, J=6 Hz), 7.54 (1H, d, J=9 Hz), 7.48 (1H, d, J=2 Hz), 7.28 (3H, m), 7.17 (1H, t, J=7 Hz), 7.10 (2H, m), 3.49 (2H, q, J=6 Hz), 3.37 (2H, t, J=6 Hz), 3.16 (3H, s).

EXAMPLE 15

Preparation of N-4-Pyridylmethyl-5-chloro-3-phenyl-thioindole-2-carboxamide

The title compound was prepared according to the procedure described in Example 1, Step B, except substituting 4-aminomethylpyridine for 3-amino-methylpyridine. The dimethylformamide was removed *in vacuo*, and the residue triturated with 1:1 ethyl acetate-hexane and filtered. Recrystallization from acetonitrile gave the title compound, mp 228-229°C.

Analysis calculated for $C_{21}H_{16}ClN_3OS$: 0.2 H_2O
C, 63.45; H, 4.16; N, 10.57
Found: C, 63.33; H, 4.02; N, 10.50

NMR (DMSO-d_6): δ 12.56 (1H, s), 8.92 (1H, t, J= 6 Hz), 8.38 (1H, d, J=4 Hz), 7.55 (1H, d, J=8 Hz), 7.47 (1H, s), 7.31 (1H, dd, J=8, 2 Hz), 7.25 (1H, d, J=7 Hz), 7.17 (2H, m), 7.05 (1H, d, J=7 Hz), 4.58 (2H, d, J=6 Hz).

EXAMPLE 16

Preparation of N-2-Hydroxyethyl-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in Example 1, Step B, except substituting 2-hydroxyethylamine for 3-amino-methylpyridine. The dimethyl-formamide was removed *in vacuo*, and the residue triturated with 1:1 ethyl acetate-hexane and filtered. Chromatography on silica gel with 2% methanol in chloroform gave the title compound, mp 222-223°C.

Analysis calculated for $C_{17}H_{15}ClN_2O_2S$: 0.3 H_2O
C, 57.96; H, 4.46; N, 7.95
Found: C, 57.99; H, 4.26; N, 7.90

NMR (DMSO-d_6): δ 12.50 (1H, s), 8.46 (1H, m), 7.55 (1H, d, J=9 Hz), 7.45 (1H, d, J=1 Hz), 7.28 (3H, m), 7.17 (1H, t, J=6 Hz), 7.13 (2H, m), 4.85 (1H, t), 3.49 (1H, m), 3.43 (1H, m).

EXAMPLE 17

Preparation of 5-Chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in Example 1, Step B, except substituting an excess of ammonia gas for 3-aminomethylpyridine and triethylamine. The dimethylformamide and excess ammonia were removed *in vacuo* and the residue partitioned between ethyl acetate and 10% hydrochloric acid. The organic phase was washed with water, 5% sodium hydroxide and saturated brine, and then dried over magnesium sulfate. Filtration and evaporation gave a crude product which was chromatographed on silica gel with 30% ethyl acetate in hexane. The title compound was obtained as a white solid mp 213-215°C.

Analysis calculated for $C_{15}H_{11}ClN_2OS \cdot 1/3H_2O$
C, 58.35; H, 3.81; N, 9.07
Found: C, 58.33; H, 3.64; N, 9.11

NMR (DMSO-d_6): δ 12.52 (1H, bs), 8.06 (1H, s), 7.76 (1H, s), 7.55 (1H, d, J=9 Hz), 7.44 (1H, s), 7.28 (3H, m), 7.15 (1H, t, J=6 Hz), 7.06 (2H, d, J=8 Hz).

EXAMPLE 18

Preparation of 5-Chloro-3-phenylthioindole-2-thiocarboxamide

A solution of 5-chloro-3-phenylthioindole-2-carboxamide (3.8 g, 12.5 mmol) and [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (5.0 g, 12.5 mmol) in dry THF (110 mL) was refluxed under nitrogen for 16 h. The solvent was removed *in vacuo* and the residue chromatographed on silica gel with 10% ethyl acetate in hexane. The chromatographed product was triturated with hexane and the yellowish solid collected and dried to give the title compound, mp 217°C (decomposed).

Analysis calculated for $C_{15}H_{11}ClN_2S$
C, 56.50; H, 3.48; N, 8.79
Found: C, 56.75; H, 3.64; N, 8.59

NMR (DMSO-d_6): δ 12.22 (1H, s), 10.31 (1H, s), 9.48 (1H, s), 7.50

(1H, d, J=8 Hz), 7.39 (1H, s), 7.25 (3H, m), 7.13 (1H, t, J=7 Hz), 7.01 (2H, d, J=7 Hz).

EXAMPLE 19

Preparation of N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-thiocarboxamide

The title compound was prepared according to the procedure described for 5-chloro-3-phenyl-thioindole-2-thiocarboxamide except substituting N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-carboxamide for 5-chloro-3-phenylthioindole-2-carboxamide. The crude product was chromatographed on silica gel with 3% ethyl acetate in hexane. The title compound was obtained as a bright yellow solid, mp 143-144°C.

Analysis calculated for $C_{20}H_{15}ClN_2OS_2 \cdot H_2O$
C, 57.61; H, 3.62; N, 6.72
Found: C, 57.56; H, 3.58; N, 6.52

NMR (DMSO-d_6): δ 12.27 (1H, s), 10.73 (1H, s), 7.55 (2H, m), 7.39 (1H, s), 7.21 (4H, m), 6.98 (2H, d, J=7 Hz), 6.36 (2H, 4.96 (2H, s).

EXAMPLE 20

Preparation of N-[1-(2(R)-hydroxypropyl)]-5-chloro-3-phenylthio-indole-2-carboxamide

The title compound was prepared according to the procedure described in Example 1, Step B, except substituting 2(R)-hydroxy-1-propylamine for 3-amino-methylpyridine. The dimethylformamide was removed *in vacuo* and the residue triturated first with 20% ethyl acetate in hexane then by acetonitrile. The title compound was obtained as an off-white solid, mp 202-203°C.

Analysis calculated for $C_{18}H_{17}ClN_2O_2S \cdot 0.3\ H_2O$
C, 59.01; H, 4.67; N, 7.65
Found: C, 58.91; H, 4.59; N, 7.50

NMR (DMSO-d_6): δ 12.52 (1H, s), 8.45 (1H, t, J=5 Hz), 7.55 (1H, d, J=8 Hz), 7.46 (1H, s), 7.25 (3H, m), 7.15 (3H, m), 4.89 (1H, d, J=5 Hz),

3.74 (1H, m), 3.38 (1H, m), 3.23 (1H, m), 1.00 (3H, d, J=6 Hz).

EXAMPLE 21

Preparation of N-(2-pyridyl)methyl-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in Example 1, Step B, except substituting 2-pyridylmethylamine for 3-aminomethylpyridine. The dimethylformamide was removed *in vacuo* and the residue triturated first with 30% ethyl acetate in hexane, then with acetonitrile. The title compound was obtained as a white solid, mp 209-210°C.

Analysis calculated for $C_{21}H_{16}ClN_3OS$
C, 64.03; H, 4.10; N, 10.67
Found: C, 63.51; H, 3.97; N, 10.41

NMR (DMSO-d_6): δ 12.58 (1H, s), 9.15 (1H, t, J=5 Hz), 8.46 (1H, d, J=5 Hz), 7.66 (1H, t, J=8 Hz), 7.57 (1H, d, J=8 Hz), 7.50 (1H, s), 7.25 (5H, m), 7.12 (3H, m), 4.68 (2H, d, J=5 Hz).

EXAMPLE 22

Preparation of N-(3-methoxy-4-pyridyl)methyl-5-chloro-3-phenylthioindole-2-carboxamide

Step 1: Preparation of 4-cyano-2-methoxypyridine

A solution of 2-chloro-4-cyanopyridine (1.25 g, 9.1 mmol), prepared as described by D. Libermann, N. Rist, F. Grumbach, S. Cals, M. Moyeux and A. Rouaix, Bull. Soc. Chim. France, 694 (1958), in methanol was treated with sodium methoxide (0.58 g, 10.9 mmol) and refluxed for 30 minutes. The reaction mixture was cooled, filtered and the filtrate concentrated *in vacuo* to obtain the crude product as an off-white solid. The crude product was chromatographed on silica gel with 20% ethyl acetate in hexane. The title compound was obtained as a white powder.

Step 2: Preparation of 4-aminomethyl-2-methoxypyridine

A solution of 4-cyano-2-methoxypyridine (0.55 g, 4.1 mmol) in ethanol was hydrogenated at 60 psi H_2 in the presence of 10% Pd/C (100 mg). After 3.5 h the catalyst was removed by filtration through Super-Cel and the filtrate evaporated to give the title compound as a foam.

Step 3: Preparation of N-(3-methoxy-4-pyridylmethyl)-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in Example 1, Step B, except substituting 4-aminomethyl-2-methoxypyridine for 3-aminomethylpyridine. The dimethylformamide was removed *in vacuo* and the crude product purified by chromatography on silica gel with 20-40% ethyl acetate in hexane. The title compound was obtained as a white solid, mp 227-228°C.

Analysis calculated for $C_{22}H_{18}ClN_3O_2S$
C, 62.33; H, 4.28; N, 9.91
Found: C, 62.63; H, 4.21; N, 9.92

NMR (DMSO-d_6): δ 12.58 (1H, s), 8.93 (1H), 8.37 (2H, d), 7.56 (1H, d), 7.47 (1H, s), 7.27 (3H, m), 7.18 (2H, m), 7.05 (2H, d), 4.59 (2H, d), 3.30 (3H, s).

EXAMPLE 23

Preparation of N-(3-hydroxymethyl)benzyl-5-chloro-3-phenylthio-indole-2-carboxamide

The title compound was prepared according to the procedure described in Example 1, Step B, except substituting 3-hydroxymethylbenzylamine for 3-amino-methylpyridine. The dimethylformamide was removed *in vacuo* and the crude product recrystallized from acetonitrile. The title compound was obtained as a white solid, mp 229-230°C.

Analysis calculated for $C_{22}H_{17}ClN_2O_2S$
C, 64.61; H, 4.19; N, 6.85
Found: C, 64.20; H, 4.09; N, 6.85
NMR (DMSO-d_6): δ 12.69 (1H, s), 10.33 (1H, s), 7.60 (3H, m), 7.49 (1H, s), 7.30 (4H, m), 7.15 (4H, m), 5.22 (1H, t, J=7 Hz), 4.50 (2H, d, J=7 Hz).

EXAMPLE 24

Preparation of N-(3-hydroxybenzyl)-5-chloro-3-phenylthioindole-2-carboxamide

The title compound was prepared according to the procedure described in Example 1, Step B, except substituting 3-hydroxybenzylamine for 3-aminomethyl-pyridine. The dimethyl-formamide was removed *in vacuo* and the crude product was chromatographed on silica gel with 10% methanol in chloroform. The title compound was obtained as a white solid, mp 214-216°C.
Analysis calculated for $C_{22}H_{17}ClN_2O_2S \cdot 0.3\ H_2O$
C, 63.77; H, 4.04; N, 6.76
Found: C, 63.92; H, 3.88; N, 6.49
NMR (DMSO-d_6): δ 12.55 (1H, s), 9.34 (1H, s), 8.75 (1H, t, J=5 Hz), 7.53 (1H, d, J=8 Hz), 7.45 (1H, s), 7.1-7.65 (4H, m), 7.06 (2H, d, J=7 Hz), 7.01 (1H, t, J=8 Hz), 6.70 (1H, s), 6.62 (2H, m), 4.48 (2H, d, J=5 Hz).

EXAMPLE 25

Preparation of 5-Chloro-3-phenylsulfonylindole-2-carboxamide (Compound 18)

5-Chloro-3-phenylthioindole-2-carboxamide (0.177 g, 0.584 mmol) was dissolved in 25 mL chloroform and cooled to 0°C. 50% by weight meta-chloroperoxybenzoic acid (503 mg, 1.46 mmol) was added and the reaction stirred at 20°C for 6 hours. A 10% aqueous solution of sodium thiosulfate was added and the reaction vigorously stirred for 10 minutes. The layers were separated and the organic phase

washed with saturated sodium chloride then dried over magnesium sulfate. The crude product was chromatographed over silica gel eluting with 40% ethyl acetate in hexane. The title compound was obtained as a white powder, mp 255-257°C.

NMR (300 MHz, DMSO-d6): δ 13.05 (1H,s), 8.48(1H,s), 8.25(1H,s), 8.03(2H,d,J=8 Hz), 7.95(1H,s), 7.60(4H,m), 7.34(1H,d,J=8 Hz).

Analysis calculated for $C_{15}H_{11}ClN_2O_3S$

C, 53.82; H, 3.31; N, 8.37

Found: C, 53.74; H, 3.29; N, 8.34

EXAMPLE 26

Preparation of 5-Chloro-3-phenylsulfinylindole-2-carboxamide (Compound 17)

A solution of magnesium monoperoxyphthalic acid (85% peracid) (11.8 mg, 0.024 mmol) in methanol (2 mL) was added dropwise to a solution of 5-chloro-3-phenylthioindole-2-carboxamide (14.5 mg, 0.048 mmol) in methanol (2 mL) at 0°C. The reaction was stirred at 20°C for 4 hours. A solution of 10% aqueous sodium thiosulfate was added and the reaction stirred vigorously for 10 minutes. Methanol was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The ethyl acetate extract was washed with brine and dried over magnesium sulfate. The crude product was purified by column chromatography on silica gel with 30-40% ethyl acetate in hexane. The title compound was obtained as a white solid.

NMR (DMSO-d6, 300 MHz) δ 12.53(1H, s), 8.35(1H,br s), 8.08(1H,br s), 7.83(1H,d,J=2 Hz), 7.71(2H,d,J=8 Hz), 7.52(4H,m), 7.30(1H,dd,J=9,2 Hz).

EXAMPLE 27

Preparation of N-(2,6-difluorobenzyl)-5-chloro-3-phenyl-sulfonyl-indole-2-carboxamide

Step A: 5-chloro-3-phenylsulfonylindole-2-carboxylic acid

To a suspension of 5-chloro-3-phenylthio-indole-2-carboxylic acid (4.84 g, 0.016 mol) in chloroform (1200 mL) was added 55% m-chloroperoxybenzoic acid (12.5 g, 0.04 mol). The mixture was allowed to stir at room temperature for 40 hours. Filtration afforded the title compound as a colorless solid, mp 277-280°C (dec). On partial evaporation a second crop of product was obtained.

Step B: Product of reaction of 5-chloro-3-phenyl-sulfonylindole-2-carboxylic acid with oxalyl chloride

To a suspension of 5-chloro-3-phenylsulfonyl-indole-2-carboxylic acid (5.04 g, 0.015 mol) in chloroform (200 mL) was added oxalyl chloride (3.81 g, 0.03 mol). After addition of a catalytic amount of dimethylformamide (0.1 mL) the mixture was heated at a bath temperature of 60°C for 50 minutes. After cooling, the solid product, mp >300°C, was utilized directly without further purification. While based on mass spectral and NMR data, this product appears to be a symmetrical dimer, it behaves as a typical acid chloride in reactions with primary amines.

Step C: N-(2,6-difluorobenzyl)-5-chloro-3-phenyl-sulfonylindole-2-carboxamide

2,6-Difluorobenzylamine (0.430 g, 3.0 mmol) was added dropwise to the solution of the "acid chloride equivalent" from Step B (0.354 g, 1.0 mmol) in tetrahydrofuran solution (10 mL) cooled in an ice-acetone bath. The reaction mixture was allowed to warm to room temperature and left overnight. For work-up, ethyl acetate and water were added. The ethyl acetate phase was washed well with dilute

hydrochloride acid, saturated aqueous sodium bicarbonate, and brine. After drying over magnesium sulfate and evaporation of the solvent, the residue was slurried with ethyl acetate and filtered to give the title compound, mp 274-280°C.

Analysis calculated for $C_{22}H_{15}ClF_2N_2O_3S \cdot 0.5H_2O$
C, 56.24; H, 3.43; N, 5.96
Found: C, 56.12; H, 3.31; N, 5.97

NMR (DMSO-d_6) δ 13.06 (1H, s), 9.41 (1H, t, J=5.5Hz), 7.95 (3H, m), 7.41-7.67 (m, 5H), 7.34 (1H, dd, J=9, 2Hz), 7.18 (2H, t, J=8Hz), 4.64 (2H, d, J=5.5Hz).

EXAMPLE 28

Preparation of N-(4-pyridylmethyl)-5-chloro-3-phenyl-sulfinylindole-2-carboxamide (29)

Step A: Preparation of 5-chloro-3-phenylsulfinyl-indole-2-carboxylic acid

To a suspension of 5-chloro-3-phenylthioindole-2-carboxylic acid (2.14 g, 0.007 mol) in chloroform (600 mL) was added 55% m-chloroperoxybenzoic acid (2.32 g, 0.0074 mol). The mixture cleared briefly and then solids appeared. After stirring overnight at room temperature, the title compound was obtained in pure form on filtration, mp 183-185°C.

Step B: N-(4-pyridylmethyl)-5-chloro-3-phenylsulfinylindole-2-carboxamide

To a mixture of 5-chloro-3-phenylsulfinylindole-2-carboxylic acid (0.096 g, 0.3 mmol), triethylamine (0.061 g, 0.6 mmol), 4-aminomethylpyridine (0.043 g, 0.4 mmol) in dry dimethylformamide was added benzotriazol-1-yloxytris(dimethyl-amino)phosphonium hexafluorophosphate (BOP reagent) (0.155 g, 0.35 mmol). The mixture was stirred at room temperature under nitrogen for three days. Following evaporation, the residue was partitioned between ethyl acetate and water. The ethyl acetate phase was separated

and washed with dilute hydrochloric acid. The acidic extract was neutralized with aqueous sodium bicarbonate and the product extracted into ethyl acetate. The ethyl acetate extract was washed well with aqueous sodium bicarbonate, then brine, and dried over magnesium sulfate. Evaporation afforded a solid residue which was recrystallized from ethyl acetate to give the title compound, mp 233-235°C.

Analysis calculated for $C_{21}H_{16}ClN_3O_2S$
C, 61.54; H, 3.93; N, 10.25
Found: C, 61.39; H, 3.95; N, 10.36

NMR (DMSO-d_6) δ 9.62 (1H, t, J=6 Hz), 8.53 (2H, d, J=6Hz), 7.80 (1H, d, J=2 Hz), 7.67 (2H, m), 7.64 (2H, d, J=9 Hz), 7.44-7.54 (3H, m), 7.33 (3H, m), 4.60 (2H, dq, J=9, 6 Hz).

EXAMPLE 29

Preparation of N-[(S)-1-phenyl-2-hydroxyethyl]-5-chloro-3-phenylsulfonylindole-2-carboxamide (32)

To a solution of the acid chloride dimer product from Example 27, Step B, (0.354 g, 1.0 mmol) in tetrahydrofuran (10 mL), cooled in an ice-acetone bath, was added a solution of (S)-(+)-2-phenylglycinol (0.343 g, 2.5 mmol). The mixture, after warming gradually to room temperature, was allowed to sit overnight. Ethyl acetate and water were added. The ethyl acetate phase was washed successively with dilute hydrochloric acid, water, saturated sodium bicarbonate and brine. After drying over magnesium sulfate and evaporation, the product was chromatographed on a 20 mm column containing 6 inches of 230-400 mesh silica gel. Elution with 40% ethyl acetate-methylene chloride gave pure title compound which, after evaporation, was crystallized from ethyl acetate-hexane to give the title compound, mp 155-160°C.

Analysis calculated for $C_{23}H_{19}ClN_2O_4S$
C, 60.72; H, 4.21; N, 6.16
Found: C, 60.33; H, 4.13; N, 6.16

NMR (DMSO-d_6): δ 13.05 (1H, s), 9.52 (1H, d, J=7.5 Hz), 7.95-8.48

(3H, m), 7.26-7.68 (10H, m), 5.13 (1H, q, J=7.5 Hz), 5.07 (1H, t=6 Hz), 3.75 (2H, 6Hz).

EXAMPLE 30

N-(3-methoxybenzyl)-5-chloro-3-(2-thiazolyl)sulfonyl-indole-2-carboxamide (31)

Step A: Preparation of 5-Chloro-3-(2-thiazolyl)thioindole-2-carboxylic Acid

Using the procedure of Example 1, Step A, but substituting di-(2-thiazolyl)disulfide for phenyldisulfide, there was obtained the title compound, mp 242-244°C.

Step B: Preparation of 5-Chloro-3-(2-thiazolyl)-sulfonylindole-2-carboxylic Acid

Using the procedure of Example 27, Step A, but substituting 5-chloro-3-(2-thiazolyl)thioindole-2-carboxylic acid for 5-chloro-3-phenylthioindole-2-carboxylic acid, there was obtained the title compound, mp 260-261°C.

Step C: Product of Reaction of 5-Chloro-3-(2-thiazolyl)sulfonyl-indole-2-carboxylic Acid with Oxalyl Chloride

Using the procedure of Example 27, Step B, but substituting 5-chloro-3-(2-thiazolyl)sulfonylindole-2-carboxylic acid for 5-chloro-3-phenylsulfonylindole-2-carboxylic acid, there was obtained a solid product, mp>290°C, which was utilized directly in the next step.

Step D: N-(3-methoxybenzyl)-5-chloro-3-(2-thiazolyl-sulfonyl)-indole-2-carboxamide

To a solution of the 'acid chloride' product from Step C (0.181 g, 0.5 mmol) in tetrahydrofuran (5 mL), cooled in an ice-acetone bath, was added 3-methoxybenzylamine (0.205 g, 1.5 mmol). The mixture was allowed to warm to room temperature and then was

left overnight with stirring. Ethyl acetate and water were added. The ethyl acetate layer, after separation, was washed with dilute hydrochloric acid, saturated sodium bicarbonate, and brine. After drying (magnesium sulfate) and evaporation, the solid residue was allowed to stand in a small volume of ethyl acetate. Filtration gave the title product, mp 205-209°C.

Analysis calculated for $C_{20}H_{16}ClN_3O_4S_2$
C, 52.00, H, 3.49, N, 9.10
Found: C, 51.88, H, 3.42, N, 9.07

(DMSO-d_6) δ 9.43 (1H, t, J=6 Hz), 8.18 (1H, d, J=3 Hz), 8.02 (1H, d, J=3 Hz), 8.00 (1H, d, J=2 Hz), 7.58 (1H, d, J=8.5 Hz), 7.40 (1H, dd, J=8.5, 2 Hz), 7.28 (1H, t, J=8 Hz), 6.98-7.05 (2H, m), 6.85 (1H, dd, J=8, 2.5 Hz), 4.54 (2H, d, J=3.76 Hz).

EXAMPLE 31

5-Chloro-3-(2-thiazolyl)sulfonylindole-2-carboxamide

A solution of the 'acid chloride' product of Example 30, Step C, (0.50 g, 1.4 mmol) in tetrahydrofuran (25 mL) was added slowly to a solution of tetrahydrofuran saturated with ammonia at -10°C. The reaction mixture was allowed to warm gradually to room temperature and then was stirred overnight. After evaporation of the solvent, the residue was partitioned between ethyl acetate and water. The ethyl acetate extract was washed with saturated sodium bicarbonate and brine, and dried with magnesium sulfate. After evaporation of solvent, the residue was slurried in ethyl acetate and filtered to give the title compound, mp 292-294°C (dec).

Analysis calculated for $C_{12}H_8ClN_3O_3S_2$
C, 42.17; H, 2.36; N, 12.29
Found: C, 42.23; H, 2.35; N, 11.85

NMR (DMSO-d_6) δ 8.39 (1H, br s), 8.34 (1H, br s), 8.24 (1H, d, J=3 Hz), 8.07 (1H, d, J=3 Hz), 8.00 (1H, dd, J=2, 0.6 Hz), 7.57 (1H, dd, J=9, 0.6 Hz), 7.40 (1H, dd, J=9, 2Hz).

EXAMPLE 32

5-Chloro-3-phenylsulfonylindole-2-thiocarboxamide

Reaction of 5-chloro-3-phenylsulfonylindole-2-carboxamide with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane (Lawesson's reagent) according to the procedure of Example 18 gave the title compound. Chromatographic purification on silica gel was carried out using 30% ethyl acetate-methylene chloride, followed by 50% ethyl acetate-methylene chloride. The pure product had mp 207-210°C.

Analysis calculated for $C_{15}H_{11}ClN_2O_2S_2$
C, 51.35; H, 3.16; N, 7.98
Found: C, 50.84; H, 3.08; N, 8.04

NMR (DMSO-d6) δ 12.90 (1H, s), 10.71 (1H, s), 10.70 (1H, s), 8.0-8.6 (2H, m), 7.84 (1H, d, J=2Hz), 7.54-7.66 (3H, m), 7.46 (1H, d, J=8.5Hz), 7.30 (1H, dd, J=8.5, 2Hz).

EXAMPLE 33

Preparation of 3-phenylsulfonyl-5-chloroindole-2-carboxamide

Step A: N-(phenylthio)succinimide

To a partial solution of N-chlorosuccinimide (3.34 g, 25 mmol) in dry methylene chloride (30 mL), cooled in an ice bath and under an inert atmosphere, was added thiophenol (2.05 mL, 20 mmol) via syringe. After stirring for 1 hour, additional N-chlorosuccinimide (0.40 g, 3 mmol) was added. After 2.5 hours total, triethylamine (3.9 mL, 28 mmol) was added dropwise. Within 15 minutes the reaction mixture was diluted with methylene chloride, the solvent washed with dilute aq. HCl and the solvent then dried (Na_2SO_4), filtered through a pad of charcoal and evaporated. The residue was triturated with diethyl ether and the product collected by filtration to yield the title compound mp 115-116°C [lit. mp 115-116°C, J. Org. Chem., 34, 51 (1969)]. This material was used as is.

Step B: Ethyl 3-phenylthio-5-chloroindole-2-carboxylate

To a partial suspension of ethyl 5-chloroindole-2-carboxylate (698 mg, 3.1 mmol) and N-(phenylthio)succinimide (683 mg, 3.3 mmol) in anhydrous methylene chloride (20 mL) at ambient temperature under an inert gas atmosphere was added boron trifluoride etherate (0.12 mL, 1.0 mmol). The reaction was monitored by tlc (thin layer chromatography) until complete. After 2 hours, the reaction was diluted with chloroform and neutralized with aq. $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered through a pad of charcoal, and the solvents evaporated. The residue was triturated with hexanes as the product crystallized out to yield the title product, mp 160-162°C [see Table II, mp 163-164°C]. This material was used as is.

Step C: Ethyl 3-phenylsulfonyl-5-chloroindole-2-carboxylate

Ethyl 3-phenylthio-5-chloroindole-2-carboxylate (642 mg, 1.94 mmol) was dissolved in chloroform (35 mL) and a dried (Na_2SO_4) solution of m-chloroperoxybenzoic acid (55% pure, 1.30 g, 4.1 mmol) in chloroform (20 mL) was added dropwise. The progress of the oxidation was monitored by tlc until complete. After 5 hours, the reaction was diluted with chloroform and some methanol and the solution washed with aq. $NaHCO_3$ and aq. Na_2CO_3. The dried (Na_2SO_4) organic layer was filtered through a pad of charcoal and the solvents removed under reduced pressure. The residue was triturated with diethyl ether to yield the product. Crystallization from methylene chloride and diethyl ether gave analytically pure material, mp 201-202°C.

^1H NMR ($CDCl_3$) δ 9.63 (br s, 1H), 8.58 (t, 1H, J=0.7 Hz), 8.07 (d, 2H, J=7 Hz), 7.46-7.56 (m, 3H), 7.40 (m, 2H), 4.39 (ABq, 2H, J=7 Hz), 1.35 (t, 3H, J=7 Hz).

Analysis calculated for $C_{17}H_{14}ClNO_4S$
C, 56.12; H, 3.88; N, 3.85
Found: C, 55.91; H, 3.95; N, 3.91

Step D: 3-Phenylsulfonyl-5-chloroindole-2-carboxamide (Compound 18)

A suspension of ethyl 3-phenylsulfonyl-5-chloroindole-2-carboxylate (596 mg, 1.64 mmol) in aqueous conc. ammonium hydroxide (10 mL) containing ammonium chloride (28 mg) was heated at 100°C for 3 hours in a sealed screw-top tube. The sealed tube was cooled in an ice bath as product crystallized out. The product was collected by filtration, rinsed with ice water, and dried to give the product, mp 253-254°C.

EXAMPLE 34

Preparation of N-[(imidazol-2-yl)methyl]-3-phenyl-sulfonyl-5-chloroindole-2-carboxamide

A suspension of 2-aminomethylimidazole dihydrochloride (256 mg, 1.5 mmol) [prepared as described in J. Org. Chem., 43, 1603 (1978)] in dry tetrahydrofuran (6 mL) containing triethylamine (.42 mL, 3.0 mmol) was stirred at room temperature under an inert atmosphere for one hour. The dimeric acid chloride (179 mg, 0.25 mmol) [see Example 27, Step B] was added, followed by additional triethylamine (0.07 mL, 0.5 mmol) and the mixture was stirred for 12-20 hours. The mixture was diluted with water and the product extracted into ethyl acetate. This organic layer was dried (Na_2SO_4), filtered, and the solvents evaporated. The residue was triturated with ethyl acetate to give the product. Recrystallization from hot ethyl acetate gave analytically pure product, mp 276-278°C.

^1H NMR (DMSO-d_6) δ 9.50 (br t, 1H, J=5.4 Hz), 8.07 (s, 1H), 8.05 (s, 1H), 8.00 (d, 1H, J=1.2 Hz), 7.52-7.67 (m, 4H), 7.37 (dd, 1H, J=1.5, 9 Hz), 7.03 (br s, 2H), 4.61 (d, 2H, J=5.4 Hz).

Analysis calculated for $C_{19}H_{15}ClN_4O_3S$
C, 55.00; H, 3.64; N, 13.50
Found: C, 54.67; H, 3.36; N, 13.37

EXAMPLE 35

Preparation of N-[(1-methylimidazol-2-yl)methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide (19)

Step A: 2-Aminomethyl-1-methylimidazole

To a suspension of lithium aluminum hydride (114 mg, 3.0 mmol) in dry tetrahydrofuran (15 mL) at room temperature in an inert atmosphere was added solid 1-methylimidazole-2-carboxamide (185 mg, 1.5 mmol) [prepared according to J. Org. Chem., 52, 4379 (1987)] in portions. After stirring the reaction mixture for 0.5 hour, the temperature was raised to 50°C for 3.5 hours. After cooling this reaction, satd. aq. Na_2SO_4 (2 mL) was added to quench reaction and then powdered anhyd. Na_2SO_4. Filtration of this mixture to remove salts gave a dry solution of 2-aminomethyl-1-methyl-imidazole in tetrahydrofuran (~25 mL) which was used as is.

Step B: N-[(1-methylimidazol-2-yl)methyl]-3-phenyl-sulfonyl-5-chloroindole-2-carboxamide

A solution of the dimeric indole acid chloride (see Example 27, Step B) (358 mg, 0.5 mmol) in dry tetrahydrofuran (7 mL) was added dropwise to the above solution of 2-aminomethyl-1-methyl-imidazole in tetrahydrofuran, which was cooled in an ice bath. After 15 min. triethylamine (0.2 mL, 1.4 mmol) was added and the reaction mixture slowly warmed to room temperature over 12-20 hours. The reaction was diluted with water and the product extracted into 10% methanol/ethyl acetate. The extract was dried (Na_2SO_4), filtered through charcoal, and the solvents evaporated. The residue was triturated with ethyl acetate and the product collected by filtration. Recrystallization from hot methanol/ethyl acetate gave analytically pure material, mp 273-275°C.

^1H NMR (DMSO-d_6) δ 9.48 (br t, 1H, J=5 Hz), 8.05 (d, 2H, J=7 Hz), 7.98 (d, 1H, J=2 hz), 7.52-7.67 (m, 4H), 7.35 (dd, 1H, J=2, 9 Hz), 7.18

(d, 1H, J=1 Hz), 6.88 (d, 1H, J=1 Hz), 4.66 (d, 2H, J=5 Hz), 3.71 (s, 3H).

Analysis calculated for $C_{20}H_{17}ClN_4O_3S$
C, 56.00; H, 4.00; N, 13.06
Found: C, 55.77; H, 3.97; N, 13.41

The hydrochloride salt was obtained by addition of one equivalent of ethanolic HCl to the free base, mp 284-285°C with decomposition.

Analysis calculated for $C_{20}H_{17}ClN_4O_3S \cdot HCl$
C, 51.62; H, 3.90: N, 12.04
Found: C, 51.21; H, 3.92; N, 11.55

EXAMPLE 36

Alternate Preparation of N-[(1-methylimidazol-2-yl)-methyl] 3-phenylsulfonyl-5-chloroindole-2-carboxamide

To a partial suspension of N-[(imidazol-2-yl)-methyl] 3-phenylsulfonyl-5-chloroindole-2-carboxamide (Example 35) (42 mg, 0.1 mmol) in 1:1 methanol/tetrahydrofuran (4 mL) was added iodomethane (.05 mL, 0.8 mmol). The reaction was stirred for three days at room temperature. The solvents were removed under reduced pressure, aq. $NaHCO_3$ added and the product extracted into ethyl acetate/methanol. The organic layer was dried (Na_2SO_4), filtered, and the solvents evaporated. The residue was purified by chromatography and the product eluted with 3% methanol/chloroform. Appropriate fractions were combined, the solvents evaporated, and the residue triturated with methylene chloride to give pure product.

EXAMPLE 37

Preparation of N-[2-(imidazol-4-yl)ethyl]-3-phenyl-sulfonyl-5-chloro-indole-2-carboxamide (24)

Carbonyldiimidazole (180 mg, 1.11 mmol) was added to a solution of 5-chloro-3-phenylsulfonylindole-2-carboxylic acid (Example 27, Step A) (336 mg, 0.5 mmol) cooled in an ice bath under an inert

atmosphere. After 0.5 hours, histamine (125 mg, 1.12 mmol) was added to the yellow solution. After 5 hours the reaction was diluted with water and the product extracted into ethyl acetate. This organic layer was washed with dilute aq. $NaHCO_3$, dried (Na_2SO_4), filtered through charcoal and the solvents evaporated. Trituration of this residue with methylene chloride gave the crude product. Crystallization from hot ethyl acetate gave analytically pure product, mp 220-221.5°C.
^1H NMR (DMSO-d_6) δ 9.11 (br t, 1H, J=5.4 Hz), 8.00 (s, 1H), 7.98 (s, 1H), 7.95 (d, 1H, J=2.1 Hz), 7.52-7.67 (m, 5H), 7.35 (dd, 1H, J=2.1, 8.7 Hz), 6.94 (s, 1H), 3.60 (q, 2H, J=7.2 Hz), 2.83 (t, 2H, J=7.2 Hz).

Analysis	calculated for $C_{20}H_{17}ClN_4O_3S$
	C, 56.00; H, 4.00; N, 13.05
Found:	C, 55.74; H, 4.04; N, 13.35

EXAMPLE 38

Preparation of N-(3-methoxybenzyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide

A solution of dimeric acid chloride (Example 27, Step B) (1.77 g, 2.5 mmol) in dry tetrahydrofuran (25 mL) was added dropwise to a solution of 3-methoxybenzylamine (1.3 mL, 10 mmol) in dry tetrahydrofuran (20 mL) cooled with an ice acetone bath. The reaction was stirred for 12-20 hours and then diluted with 10% methanol/ethyl acetate. This organic layer was washed with dilute HCl, dried (Na_2SO_4), filtered, and the solvents evaporated. The residue was triturated with diethyl ether to give flocculent white product. Recrystallization from hot methanol/ethyl acetate gave analytically pure product, mp 203-204°C.
^1H NMR (DMSO-d_6) δ 9.47 (br t, 1H, J=6 Hz), 8.03 (s, 1H), 8.01 (s, 1H), 7.94 (d, 1H, J=2.1 Hz), 7.63 (t, 1H, J=6.9 Hz), 7.52-7.58 (m, 3H), 7.35 (dd, 1H, J=2.1, 8.7 Hz), 7.29 (t, 1H, J=7.8 Hz), 7.06 (s, 1H), 7.05 (d, 1H, J=6.6 Hz), 6.86 (dd, 1H, J=2.7, 7.5 Hz), 4.57 (q, 2H, J=6 Hz), 3.76 (s, 3H).

Analysis calculated for $C_{23}H_{19}ClN_2O_4S$
C, 60.72; H, 4.21; N, 6.16
Found: C, 60.60; H, 4.17; N, 6.12

EXAMPLE 39

Preparation of N-(3-hydroxybenzyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide

To a saturated solution of N-(3-methoxybenzyl) 3-phenylsulfonyl-5-chloroindole-2-carboxamide (1.37 g, 3.0 mmol) in dry methylene chloride (140 mL) under an inert atmosphere was added boron tribromide in hexane (1 M, 10 mL, 10 mmol). After stirring for 12-20 hours, the reaction was neutralized by addition of aq. $NaHCO_3$. After two hours, the solution was made weakly acidic by addition of dilute HCl. The precipitated product was collected by filtration and then the aqueous filtrate extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered, and the solvent evaporated. The residue was triturated with diethyl ether to give additional product. The solids were combined and crystallized from hot methanol/ethyl acetate to give analytically pure product, mp 273.5-274.5°C.
^1H NMR (DMSO-d_6) δ 9.43 (t, 1H, J=6 Hz), 8.01 (s, 1H), 7.98 (s, 1H), 7.97 (d, 1H, J=2.1 Hz), 7.63 (t, 1H, J=6 Hz), 7.52-7.58 (m, 3H), 7.35 (dd, 1H, J=2, 1, 9 Hz), 7.17 (t, 1H, J=7.8 Hz), 6.89 (s, 1H), 6.86 (s, 1H), 6.84 (s, 1H), 6.70 (dd, 1H, J=2.1, 8.4 Hz), 4.50 (d, 2H, J=6 Hz).
Analysis calculated for $C_{22}H_{17}ClN_2O_4S$
C, 59.93; H, 3.89; N, 6.36
Found: C, 59.91; H, 3.86; N, 6.51

EXAMPLE 40

Preparation of N-(3-nitrobenzyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Using the procedure described in Example 34, except for substituting 3-nitrobenzylamine hydrochloride for 2-aminomethyl-imidazole dihydrochloride and adjusting the amount of triethylamine

accordingly, the title compound was obtained, mp 253-254°C.
Analysis calculated for $C_{22}H_{16}ClN_3O_5S$
C, 56.23; H, 3.43; N, 8.94
Found: C, 55.98; H, 3.37; N, 8.85

EXAMPLE 41

Preparation of N-(3-aminobenzyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide (30)

A solution of N-(3-nitrobenzyl) 3-phenyl-sulfonyl-5-chloroindole-2-carboxamide (353 mg, 0.75 mmol) in tetrahydrofuran (25 mL) and methanol (10 mL) containing platinum oxide (70 mg) was hydrogenated with an atmospheric pressure of hydrogen for 3 hours. The degassed solution was filtered to remove catalyst and the solvents evaporated. The residue was triturated with diethyl ether to give the product. Crystallization from acetonitrile gave analytically pure product, mp 247-249°C.
^{1}H NMR (DMSO-d_6) δ 9.38 (t, 1H, J=6 Hz), 7.98 (s, 1H), 7.96 (d, 1H, J=2.1 Hz), 7.53-7.60 (m, 4H), 7.35 (dd, 1H, J=2.1, 9 Hz), 7.02 (t, 1H, J=7.5 Hz), 6.61 (s, 1H), 6.60 (d, 1H, J=6 Hz), 6.50 (dd, 1H, J=2.1, 8.1 Hz), 4.43 (d, 2H, J=6 Hz).
Analysis calculated for $C_{22}H_{18}ClN_3O_3S \cdot 0.25H_2O$
C, 59.45; H, 4.20; N, 9.46
Found: C, 59.43; H, 4.08; N, 9.54

EXAMPLE 42

Preparation of N-(2-methoxybenzyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Using the procedure described in Example 38, except substituting 2-methoxybenzylamine for 3-methoxybenzylamine, the title compound was obtained, mp 235-237°C.
^{1}H NMR (DMSO-d_6) δ 9.39 (t, 1H, J=6 Hz), 7.99 (d, 1H, J=2.1 Hz), 7.95 (s, 1H), 7.93 (s, 1H), 7.63 (t, 1H, J=7.2 Hz), 7.50-7.57 (m, 3H), 7.29-7.44 (m, 3H), 7.06 (d, 1H, J=7.5 Hz), 6.97 (dt, 1H, J=0.9, 7.2 Hz),

4.55 (d, 2H, J=5.7 Hz), 3.85 (s, 3H).
Analysis calculated for $C_{23}H_{19}ClN_2O_4S \cdot 0.2H_2O$
C, 60.24; H, 4.26; N, 6.11
Found: C, 60.19; H, 4.40; N, 6.11

EXAMPLE 43

Preparation of N-(2-hydroxybenzyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Using the procedure described in Example 39, except substituting the 2-methoxy isomer (Example 42) for the 3-methoxy isomer described, the title compound was obtained, mp 243-244.5°C.
^1H NMR (DMSO-d_6) δ 7.99 (d, 1H, J=3 Hz), 7.98 (s, 1H), 7.97 (s, 1H), 7.63 (t, 1H, J=6 Hz), 7.51-7.57 (m, 3H), 7.33-7.38 (m, 2H), 7.14 (dt, 1H, J=1.2, 7.8 Hz), 6.89 (d, 1H, J=7.2 Hz), 6.81 (t, 1H, J=7.2 Hz), 4.52 (s, 2H).
Analysis calculated for $C_{22}H_{17}ClN_2O_4S \cdot 0.2H_2O$
C, 59.44; H, 3.95; N, 6.30
Found: C, 59.38; H, 3.70; N, 6.39

EXAMPLE 44

Preparation of N-(4-methoxybenzyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Using the procedure described in Example 38, except substituting 4-methoxybenzylamine for 3-methoxybenzylamine, the title compound was obtained, mp 205-206°C.
^1H NMR (DMSO-d_6) δ 9.42 (br t, 1H, J=6 Hz), 8.01 (s, 1H), 7.98 (s, 1H), 7.95 (d, 1H, J=1.8 Hz), 7.64 (t, 1H, J=7.2 Hz), 7.52-7.58 (m, 3H), 7.33-7.40 (m, 3H), 6.95 (d, 2H, J=9 Hz), 4.51 (d, 2H, J=6 Hz), 3.76 (s, 3H).
Analysis calculated for $C_{23}H_{19}ClN_2O_4S$
C, 60.72; H, 4.21; N, 6.16
Found: C, 60.59; H, 4.14; N, 6.11

EXAMPLE 45

Preparation of N-(4-hydroxybenzyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Using the procedure described in Example 39, except substituting the 4-methoxy isomer (Example 44) for the methoxy isomer described, the title compound was obtained, mp 249-250°C. ^{1}H NMR (DMSO-d_6) δ 9.35 (t, 1H, J=6 Hz), 7.95-7.99 (m, 3H), 7.62 (t, 1H, J=6.9 Hz), 7.52-7.57 (m, 3H), 7.35 (dd, 1H, J=1.8, 8.7 Hz), 7.25 (d, 2H, J=8.7 Hz), 6.76 (d, 2H, J=8.1 Hz), 4.46 (d, 2H, J=6 Hz).

Analysis calculated for $C_{22}H_{17}ClN_2O_4S$
C, 59.93; H, 3.89; N, 6.36
Found: C, 59.37; H, 3.85; N, 6.25

EXAMPLE 46

Preparation of N-(3-acetylaminobenzyl)-3-phenyl-sulfonyl-5-chloro-indole-2-carboxamide

A solution of N-(3-aminobenzyl) 3-phenyl-sulfonyl-5-chloroindole-2-carboxamide (Example 41) (176 mg, 0.4 mmol) in dry tetrahydrofuran (7 mL) containing acetic anhydride (0.05 mL, 0.5 mmol) was stirred at room temperature for 16 hours. The reaction was diluted with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered through charcoal, and the solvents evaporated. The residue was triturated with methylene chloride and the solid collected by filtration to give the product, mp 249-250°C. ^{1}H NMR (DMSO-d_6) δ 9.98 (br s, 1H), 9.39 (v br s, 1H), 7.96-8.00 (m, 3H), 7.51-7.62 (m, 6H), 7.30 (t, 2H, J=8 Hz), 7.14 (d, 1H, J=8 Hz), 4.53 (br s, 2H), 2.04 (s, 3H).

Analysis calculated for $C_{24}H_{20}ClN_3O_4S$
C, 59.81; H, 4.18; N, 8.72
Found: C, 59.41; H, 4.09; N, 8.62

EXAMPLE 47

Preparation of N-(3-methylsulfonylaminobenzyl)-3-phenyl-sulfonyl-5-chloroindole-2-carboxamide (34)

To a solution of N-(3-aminobenzyl) 3-phenyl-sulfonyl-5-chloroindole-2-carboxamide (174 mg, 0.4 mmol) in dry tetrahydrofuran (7 mL) at room temperature under an inert atmosphere was added methanesulfonyl chloride (.035 mL, .45 mmol) and triethylamine (0.7 mL, .50 mmol). Over a period of 20 hours, the reaction progress was monitored by tlc. Additional equivalents of methanesulfonyl chloride and triethylamine were added twice over this period to obtain complete reaction with the carboxamide. The reaction was diluted with water, acidified with dilute HCl, and the product extracted into chloroform. This organic layer was dried (Na_2SO_4), filtered, and the solvent evaporated. The residue was purified by chromatography on silica gel. Elution with 1% methanol/chloroform gave the bis-sulfonylated product as evidenced by two methyl group resonances in the NMR at δ 3.47 and 2.98.

This material was dissolved in dimethoxyether (3 mL) and water (2 mL) and lithium hydroxide monohydrate (66 mg, 1.57 mmol) was added. The solution was heated at 60°C for two hours. The cooled reaction was acidified with dilute HCl. Upon stirring for 2-3 hours, the product crystallized out and was collected by filtration and dried. Recrystallization from hot methanol/ethyl acetate gave analytically pure product, mp 252-253°C.

^1H NMR (DMSO-d_6) δ 9.48 (br t, 1H, J=5.4 Hz), 8.01 (s, 1H), 7.98 (s, 1H), 7.95 (d, 1H, J=1.8 Hz), 7.63 (t, 1H, J=7.2 Hz), 7.52-7.58 (m, 3H), 7.33-7.38 (m, 2H), 7.27 (br s, 1H), 7.23 (br d, 1H, J=7.8 Hz), 7.15 (d, 1H, J=7.8 Hz), 4.55 (d, 2H, J=5.4 Hz), 3.00 (S, 3H).

Analysis calculated for $C_{23}H_{20}ClN_3O_5S_2$
C, 53.33; H, 3.89; N, 8.11
Found: C, 53.26; H, 3.86; N, 8.12

EXAMPLE 48

Preparation of N-benzyl-3-phenylsulfonyl-5-chloroindole-2-carboxamide

A solution of the dimeric acid chloride (Example 27, Step B) (170 mg, 0.25 mmol) in dry tetrahydrofuran (2 mL) was added dropwise to a solution of benzylamine (.28 mL, 2.5 mmol) in dry tetrahydrofuran (3 mL) cooled in an ice/acetone bath. The reaction mixture was left to stir for 12-20 hours as the temperature rose to ambient. The solvents were removed under vacuum and the residue partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried (Na_2SO_4), and the solvent evaporated. The residue was crystallized from ethyl acetate/methanol to give analytically pure product, mp 249-251°C.
^1H NMR (DMSO-d_6) δ 9.47 (t, 1H, J=6 Hz), 8.02 (s, 1H), 8.00 (s, 1H), 7.95 (d, 1H, J=2.1 Hz), 7.33-7.57 (m, 10 H), 4.59 (d, 2H, J=6 Hz).
Analysis calculated for $C_{22}H_{17}ClN_2O_3S$
C, 62.19; H, 4.03; N, 6.59
Found: C, 62.14; H, 4.13; N, 6.62

EXAMPLE 49

Preparation of N-(3-pyridylmethyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide (28)

Using the procedure in Example 48, except substituting 3-aminomethylpyridine for benzylamine, the title compound was obtained, mp 263-264°C.
Analysis calculated for $C_{21}H_{16}ClN_3O_3S$
C, 59.22; H, 3.79; N, 9.87
Found: C, 59.01; H, 3.79; N, 9.87

EXAMPLE 50

Preparation of N-(2-pyridylmethyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Using the procedure described in Example 48, except substituting 2-aminomethylpyridine for benzylamine, the title compound was obtained, mp 250-251°C.

Analysis calculated for $C_{21}H_{16}ClN_3O_3S$
C, 59.22; H, 3.79; N, 9.87
Found: C, 59.04; H, 3.73; N, 10.06

EXAMPLE 51

Preparation of N-[2-(pyridin-4-yl)ethyl]-3-phenyl-sulfonyl-5-chloroindole-2-carboxamide

Using the procedure described in Example 48, except substituting 4-(2-aminoethyl)pyridine for benzylamine, the title compound was obtained, mp 258-260°C.

Analysis calculated for $C_{22}H_{18}ClN_3O_3S$
C, 60.07; H, 4.12; N, 9.55
Found: C, 59.68; H, 3.84; N, 9.30

EXAMPLE 52

Preparation of N-(2-hydroxyethyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Using the procedure described in Example 48, except substituting 2-hydroxyethylamine for benzylamine, the title compound was obtained, mp 198-200°C.

Analysis calculated for $C_{17}H_{15}ClN_2O_4S$
C, 53.90; H, 3.99; N, 7.39
Found: C, 54.09; H, 3.94; N, 7.25

EXAMPLE 53

Preparation of N-ethyl-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Using the procedure described in Example 48, except substituting ethylamine for benzylamine, the title compound was obtained, mp 259-260°C.

Analysis calculated for $C_{17}H_{15}ClN_2O_3S$
C, 56.28; H, 4.17; N, 7.72
Found: C, 56.07; H, 4.11; N, 7.73

EXAMPLE 54

Preparation of N-[(2-chloropyridin-4-yl)methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Using the procedure described in Example 35, Step B, except substituting 2-chloro-4-aminomethyl-pyridine for 2-aminomethyl-1-methylimidazole, the title compound was obtained, mp 263-265°C.

Analysis calculated for $C_{21}H_{15}Cl_2N_3O_3S$
C, 54.79; H, 3.28; N, 9.13
Found: C, 54.38; H, 3.18; N, 9.03

EXAMPLE 55

Preparation of N-cyclopropyl-5-chloro-3-phenylsulfonyl-indole-2-carboxamide (26)

Using the procedure described in Example 48, except substituting cyclopropylamine for benzylamine, the title compound was obtained, mp 242-243°C.

Analysis calculated for $C_{18}H_{15}ClN_2O_3S$
C, 57.68; H, 4.03; N, 7.47
Found: C, 57.40; H, 3.94; N, 7.43

EXAMPLE 56

Preparation of N-(cyclopropylmethyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Using the procedure described in Example 48, except substituting cyclopropylmethylamine for benzylamine, the title compound was obtained, mp 232-234°C.

Analysis calculated for $C_{19}H_{17}ClN_2O_3S$
C, 57.88; H, 4.50; N, 7.11
Found: C, 57.92; H, 4.34; N, 7.09

EXAMPLE 57

Preparation of 3-(4-chlorophenylsulfonyl)-5-chloro-indole-2-carboxamide

Using the procedure described in Example 30 and 31, except substituting bis(4-chlorophenyl)disulfide for di(2-thiazolyl)-disulfide, the title compound was obtained, mp 275-277°C.

Analysis calculated for $C_{15}H_{10}Cl_2N_2O_3S$
C, 48.32; H, 2.81; N, 7.51
Found: C, 48.23; H, 2.84; N, 7.91

EXAMPLE 58

Preparation of 3-(3-chlorophenylsulfonyl)-5-chloro-indole-2-carboxamide

Using the procedure described in Example 30 and 31, except substituting bis(3-chlorophenyl)disulfide for di(2-thiazolyl)-disulfide, the title compound was obtained, mp 272-273°C.

Analysis calculated for $C_{15}H_{10}Cl_2N_2O_3S$
C, 48.79; H, 2.73; N, 7.59
Found: C, 48.39; H, 2.70; N, 7.44

EXAMPLE 59

Preparation of 3-(3,5-dichlorophenylsulfonyl)-5-chloro-indole-2-carboxamide

Using the procedure described in Example 30 and 31, except substituting bis(3,5-dichlorophenyl)-disulfide for di(2-thiazolyl)-disulfide, the title compound was obtained, mp 258-260°C.

Analysis calculated for $C_{15}H_9Cl_3N_2O_3S$
C, 44.63; H, 2.25; N, 6.94
Found: C, 44.49; H, 2.24; N, 7.04

EXAMPLE 60

Preparation of 3-(2-chlorophenylsulfonyl)-5-chloro-indole-2-carboxamide

Using the procedure described in Example 33, except substituting 2-chlorothiophenol for thiophenol, the title compound was obtained, mp 267°C.

Analysis calculated for $C_{15}H_{10}Cl_2N_2O_3S$
C, 48.79; H, 2.73; N, 7.59
Found: C, 48.69; H, 2.73; N, 7.62

EXAMPLE 61

Preparation of 3-(pyridin-2-ylsulfonyl)-5-chloroindole-2-carboxamide

Using the procedure described in Example 30 and 31, except substituting bis(pyridin-2-yl)disulfide for di(2-thiazolyl)-disulfide, the title compound was obtained, mp 244-246°C.

Analysis calculated for $C_{14}H_{10}ClN_3O_3S$
C, 50.08; H, 3.00; N, 12.51
Found: C, 50.31; H, 3.00; N, 12.55

EXAMPLE 62

Preparation of 3-(pyridin-3-ylsulfonyl)-5-chloroindole-2-carboxamide

Using the procedure described in Example 30 and 31, except substituting bis(pyridin-3-yl)disulfide for di(2-thiazolyl)-disulfide, the title compound was obtained, mp 300°C dec.
FAB mass spectrum: m/e = 336 (M+1)

EXAMPLE 63

Preparation of 3-(pyridin-4-ylsulfonyl)-5-chloroindole-2-carboxamide

Using the procedure described in Example 30 and 31, except substituting bis(pyridin-4-yl)disulfide for di(2-thiazolyl)-disulfide, the title compound was obtained, mp>260°C dec.
FAB mass spectrum: m/e = 336 (M+1)

EXAMPLE 64

Preparation of 3-[(1-methylimidazol-2-yl)sulfonyl]-5-chloroindole-2-carboxamide

Using the procedure described in Example 30 and 31, except substituting bis(1-methylimidazol-2-yl)-disulfide for di(2-thiazolyl)disulfide, the title compound was obtained, mp 255-256°C dec.

Analysis	calculated for $C_{13}H_{11}ClN_4O_3S$
	C, 46.09; H, 3.27; N, 16.54
Found:	C, 46.02; H, 3.28; N, 16.27

EXAMPLE 65

Preparation of N-(3-methoxybenzyl-3-(3-chlorophenylsulfonyl)-5-chloroindole-2-carboxamide

Using the procedure described in Example 38, except substituting the dimeric acid chloride derived from 3-(3-chlorophenylsulfonyl)-5-chloroindole-2-carboxylic acid for that derived from 3-(phenyl-sulfonyl)-5-chloroindole-2-carboxylic acid, the title

compound was obtained, mp 225-226.5°C.

Analysis calculated for $C_{23}H_{18}Cl_2N_2O_4S$
C, 56.45; H, 3.71; N, 5.73
Found: C, 56.52; H, 3.70; N, 5.83

EXAMPLE 66

Preparation of N-(3-hydroxybenzyl)-3-(3-chlorophenylsulfonyl)-5-chloroindole-2-carboxamide

Using the procedure described in Example 39, N-(3-methoxybenzyl)-3-(3-chlorophenylsulfonyl)-5-chloroindole-2-carboxamide was demethylated to obtain the title compound, mp 230-231°C.

Analysis calculated for $C_{22}H_{16}Cl_2N_2O_4S$
C, 55.58; H, 3.39; N, 5.89
Found: C, 55.59; H, 3.36; N, 5.66

EXAMPLE 67

Preparation of N-[(1-methylimidazol-2-yl)methyl]-3-(3-chlorophenylsulfonyl)-5-chloroindole-2-carboxamide (23)

Using the procedure described in Example 35, except for substituting the dimeric acid chloride derived from 3-(3-chlorophenylsulfonyl)-5-chloroindole-2-carboxylic acid for that derived from 3-(phenylsulfonyl)-5-chloroindole-2-carboxylic acid, the title compound was obtained, mp 232-234°C.

Analysis calculated for $C_{20}H_{16}Cl_2N_4O_3S$
C, 51.84; H, 3.48; N, 12.09
Found: C, 51.46; H, 3.38; N, 11.78

EXAMPLE 68

Preparation of 2-carboxamido-5-chloroindole-3-cyclo-propyl-sulfonamide

Step A: 2-Carboethoxy-5-chloro-1-phenylsulfonylindole-3-sulfonic acid

Concentrated sulfuric acid (2.50 ml, 90 mmol) was added dropwise over 5 min at 0°C to a stirred solution of 2-carboethoxy-5-chloro-1-phenylsulfonylindole (7.28 g, 20.0 mmol) in acetic anhydride (10 ml) and dry dichloromethane (50 ml). The resulting tan solution was warmed to RT (room temperature) and after 3 hours was poured onto ice and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo* to a syrup. Residual acetic anhydride was removed by azeotroping with toluene (3 x 50 ml), and the residue was crystallized from dichloromethane. The dichloromethane was evaporated *in vacuo* to give the title compound as a tan powder:
^1H NMR (d_6 DMSO) δ 1.33 (t, J=7.1 Hz, 3H), 4.33 (q, J=7.1 Hz, 2H), 7.44 (dd, J=8.9 and 2.2 Hz, 1H), 7.63 (t, J=7.6 Hz, 2H), 7.73 (t, J=7.4 Hz, 1H), 7.77 (d, J=2.2 Hz, 1H), 7.96 (d, J=8.9 Hz, 1H), 8.00 (d, J=7.6 Hz, 2H).

Step B: 2-Carboethoxy-5-chloro-1-phenylsulfonyl-indole-3-cyclopropylsulfonamide

Oxalyl chloride (0.90 ml, 10.3 mmol) was added to a stirred solution of 2-carboethoxy-5-chloro-1-phenylsulfonylindole-3-sulfonic acid (1.505 g, 3.39 mmol) in dry dichloromethane (15 ml) at 0°C. DMF (2 drops) was added and the solution was warmed to room temperature. More DMF (1 drop) was added and the reaction was heated to reflux. After 2 hours, the solution was cooled and evaporated *in vacuo* to give the sulfonylchloride as a tan solid. This was dissolved in dichloromethane (15 ml) and cyclopropylamine (0.94 ml, 13.56 mmol) and pyridine (0.5 ml) were added. The solution was heated to

reflux and after 15 min was cooled, diluted with ethyl acetate and was washed with 1 M HCl solution, sodium hydrogen carbonate solution and brine, dried (Na_2SO_4) and evaporated *in vacuo* to a gum. Methanol (5 ml) was added to give a colorless solid, and the mixture was stirred and heated to reflux for 5 min. The solids were filtered cold, washing with cold methanol (3x5 ml), and were dried *in vacuo* to give the title compound as colorless crystals: mp 189-191°C;
^1H NMR ($CDCl_3$) δ 0.61 (m, 4H), 1.48 (t, J=7.1 Hz, 3H), 2.26 (m, 1H), 4.58 (q, J=7.1 Hz, 2H), 5.06 (br s, 1H), 7.42 (dd, J=9.0 and 2.0 Hz, 1H), 7.54 (t, J=7.6 Hz, 2H), 7.66 (t, J=7.5 Hz, 1H), 7.97 (d, J=9.0 Hz, 1H), 7.98 (d, J=2.0 Hz, 1H), 8.09 (d, J=7.6 Hz, 2H).

Step C: 2-Carboxamido-5-chloroindole-3-cyclopropyl-sulfonamide

A mixture of 2-carboethoxy-5-chloro-1-phenyl-sulfonyl-indole-3-cyclopropylsulfonamide (0.42 g, 0.870 mmol) and 2:1:1 10% potassium hydroxide solution/methanol/THF (20 ml) was heated to reflux to give a clear tan solution. After 0.5 hour reflux the solution was cooled and was concentrated *in vacuo* to 1/2 volume. The solution was acidified with 1 M HCl, and the resulting mixture was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4) and evaporated *in vacuo* to a gum. The crude product was dissolved in 2% sodium hydroxide solution which was acidified with 1 M HCl. The solid material was collected by filtration, washed with 1 M HCl solution, and dried *in vacuo* to give 3-cyclopropylsulfonamido-5-chloroindole-2-carboxylic acid. Oxalyl chloride (0.58 ml, 6.65 mmol) and DMF (1 drop) were added to a stirred suspension of the acid in dry dichloromethane (10 ml). After 1 hour at room temperature the mixture was heated to reflux for 1 hour, cooled and evaporated *in vacuo* to a tan solid. The solid was suspended in acetone (10 ml) and 9:1 ammonium hydroxide/acetone solution (20 ml) was added. After 15 min the solution was evaporated *in vacuo* to 2 ml in volume and the residue was acidified with 1 M HCl solution and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4) and evaporated *in*

vacuo. The resulting tan solid was purified by flash chromatography on silica (dry loaded, eluting with a chloroform/methanol gradient, 2-10% methanol), to give the title compound as colorless crystals (from ethyl acetate/hexanes): mp 236-238°C;
^{1}H NMR (d_6 DMSO) δ 0.40 (m, 4H), 2.07 (m, 1H), 7.35 (dd, J=8.7 and 2.1 Hz, 1H), 7.56 (d, J=8.7 Hz, 1H), 8.01 (d, J=1.7 Hz, 1H), 8.10 (d, J=2.1 Hz, 1H), 8.22 (br s, 1H), 8.47 (br s, 1H).

EXAMPLE 69

Preparation of 2-carboxamido-5-chloroindole-3-phenyl-sulfonamide

Step A: 2-Carboethoxy-5-chloro-1-phenylsulfonylindole-3-phenylsulfonamide

In the manner outlined in Example 68, Step B, aniline (0.63 ml, 6.91 mmol) was added to 2-carboethoxy-5-chloro-1-phenyl-sulfonylindole-3-sulfonylchloride to give, after flash column chromatography on silica (dry loaded, eluting with an ethyl acetate/hexanes gradient, 20-30% ethyl acetate) the title compound as colorless crystals;
^{1}H NMR ($CDCl_3$) δ 1.47 (t, J=7.1 Hz, 3H), 4.58 (q, J=7.1 Hz, 2H), 6.74 (br s, 1H), 7.11 (m, 5H), 7.31 (dd, J=9.0 and 2.2 Hz, 1H), 7.51 (t, J=8.1 Hz, 2H), 7.57 (d, J=1.7 Hz, 1H), 7.65 (t, J=7.5 Hz, 1H), 7.87 (d, J=9.0 Hz, 1H), 7.99 (d, J=7.6 Hz, 2H).

Step B: 5-Chloro-3-phenylsulfonamidoindole-2-carboxylic acid

2-Carboethoxy-5-chloro-1-phenylsulfonylindole-3-phenylsulfonamide (0.39 g, 0.75 mmol) was dissolved in 2:1:1 10% sodium hydroxide solution/methanol/THF (20 ml) and after 2 hours the solution was acidified with 1 M HCl, and the resulting mixture was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4) and evaporated *in vacuo* to a glass. Dichloromethane (5 ml) was added to give a colorless solid, and the mixture was stirred and heated to reflux for 5 min. The solids were filtered cold, washing with cold dichloro-

methane, and were dried *in vacuo* to give the title compound as colorless crystals;
^{1}H NMR (d_6 DMSO) δ 7.28 (t, J=7.1 Hz, 1H), 7.4 (d, J=7.2 Hz, 2H), 7.51 (t, J=7.1 Hz, 2H), 7.72 (dd, J=8.8 and 2.1 Hz, 1H), 7.86 (d, J=8.8 Hz, 1H), 8.43 (d, J=2.1 Hz, 1H), 10.25 (br s, 1H).

Step C: 2-Carboxamido-5-chloroindole-3-phenyl-sulfonamide

Oxalyl chloride (0.087 ml, 1.00 mmol) and DMF (1 drop) were added to a stirred solution of 5-chloro-3-phenylsulfonamido-indole-2-carboxylic acid (123 mg, 0.35 mmol) in dry THF (3 ml) at 0°C. After 1 hour at room temperature the solution was evaporated *in vacuo* to give a tan solid. The solid was dissolved in acetone (1 ml) and 9:1 ammonium hydroxide/acetone solution (2 ml) was added. After 0.5 hours the solution was evaporated *in vacuo* to a gum which was dissolved in ethyl acetate, washed with 1 M HCl and brine, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting tan solid was purified by flash column chromatography on silica (dry loaded, eluting with an ethyl acetate/hexanes gradient, 20-70% ethyl acetate) to give the title compound as colorless crystals (from dichloromethane); mp 225-227°C: ^{1}H NMR (d_6 DMSO) δ 7.00 (m, 3H), 7.17 (t, J=7.3 Hz, 2H), 7.30 (dd, J=8.8 and 2.0 Hz, 1H), 7.48 (d, J=8.8 Hz, 1H), 7.93 (d, J=2.0 Hz, 1H), 8.21 (br s, 1H), 8.28 (br s, 1H), 10.34 (br s, 1H).

EXAMPLE 70

Preparation of 2-carboxamido-5-chloroindole-3-methyl-(phenyl)-sulfon-amide

Step A: 2-Carboethoxy-5-chloro-1-phenylsulfonylindole-3-methyl(phenyl)sulfonamide

In the manner outlined in Example 68, Step B, N-methyl-aniline was added to 2-carboethoxy-5-chloro-1-phenyl-sulfonylindole-3-sulfonylchloride to give, after flash column chromatography on silica (dry loaded, eluting with an ethyl acetate/hexanes gradient, 10-30%

ethyl acetate) the title compound as colorless crystals (from dichloromethane/hexanes);
^{1}H NMR ($CDCl_3$) δ 1.46 (t, J=7.1 Hz, 3H), 3.30 (s, 3H), 4.55 (q, J=7.1 Hz, 2H), 6.69 (d, J=2.0 Hz, 1H), 7.11 (d, J=7.0 Hz, 2H), 7.26 (m, 4H), 7.54 (t, J=7.6 Hz, 2H), 7.66 (t, J=7.4 Hz, 1H), 7.87 (d, J=8.8 Hz, 1H), 8.08 (d, J=7.6 Hz, 2H).

Step B: 5-Chloro-3-methyl(phenyl)sulfonamidoindole-2-carboxylic acid

In the manner outlined in Example 69, Step B, 2-carboethoxy-5-chloro-1-phenylsulfonylindole-3-methyl-(phenyl)-sulfonamide (0.39 g, 0.75 mmol) was hydrolysed in 2:1:1 10% sodium hydroxide solution/methanol/THF (20 ml, 14 h at RT (room temperature) followed by 5 min at reflux), to give the title compound (from ethyl acetate);
^{1}H NMR (d_6 DMSO) δ 3.26 (s, 3H), 7.03 (d, J=2.2 Hz, 1H), 7.21 (m, 6H), 7.46 (d, J=8.8 Hz, 1H).

Step C: 2-Carboxamido-5-chloroindole-3-methyl(phenyl)-sulfonamide

In the manner outlined in Example 69, Step C, starting with 5-chloro-3-methyl(phenyl)sulfonamidoindole-2-carboxylic acid, and after purification by flash column chromatography on silica (dry loaded, eluting with 2% methanol/chloroform), the title compound was obtained as colorless crystals (from ethyl acetate); mp 240-242°C.
^{1}H NMR (d_6 DMSO) δ 3.13 (s, 3H), 7.06 (d, J=2.1 Hz, 1H), 7.09 (m, 2H), 7.23 (dd, J=8.8 and 2.1 Hz, 1H), 7.26 (m, 3H), 7.48 (d, J=8.8 Hz, 1H), 8.01 (br s, 1H), 8.06 (br s, 1H).

EXAMPLE 71

Preparation of N-[2-(1-methylimidazol-4-yl)ethyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide (25)

Reaction of 3-phenylsulfonyl-5-chloroindole-2-carboxylic

acid with 1-methylhistamine under the conditions of Example 37 provides the title compound.

EXAMPLE 72

Preparation of N-[2-(3-methylimidazol-4-yl)ethyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Reaction of 3-phenylsulfonyl-5-chloroindole-2-carboxylic acid with 3-methylhistamine under the conditions of Example 37 gave the title compound, mp 257-258.5°C.

EXAMPLE 73

Preparation of N-[(imidazol-4-yl)methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Reaction of the dimeric acid chloride (Example 27, Step B) with 4-aminomethylimidazole under the conditions of Example 34 provides the title compound.

EXAMPLE 74

Preparation of N-[3-(imidazol-1-yl)propyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Reaction of the 3-phenylsulfonyl-5-chloroindole-2-carboxylic acid with 1-(3-aminopropyl)-imidazole under the conditions of Example 37 gave the title compound, mp 216-217.5°C.

EXAMPLE 75

Preparation of 3-phenylsulfonyl-5-methylsulfonylamino-indole-2-carboxamide (36)

Step A: 3-Phenylsulfonyl-5-nitroindole-2-carboxamide

Reaction of ethyl 5-nitroindole-2-carboxylate (J. Amer.

Chem. Soc. 80, 4621 (1958)) with N-(phenyl-thio)succinimide under the conditions of Example 33, Step B, followed by oxidation to the sulfonyl product (Step C) provides a product which may be converted to the title compound with ammonium hydroxide at elevated temperature and pressure.

Step B: 3-Phenylsulfonyl-5-aminoindole-2-carboxamide

Reduction of 3-phenylsulfonyl-5-nitroindole-2-carboxamide with hydrogen under the conditions of Example 41 provides the title compound.

Step C: 3-Phenylsulfonyl-5-methylsulfonylaminoindole-2-carboxamide

Reaction of 3-phenylsulfonyl-5-aminoindole-2-carboxamide with methanesulfonyl chloride under the conditions of Example 47 provides the title compound.

EXAMPLE 76

Preparation of 4-[(5-chloro-3-phenylsulfonylindole-2-carboxamido)-methyl]pyridin-2(1H)-one (37)

Step A: N-(2-methoxy-4-pyridylmethyl)-5-chloro-3-phenylsulfonylindole-2-carboxamide

Reaction of the 'acid chloride dimer' product of Example 27, Step B, with 2-methoxy-4-pyridylmethylamine under the conditions of Example 27, Step C, provides the title compound.

Step B: 4-[(5-Chloro-3-phenylsulfonylindole-2-carboxamido)-methyl]-pyridin-2(1H)-one

Reaction of N-(2-methoxy-4-pyridylmethyl)-5-chloro-3-phenylsulfonylindole-2-carboxamide with boron tribromide in methylene chloride at 0°C to room temperature, according to the procedure described in Example 39, provides the title compound.

EXAMPLE 77

Preparation of N-(2-amino-4-pyridylmethyl)-5-chloro-3-phenylsulfonylindole-2-carboxamide (38)

Step A: 2-Amino-4-aminomethylpyridine

2-Aminopyridine-4-carbonitrile (L.W. Deady et al., Aust. J. Chem., 35, 2025 (1982)) is reduced catalytically according to the procedure of D.E. Beattie et al. for the preparation of 2-amino-3-aminomethyl pyridine (J. Med. Chem., 20, 718, (1977)) to give the title compound.

Step B: N-(2-Amino-4-pyridylmethyl)-5-chloro-3-phenylsulfonyl-indole-2-carboxamide

Reaction of 2-amino-4-aminomethylpyridine with the dimeric acid chloride from Example 27, Step B, according to the procedure of Example 27, Step C, provides the title compound.

EXAMPLE 78

Preparation of N-(2-aminothiazol-4-ylmethyl)-5-chloro-3-phenylsulfonyl-indole-2-carboxamide

Reaction of the dimeric acid chloride from Example 27, Step B, with 2-aminothiazol-4-ylmethylamine (Chem. Ab. 58, 4534 (1962)) under the conditions of Example 27, Step C, provides the title compound.

EXAMPLE 79

Preparation of N-cyano-5-chloro-3-phenylsulfonylindole-2-carboximid-amide (35)

Step A: 5-Chloro-3-phenylsulfonylindole-2-carbonitrile

5-Chloro-3-phenylsulfonylindole-2-carboxamide reacts with methyl (carboxysulfamoyl)triethylammonium hydroxide inner salt (Burgess reagent) in tetrahydrofuran (THF) solvent as described by D.A. Claremon and B.T. Phillips (Tetrahedron Lett., 29, 2155 (1988)) to provide the title compound.

Step B: Ethyl 5-chloro-3-phenylsulfonylindole-2-carboximidate

5-Chloro-3-phenylsulfonylindole-2-carbonitrileis allowed to react with ethanol saturated with hydrogen chloride at 0-10°C for 7 days. Evaporation to dryness affords the title compound as a hydrochloride salt. The title compound is obtained as a free base by adding the reaction mixture to an ice cold solution of excess potassium carbonate and extracting the product with chloroform.

Step C: N-Cyano-5-chloro-3-phenylsulfonylindole-2-carboximid-amide

Ethyl 5-chloro-3-phenylsulfonylindole-2-carboximidate is reacted with an equimolar amount of cyanamide in absolute methanol (according to the procedure of K.R. Huffman and F.C. Schaefer (J. Org. Chem., 28, 1812 (1963)). After 30-60 minutes the solvent is removed and the residue purified by silica gel chromatography to afford the title compound.

EXAMPLE 80

Preparation of N-cyclobutyl-5-chloro-3-phenylsulfonylindole-2-carboxamide (27)

Using the procedure of Example 48 but substituting cyclobutylamine for benzylamine, there is obtained the title compound.

EXAMPLE 81

Preparation of N-cyclopropyl-5-chloro-3-phenylsulfinylindole-2-carboxamide (39)

Using the procedure of Example 28, Step B, but substituting cyclopropylamine for 4-aminomethylpyridine, there is obtained the title compound.

EXAMPLE 82

Preparation of N-[(1-methylimidazol-2-yl)methyl]-3-phenylsulfinyl-5-chloroindole-2-carboxamide (20)

Using the procedure of Example 28, Step B, but substituting 2-aminomethyl-1-methylimidazole for 4-aminomethyl-pyridine, there is obtained the title compound.

EXAMPLE 83

Preparation of N-[(1-methylimidazol-4-yl)methyl-3-phenylsulfonyl-5-chloroindole-2-carboxamide (21) and N-[(1-methylimidazol-5-yl)methyll-3-phenylsulfonyl-5-chloroindole-2-carboxamide (22)

Step A: N-[(Imidazol-4(or 5)-ylmethyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Employing the procedure of Example 34, but substituting 4(or 5)-aminomethylimidazole dihydrochloride for 2-aminomethyl-imidazole dihydrochloride, there is obtained the title compound.

Step B: N-[(1-methylimidazol-4-yl)methyl]-3-phenylsulfonylindole-5-chloroindole-2-carboxamide; N-[(1-methylimidazol-5-yl)methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide

Employing the procedure of Example 36, but substituting N-[(imidazol-4(or 5)-yl)methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide for N-[(imidazol-2-yl)methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide, there is obtained each of the title compounds which are obtained pure by chromatography on silica gel.

EXAMPLE 84

Preparation of N-[(R)-1-phenylethyl]-5-chloro-3-phenylsulfonyl-indole-2-carboxamide (33)

Employing the procedure of Example 29, but substituting (R)-(+)-a-methylbenzylamine for (S)-(+)-2-phenylglycinol, there was obtained the title compound, mp 149°C.

Analysis calculated for $C_{23}H_{19}ClN_2O_3S \cdot 0.15\ C_2H_4O_2 \cdot 0.15H_2O$
C, 62.32; H, 4.54; N, 6.16
Found: C, 62.39; H, 4.54; N, 6.01

^1H NMR (DMSO-d_6) δ 3.06 (1H, s); 9.43 (1H, d, J=8Hz); 7.94-8.02 (3H, m); 7.46-7.67 (6H, m); 7.25-7.42 (4H, m); 5.21 (1H, q,J =7Hz); 1.53 (3H, d, J=7Hz).

EXAMPLE 85

Preparation of N-[(1-ethylimidazol-2-yl)methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide

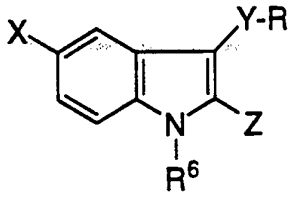
Using the procedure described in Example 35, except substituting 2-aminomethyl-1-ethylimidazole for the 2-aminomethyl-1-methylimidazole (Step A), the title compound was obtained, mp 204-205.5°C.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of

illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations, and modifications, as come within the scope of the following claims and its equivalents.

WHAT IS CLAIMED IS:

1. A compound of formula A,



A

wherein

X is -H, -Cl, -F, -Br, -NO_2, -CN, -OR^2, -NR^2R^2, -$NHSO_2$-C_{1-3}alkyl, or -NHCO-C_{1-3}alkyl;

Y is -$S(O)_n$- or -O-, wherein n is zero, 1 or 2;

R is

1) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
   a) -C_{1-5}alkyl,
   b) -C_{1-5}alkoxy,
   c) -OH, or
   d) aryl, unsubstituted or substituted with one or more of:
      i) -C_{1-5}alkyl,
      ii) -C_{1-5}alkoxy,
      iii) -OH,
      iv) halogen, or
      v) -NR^2R^2,

2) aryl, unsubstituted or substituted with one or more of:
   a) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
      i) -OH or
      ii) -C_{1-5}alkoxy,
   b) -C_{1-5}alkoxy,
   c) -OH,
   d) halogen, or

e) $-NR^2R^2$,

3) heterocycle, unsubstituted or substituted with one or more of:

a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:

i) -OH or

ii) $-C_{1-5}$alkoxy,

b) $-C_{1-5}$alkoxy,

c) -OH,

d) halogen, or

e) $-NR^2R^2$, or

4) $-NR^2R^3$, provided that Y is $-S(O)_n-$;

Z is

1) $-\overset{\overset{W}{\|}}{C}-NR^2R^3$,

wherein W is O, S, -N-CN, or $-N-OR^2$,

2) $-COR^{1a}$,

3) $-COOR^{1b}$,

4) $-CR^2R^2-S(O)_n-R^{1a}$,

wherein n is defined above,

5) $-CR^2R^2NHR^4$,

6) $-CR^2R^2-CO-R^5$,

7) $-C_{1-3}$alkyl substituted with one or more of:

a) aryl, unsubstituted or substituted with one or more of:

i) -C_{1-5}alkyl,
ii) -C_{1-5}alkoxy,
iii) -OH,
iv) halogen, or
v) -NR^2R^2, or

b) heterocycle, unsubstituted or substituted with one or more of:
i) -C_{1-5}alkyl,
ii) -C_{1-5}alkoxy,
iii) -OH,
iv) halogen, or
v) -NR^2R^2, or

8) -CN;

R^1 is

1) hydrogen,
2) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
a) -C_{1-5}alkyl,
b) -C_{1-5}alkoxy,
c) -OH,
d) aryl, unsubstituted or substituted with one or more of:
i) -C_{1-5}alkyl,
ii) -C_{1-5}alkoxy,
iii) -OH,
iv) halogen, or
v) -NR^2R^2, or
e) heterocycle, unsubstituted or substituted with one or more of:
i) -C_{1-5}alkyl,
ii) -C_{1-5}alkoxy,
iii) -OH,
iv) halogen, or

v) $-NR^2R^2$, or

3) aryl, unsubstituted or substituted with one or more of:
   a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
      i) -OH or
      ii) $-C_{1-5}$alkoxy,
   b) $-C_{1-5}$alkoxy,
   c) -OH,
   d) halogen,
   e) -CN,
   f) $-NO_2$, or
   g) $-NR^2R^2$; or

4) heterocycle, unsubstituted or substituted with one or more of:
   a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
      i) -OH or
      ii) $-C_{1-5}$alkoxy,
   b) $-C_{1-5}$alkoxy,
   c) -OH,
   d) halogen, or
   g) $-NR^2R^2$;

R^{1a} is

1) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
   a) $-C_{1-5}$alkyl,
   b) $-C_{1-5}$alkoxy,
   c) -OH,
   d) aryl, unsubstituted or substituted with one or more of:
      i) $-C_{1-5}$alkyl,
      ii) $-C_{1-5}$alkoxy,
      iii) -OH,

iv) halogen, or
v) $-NR^2R^2$, or

e) heterocycle, unsubstituted or substituted with one or more of:
i) $-C_{1-5}$alkyl,
ii) $-C_{1-5}$alkoxy,
iii) -OH,
iv) halogen, or
v) $-NR^2R^2$, or

2) aryl, unsubstituted or substituted with one or more of:
a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
i) -OH or
ii) $-C_{1-5}$alkoxy,
b) $-C_{1-5}$alkoxy,
c) -OH,
d) halogen,
e) -CN,
f) $-NO_2$, or
g) $-NR^2R^2$;

3) heterocycle, unsubstituted or substituted with one or more of:
a) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
i) -OH or
ii) $-C_{1-5}$alkoxy,
b) $-C_{1-5}$alkoxy, or
c) -OH,
d) halogen, or
e) $-NR^2R^2$, or

4) C_{3-6}cycloalkyl;

R^{1b} is

1) $-C_{1-5}$alkyl substituted with one or more of:
a) $-C_{1-5}$alkoxy,

b) -OH,
c) aryl, unsubstituted or substituted with one or more of:
i) -C_{1-5}alkyl,
ii) -C_{1-5}alkoxy,
iii) -OH,
iv) halogen, or
v) -NR^2R^2, or
d) heterocycle, unsubstituted or substituted with one or more of:
i) -C_{1-5}alkyl,
ii) -C_{1-5}alkoxy,
iii) -OH,
iv) halogen, or
v) -NR^2R^2,

2) aryl, unsubstituted or substituted with one or more of:
a) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
i) -OH or
ii) -C_{1-5}alkoxy,
b) -C_{1-5}alkoxy,
c) -OH,
d) halogen,
e) -CN,
f) -NO_2, or
g) -NR^2R^2; or

3) heterocycle, unsubstituted or substituted with one or more of:
a) -C_{1-5}alkyl, unsubstituted or substituted with one or more of:
i) -OH or
ii) -C_{1-5}alkoxy,
b) -C_{1-5}alkoxy,
c) -OH,

d) halogen, or
e) $-NR^2R^2$;

R^2 is hydrogen or C_{1-3}alkyl;

R^3 is

1) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of:
a) $-C_{1-5}$alkyl,
b) $-C_{1-5}$alkoxy, unsubstituted or substituted with -OH,
c) -OH,
d) $-OC(O)R^7$;
e) $-COOR^2$
f) aryl, unsubstituted or substituted with one or more of:
i) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of -OH,
ii) $-C_{1-5}$alkoxy,
iii) -OH,
iv) halogen,
v) $-NO_2$,
vi) $-NR^2R^2$,
vii) $-NHCO-C_{1-3}$alkyl, or
viii) $-NHSO_2-C_{1-3}$alkyl,
g) heterocycle, unsubstituted or substituted with one or more of:
i) $-C_{1-5}$alkyl,
ii) $-C_{1-5}$alkoxy,
iii) -OH,
iv) C_{1-3}alkyl-NR^2R^2,
v) halogen,
vi) oxo,
vii) $-NO_2$,
viii) $-NR2R^2$,

ix) -NHCO-C_{1-3}alkyl, or
x) -NHSO$_2$-C_{1-3}alkyl,

h) -NR^2R^2,
i) -C_{3-6}cycloalkyl,

2) aryl, unsubstituted or substituted with one or more of:
a) -C_{1-5}alkyl,
b) -C_{1-5}alkoxy,
c) -OH,
d) halogen, or
e) -NR^2R^2,

3) heterocycle, unsubstituted or substituted with one or more of:
i) -C_{1-5}alkyl,
ii) -C_{1-5}alkoxy,
iii) -OH,
iv) halogen, or
v) -NR^2R^2,

4) -C_{1-5}alkoxy,
5) -OH,
6) -C_{3-6}cycloalkyl, or
7) hydrogen;

R^4 is
1) R^1 or
2) -COR^1;

R^5 is
1) R^1,
2) -C_{1-5}alkoxy,
3) -NHR^1, or

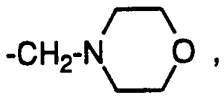
4) heterocycle, unsubstituted or substituted with one or more of:
   i) $-C_{1-5}$alkyl,
   ii) $-C_{1-5}$alkoxy,
   iii) -OH,
   iv) halogen, or
   v) $-NR^2R^2$;

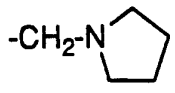
R^6 is
1) hydrogen,
2) $-COR^1$,
3) $-CONHR^1$;

R^7 is
1) aryl, unsubstituted or substituted with one or more of -Cl, -Br, -OH, $-OCH_3$, or -CN, or
2) $-C_{1-5}$alkyl, unsubstituted or substituted with one or more of -OH or $-NR^2R^2$; and

with the proviso that when X is -H, Y is -S, R is unsubstituted phenyl and R^6 is -H,

Z is not $-CH_2$-SO-Ph, -COH,



, or 

;

or a pharmaceutically acceptable salt or ester thereof.

2. The compound according to Claim 1 wherein:

X is -H, -Cl or -F;
Y is $-S(O)_n-$;
R is -Ph, -tolyl, 3-Cl-phenyl, 2-pyridyl or 2-thiazolyl;

R^6 is -H; and

Z is

$-\overset{\overset{W}{\|}}{C}-NR^2R^3$, $-COOR^{1b}$, $-COR^{1a}$,

$-CR^2R^2-S(O)_n-R^{1a}$ or

$-C_{1-3}$alkyl substituted with heterocycle.

3. The compound according to Claim 2 wherein:

X is -H or -Cl;

Y is $-S(O)_n-$;

R is -Ph, -tolyl, 3-Cl-phenyl or 2-thiazolyl;

R^6 is -H; and

Z is

1) $-\overset{\overset{W}{\|}}{C}-NR^2R^3$,

wherein R^2 is -H and W is -O, -S or -NCN, or

2) $-CR^2R^2-SO$-aryl, wherein the aryl group is unsubstituted or substituted with one or more of C_{1-5}alkyl.

4. The compound according to Claim 3 wherein:

X is -Cl;

Y is $-S(O)_n-$;

n is 1 or 2;

R is -Ph, 3-Cl-phenyl or 2-thiazolyl;

R^6 is -H;

Z is

$-\overset{\overset{W}{\|}}{C}-NR^2R^3$,

wherein R^2 is -H, and W is -O, -S or -NCN; and

R^3 is

1) -C_{1-5}alkyl, unsubstituted or substituted with one or more of
   a) -C_{1-5}alkoxy, unsubstituted or substituted with -OH,
   b) -OH,
   c) -$OC(O)R^7$,
   d) aryl, unsubstituted or substituted with one or more of:
      i) -C_{1-5}alkyl, unsubstituted or substituted with one or more of -OH,
      ii) -C_{1-5}alkoxy,
      iii) -OH,
      iv) halogen, or
      v) -NR^2R^2,
   e) heterocycle, unsubstituted or substituted with one or more of:
      i) -C_{1-5}alkyl,
      ii) -C_{1-5}alkoxy, or
      iii) -OH,
      iv) halogen, or
      v) -NR^2R^2, or
   f) C_{3-6}cycloalkyl,

2) heterocycle, unsubstituted or substituted with one or more of:
   i) -C_{1-5}alkyl,
   ii) -C_{1-5}alkoxy,
   iii) -OH,
   iv) halogen, or
   v) -NR^2R^2,
3) hydrogen, or
4) C_{3-6} cycloalkyl.

5. The compound according to Claim 1 wherein X is selected from the group consisting of:

1) $-NR^2R^2$,
2) $-NHSO_2-C_{1-3}$alkyl and
3) $-NHCO-C_{1-3}$alkyl.

6. The compound according to Claim 1 wherein Z is $-C(=W)-NR^2R^3$ and R^3 is selected from the group consisting of:

1) C_{1-3}alkyl substituted with phenyl wherein phenyl is substituted with one or more of
   a) $-NO_2$,
   b) $-NR^2R^2$,
   c) $-NHCO-C_{1-3}$alkyl or
   d) $-NHSO_2-C_{1-3}$alkyl, and

2) C_{1-3}alkyl substituted with heterocycle wherein heterocycle is substituted with one or more of:
   a) halogen,
   b) oxo,
   c) $-NO_2$,
   d) $-NR^2R^2$,
   e) $-NHCO-C_{1-3}$alkyl or
   f) $-NHSO_2-C_{1-3}$alkyl.

7. The compound according to Claim 1 wherein Y is $-S(O)_n-$ and R is $-NR^2R^3$.

8. A compound selected from the group consisting of:
N-ethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-hydroxyethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-methoxyethyl-5-chloro-3-phenylthioindole-2-carboxamide,

N-3-methoxybenzyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-4-pyridylmethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-3-pyridylmethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-3-pyridyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-[1-(2(R)-hydroxypropyl)]-5-chloro-3-phenylthioindole-2-carboxamide,
N-(2-pyridyl)methyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-(3-methoxy-4-pyridyl)methyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-(3-hydroxymethyl)benzyl-5-chloro-3-phenylthioindole-2-carboxamide,
5-chloro-3-phenylthioindole-2-carboxamide,
N-(3-hydroxybenzyl)-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-thiocarboxamide,
5-chloro-3-phenylthioindole-2-thiocarboxamide,
5-chloro-3-phenylsulfinylindole-2-carboxamide, and
5-chloro-3-phenylsulfonylindole-2-carboxamide,

or a pharmaceutically acceptable salt or ester thereof.

9. A compound selected from the group consisting of:
N-ethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-hydroxyethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-methoxyethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-3-methoxybenzyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-4-pyridylmethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-3-pyridylmethyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-carboxamide, and
N-3-pyridyl-5-chloro-3-phenylthioindole-2-carboxamide,

or a pharmaceutically acceptable salt or ester thereof.

10. A compound selected from the group consisting of:
N-[1-(2(R)-hydroxypropyl)]-5-chloro-3-phenyl-thioindole-2-carboxamide,
N-(2-pyridyl)methyl-5-chloro-3-phenylthioindole-2-carboxamide,
N-(3-methoxy-4-pyridyl)methyl-5-chloro-3-phenyl-thioindole-2-carboxamide,
N-(3-hydroxymethyl)benzyl-5-chloro-3-phenyl-thioindole-2-carboxamide,
5-chloro-3-phenylthioindole-2-carboxamide,
N-(3-hydroxybenzyl)-5-chloro-3-phenylthioindole-2-carboxamide,
N-2-furanylmethyl-5-chloro-3-phenylthioindole-2-thiocarboxamide, and
5-chloro-3-phenylthioindole-2-thiocarboxamide,

or a pharmaceutically acceptable salt or ester thereof.

11. A compound selected from the group consisting of:
5-chloro-3-phenylsulfinylindole-2-carboxamide, and
5-chloro-3-phenylsulfonylindole-2-carboxamide,

or a pharmaceutically acceptable salt thereof.

12. A compound selected from the group consisting of:
N-[(1-methylimidazol-2-yl)methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide,
N-[(1-methylimidazol-2-yl)methyl]-3-phenylsulfinyl-5-chloroindole-2-carboxamide,
N-[(1-methylimidazol-4-yl)methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide,
N-[(1-methylimidazol-5-yl)methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide,
N-[(1-methylimidazol-2-yl)methyl]-3-(3-chlorophenylsulfonyl)-5-chloroindole-2-carboxamide,
N-[2-(imidazol-4-yl)ethyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide,

N-[2-(1-methylimidazol-4-yl)ethyl]-3-phenyl-sulfonyl-5-chloroindole-2-carboxamide,
N-cyclopropyl-5-chloro-3-phenylsulfonylindole-2-carboxamide,
N-cyclobutyl-5-chloro-3-phenylsulfonylindole-2-carboxamide,
N-(3-pyridylmethyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide,
N-(4-pyridylmethyl)-5-chloro-3-phenylsulfinyl-indole-2-carboxamide,
N-(3-aminobenzyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide,
N-(3-methoxybenzyl)-5-chloro-3-(2-thiazolyl)-sulfonylindole-2-carboxamide,
N-[(S)-1-phenyl-2-hydroxyethyl]-5-chloro-3-phenylsulfonylindole-2-carboxamide,
N-[(R)-1-phenylethyl]-5-chloro-3-phenylsulfonyl-indole-2-carboxamide,
N-(3-methylsulfonylaminobenzyl)-3-phenylsulfonyl-5-chloroindole-2-carboxamide,
N-cyano-5-chloro-3-phenylsulfonylindole-2-carboximidamide,
3-phenylsulfonyl-5-methylsulfonylaminoindole-2-carboxamide,
4-[(5-chloro-3-phenylsulfonylindole-2-carboxamido)-methyl]pyridin-2(1H)-one,
N-(2-amino-4-pyridylmethyl)-5-chloro-3-phenyl-sulfonylindole-2-carboxamide, and
N-cyclopropyl-5-chloro-3-phenylsulfinylindole-2-carboxamide, or

a pharmaceutically acceptable salt or ester thereof.

13. The compound N-[(1-methylimidazol-2-yl)-methyl]-3-phenylsulfonyl-5-chloroindole-2-carboxamide, or

a pharmaceutically acceptable salt thereof.

14. A method of inhibiting HIV reverse transcriptase, comprising administering to a mammal an effective amount of a compound of Claim 1.

15. A method of preventing infection of HIV, or of treating infection by HIV or of treating AIDS or ARC, comprising administering to a mammal an effective amount of a compound of Claim 1.

16. A pharmaceutical composition useful for inhibiting HIV reverse transcriptase, comprising an effective amount of a compound of Claim 1, and a pharmaceutically acceptable carrier.

17. A pharmaceutical composition useful for preventing or treating infection of HIV or for treating AIDS or ARC, comprising an effective amount of a compound of Claim 1, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

In. ..ational application No.
PCT/US94/01694

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :C07D 209/30; A61K 31/40
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/235.2, 339, 365, 394, 397, 418; 544/143; 546/273; 548/205, 305.1, 312.1, 312.1, 465

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Computer Search
1966 - To Date

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Pharmaceutical Bulletin, Vol. 24, issued 1976, Inaba et al., "Benzodiazepine. XIII. Synthesis of 1, 4-Benzodiazepine Derivatives," pages 1076-1082.	1-13
A	Synthesis, issued June 1988, Atkinson et al., "A New Synthesis of 3-Arylthiandoles", pp. 480-481.	1-13
A	Synthesis, issued November 1982, Nagarathram et al., "A Convienent Synthesis of 2-(2-Arylethyl)-3-ethoxy carbony)-5-methoxyindoles via the Wittig-Horner Reaction", pp. 926-927.	1-13
A	Synthesis, issued February 1985, Mohan et al., "Synthesis of 2(2Aryl ethyl)-indoles", pp. 188-190.	1-13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
10 MAY 1994

Date of mailing of the international search report
01 JUN 1994

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

In...national application No.
PCT/US94/01694

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Tetrahedron letters, Vol. 24, No. 33, issued 1983, Vedachalam et al., "A Facile Preparation of 2-Alkyl-indoles - Potential Intermediates for Alkoids", pp. 3531-3532.	1-13
A	Synthesis, issued February 1983, Nagarathinam et al., "1-Benzenesulfonyl-2-bromoethyl-3-phenylthioindole as a synthon for 2-substituted Indoles: A New Synthesis of 2-Aminomethy Indoles", pp. 156-157.	1-13
X	J. Medicinal Chemistry, Vol. 12, issued 12 April 1969, Savena et al., "Synthesis of 3-hydroxy and 3-methoxy-indole-2-carboxamides and esters," pp. 1120-1122, see Table 1, compound 6.	1-13
X	Chemical Abstracts, Vol. 110, No. 25, issued 19 June 1989, Uhlendorf et al., "Preparation of N-substituted indole carboxamides and indolemethyl amines as nervous systems agents", see formula 1, abstract no. 231432y.	1-13
A	WO,A, 91/09849 (Romero et al.) 11 July 1991.	14-17
A	WO,A, 88/08424 (McCall et al.) 03 November 1988.	1-13
A	EP,A, 0,000,972 (Steinman et al.) 07 March 1979.	1-13
A	EP,A, 0,275,667 (Gillar et al.) 27 July 1988.	1-13
A	WO,A, 91/05761 (Harrison et al.) 02 May 1991.	14-17
A	DE,A, 1,935,671 (Yamamoto et al.) 05 March 1970.	1-13
A	US,A, 4,255,442 (Steinman et al.) 10 March 1981.	1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/01694

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/235.2, 339, 365, 394, 397, 418; 544/143; 546/273; 548/205, 305.1, 312.1, 312.1, 465