Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2308994 A1 2001/11/19

(21) 2 308 994

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(22) Date de dépôt/Filing Date: 2000/05/19

(41) Mise à la disp. pub./Open to Public Insp.: 2001/11/19

(51) Cl.Int.^{7}/Int.Cl.^{7} C07D 471/22, A61K 31/706, A61K 31/7056, A61K 31/4375, A61K 31/437, A61P 35/00, A61P 25/00, A61K 31/4045, A61P 9/10, C07H 5/06, C07D 471/04, C07D 403/04, C07D 487/14, C07D 409/14, C07D 403/14

(71) Demandeur/Applicant:
AEGERA THERAPEUTICS INC., CA

(72) Inventeurs/Inventors:
GILLARD, John W., CA;
JAQUITH, James B., CA

(74) Agent: BORDEN LADNER GERVAIS LLP

(54) Titre : COMPOSES NEUROPROTECTEURS
(54) Title: NEUROPROTECTIVE COMPOUNDS

(57) Abrégé/Abstract:
This invention features ring-substituted β-carboline derivatives of the indolocarbazole K252a, and ring-substitution and structural derivatives of 3-(1H-indol-3-yl)-1H-pyrroledione which are useful as neuroprotective compounds. Also disclosed are methods for the preparation of these compounds, selected biological profiles, and uses of these compounds in the treatment of various neurodegenerative and inflammatory diseases, and in the treatment of various other disorders characterized by loss of growth and cellular differentiation control; cancer, inflammation, and various human and viral signal transduction processes.

Abstract

This invention features ring-substituted β-carboline derivatives of the indolocarbazole K252a, and ring-substitution and structural derivatives of 3-(1*H*-indol-3-yl)-1*H*-pyrroledione which are useful as neuroprotective compounds. Also disclosed are methods for the preparation of these compounds, selected biological profiles, and uses of these compounds in the treatment of various neurodegenerative and inflammatory diseases, and in the treatment of various other disorders characterized by loss of growth and cellular differentiation control; cancer, inflammation, and various human and viral signal transduction processes.

NEUROPROTECTIVE COMPOUNDS

FIELD OF THE INVENTION

This invention features derivatives of the indolocarbazole K252a, and derivatives of pyrroledione which are useful in prevention and treatment of neurodegenerative and inflammatory diseases, as well as in treatment and prevention of cancer, inflammation, and various human and viral signal transduction processes.

BACKGROUND OF THE INVENTION

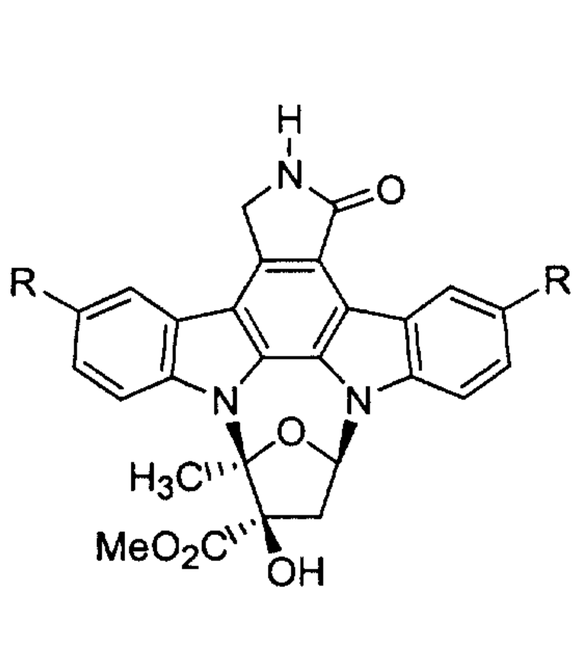
The regulation of neuronal responses to ischemic, excitotoxic or chemotoxic stresses in the central nervous system (CNS), including for example, the brain and the spinal cord, is a major frontier of modern medicine. Neurons are non-proliferating cells whose progressive or abrupt loss can result in diseases exemplified by Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic laterial sclerosis ("ALS" or "Lou Gehrig's disease"), Huntington's disease (HD), ischemia, multiple sclerosis (MS), spinal muscular atrophy (SMA), and stroke. These diseases and disorders are individually or collectively referred to herein as "neurodegenerative diseases." Progressive in nature, the incidence of neurodegenerative diseases increases with age. For example, less than 5% of the population under the age of 65 display signs of AD. An exponential increase is observed over the age of 65, with as much as 47% of the population displaying some form of AD over the age of 85. *See*. Katzman et al, *FASEB*, *5*:278-286 (1991); Evans et al, *JAMA*, *262*:2551-2556 (1989). Even in the absence of disease, aging and neuronal loss may be positively correlated in most individuals over the age of 80, with a significant number of these individuals showing some sign of age- and/or disease related loss of neurons. *See*, Matsuyama et al, *Proceedings of the Fifth International Congress of Neuropathy* (Exerpta Medicca International Congress Series No. 100 eds, Luthy et al) 979-980 (1966). Symptoms resulting from these diseases may include memory loss, loss of muscle control, muscle wasting,

and paralysis. The mode of action underlying such neuronal death involves programmed cell death, or apoptosis.

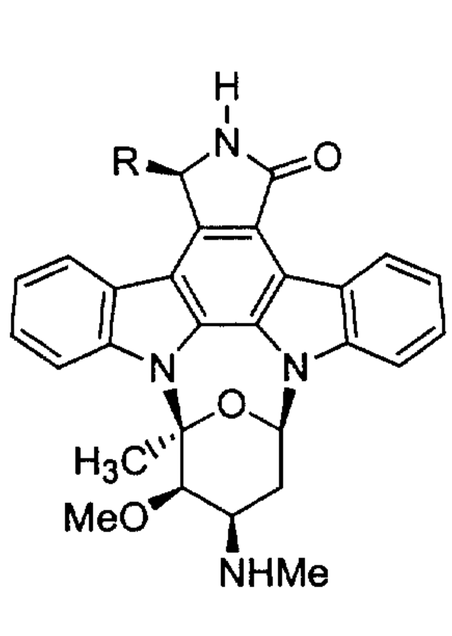
Scientists at Apoptogen have recently discovered a new family of genes known as the IAPs (Inhibitor of Apoptosis Proteins), which are responsible for modulating apoptosis. NAIP (Neuronal Apoptosis Inhibitory Protein) is a member of this gene family whose primary function appears to be the regulation of neuronal apoptosis (Xu, D.G. *et al. Nature Medicine* **1997**, *3*, 997; MacKenzie et al, **US**; MacKenzie et al, **US**). NAIP is primarily expressed in neurons where it serves to protect the post-mitotic cells against environmental and metabolic stress. Deletions in the NAIP gene were found to be causally related to the severity of the childhood genetic disease SMA.

The over expression of NAIP in the brains of experimental animals, through a gene therapy vectoring approach, protects against neurodegeneration induced by ischemia, kainic acid, quinolinic acid, MPTP, and 6OH-dopamine, all of which are models for stroke, epilepsy, Huntington's disease, and Parkinson's disease, respectively (MacKenzie et al, **US**).

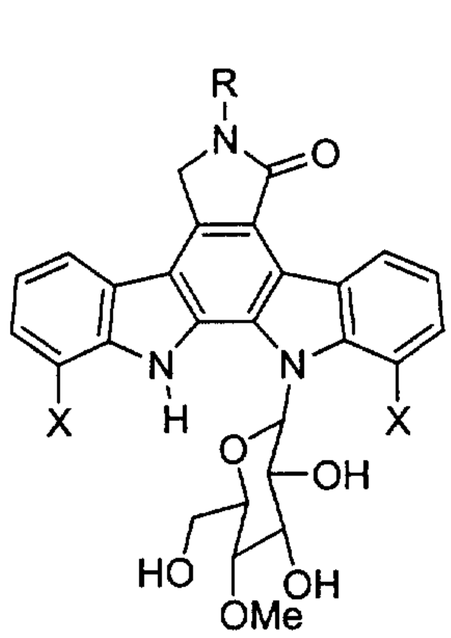
Scientists at the University of Ottawa have shown that it is possible to modulate the expression of the NAIP gene, in the brain, through the systemic administration of the neuroprotective alkaloid K252a (Sezaki, M. *J. Antibiot.* **1986**, *39*, 1066).



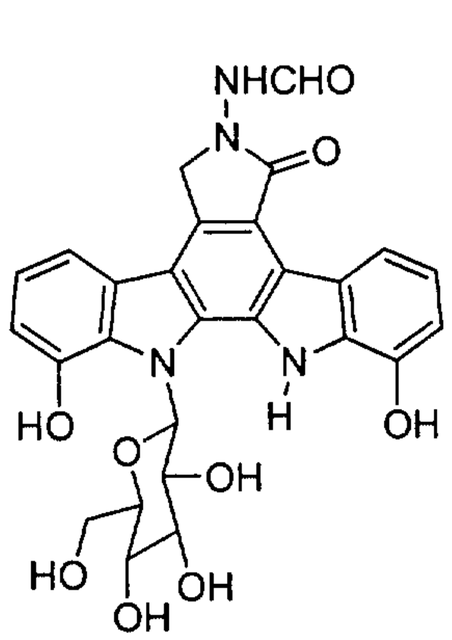
(+)-K252a; R=H
CEP 1347; R=CH_2SEt



Staurostorine; R = H
UNC 011; R = OH



Rebeccamycin; R = H, X = Cl
R-3; R = OH, X = H



NB 506

In vivo studies demonstrated increased expression of NAIP in hippocampal neurons after K252a administration to rats. These results correlate well with increased protection to ischemic insults (for the Apoptogen discoveries see – Xu, D.G. *et al. Nature Medicine* **1997**, *3*, 997 and references cited therein). Knock-out mice lacking the expression of NAIP displayed dramatic

neuronal sensitivity to such ischemic insults. Therefore, we hypothesize that small molecule induced upregulation of NAIP expression in neurons will provide protection against cytotoxic insults. A distinct benefit of such compounds, compared to neurotrophic proteins, is the ease with which these and related compounds cross the blood-brain barrier.

The mechanism by which K252a upregulates the NAIP gene expression is not known. However, it is known that K252a inhibits several classes of protein kinases (for a review see Woodgett, J.R. Protein Kinases, Oxford University Press, 1994). The X-ray crystal structure of staurosporine bound to the protein kinases CDK2 and cAPK (for a review see Lydon, N. B. *et al. Structure* 1997, 5151) confirmed that staurosporine acts as a competitive inhibitors for the binding site of adenosine triphosphate (ATP) (for a general review of the chemistry and properties of these alkaloids see Gribble, G. W.; Berthel, S. J. "Studies in Natural Products Chemistry", 1993, *12*, 365. For synthetic studies see Wood, J. L. *et al. J. Am. Chem. Soc.* **1997**, *119*, 9641; Danishefsky, S. *et al. J. Am. Chem. Soc.* **1996**, *118*, 2825). Several groups have suggested that K252a and its structural analogues, the indolocarbazoles, also bind to the ATP binding site of various protein kinases. A large number of natural products related to the K252a structure also inhibit various serine-threonine protein kinases. Many of these compounds have undesirable cytotoxic effects due to their lack of kinase specificity. Unfortunately, K252a also displays significant cytotoxicity at low doses *in vitro*, leading to difficulty in interpreting its mechanism as an inducer of the IAPs. Its metabolic disposition *in vivo* is also a concern, given the distinctive differences in kinase inhibitory profile seen by several hydroxylated *bis*-(indolyl)maleimide metabolites (eg. UCN011, R3, and NB506).

Due to the toxicity related to K252a in cellular systems the upregulation of NAIP expression was not observed *in vitro* when K252a was administered to either cultured neuroblastomas cells or cerebellar granule neurons (CGN) (Apoptogen, unpuplished results). Clearly a dichotomy exists between the different IAP profiles observed *in vivo* and *in vitro*. We feel that K252a itself may not be responsible for the upregulation of the IAP expression observed *in vivo*, however, one or several of its metabolites may. Several possible sites of enzymatic oxidation are apparent in the structure of K252a and are similar to those seen in the more selective protein kinases UCN011, R3, and NB506.

These observations lead to the hypothesis that inhibition of kinases in the apoptotic neuronal death signalling pathway (MERK, MLK 1-3, MCK 1-3, JNK 1-3; see Wang, C. Y. *et*

al. Science **1988**, *281*, 1680) may result in the induction of NAIP gene expression. Non-specific compounds may interrupt the survival signalling pathway through inhibition of the closely related JNK 1 & 2 isoforms, or by inhibiting PKB or PKC, all of which are on survival pathways, thereby eliminating any beneficial effects. In fact, protein kinase deregulation has been implicated in various neurodegenerative disorders (Bradshaw, D. *et al. Agents and Actions* **1993**, *38*, 137; Rasouly, D. *et al.* The Toxic Action of Marine and Terrestrial Alkaloids, Ed. Blum, M. S., **1995**, 161; Knusel B.; Heft F. J. *Neurochem.* **1992**, *59*, 1987). These findings suggest that highly specific compounds will be required in order to have pharmaceutical potential in regulating either a pro-apoptotic or anti-apoptotic action in various cell lines.

Various K252a derivatives have been implicated in the treatment of neurodegenerative disorders. Roder *et al.* have reported that K252a derivatives incorporating a carbon at the tetrahydrofuran oxygen position of the K252a sugar moiety prevents tau hyperphosphorylation by the direct inhibition of the ERK family of protein kinases, also known as the MAP kinases (Roder *et al*, US 6,013,646). Tau hyperphosphorylation results in the destabilization of regular microtubular organization and the formation of neurofibular tangles (Iqbal, K. *et al.* FEBS Lett., **1994**, 349, 104; Garver, T. D. *et al.*, *J. Neurosci. Res.*, **1996**, *44*, 12). Neurofibular tangles has been found to be causative in neurodegenerative diseases such as AD and PD. Aberrant ERK activation has also been implicated in the treatment of various other disorders characterized by loss of growth and cellular differentiation control; cancer, inflammation, and various human and viral signal transduction processes. Additionally, these compounds inhibit cdc2 and its isoforms, again suggestion potential utility cancer treatment.

A recent report (Murakata, C. *et al. J. Med Chem.* **1997**, *40*, 1863) established that the K252a analogue CEP 1347 is a selective neurotrophic agent in which the undesirable NGF (trk A kinase) and PKC inhibitory activities have been reduced, as demonstrated in a ChAt assay. Additionally, this class of compounds appears to inhibit the production of the neurotrofin TNF-α (tumour necrosis factor), which is intimately involved in the initiation of neuronal apoptosis. At the same time CEP 1347 and related compounds upregulate the production of IL-1β (Mallamo et al, WO96/31515; Hudkins et al, WO 97/46565; Engber et al, WO97/49406). Recently, CEP 1347 was shown to inhibit MLK1 and JNK1 (Maroney, A. C. *et al.*, *J. Neurosci.*, **1998**, *18*, 104), thereby preventing caspase induced apoptosis. The MLK proteins 1 through 3 are found in most

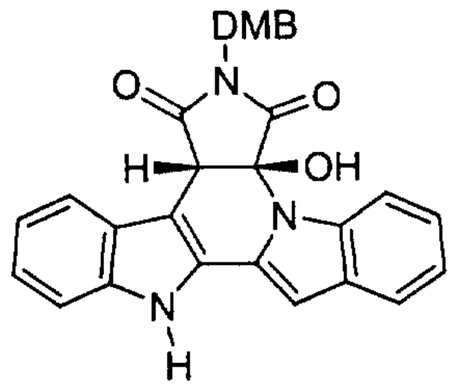
mammalian organs, however, a 70% increase in MLK1 expression is observed in neuronal cells, allowing for increased therapeutic targeting.

Other reports of indolocarbazole derivatives include Glicksman, M. A. *et al.* WO 95 07911, Lewis, M. E. WO 94 02488, Lewis, M. E. *et al.* US 5,756,494, Lewis, M. E. *et al.* US 5,741,808, and Lewis, M. E. *et al.* US 5,621,101. Many of the compounds disclosed are highly lipophilic, allowing for penetration of the blood brain barrier, but poor water solubility of these compounds would result in various pharmokinetic and formulation problems.

Indolocarbazole derivatives have also been implicated in the treatment of cancer (EP 0 323 171, EP 0 643 966, US 4,923,986, US 4,877,776, WO 94 27982), as antimicrobial agents (Prudhomme *et al*, *J. Antibiotics*, **1994**, *47*, 792), and in the treatment of hypertension (Hachisu *et al. Life Sciences* **1989**, *44*, 1351).

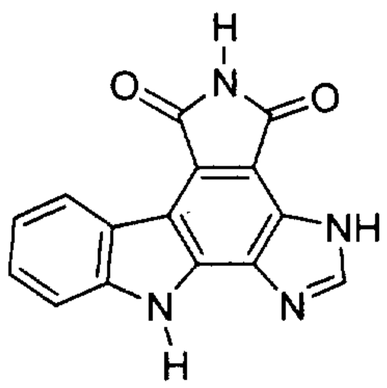
A variety of synthetic procedures have been reported in the literature for the preparation of *bis*(indolyl)pyrrole-2,5-diones and indolocarbazoles, which are structurally related to the disclosed β-carbolines; Bit et al., *J. Med. Chem.*, **1993**, *63*, 21; Bit *et al.*, *Tetrahedron Lett.*, **1993**, *34*, 5423; Bergman *et al.*, *Tetrahedron Lett.*, **1987**, *28*, 4441; Davis *et al.*, *Tetrahedron Lett.*, **1990**, *31*, 2353; Davis *et al.*, *Tetrahedron Lett*, **1990**, *31*, 5201; Faul, M. M. *et al.*, *Tetrahedron Lett.*, 1999, 40, 1109; Faul M.M. *et al.* US 5,859,261, 5,919,946, 6,037,475.

Intermediate (**a**) shown was reported by Wood *et al.* as an undesirable reaction product (Wood, J. L. *et al.*, *J. Am. Chem. Soc.*, **1997**,*119*, 9641). No further reactions involving intermediate (**a**), or any biological activity was reported for this compound.

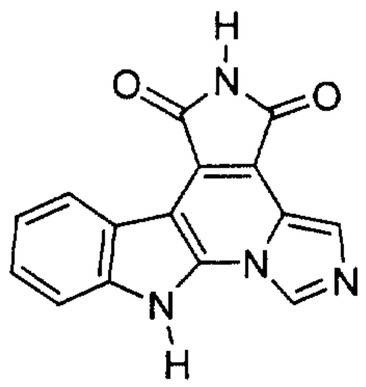


(a)

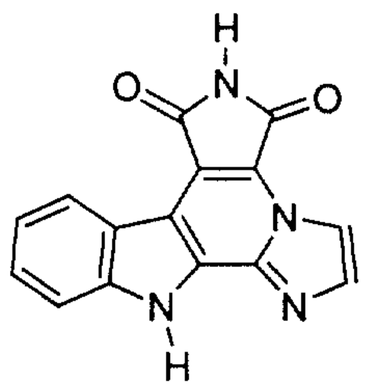
A class of indolocarbazoles having fused imidazolyl ring systems has been described. These compounds and are known as the granulatimides (Piers, E. *et al. J. Org. Chem.*, **2000**,). *Iso*-granulatimide has been shown to be an effective G2 check point inhibitor.



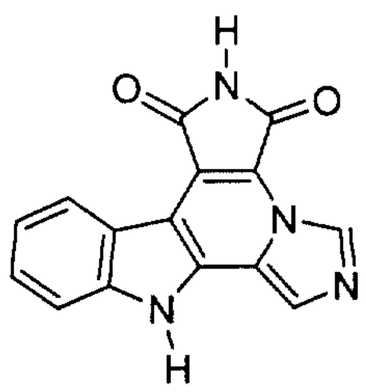
granulatimide



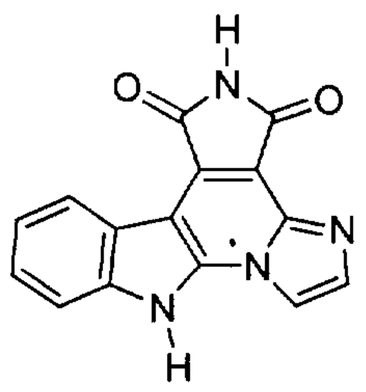
iso-granulatimide



iso-granulatimide A



iso-granulatimide B



iso-granulatimide C

A variety of synthetic procedures have been reported in the literature for the preparation of 3-(1H-indol-3-yl)-1H-pyrrole-2,5-diones involving the condensation of indole with maleimide (Bergman, J. *et al. Tetrahedron*, **1999**, *55*).

Most of the above synthetic procedures have distinct limitations with regards to the use of harsh reaction conditions, the functional groups tolerated during the coupling reactions, the need for protection of the pyrrole-2,5-dione nitrogen, and the total number of synthetic steps required for the preparation of the desired indolocarbazole nuclei.

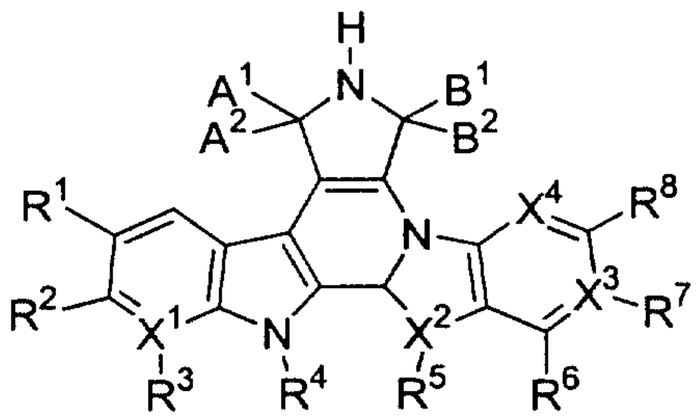
SUMMARY OF THE INVENTION

The present invention is directed, *inter alia*, to selected ring-substitution and β-carboline derivatives of the indolocarbazole K252a, and selected ring-substitution and structural derivatives of 3-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-diones, for the treatment of neurodegenerative diseases, for facilitating either the up or down regulation of the IAPs, including but not limited to NAIP, for the inhibition of various serine-threanine protein kinases, including but not limited to ERK (MAP kinase), PKC, cdc2 and its isoforms, JNK, and MLK, for inhibiting the degradation, dysfunction, or loss of neurons of the CNS, or enhancing the phenotype of neuronal cells and neuronal progress either in the brain or in the peripheral nervous system (PNS).

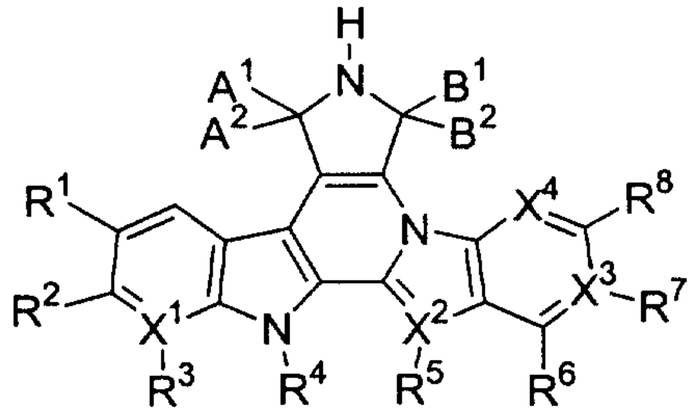
These compounds may also be useful in the treatment of various other disorders characterized by loss of growth and cellular differentiation control; cancer, inflammation, and various human and viral signal transduction processes.

Also included are selected methods for the preparation of these compounds.

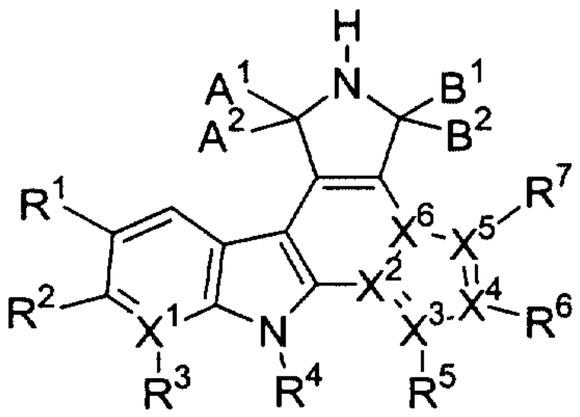
The indolo-β-carboline analogues of the present invention include compounds of formula I, II, and III:



I

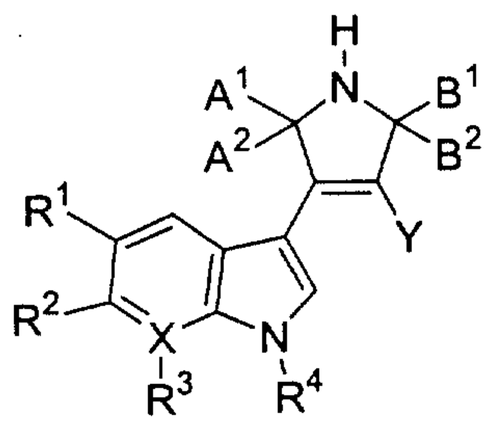


II



III

The 3-(indol-3-yl)-1*H*-pyrrole-2,5-diones analogues of the present invention include compounds of formula IV:



IV

DETAILED DESCRIPTION

I. Drawings

insert/describe drawings of:

a) high/low potassium CGNs for best compounds.

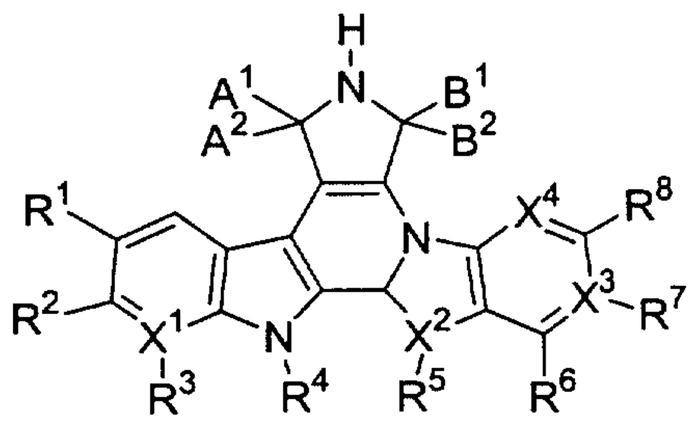
b) beta-amyloid saves for CGNs.

c) cisplatin kills on CGNs.

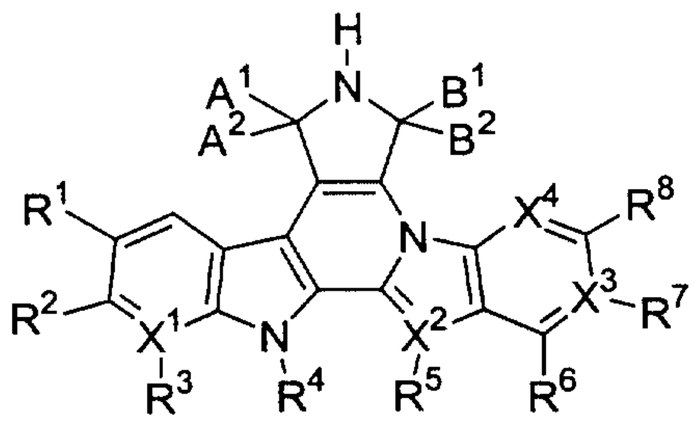
d) caspase down regulation during high/low potassium in CGNs for best compounds.

II. Selected ring-substitution and structural derivatives of the indolocarbazoles K252a

Disclosed herein are the selected ring-substitution and structural derivatives of the indolocarbazoles K252a, which are represented by the following formulas:



I



II

or a pharmaceutically acceptable salt thereof

wherein:

II is the fully oxidized derivative of I;

A^1 and A^2 are hydrogen, A^1 and A^2 together represent oxygen, or A^1 is hydroxyl and A^2 is hydrogen;

B^1 and B^2 are hydrogen, B^1 and B^2 together represent oxygen, or A^1 is hydroxyl and A^2 is hydrogen;

R^1, R^2, R^3 (when X^1 is C), R^6, R^7 (when X^3 is C), and R^8 is selected from, or a combination of, the groups consisting of:

a) hydrogen, lower alkyl, halogen, nitro, NRR (wherein R and R is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl; carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl);

b) -OR, wherein R is selected from the group consisting of;

1) hydrogen, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

c) $-O(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of:

1) hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl;

2) OR;

3) SR;

d) -SR, wherein R is selected from the group consisting of;

1) hydrogen, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

e) $-S(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of:

1) hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl;

2) OR;

3) SR;

f) -CH=CH-R, wherein the stereochemisrty is either E or Z, and R is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively);

g) $-(CH_2)_jR$, wherein j is 2 to 6, and R is hydrogen, halogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted

heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively);

h) $-CH_2OR$, wherein R is hydrogen, substituted lowed alkyl, unsubstituted lower alkyl;

R^4 is selected from the group consisting of:

a) H, substituted lower alkyl, unsubstituted lower alkyl; substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

b) $-(CH_2)_jCH_2OR$, where j is 0 to 4 and where R and R is selected from the group consisting of:

1) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylcarbonyl, substituted arylcarbonyl or unsubstituted arylcarbonyl, CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, a sugar moiety as described in f) below;

c) $-CH_2CH(OR)CH_2OR$, where R and R is selected from the group consisting of;

1) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle;

d) $CO(CH_2)_jR$, wherein j is 1 to 6, and R is selected from the group consisting of;

1) hydrogen or a halogen;

2) NRR, werein R and R independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, or R and R are joined in a ring with the nitrogen atom to form a heterocyclic group;

3) substituted aryl, unsubstituted aryl, substituted heterocycle, unsubstituted heterocycle;

4) COR, wherein R is selected from the group consisting of;

i) OH;

ii) R is the same as R;

iii) NRR, wherein R and R are the same as R and R, respectively;

e) SO_2R, wherein R is selected from the group consisting of;

1) $-(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of;

a) H, halogen;

b) OR, wherein R is selected from the group consisting of;

i) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylcarbonyl, substituted arylcarbonyl or unsubstituted arylcarbonyl, CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, a sugar moiety as described in f) above;

b) NRR, werein R and R independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-substituted heterocycle, or R and R are joined in a ring with the nitrogen atom to form a heterocyclic group.

2) unsubstituted aryl, substituted aryl, unsubstituted heteroaryl, substituted heteroaryl;

f) a sugar moiety being of either the α- or β-antipoid, including, but not limited to the substitited or unsubstituted sugars glucose, fructose, galactose, maltose, ribose, and glucosamine;

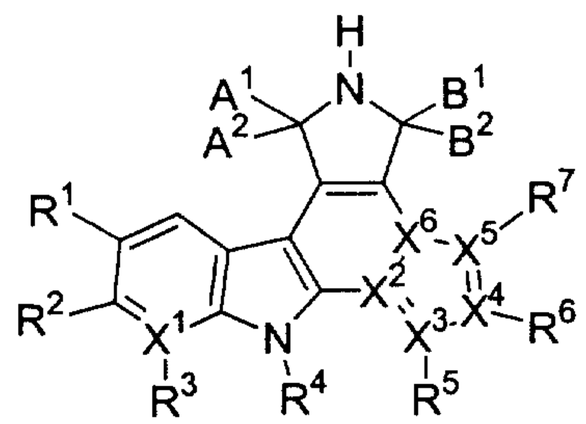
when X^2 is C, R^5 is selected from the group consisting of:

X^1, X^2, and X^3 are either C or N, such that R^3 is a lone pair when X^1 is N, R^5 is a lone pair when X^2 is N, and R^7 is a lone pair when X^3 is N;

X^4 is either CH or N.

Notably, within the structures of compounds I and II, any of the outer four positions of either indole benzene ring may be C or N. Thus, the indole benzene rings may have one or more N present at any of the outer four positions, not just at positions noted as X^1, X^3 and X^4, as shown in the above formulae. Such structures are within the scope of the invention.

Disclosed herein are the selected ring-substitution and structural derivatives of K252a, which are represented by the following formula:



III

or a pharmaceutically acceptable salt thereof

wherein:

A^1 and A^2 are hydrogen, A^1 and A^2 together represent oxygen, or A^1 is hydroxyl and A^2 is hydrogen;

B^1 and B^2 are hydrogen, B^1 and B^2 together represent oxygen, or A^1 is hydroxyl and A^2 is hydrogen;

R^1, R^2, R^3 (when X^1 is C), R^5 (when X^3 is C), R^6 (when X^4 is C), and R^7 (when X^5 is C), is selected from, or a combination of, the groups consisting of:

a) hydrogen, lower alkyl, halogen, nitro, NRR (wherein R and R is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl);

b) -OR, wherein R is selected from the group consisting of;

1) hydrogen, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

c) $-O(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of:

1) hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl;

2) OR;

3) SR;

d) -SR, wherein R is selected from the group consisting of;

1) hydrogen, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

e) $-S(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of:

1) hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl;

2) OR;

3) SR;

f) -CH=CH-R, wherein the stereochemisrty is either E or Z, and R is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively);

g) $-(CH_2)_jR$, wherein j is 2 to 6, and R is hydrogen, halogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively);

h) $-CH_2OR$, wherein R is hydrogen, substituted lowed alkyl, unsubstituted lower alkyl;

R^4 is selected from the group consisting of:

a) H, substituted lower alkyl, unsubstituted lower alkyl;

b) -$(CH_2)_jCH_2OR$, where j is 0 to 4 and where R and R is selected from the group consisting of:

1) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylcarbonyl, substituted arylcarbonyl or unsubstituted arylcarbonyl, CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, a sugar moiety as described in f) below;

c) -$CH_2CH(OR)CH_2OR$, where R and R is selected from the group consisting of;

1) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle;

d) $CO(CH_2)_jR$, wherein j is 1 to 6, and R is selected from the group consisting of;

1) hydrogen or a halogen;

2) NRR, werein R and R independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, or R and R are joined in a ring with the nitrogen atom to form a heterocyclic group;

3) substituted aryl, unsubstituted aryl, substituted heterocycle, unsubstituted heterocycle;

4) COR, wherein R is selected from the group consisting of;

i) OH;

ii) R is the same as R;

iii) NRR, wherein R and R are the same as R and R, respectively;

e) SO_2R, wherein R is selected from the group consisting of;

1) -$(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of;

a) H, halogen;

b) OR, wherein R is selected from the group consisting of;

i) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylcarbonyl, substituted arylcarbonyl or unsubstituted arylcarbonyl, CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, a sugar moiety as described in f) above;

b) NRR, werein R and R independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-substituted heterocycle, or R and R are joined in a ring with the nitrogen atom to form a heterocyclic group.

2) unsubstituted aryl, substituted aryl, unsubstituted heteroaryl, substituted heteroaryl;

f) a sugar moiety being of either the α- or β-antipoid, including, but not limited to the substitited or unsubstituted sugars glucose, fructose, galactose, maltose, ribose, and glucosamine;

when X^2 is C, R^5 is selected from the group consisting of:

X^1, X^2, and X^3 are either C or N, such that R^3 is a lone pair when X^1 is N, R^5 is a lone pair when X^2 is N, and R^7 is a lone pair when X^3 is N;

X^4 is selected from the group consisting of;

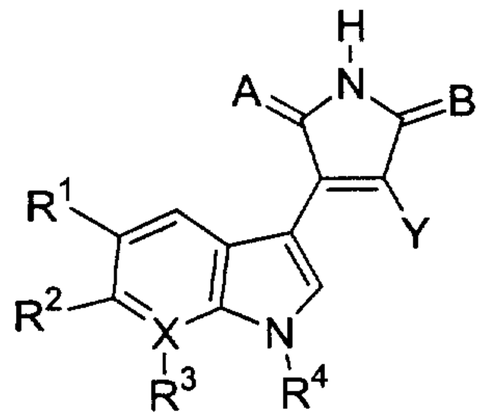
a) C;

b) N;

c) NR, wherein R is hydrogen, halogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively).

Notably, within the structure of compound III, any of the outer four positions of the indole benzene ring may be C or N. Thus, the indole benzene may have one or more N present at any of the outer four positions, not just at positions noted as X^1, as shown in the above formulae. Such structures are within the scope of the invention.

Disclosed herein are the selected ring-substitution and structural derivatives of 3-(indol-3-yl)-1*H*-pyrrole-2,5-diones, which are represented by the following formula:



IV

or a pharmaceutically acceptable salt thereof

wherein:

A^1 and A^2 are hydrogen, A^1 and A^2 together represent oxygen, or A^1 is hydroxyl and A^2 is hydrogen;

B^1 and B^2 are hydrogen, B^1 and B^2 together represent oxygen, or A^1 is hydroxyl and A^2 is hydrogen;

R^1, R^2, R^3 (when X is C), is selected from, or a combination of, the groups consisting of:

a) hydrogen, lower alkyl, halogen, nitro, NRR (wherein R and R is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl);

b) -OR, wherein R is selected from the group consisting of;

1) hydrogen, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

c) $-O(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of:

1) hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl;

2) OR;

3) SR;

d) -SR, wherein R is selected from the group consisting of;

1) hydrogen, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

e) $-S(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of:

1) hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl;

2) OR;

3) SR;

f) -CH=CH-R, wherein the stereochemisrty is either E or Z, and R is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively);

g) $-(CH_2)_jR$, wherein j is 2 to 6, and R is hydrogen, halogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively);

h) $-CH_2OR$, wherein R is hydrogen, substituted lowed alkyl, unsubstituted lower alkyl;

R^4 is selected from the group consisting of:

a) H, substituted lower alkyl, unsubstituted lower alkyl;

b) -$(CH_2)_jCH_2OR$, where j is 0 to 4 and where R and R is selected from the group consisting of:

1) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylcarbonyl, substituted arylcarbonyl or unsubstituted arylcarbonyl, CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, a sugar moiety as described in f) below;

c) -$CH_2CH(OR)CH_2OR$, where R and R is selected from the group consisting of;

1) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle;

d) $CO(CH_2)_jR$, wherein j is 1 to 6, and R is selected from the group consisting of;

1) hydrogen or a halogen;

2) NRR, werein R and R independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, or R and R are joined in a ring with the nitrogen atom to form a heterocyclic group;

3) substituted aryl, unsubstituted aryl, substituted heterocycle, unsubstituted heterocycle;

4) COR, wherein R is selected from the group consisting of;

i) OH;

ii) R is the same as R;

iii) NRR, wherein R and R are the same as R and R, respectively;

e) SO_2R, wherein R is selected from the group consisting of;

1) -$(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of;

a) H, halogen;

b) OR, wherein R is selected from the group consisting of;

i) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylcarbonyl, substituted arylcarbonyl or unsubstituted arylcarbonyl, CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, a sugar moiety as described in f) above;

b) NRR, werein R and R independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-substituted heterocycle, or R and R are joined in a ring with the nitrogen atom to form a heterocyclic group.

2) unsubstituted aryl, substituted aryl; unsubstituted heteroaryl, substituted heteroaryl;

f) a sugar moiety being of either the α- or β-antipoid, including, but not limited to the substitited or unsubstituted sugars glucose, fructose, galactose, maltose, ribose, and glucosamine;

X is C or N, such that R^3 is a lone pair when X^1 is N;

Y is hydrogen or halogen.

Notably, within the structure of compound IV, any of the outer four positions of the indole benzene ring may be C or N. Thus, the indole benzene may have one or more N present at any of the outer four positions, not just at positions noted as X, as shown in the above formulae. Such structures are within the scope of the invention.

The compounds represented by folmula (I) are hereinafter referred to as Compound (I), and the same applies to the compounds of other formula numbers.

In the definitions of the groups of formula I, II, III, and IV, lower alkyl means a straight-chain or branched alkyl group having 1 to 8 carbon atoms, such as methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-amyl, neopentyl, 1-ethylpropyl, hexyl, and octyl. The lower alkyl moiety of lower alkoxy, lower alkylsulfonyl, lower alkoxylcarbonyl, lower alkylaminocarbonyl has the same meaning as lower alkyl defined above. The acyl maoiety of the acyl and the acyloxy group means a straight-chain or branched alkanoyl group having 1 to 6 carbon atoms, such as formyl, acetyl, propanoyl, butyryl, valeryl, pivaloyl and hexanoyl, and arylcarbonyl group described below, or a heteroarylcarbonyl group described below. The aryl moiety of the aryl, the arylcarbonyl and arylaminocarbonyl groups means a group having 6 to 12 carbon atoms such as phenyl, biphenyl, or naphthyl. The heteroaryl moiety of the heteroarylcarbonyl groups contain at least one hetero atom from O, N, and S, and include pyridyl, pyrimidyl, pyrroleyl, furyl, thienyl, imidazolyl, triazolyl, quinolyl, iso-quinolyl, benzoimidazolyl, thiazolyl, and benzothiazolyl. The aralkyl moiety of the aralkyl and the aralkyloxy groups having 7 to 15 carbon atoms, such as benzyl, phenethyl, benzhydryl, and naphthylmethyl. The substituted lower alkyl group has 1 to 3 independently-substitutuents, such as hydroxyl, lower alkyloxy, carboxyl, lower alkylcarbonyl, nitro, amino, mono- or di-lower alkylamino, dioxolane, dioxane, dithiolane, and dithione. The lower alkyl moiety of the substituted lower alkyl, and the lower alkyl moeity of the lower alkoxy, the lower alkoxycarbonyl, and the mono- and di-lower alkylamino in the substituents of the substituted lower alkyl group have the same meaning as lower alkyl defined above. The substituted aryl, the substituted heteroaryl and the substituted aralkyl groups each has 1 to 3 independently-selected substitutents, such as lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, nitro, amino, mono or di-lower alkylamino, and haloden. The lower alkyl moiety of the lower alkyl, the lower alkoxy, the lower alkylamino, and the mono- and di-lower alkylamino groups amoung the susbtituents has the same meaning as lower alkyl defined above. The heterocyclic group formed with a nitrogen atom includes pyrroleyl, piperidinyl, piperidino, morpholinyl, morpholino, thiomorpholino, N-methylpiperazinyl, indolyl, and isoindolyl. The cycloalkyl moeity means a cycloalkyl group of the indicated number of carbon atoms, containing one or more rings anywhere in the structure, such as cycloalkyl groups include cyclopropyl,

cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-norbornyl, 1-adamantyl and the like. The lower fluoroalkyl moiety means a lower fluoroalkyl group in which aone or more hydrogens of the corresponding lower alkyl group, as defined above, is replaced by a fluorine atom, such as CH_2F, CHF_2, CF_3, CH_2CF_3. The α-amino acid groups include glycine, alanine, proline, glyutamic acid, and lysine, which may be in the L-form, or the D-form, or in the form of racemates. The polypeptide groups include any linear combination of the above α-amino acids. Halogen includes fluorine, chlorine, bromine, and iodine.

Some of the compounds described herein contain one or more chiral centres and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic, resolved and enantiomerically pure forms, and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z isomers.

The following section summarizes the biological profiles of the compounds defined as formula I through IV, in cultured CGN and SHSY-5Y cell lines, treated with various pro-apoptotic triggers.

The compounds defined by formula I through IV have been shown to protect CGNs to several pro-apoptotic triggers, including high/low potassium (HK/LK), β-amyloid (Aβ) fibril formation, ceramide, glutamate, and cisplatin. Additionally, these compounds have been shown to down regulate the dramatic increase in caspase induction observed during HK/LK treatments, suggesting they prevent cell death by interfering in the apoptotic cascade at a point upstream of the caspases, ie. inhibition of one or several of the serine/threonine protein kinases directly upstream of the caspases, typified by MEKK1, MKL, c-jun, JNK, and P_{53}. The compounds defined by formula I through IV display low levels of *in vitro* (CGNs and SHSY-5Y cell lines) and *in vivo* toxicity. The compounds defined by formula I through IV provided little or no protection against etoposide induced apoptosis in CGNs and SHSY-5Y cell lines.

Cultured CGNs which are maintained in medium containing 26 mM potassium (high K^+ or HK) undergo cell death when the medium is changed to one containing 5 mM potassium (low K^+ or LK). HK maintains the cells in a highly polarized state, duplicating that of fully innervated neurons. The switch to LK (5 mM is more representative of physiological conditions) results in depolarization of the cells, mimicking the loss of neuronal conductivity. Cell death under these conditions displays typical features of apoptotic cell death, both in morphology and in the upregulation of various killer genes including c-jun and the caspases 1 and 3 (Ikeuchi, T. *Hum. Cell*, **1998**, *11*, 125). As these killer genes are turned on by various types of neuronal insult as observed in AD, PD, and stroke, HK/LK is a general *in vitro* model for neuronal degradation, blanketing a wide range of neurodegenerative diseases. Compounds which protect against HK/LK in CGNs would therefore be expected to be efficacious in various neurodegenerative disease states.

The compounds disclosed in this invention have been found to inhibit HL/LK apoptotic cell death in CGNs under two different scenarios. The first involves a 24 hour pretreatment of the

cells with compound (prophylactic treatment), and the second involves addition of the compound at the time of the medium change (acute treatment). Similar protection was observed under both scenarios with selected compounds protecting upwards of 100% of the neurons at 10 μm drug concentrations. The toxicity of these compounds varied, however, in those compounds displaying significant levels of protection, toxicity was generally less than 5%, based on *in vitro* controls.

Various mechanisms have been put forward in order to account for the acute neurotoxicity related to extracellular Aβ fibril formation. Some of these include altered enzyme activity and disrupted calcium homeostasis leading to calpain and caspase activation (Chan, S. L, Mattson, M. P. *J. Neurosci. Res.*, **1999**, *58*, 167), increased free radical formation, and more recently, Aβ has been shown to interact with various receptor sites and to physically insert into the cell membrane (Kanfer, J. N. *et al. Neurochem Res.*, **1999**, *24*, 1621). Regardless of the mode of action, extracellular Aβ fibril formation acts as an effective apoptotic trigger for neuronal cells and serves as an *in vitro* model for various neurodegenerative diseases characterized by extracellular protein fibril formation, typified by diseases such as AD and PD.

We and others have observed that linear Aβ rapidly aggregates in CGN cultures, leading to the apoptotic cell death of approximately 50% of the neurons after 5 days. Addition of selected compounds of the formula I through IV save upwards of 100% of these cells at drug concentrations of 10 μM. These compounds may be added to the CGN culture 24 hours prior to linear Aβ addition or at the time of linear Aβ addition. Similar saves were observed under these two scenarios. The most active compounds displayed limited toxicity, less than 5%, in their respective *in vitro* controls.

Ceramide is a native protein found in most mammalian cells. The upregulation of endogenous ceramide has been linked to caspase 1 (ICE) induced apoptosis (Suzuki, A. *et al. Exp. Cel. Res.*, **1997**, *233*, 41). In a simmilar fashion, the addition of ceramide to cultured CGNs results in caspase induced apoptosis, and is therefore considered an effective *in vitro* model for the various neurodegenerative diseases described above, which are characterized by caspase induced apoptosis. Addition of selected compounds of the formula I through IV, 24 hours prior to the

addition of ceramide, to cultured CGNs provided modest protection against apoptosis, with 10 to 50% of the cells being saved at 10 μM drug concentrations.

Glutaminergic neurons secrete the neurotransmitter glutamate as a part of normal cell signalling processes. Intracelular glutamate levels are regulated by glial cell uptake and conversion to glutamine. Under conditions of oxidative stress, as observed in various neurodegenerative diseases such as stroke, ALS, PD, and HD, glutaminergic neurons release massive amounts of glutamate into the intracellular fluid, overwhelming the surrounding cells. Stimulation of both NMDA and non-NMDA-type glutamate excitory receptors leads to sustained depolarization of postsynaptic dendrosomal membranes, increased membrane permeability, and impaired ion homeostasis, all leading to either apoptotic or necrotic cell death.

Addition of selected compounds of the formula I through IV, either at the time of glutamate addition or 24 hours prior to the addition of ceramide, to cultured CGNs provided protection against neuronal cell death, with 10 to 20% of the cells being saved at 10 μM drug concentrations.

Cisplatin has been used exensively in the treatment of various cancers. One side effect of this chemotherapeutic agent is related to hearing loss as a result of its toxicity to auditory neurons. We have shown that cisplatin is also toxic to CGNs *in vitro*. Melatonin has been shown to protect auditory neurons during cisplatin treatments *in vivo*, and this combination therapy is currently in clinical trial. We have shown that at high doses melatonin will also protect CGNs, suggesting that protection of CGNs may serve as an *in vitro* model for cisplatin induced neurotoxicity to auditory neurons, as these two cell types may share a similar cisplatin induced mechanism of apoptosis.

Addition of selected compounds of the formula I through IV, 24 hours prior to the addition of cisplatin (25 mg/mL), to cultured CGNs protected against neuronal apoptosis, with upwards of 75% of the cells being saved at 10 μM drug concentrations.

Etoposide is a well known topoisomerase I inhibitor which induces cellular apoptosis by inhibition of the regular cell cycle and DNA fragmentation. Addition of selected compounds of the formula I through IV, 24 hours prior to the addition of etoposide, to cultured CGNs provided modest protection against apoptosis, with not more than 20% of the cells being saved at 10 μM drug concentrations. Similar results were observed for SHSY-5Y cell lines (a neuroblastoma cell line) pretreated for 24 hours with selected compounds of the formula I through IV. As various topoisomerase I inhibitors are currently in clinical trial as anti-cancer agents, it is clear that concurrent administration of selected compounds of the formula I through IV with specific topoisomerase I inhibitors would not interfer with topoisomerase I induced cell death. However, the selected compounds of the formula I through IV will provide protection to various non-differentiating neurons which may be adversely affected by the topoisomerase I inhibitor therapy.

The invention also involves intermediates for manufacturing the above compounds I to IV, as described herein. Mixtures including isomeric mixtures also may result depending upon the symmetry of the starting molecule. Such mixtures are within the scope of the invention.

To prepare the full range of compounds of the invention, only the chemistry described below, together with chemistry well known to those of ordinary skill in the art is required. In particular, modifications of the core structures can be accomplished using routine chemistry such as that used to make similar modifications to K252a, as detailed in WO94/02488,WO94/27982, WO94/04541.

The term "subject" or "patient" as used herein may refer to mammals including humans, primates, horses, cows, pigs, sheep, goats, dogs, cats and rodents.

The pharmaceutical compositions of the invention are administered to subjects in effective amounts. An effective amount means that amount necessary to delay the onset of, inhibit the progression of, halt altogether the onset or progression of or diagnose the particular condition or symptoms of the particular condition being treated. In general, an effective amount for treating a

neurological disorder is that amount necessary to affect any symptom or indicator of the condition In general, an effective amount for treating cancer will be that amount necessary to favorably affect mammalian cancer cell proliferation *in situ*. When administered to a subject, effective amounts will depend, of course, on the particular condition being treated; the severity of the condition; individual patient parameters including age, physical condition, size and weight; concurrent treatment; frequency of treatment; and the mode of administration. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to sound medical judgment.

A variety of administration routes are available. The particular mode selected will depend, of course, upon the particular condition being treated, the particular drug selected, the severity of the condition being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal, intradermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Oral routes are preferred.

Dosage may be adjusted appropriately to achieve desired drug levels, locally or systemically. Generally, daily oral doses of active compounds will be from about 0.01 mg/kg per day to 1000 mg/kg per day. It is expected that IV doses in the range of about 1 to 1000 mg/m2 per day will be effective. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the conjugates of the invention into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately

bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active compound. Other compositions include suspensions in aqueous liquors or non-aqueous liquids such as a syrup, an elixir, or an emulsion.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the active compounds of the invention, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer based systems such as polylactic and polyglycolic acid, polyanhydrides and polycaprolactone; nonpolymer systems that are lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono-, di and triglycerides; hydrogel release systems; silastic systems; peptide based systems; wax coatings, compressed tablets using conventional binders and excipients, partially fused implants and the like. In addition, a pump-based hardware delivery system can be used, some of which are adapted for implantation.

A long-term sustained release implant also may be used. "Long-term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 30 days, and preferably 60 days. Long-term sustained release implants are well known to those of ordinary skill in the art and include some of the release systems described above. Such implants can be particularly useful in treating solid tumors by placing the implant near or directly within the tumor, thereby affecting localized, high-doses of the compounds of the invention.

When administered, the formulations of the invention are applied in pharmaceutically acceptable compositions. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic ingredients. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may

conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, *p*-toluenesulfonic, tartaric, citric, methane sulfonic, formic, malonic, succinic, naphthalene-2-sulfonic, and benzene sulfonic. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Suitable buffering agents include: acetic acid and a salt (1-2% W/V); citric acid and a salt (1-3% W/V); and phosphoric acid and a salt (0.8-2% W/V), as well as others known in the art.

Suitable preservatives include benzalkonium chloride (0.003-0.03% W/V); chlorobutanol (0.3-0.9% W/V); parabens (0.01-0.25% W/V) and thimerosal (0.004-0.02% W/V), as well as others known in the art.

Suitable carriers are pharmaceutically-acceptable carriers. The term pharmaceutically-acceptable carrier means one or more compatible solid or liquid filler, dilutants or encapsulating substances which are suitable for administration to a human or other animal. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions are capable of being commingled with the molecules of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy. Carrier formulations suitable for oral, subcutaneous, intravenous, and intramuscular administration etc., are those which are known in the art.

The compounds of the invention may be delivered with other therapeutic agents. The invention additionally includes co-administration of any of the compounds I to IV of the invention with other compounds known to be useful in treating neurodegenerative diseases, typified by but not limited to L-dopa for treating Parkinson's disease.

Compounds I through IV have been shown to protect CGNs to cisplatin induced apoptosis. It is expected that this protection will extend to the protection of peripheral neurons to various neurotoxins and chemotherapeutic agent which induce peripheral neurotoxicity.

In the case of peripheral neuropathy induced by a toxic agent, the compounds I through IV would be delivered separately before, simultaneously with (ie. in the form of anti-cancer coctails, see below), or after exposure to the toxic agent. Preferably, compounds I through IV and the chemotherapeutic agent are each administered at effective time intervals, during an overlapping period of treatment in order to prevent or restore at least a portion of the neurofunction destroyed by the neurotoxic or chemotherapeutic agent. The chemotherapeutic can be any chemotherapetic agent that causes neurotoxicity, such as vincristine, taxol, dideoxyinosine, or *cisplatin*.

By "toxic agent" or "neurotixic agent" is meant a substance that through its chemical action injures, impairs, or inhibits the activity of a component of the nervous system. The list of neurotoxic agents that cause neuropathies is lengthy (see a list of candidate agents provided in Table 1). Such neurotoxic agents include, but are not limited to, neoplastic agents such as vincristine, vinblastine, cisplatin, taxol, or dideoxy-compounds, eg., dideoxyinosine; alcohol; metals; industrial toxins involved in occupational or environmental exposure; contaminants in food or medicinals; or over-doses of vitamines or therapeutic drugs, eg. Antibiotics such as penicillin or chloramphenicol, or mega-doses of vitamins A, D, or B6.

Table 1: Neurotoxic Agents

AGENT	ACTIVITY	AGENT	ACTIVITY
actazolimide	diuretic	imipramine	antidepressant
acrylamide	flocculant, grouting agent	indolmethacin	anti-inflammatory
adriamycin	antineoplastic	inorganic lead	toxic metal in paint, etc.
alcohol (ie. ethanol)	solvent, recreational drug	iso-niazid	antituberculousis
almitine	respiratory stimulant	lithium	antidepressant
amiodarone	antiarrthymic	methylmercury	industrial waste
amphotericin	antimicrobial	metformin	antidiabetic
arsenic	herbicide, insecticide	methylhydrazine	synthetic intermediate
aurothioglucose	antirheumatic	metronidazole	antiprotozoal

barbiturates	anticonvulsive, sedative	misonidazole	radiosensitizer
buckthorn	toxic berry	nitrofurantoin	urinary antiseptic
carbimates	insecticide	nitrogen mustard	antineoplastic, nerve gas
carbon disulfide	industrial applications	nitous oxide	anesthetic
chloramphenicol	antibacterial	organophosphates	insecticides
chloroquine	antimalarial	ospolot	anticonvulsant
chlorestyramine	antihyperlipoproteinemic	penicillin	antibacterial
cisplatin	antineoplastic	perhexiline	antiarrhythmic
clioquinol	amebicide, antibacterial	perhexiline maleate	antiarrythmic
colestipol	antihyperlipoproteinemic	phenytoin	anticonvulsant
colchicine	gout suppressant	platnim	drug component
colistin	antimicrobial	primidone	anticonvulsant
cycloserine	antibacterial	procarbazine	antineoplastic
cytarabine	antineoplastic	pyridoxine	vitamin B6
dapsone	dermatological including leprosy	sodium cyanate	antisickling
dideoxycytidine	anatineoplastic	streptomycin	antimicrobial
dideoxyinosine	antineoplastic	sulphonamides	antimicrobial
dideoxythymidine	antiviral	suramin	anteneoplastic
disulfiram	antialcohol	tamoxifen	antineoplastic
doxorubicin	antineoplastic	taxol	antineoplastic
ethambutol	antibacterial	thalidomide	antileprous
ethionamide	antibacterial	thallium	rat poison
glutethimide	sedative, hypnotic	triamterene	diuretic
gold	antirheumatic	trimethyltin	toxic metal
hexacarbons	solvents	L-trypophan	health food additive
hormonal contraceptives		vincristine	antineoplastic
hexamethylolmelamine	fireprooing, crease proofing	vinblastine	antineoplastic
hydralazine	antihypertensive	vindesine	antineoplastic
hydroxychloroquine	antirheumatic	vitamine A or D	mega doses

In the case of cancer, the compounds would be delivered separately or in the form of anti-cancer cocktails. An anti-cancer cocktail is a mixture of any one of the compounds of this invention with another anti-cancer agent such as an anti-cancer drug, a cytokine, and/or supplementary potentiating agent(s). The use of cocktails in the treatment of cancer is routine. In this

embodiment, a common administration vehicle (e.g., pill, tablet, implant, injectable solution, etc.) could contain both the compounds useful in this invention (described above) and the anti-cancer drug and/or supplementary potentiating agent.

Thus, cocktails of non-Formula I through IV compounds and Formula I trough IV compounds are contemplated. Non-Formula I anti-neoplastic compounds include:
Antineoplastic: Acivicin; Aclarubicin; Acodazole Hydrochloride; Acronine; Adozelesin; Aldesleukin; Altretamine; Ambomycin; Ametantrone Acetate; Aminoglutethimide; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperlin ; Azacitidine; Azetepa; Azotomycin; Batimastat; Benzodepa; Bicalutamide; Bisantrene Hydrochloride; Bisnafide Dimesylate; Bizelesin; Bleomycin Sulfate; Brequinar Sodium; Bropirimine; Busulfan; Cactinomycin; Calusterone; Caracemide; Carbetimer; Carboplatin; Carmustine; Carubicin Hydrochloride; Carzelesin; Cedefingol; Chlorambucil; Cirolemycin ; Cisplatin; Cladribine; Crisnatol Mesylate; Cyclophosphamide ; Cytarabine ; Dacarbazine; Dactinomycin; Daunorubicin Hydrochloride; Decitabine; Dexormaplatin; Dezaguanine; Dezaguanine Mesylate; Diaziquone; Docetaxel; Doxorubicin; Doxorubicin Hydrochloride; Droloxifene; Droloxifene Citrate; Dromostanolone Propionate; Duazomycin; Edatrexate; Eflornithine Hydrochloride ; Elsamitrucin; Enloplatin; Enpromate; Epipropidine; Epirubicin Hydrochloride; Erbulozole; Esorubicin Hydrochloride; Estramustine; Estramustine Phosphate Sodium; Etanidazole; Ethiodized Oil I 131; Etoposide; Etoposide Phosphate; Etoprine; Fadrozole Hydrochloride; Fazarabine; Fenretinide; Floxuridine; Fludarabine Phosphate; Fluorouracil; Flurocitabine; Fosquidone; Fostriecin Sodium; Gemcitabine; Gemcitabine Hydrochloride; Gold Au 198; Hydroxyurea; Idarubicin Hydrochloride; Ifosfamide; Imofosine; Interferon Alfa-2a; Interferon Alfa-2b ; Interferon Alfa-n1; Interferon Alfa-n3; Interferon Beta- I a; Interferon Gamma- Ib; Iproplatin; Irinotecan Hydrochloride ; Lanreotide Acetate; Letrozole; Leuprolide Acetate ; Liarozole Hydrochloride; Lometrexol Sodium; Lomustine; Losoxantrone Hydrochloride; Masoprocol; Maytansine; Mechlorethamine Hydrochloride; Megestrol Acetate; Melengestrol Acetate; Melphalan; Menogaril; Mercaptopurine; Methotrexate; Methotrexate Sodium; Metoprine; Meturedepa; Mitindomide; Mitocarcin; Mitocromin; Mitogillin; Mitomalcin; Mitomycin; Mitosper; Mitotane; Mitoxantrone Hydrochloride; Mycophenolic Acid; Nocodazole; Nogalamycin; Ormaplatin; Oxisuran; Paclitaxel; Pegaspargase; Peliomycin; Pentamustine; Peplomycin Sulfate;

Perfosfamide; Pipobroman; Piposulfan; Piroxantrone Hydrochloride; Plicamycin; Plomestane; Porfimer Sodium; Porfiromycin; Prednimustine; Procarbazine Hydrochloride; Puromycin; Puromycin Hydrochloride; Pyrazofurin; Riboprine; Rogletimide; Safingol; Safingol Hydrochloride; Semustine; Simtrazene; Sparfosate Sodium; Sparsomycinl, Spirogermanium Hydrochloride; Spiromustine; Spiroplatin; Streptonigrin; Streptozocin; Strontium Chloride Sr 89; Sulofenur; Talisomycin; Taxane; Taxoid; Tecogalan Sodium; Tegafur; Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone; Testolactone; Thiamiprine; Thioguanine; Thiotepa; Tiazofurin; Tirapazamine; Topotecan Hydrochloride; Toremifene Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredepa; Vapreotide; Verteporfin; Vinblastine Sulfate; Vincristine Sulfate; Vindesine; Vindesine Sulfate; Vinepidine Sulfate; Vinglycinate Sulfate; Vinleurosine Sulfate; Vinorelbine Tartrate; Vinrosidine Sulfate; Vinzolidine Sulfate; Vorozole; Zeniplatin; Zinostatin; Zorubicin Hydrochloride.

Other anti-neoplastic compounds include: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue;

conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; irinotecan; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic

acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; 06-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormiaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B 1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thalidomide; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene dichloride; topotecan; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector

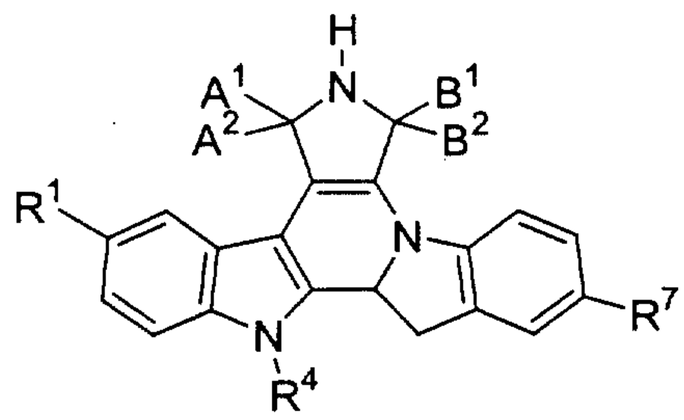
system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer.

Anti-cancer Supplementary Potentiating Agents: Tricyclic anti-depressant drugs (e.g., imipramine, desipramine, amitryptyline, clomipramine, trimipramine, doxepin, nortriptyline, protriptyline, amoxapine and maprotiline); non-tricyclic anti-depressant drugs (e.g., sertraline, trazodone and citalopram); Ca++ antagonists (e.g., verapamil, nifedipine, nitrendipine and caroverine); Calmodulin inhibitors (e.g., prenylamine, trifluoroperazine and clomipramine); Amphotericin B; Triparanol analogues (e.g., tamoxifen); antiarrhythmic drugs (e.g., quinidine); antihypertensive drugs (e.g., reserpine); Thiol depleters (e.g., buthionine and sulfoximine) and Multiple Drug Resistance reducing agents such as Cremaphor EL.

The compounds of the invention also can be administered with cytokines such as granulocyte colony stimulating factor.

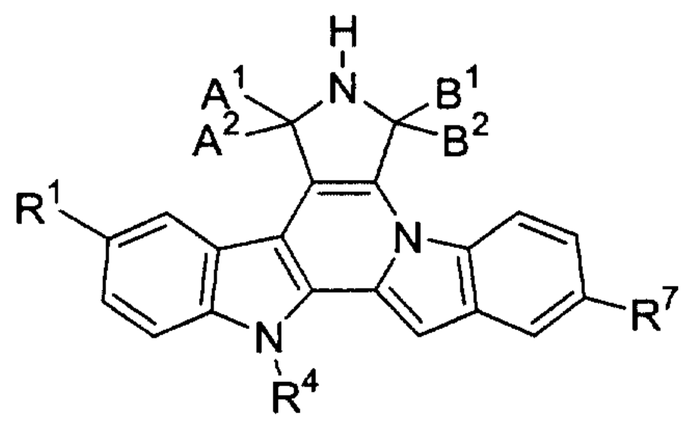
The conjugates of the invention also are useful, in general, for treating mammalian cell proliferative disorders other than cancer, including psoriasis, actinic keratosis, etc.

Examples of formula I are:



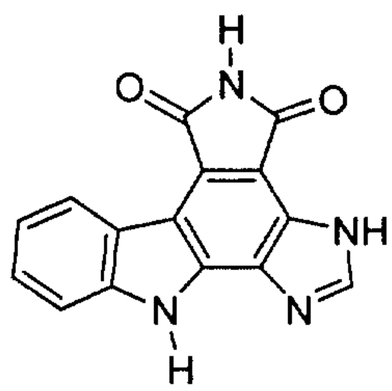
Compound	A^1/A^2	B^1/B^2	R^1	R^4	R^7
1	O	O	H	H	H
2	O	O	H	H	MeO

Examples of formula II are:

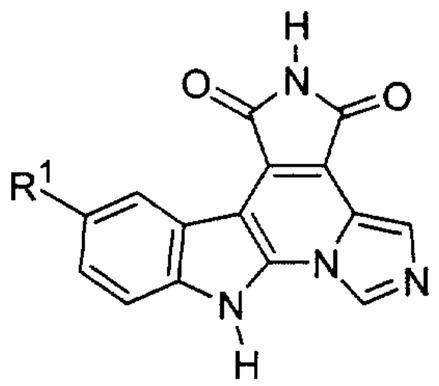


Compound	A^1/A^2	B^1/B^2	R^1	R^4	R^7
3	O	O	H	H	H
4	O	O/OH	H	H	H
5	O/OH	O	H	H	H
6	O	H/H	H	H	H
7	H/H	O	H	H	H
8	O	O	MeO	H	H
9	O	O	H	H	MeO

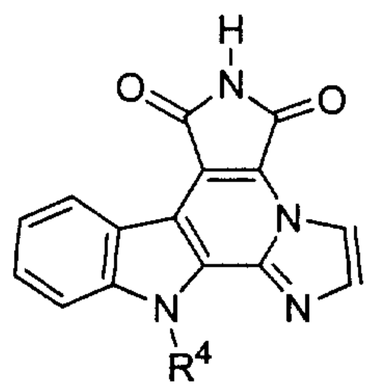
Examples of formula III:



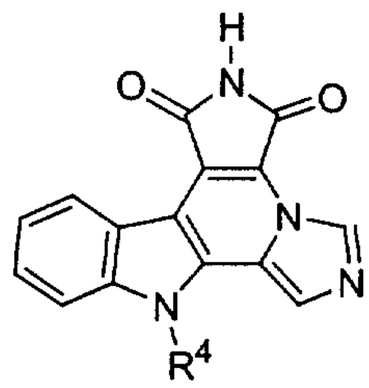
Compound 10; granulatimide



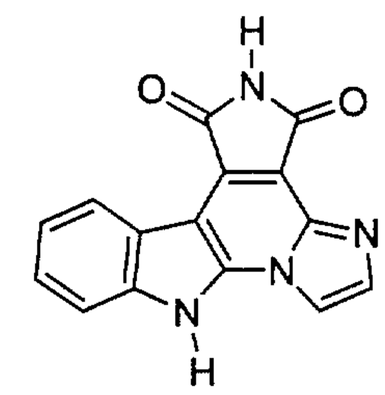
Compound 11; R^1=H; *iso*-granulatimide
Compound 12; R^1=OMe



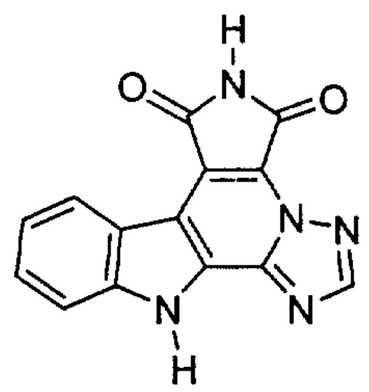
Compound 13; R^4=$CO_2{}^tBu$
Compound 14; R^4=H; *iso*-granulatimide A



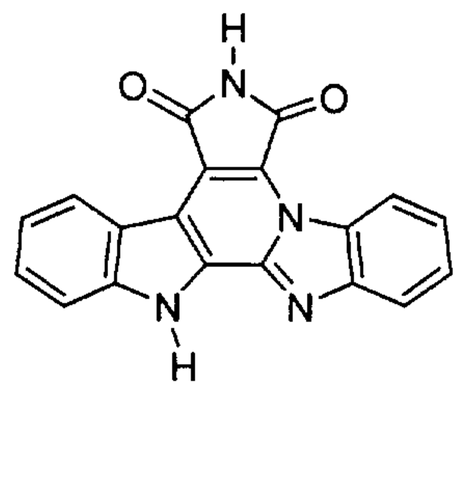
Compound 15; R^4=$CO_2{}^tBu$
Compound 16; R^4=H; *iso*-granulatimide B



Compound 17; *iso*-granulatimide C



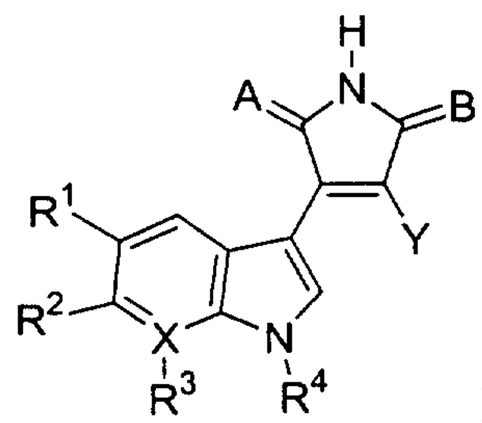
Compound 18



Compound 19

For any of the compounds having the structure of Formula III which bear similarity to those known in the art, the use of these compounds for treatment and/or prevention of neuological disorders, cancer, inflammation, or symptoms related thereto are encompassed by the invention.

Examples of formula IV are:



IV

Compound	A	B	R^1	R^2	R^3	R^4	X	Y
26	O	O	Br	H	H	H	C	H
27	O	O	Br	H	H	$-COCH_3$	C	H
28	O	O	Br	H	H	$-CONMe_2$	C	H
29	O	O	Br	H	H	Ts	C	H
30	O	O	Br	H	H	$-SO_2(1-C_{10}H_7)$	C	H
31	O	O	Br	H	H	$-SO_2(2-C_{10}H_7)$	C	H
32	O	O	Br	H	H	dansyl	C	H
33	O	O	BnO	H	H	H	C	H
34	O	O	BnO	H	H	$-COCH_3$	C	H
35	O	O	BnO	H	H	-COPh	C	H
36	O	O	BnO	H	H	$-CO(2,4-(MeO)_2Ph)$	C	H
37	O	O	BnO	H	H	Ts	C	H
38	O	O	BnO	H	H	$-SO_2(4-(NO_2)Ph)$	C	H
39	O	O	BnO	H	H	$-CH_2Ph$	C	H
40	O	O	BnO	H	H	$-CH_2(3,5-(MeO)_2Ph)$	C	H
41	O	O	BnO	H	H	$2-F(Ph)CH_2-$	C	H
42	O	O	BnO	H	H	$3-F(Ph)CH_2-$	C	H
43	O	O	BnO	H	H	$4-F(Ph)CH_2-$	C	H
44	O	O	BnO	H	H	$-CH_2Phth$	C	H
45	O	O	BnO	H	H	$-CH_2(2-C_{10}H_7)$	C	H
46	O	O	BnO	H	H	$-CH_2(C_6H_{11})$	C	H
47	O	O	BnO	H	H	$-CH_2(CH_2)_6CH_3$	C	H
48	O	O	BnO	H	H	$-CH_2CH_2OH$	C	H
49	O	O	BnO	H	H	$-CH_2CH_2OAc$	C	H
50	O	O	BnO	H	H	$-CH_2CH(OH)CH_2OH$	C	H
51	O	O	MeO	H	H	H	C	H
52	O	O	MeO	H	H	Ts	C	H
53	O	O	MeO	H	H	$-SO_2(4-(NO_2)Ph)$	C	H

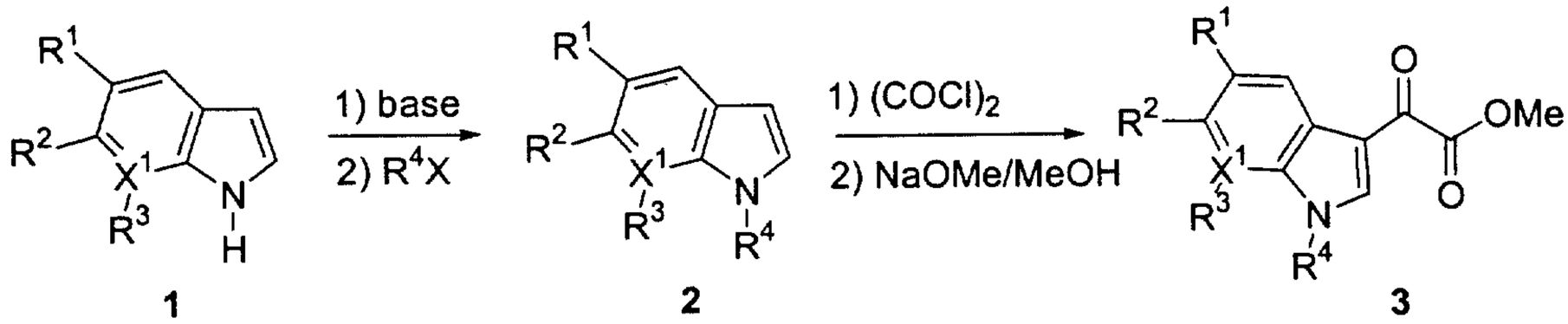
54	O	O	MeO	H	H	allyl	C	H
55	O	O	HO	H	H	allyl	C	H
56	O	O	HO	H	H	Ts	C	H
57	O	O	H	H	H	H	C	H
58	O	O	H	H	H	Ts	C	H
59	O	O	H	H	H	$-SO_2$(4-(AcNH)Ph)	C	H
60	O	O	H	H	H	$-SO_2$(2-(NO_2)Ph)	C	H
61	O	O	H	H	H	$-SO_2$(4-(NO_2)Ph)	C	H
62	O	O	H	H	H	$-SO_2$Th	C	H
63	O	O	H	H	H	$-SO_2$Bu	C	H
64	O	O	Cl	H	H	H	C	H
65	O	O	H	Cl	H	H	C	H
66	O	O	H	H	Cl	H	C	H
67	O	O	F	H	H	H	C	H
68	O	O	H	F	H	H	C	H
69	S	O	BnO	H	H	H	C	H

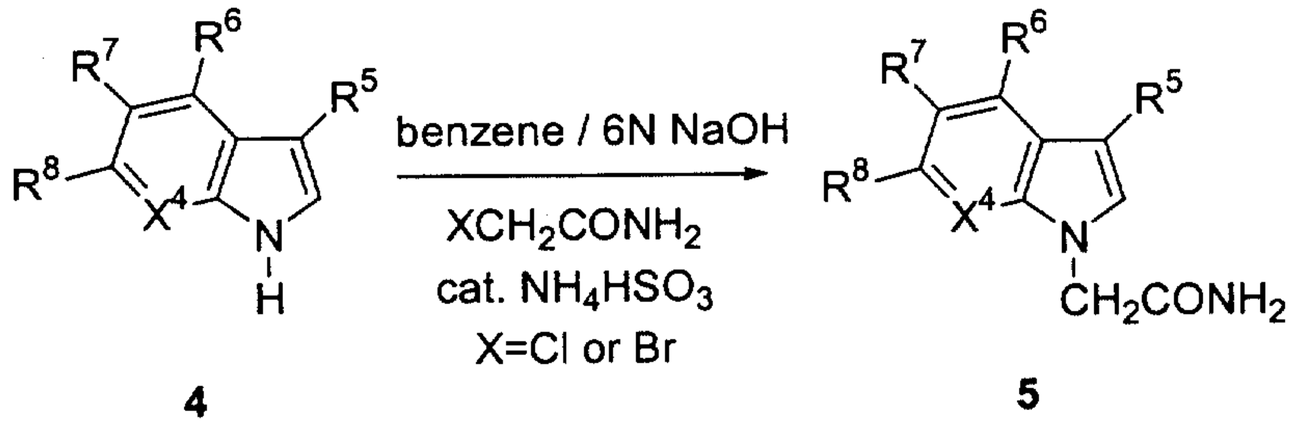
General Preparative Methods

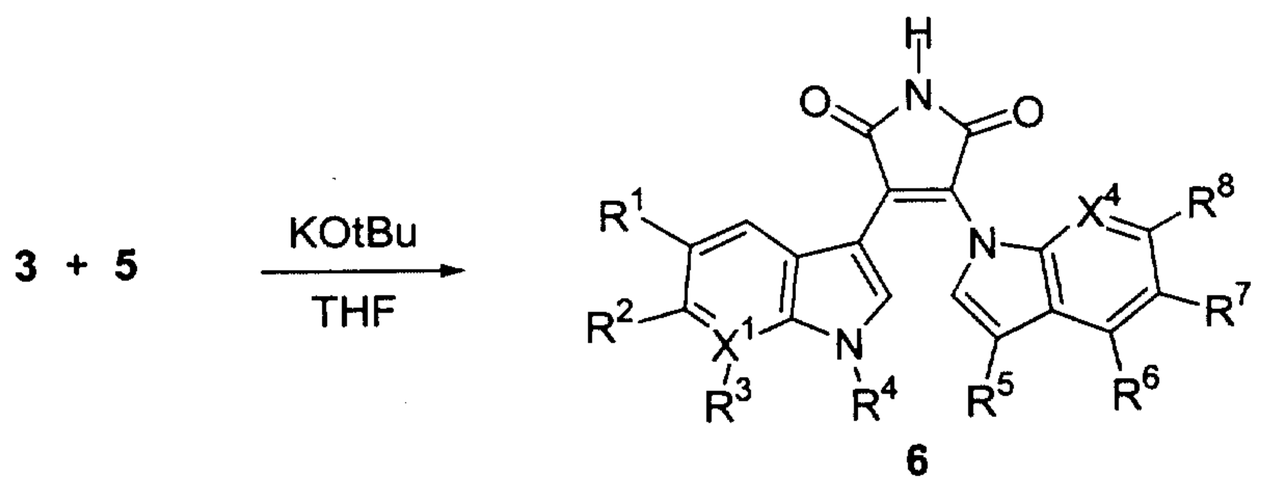
The compounds of the invention may be prepared by use of known chemical reactions and procedures. Nevertheless, the following general preparative methods are presented to aid the reader in synthesizing compounds I through IV.

Method A: Synthesis of 3-(indol-3-yl)-4-(1*N*-indolyl)-1*H*-pyrrole-2,5-diones

An appropriately substituted indole, **1**, is treated with a base such as NaH or KO^tBu in a solvent such as THF, followed by the appropriate alkylating group to provide the fully functionalized indole **2**. Subsequent treatment of **2** with oxalyl chloride in a solvent such as methylene chloride provides the 3-indolylglyoxalyl chloride hydrochloride salt, which is further treated with NaOMe in MeOH, to yield the methyl 3-indolylglyoxylate **3**. A second appropriately substituted indole, **4**, is alkylated to provide acetamide **5**, by stirring **4** with bromo- or chloroacetamide, under phase transfer conditions (benzene, 6N NaOH, catalytic NH_4HSO_3). Both **3** and **5** are dissolved in THF and treated with 3 to 4 equivalents of KO^tBu, to provide compound **6**.

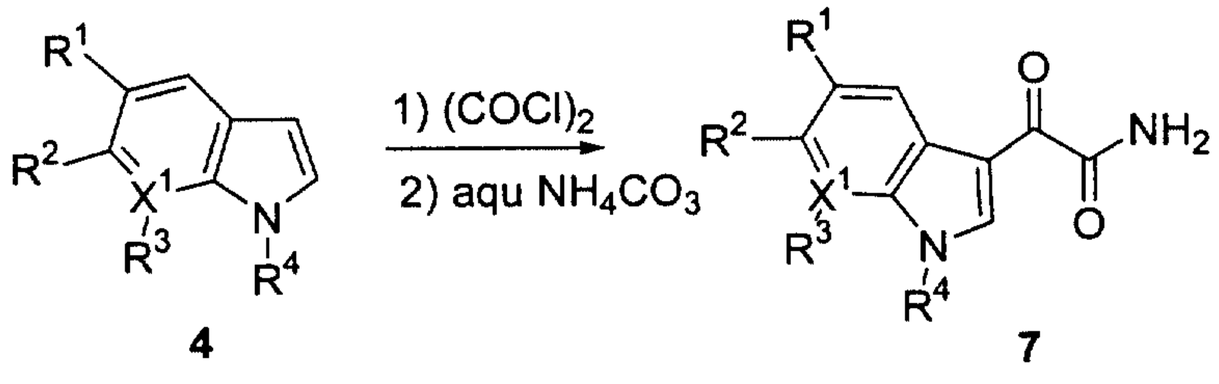




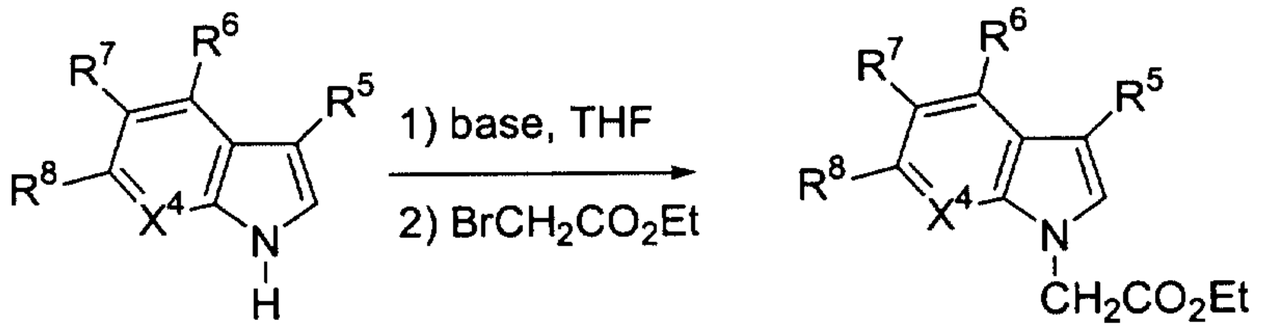


Method B: Synthesis of 3-(indol-3-yl)-4-(1*N*-indolyl)-1*H*-pyrrole-2,5-diones

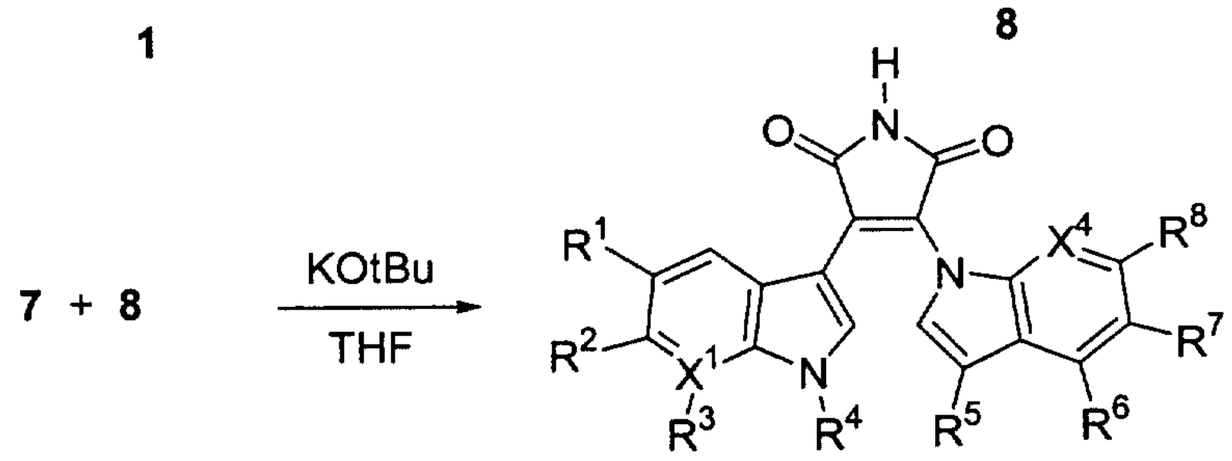
An appropriately substituted indole, **4**, is treated with oxalyl chloride in a solvent such as diethyl ether or THF. The resulting 3-indolylglyoxalyl chloride hydrochloride salt is treated with aqueous ammonium carbonate to provide acetamide **7**. A second appropriately substituted indole, **1**, is treated with a KO^{t}Bu, followed by ethyl bromoacetate to yield ester **8**. This solution of **8** is added, without isolation or workup, to a solution of **7** suspended in THF, and pretreated with 2 equiv of KO^{t}Bu. After stirring for 2 to 5 hours, an additional 3 equiv of KO^{t}Bu. After stirring over night, and quenching with conc H_2SO_4, aqueous workup and purification by silica gel chromatography yields **6**.



4 7



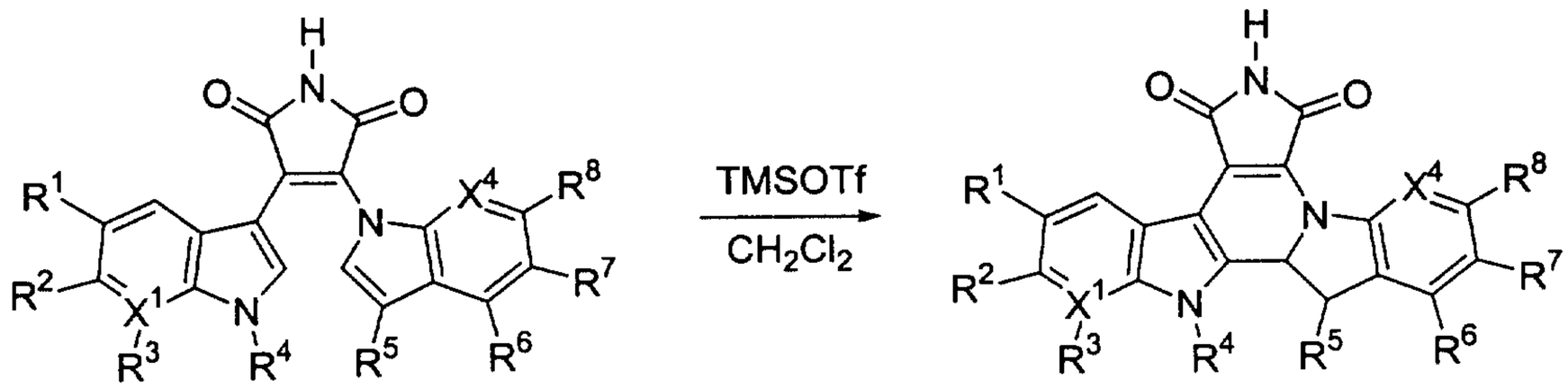
1 8



6

Method C: Cyclization of 3-(indol-3-yl)-4-(1*N*-indolyl)-1*H*-pyrrole-2,5-diones

Compound **6** was suspended in a solvent such as methlyene chloride and treated with 1.2 equiv of TMSOTf. After stirring 0 to 24 hours the solvent is removed to provide, after silica gel chromatography, compound **9**.



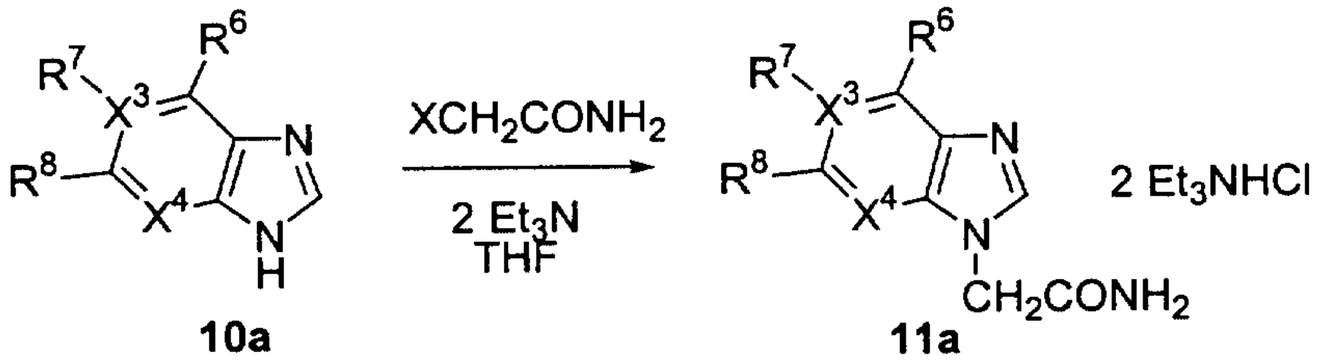
6 9

Method D: Synthesis of 3-(indol-3-yl)-4-(1*N*-purinyl)-1*H*-pyrrole-2,5-diones, 3-(indol-3-yl)-4-(1*N*-benzyimidazolyl)-1*H*-pyrrole-2,5-diones,

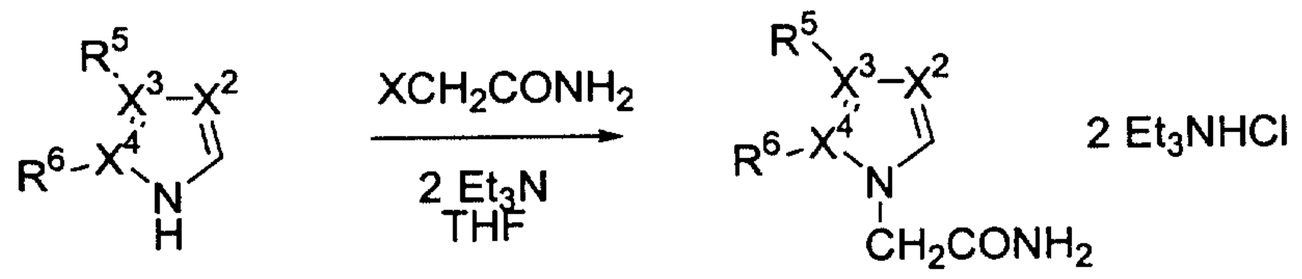
3-(indol-3-yl)-4-(1*N*-imidazolyl)-1*H*-pyrrole-2,5-diones, and

3-(indol-3-yl)-4-(1*N*-triazolyl)-1*H*-pyrrole-2,5-diones

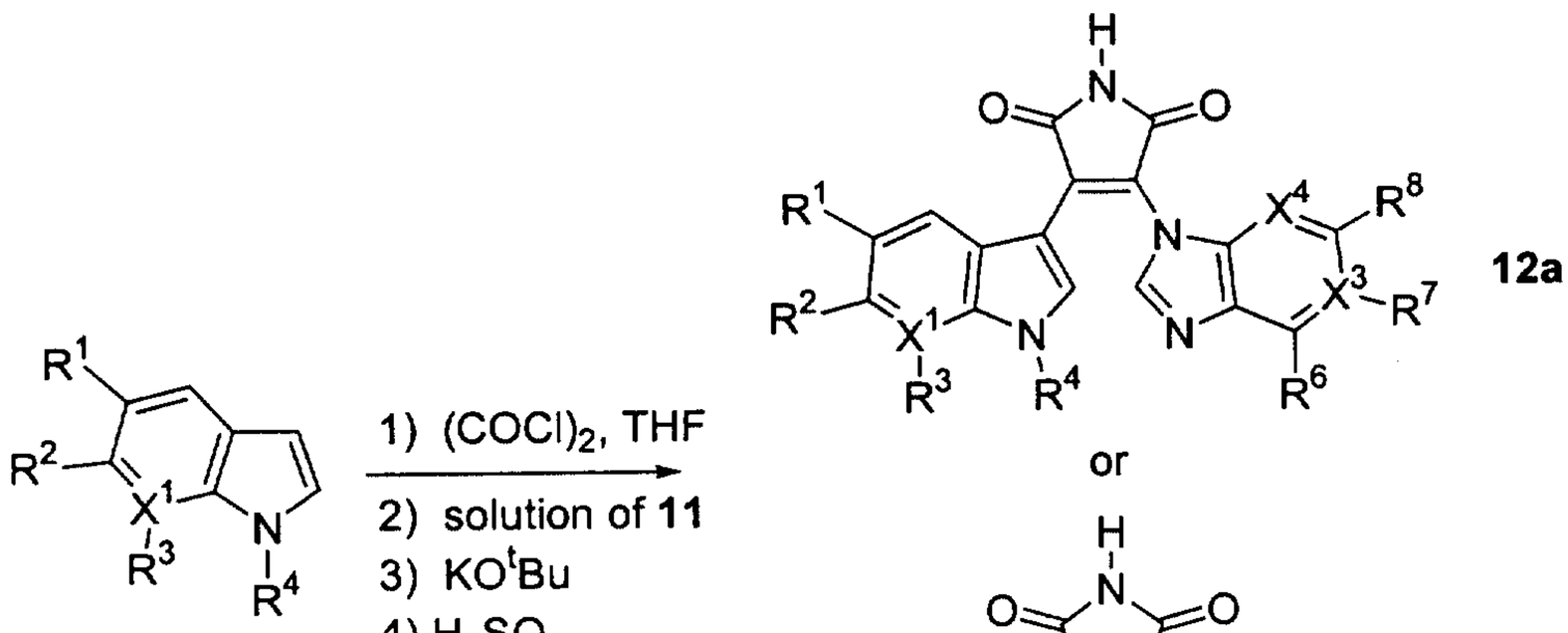
In flask **A**, an appropriately substituted purine or benzimidazole, **10a**, imidazole or triazole, **10b**, is stirred with bromo- or chloroacetamide and a base such as triethylamine, in a solvent such as THF, to yield acetamide **11**. In flask **B**, an appropriately substituted indole, **2**, dissolved in a solvent such as THF is treated with oxalyl chloride. After stirring for 1 to 24 hours, the solution of **11** in flask **A** is added to flask **B**. This mixture is stirred for 3 hours before KO^tBu (5 equiv) is added. The mixture is quenched with conc H_2SO_4 and after aqueous workup and purification either by silica gel chromatography or tituration from with the appropriate solvent, provides compound **12**.



10a **11a**



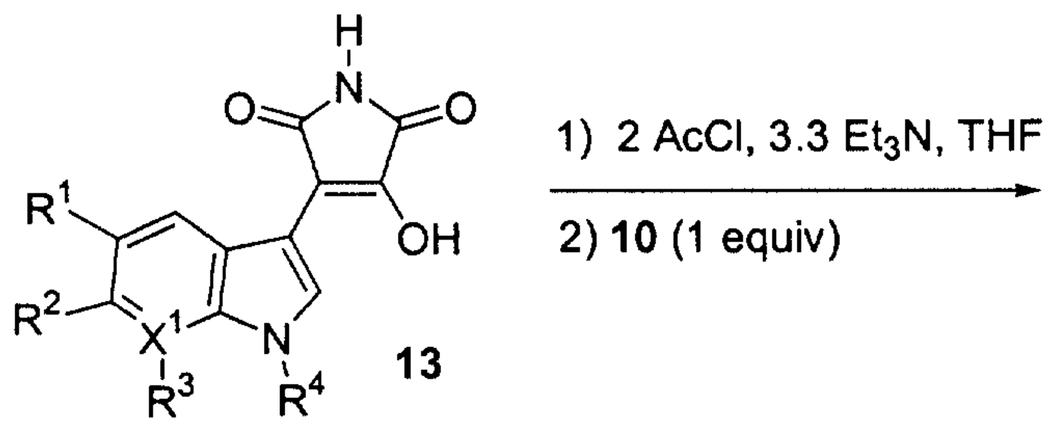
10b **11b**



1 **12a** **12b**

Method E: Synthesis of 3-(indol-3-yl)-4-(1*N*-purinyl)-1*H*-pyrrole-2,5-diones,
3-(indol-3-yl)-4-(1*N*-benzyimidazolyl)-1*H*-pyrrole-2,5-diones,
3-(indol-3-yl)-4-(1*N*-imidazolyl)-1*H*-pyrrole-2,5-diones, and
3-(indol-3-yl)-4-(1*N*-triazolyl)-1*H*-pyrrole-2,5-diones

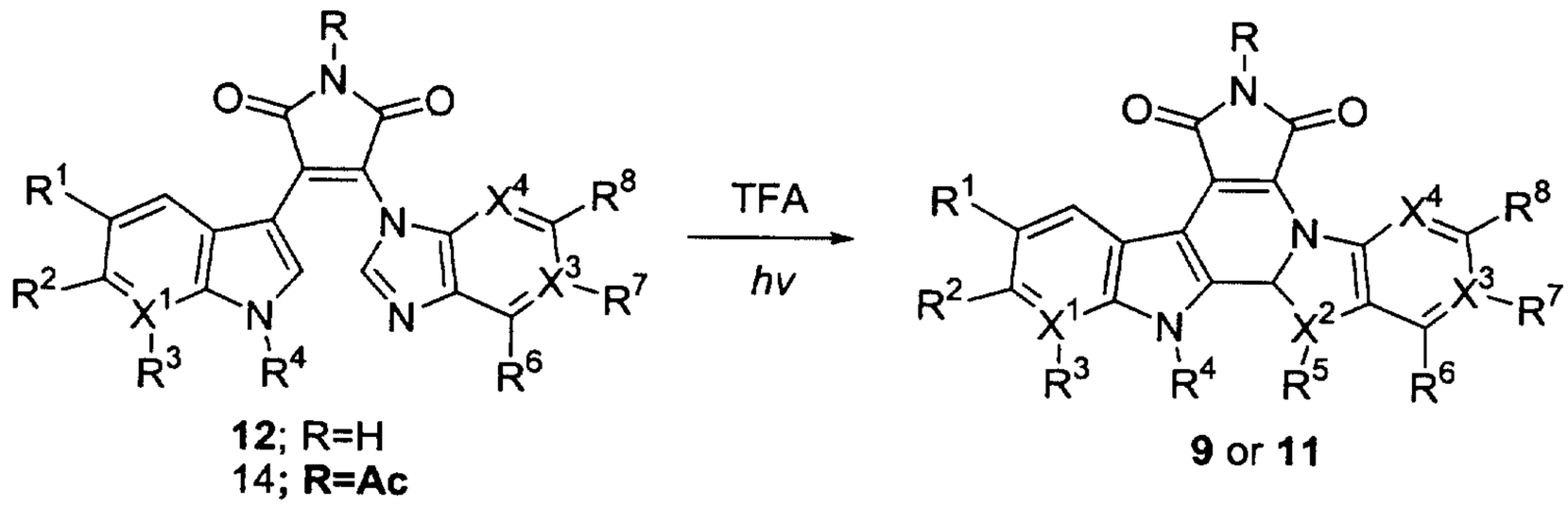
To an appropriately substituted enol **13** (prepared according to the procedure described by) dissolved in a solvent such as THF, is added 3.3 equiv of a base such as triethylamine, and 2 equiv of acetyl chloride. This solution is stirred for 2 hours before a solution of **10** in THF is added. After stirring for 2 to 24 hours compound **14** was obtained after purification by recrystallization or silica gel chromatography.



Method F: Cyclization of 3-(indol-3-yl)-4-(1*N*-purinyl)-1*H*-pyrrole-2,5-diones,
3-(indol-3-yl)-4-(1*N*-benzyimidazolyl)-1*H*-pyrrole-2,5-diones,
3-(indol-3-yl)-4-(1*N*-imidazolyl)-1*H*-pyrrole-2,5-diones, and
3-(indol-3-yl)-4-(1*N*-triazolyl)-1*H*-pyrrole-2,5-diones

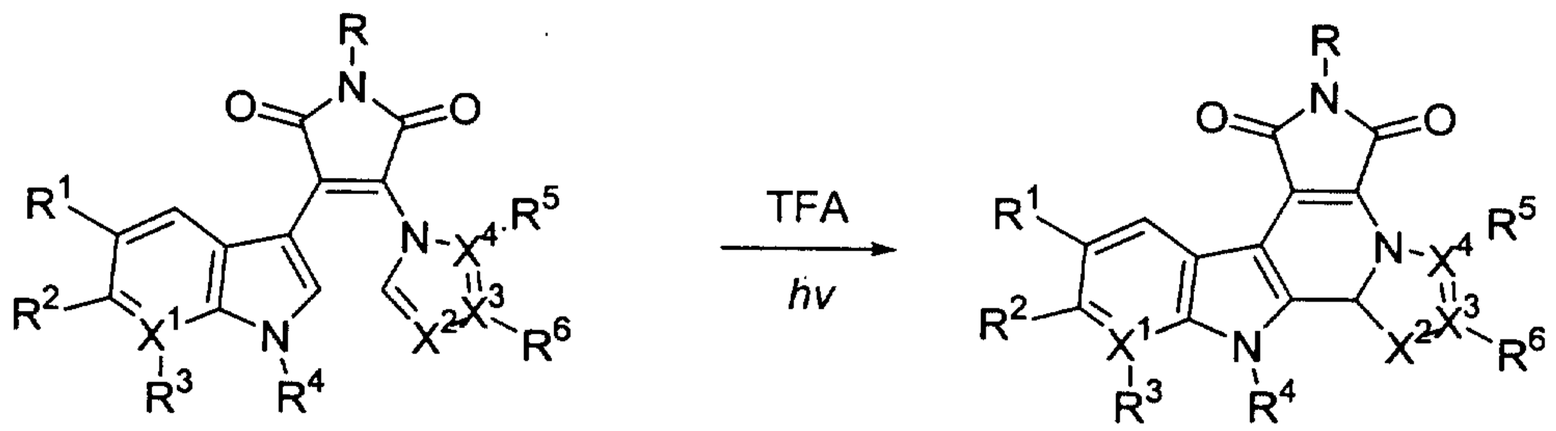
Compounds **12** or **14** is placed in a quartz tube, suspended in THF so as to make a 0.1 M solution, treated with TFA (1.5 equiv), and stirred until the solution became homogeneous. The resulting solution is irradiated at room temperature with a low pressure mercury lamp until no starting material is visible by TLC, 6 to 48 hours. Volatiles are removed under reduced pressure

and compounds , , and , respectively, are isolated by recrystallization or by purification using silica gel chromatography.



12; R=H
14; **R=Ac**

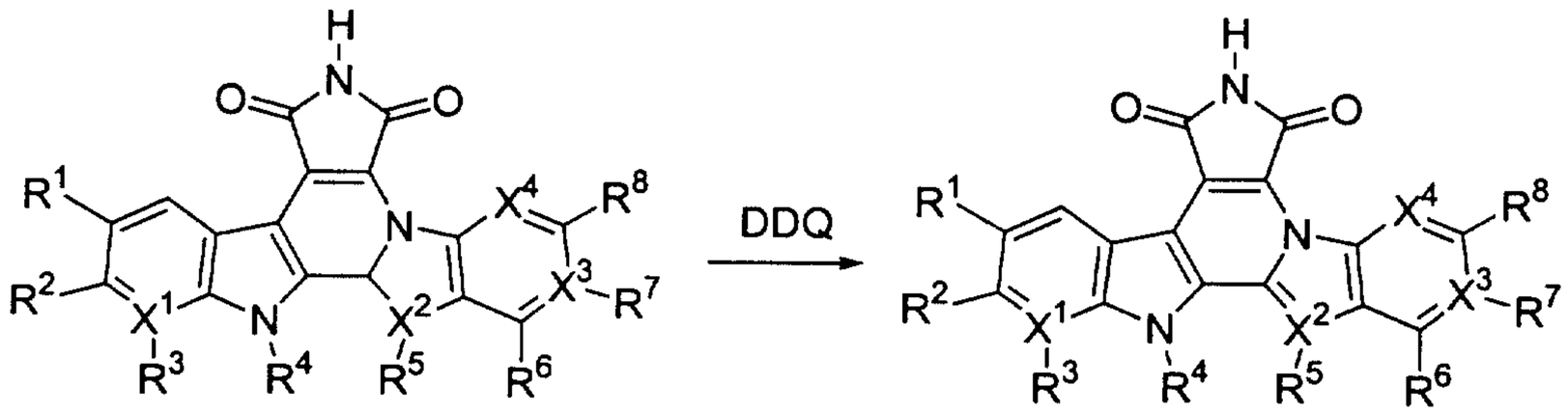
9 or **11**



12b

Method G:

Compound **9** or **11** is dissolved in a solvent such as 1,4-dioxane and treated with a dioxane solution of DDQ (2.2 equiv). Filtration and purification by silica gel chromatography provides compound **12**.



9 or **11**

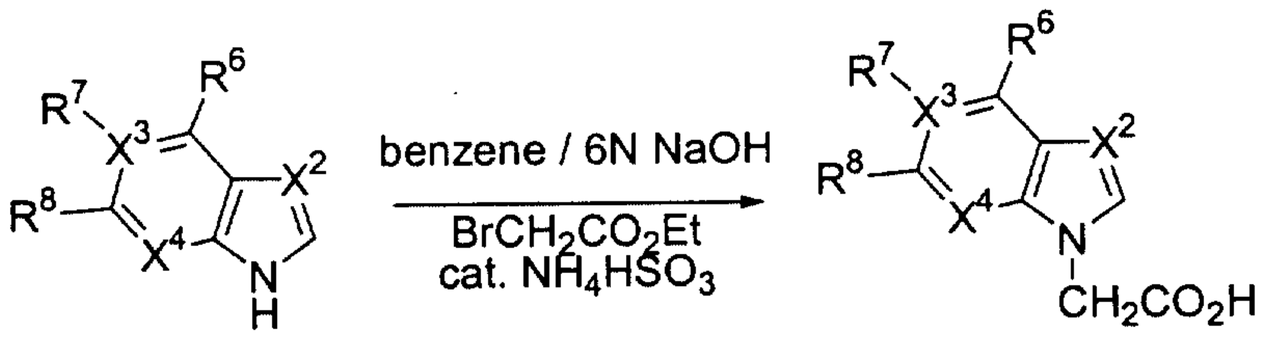
12

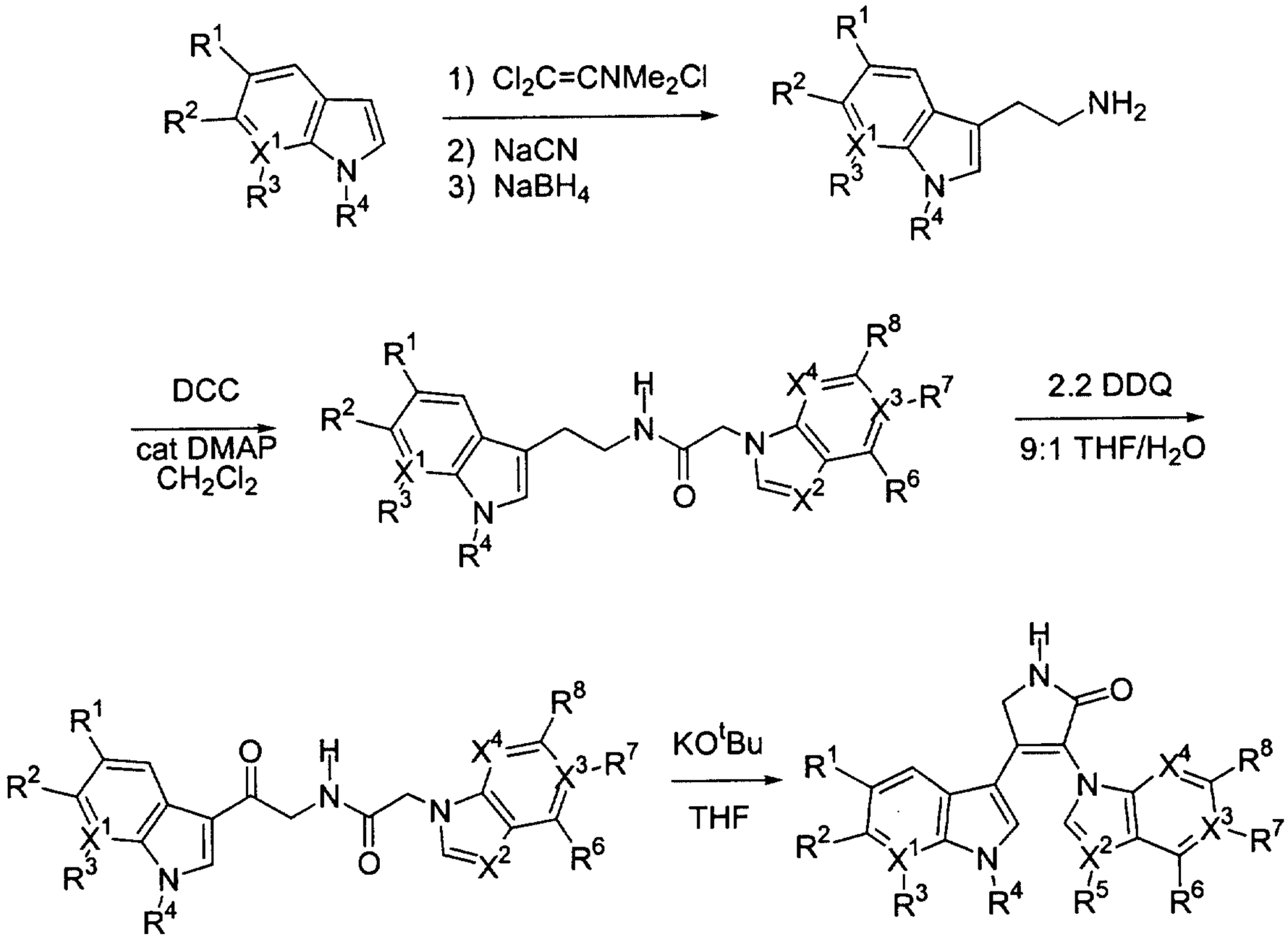
Method H: Synthesis of 3-(1*N*-indolyl)-4-(indol-3-yl)-1*H*-pyrrole-2-ones

3-(1*N*-Indolyl)-4-(indol-3-yl)-1*H*-pyrrole-2-ones were prepared according to modifications to the procedure described by Kobayashi, Y. *et al.*, *J. Am. Chem. Soc.*,**1999**, *121*, 6501.

Acid may be prepared using a variation of the procedure described by *et al.* . The appropriately substituted indole, benzimidazole, or purine is partitioned between benzene and 50% aqueous NaOH. A catalytic quantity (10 mol%) of *n*-BuN_4HSO_3 is added and the mixture is stirred vigorously for 30 minutes before ethyl bromoacetate or ethyl chloroacetate (1.5 equiv) is added. The solution is stirred for 1 to 48 hours before the layers are separated and the aqueous layer is washed with diethyl ether and acidified with 6N HCl. Filtration of the resulting solid yields acid .

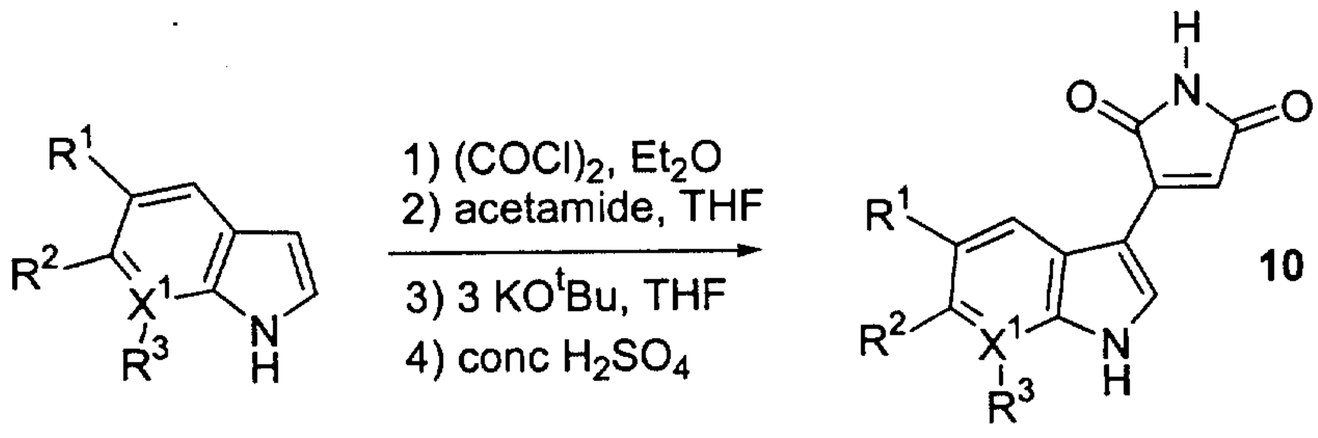
Tryptamine is prepared by using a variation of the procedure described by . The appropriately substituted indole **4** is treated with to yield the corresponding gramine, which may be converted to the corresponding 3-indolylacetonitrile. Reduction of the nitrile group with a reducing agent such as $NaBH_4$ or $LiAlH_4$ yields the desired tryptamine .


benzene / 6N NaOH
BrCH2CO2Et
cat. NH4HSO3
CH2CO2H


1) Cl2C=CNMe2Cl
2) NaCN
3) NaBH4
NH2
DCC
cat DMAP
CH2Cl2
2.2 DDQ
9:1 THF/H2O
KOtBu
THF

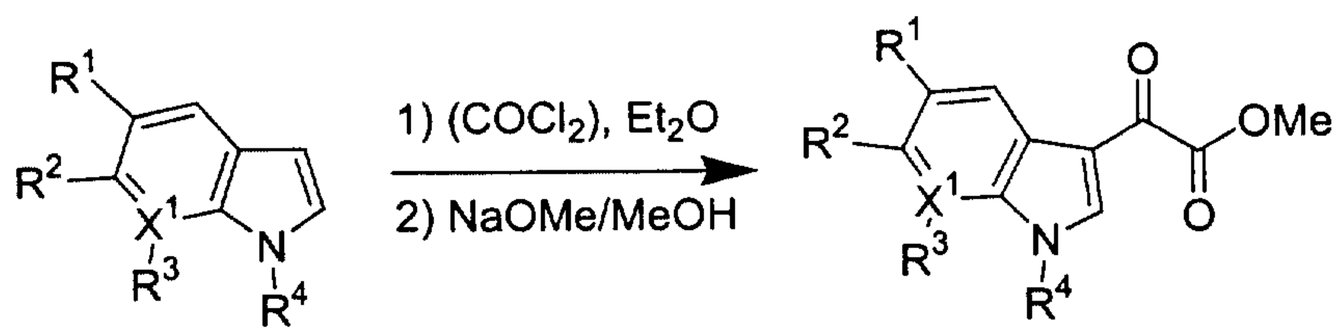
Method K: One Pot preparation of 3-(indol-3-yl)-1*H*-pyrrole-2,5-diones

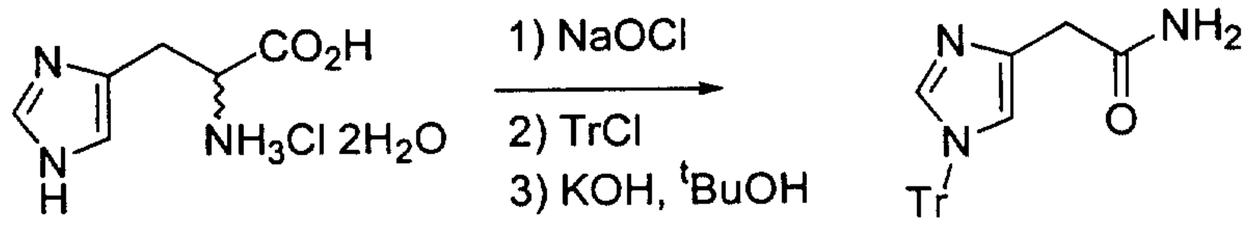
The appropriate indole (1.0 equiv) is dissolved in a solvent such as diethyl ether or THF and treated with oxalyl chloride (1.1 equiv). After stirring at room temperature for 1 to 24 hours the volatiles are removed under reduced pressure. Acetamide (3 equiv) is added to the resulting 3-indolylglyoxalyl chloride hydrochloride salt, and this mixture is taken up in dry THF. After stiring at room temperature for 2 to 3 hours a 1.0 M THF solution of KO^tBu (5 equiv) is added. Ths resulting purple solution is stirred for 3 to 24 hours before the reaction is quenched with conc H_2SO_4 (30 minutes at room temperature), followed by aqueous extraction and purification by recrystallization or silica gel chromatography.

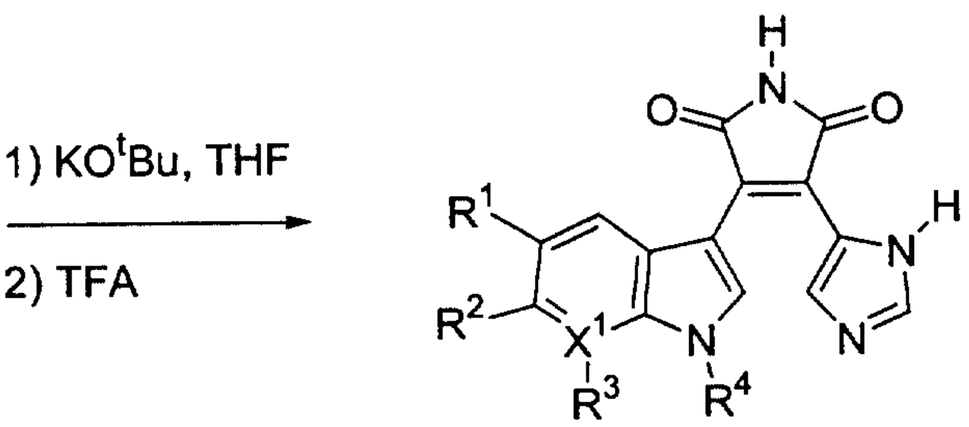


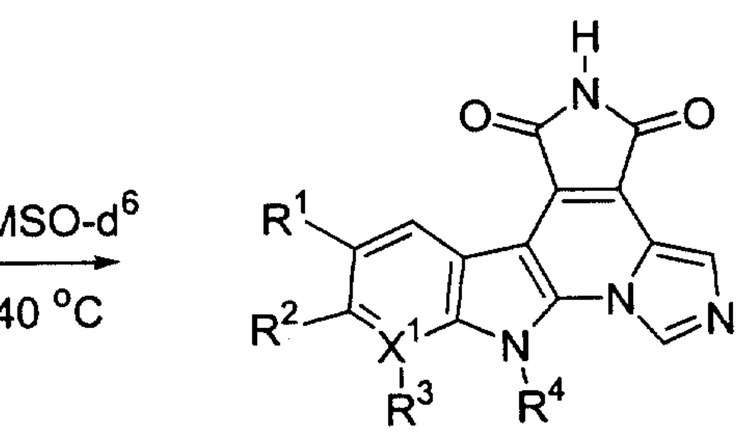
Method H: *Iso*-Granulatimide Derivatives

Compounds were prepared using the following general methodology. Didemnide A derivatives were prepared according to the procedure described by Hughes, T.V. and Cava, M.P., *Tetrahedron Lett.* (1998) 39,9629. A cyclization procedure was conducted similar to that disclosed by Piers et al., *J. Org. Chem.* 2000.


1) (COCl2), Et2O
2) NaOMe/MeOH
OMe


CO2H
NH3Cl 2H2O
1) NaOCl
2) TrCl
3) KOH, tBuOH
NH2
Tr


1) KOtBu, THF
2) TFA


DMSO-d6
140 °C

General Procedure A: Indole Alkylation

To a 0.5 mmol solution of the appropriate indole (1.0 equiv) in THF was added a 1.0M solution of K^{t}OBu (1.0 mmol) in THF. The reaction mixture was stirred at room temperature for 2 hours before the requisite alkyl halide was added (1.1 equiv). The solution was stirred for an additional 1 to 16 hours before aqueous workup with ethyl acetate. The resulting products were either purified by recrystallization, silica gel chromatography, or advanced to the next step without further purification.

General Procedure B: One Pot Preparation of 3-(Indoly-3-l)-1*H*-pyrrolee-2,5-diones and 3-(Indoly-3-l)-1*H*-pyrrolee-2-one-5-thiones

The appropriately substituted indole (1.0 mmol) was dissolved in diethyl ether (0.25 mmol solution) and cooled to 0 °C. Oxalyl chloride (1.1 equiv) was added via syringe and the resulting suspension was stirred at room temperature for 1 to 16 hours. Volatiles were removed under reduced pressure. Either acetamide, in the case of the 3-(indoly-3-l)-1*H*-pyrrolee-2-5-diones, or thioacetamide (3 equiv), in the case of the 3-(indoly-3-l)-1*H*-pyrrolee-2-one-5-thiones, was added to the resulting solid, and the mixture was taken up in THF (to make a 0.25 mmol solution based on indole). The resulting suspension was stirred for 3 hours before a 1.0M THF solution of K^{t}OBu (5 equiv) was added. The resulting deep red/black solution was stirred over night before being treated with 1 ml conc H_2SO_4 and refluxed for 30 minutes. This final solution was diluted with water and ethyl acetate and the organic layer was washed with brine. Purification by silica gel chromatography yielded the desired product.

General Procedure C: Preparation of 3-Indolylglyoxalimides

The appropriately substituted indole (1.0 mmol) was dissolved in diethyl ether (0.25 mmol solution) and cooled to 0 °C. Oxalyl chloride (1.1 equiv) was added via syringe and the resulting suspension was stirred at room temperature for 1 to 16 hours. The suspension was cooled on ice and an aqueous solution of NH_4CO_3 (2-3 equiv) was added. The bilayer was vigerously stirred for 30 minutes before being filtered, washed with water until the filtrate was neutral, cold *iso*-

propanol, and diethyl ether. The resulting solid generally required no further purification. The *iso*-propanol washed contained varied quantities of product, depending on its solubility.

General Procedure D: Preparation of 3-(Indoly-3-l)-4-(1*N*-indolyl)-1*H*-pyrrolee-2,5-diones

To a 0.5 mmol solution of the appropriate indole (1.0 equiv) in DMF was added a 1.0M solution of K^{t}OBu (1.0 mmol) in THF. The reaction mixture was stirred at room temperature for 2 hours before the ethyl bromoacetate was added (1.0 equiv). The solution was stirred over night. In a separate flask, the appropriate 3-indolylglyoxalimide was dissolved in DMF (to make a 0.25M solution) and treated with a 1.0M THF solution of K^{t}OBu (2 equiv). This solution was stirred at room temperature for 1 hour. The THF solution was added to the THF solution via cannula over approximately 5 minutes. This solution was allowed to stir over night before a 1.0M THF solution of K^{t}OBu (5 equiv) was added. This final solution was stirred for 3 hours before being diluted with water and ethyl acetate, and subjected to standard workup. Purification by silica gel chromatography yielded compound .

Example 1: 3-(*N*-indolyl)-4-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione

Step 1: Intermediate A1 was prepared according to either general procedure B or C, to provided the desired compounds as an orange solid after purification by silica gel chromatography, eluting with 3:1 petroleum ether/ethyl acetate, in 15% yield for procedure B and 34% yield for procedure C.

Step 2: Intermediate A1 ( ) was stirred with TMSOTf ( ) in CH_2Cl_2 (50 mL) for 3 hours. Removal of volatiles and purification by silica gel chromatography, eluting with 1:1 acetone/petroleum ether, yielded a deep purple solid in 95% yield.

Example 2: 3-(*N*-5-Methoxyindolyl)-4-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione

Step 1: Intermediate A1 was prepared according to either general procedure B or C, to provided the desired compounds as an orange solid after purification by silica gel chromatography, eluting with 3:1 petroleum ether/ethyl acetate, in 15% yield for procedure B and 34% yield for procedure C.

Step 2: Intermediate A1 was cyclized using general procedure C. Intermediate A1 ( ) was stirred with TMSOTf ( ) in CH_2Cl_2 (50 mL) for 3 hours. Removal of volatiles and purification by silica gel chromatography, eluting with 1:1 acetone/petroleum ether, yielded a deep purple solid in 95% yield.

Example 3:

Example 1 was oxidized using general procedure G. Compound 1 ( ) in dioxane (10 mL), was treated with a dioxane solution (5 mL) of DDQ (), and stirred for 1 hour. Workup and purification by silica gel chromatography, eluting with 1:1 acetone/petroleum ether, yielded compound 2 as a deep purple solid in 85% yield.

Example 8:

Step 1: To a solution of 5-methoxyindole (2.5 g, 16.98 mmol) in 50 mL of anh. diethyl ether cooled to 0°C was added oxallyl chloride (1.63 mL, 18.68 mmol) and subsequently warmed to room temperatue. After 3.5 hours the solution was cooled to 0°C and 50 mL of an aqueous solution of ammonium carbonate was added. After stirring overnight the precipitate was filtered off and washed with water, isopropanol and diethyl ether to afford the desired acetamide in 78% yield as a bright yellow solid.

^{1}H-NMR (200 MHz, DMSO-d_6) δ 11.3 (broad s, 1H), 8.6 (s, 1H), 8.0 (s, 1H), 7.73 (d, 1H, J=2.57 Hz), 7.68 (s, 1H), 7.4 (d, 1H, J=8.81 Hz), 6.8 (dd, 1H, J=2.56; 8.79Hz), 3.8 (s, 3H)

Step 2: 3-(5-(methoxy)indol-1-yl)-4-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione

Intermediate A2 was prepared according to either general procedure C, using ( ), ()to provided the desired compounds as an orange solid after purification by silica gel chromatography, eluting with 3:1 petroleum ether/ethyl acetate, in 34% yield.

Step 3:

The coupled product of acetamide from step 1 with N-ethylindoylyl acetate (50 mg, 0.14 mmol) was stirred with TMSOTf (32.4 μL, 0.168 mmol) in CH_2Cl_2 (5 mL) for 3 days. Removal

of volatiles and purification by silica gel chromatography, eluting with 3:2 hexanes\ethyl acetate, yielded a deep purple solid in 42% yield.

^{1}H-NMR (DMSO-D_6, 200 MHz) δ 11.8 (s, 1H), 10.9 (s, 1H), 8.0 (d, 1H, J=3.5Hz), 7.68 (s, 1H), 7.5-7.2 (m, 3H), 7.06 (m, 3H), 3.95 (s, 3H), ^{13}C-NMR (DMSO-d_6) δ 169.3, 166.7, 151.6, 136.6, 136.1, 132.1, 130.9, 129.6, 127.5, 126.4, 124.8, 122.5, 121.5, 119.9, 114.5, 112.2, 112.0, 112.0, 111.2, 105.4, 57.2

Example 9:

Example 3 was oxidized using general procedure G. Compound 3 ( ) in dioxane (10 mL), was treated with a dioxane solution (5 mL) of DDQ (), and stirred for 1 hour. Workup and purification by silica gel chromatography, eluting with 1:1 acetone/petroleum ether, yielded compound 9 as a deep purple solid in 65% yield.

Example 20: Synthesis of 3-(1*H*-5-bromoindol-3-yl)-1*H*-pyrrole-2,5-dione (J-1-113)

Oxalyl chloride (445 uL, 5.10 mmol)) was added to a THF (25) solution of 5-bromoindole (1.00 g, 5.10 mmol). After stirring at room temperature for 3 hours, volatiles were removed under reduced pressure. Solid acetamide (903 mg, 15.3 mmol) was added to the resulting solid, and the mixture was dissolved in THF . After stirring for 3 hours, a 1M solution of KO^{t}Bu (15.3 mL, 15.3 mmol) was added. The resulting, deep purple solution was stirred overnight, quenched with conc H_2SO_4 (1mL), stirred for 30 minutes before being diluted with water (20 mL) and ethyl acetate. The aqueous layer was washed with ethyl acetate and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. Purification by silica gel chromatography, eluting with 3:1 to 1:1 petroleum ether/ethyl acetate, provided compound 20 in 45% yield. Compound 20 could be further purified, where necessary, by recrystallization from methanol.

m.p. 270.5-271.0 °C.

Example 21: Synthesis of 3-(*N*-acetyl-5-bromoindol-3-yl)-1*H*-pyrrole-2,5-dione (J-1-114)

Compound 20 (80 mg, 0.275 mmol), triethylamine (42 μL, 0.3 mmol), DMAP (5 mg), and actetic anhydride (30 μL, 0.3 mmol) were stirred together in THF (5 mL) over night. Standard

aqueous workup and purification by silica gel chromatography, eluting with 3:1 petroleum ether/ethyl acetate, provided compound 21 in 51% yield, as a yellow solid.
m.p. 271.0-272.9 °C. ^{1}H NMR (200 MHz, DMSO-d^{6}) δ 11.07 (br s, 1H), 8.49 (s, 1H), 8.25 (d, J=8.8Hz, 1H), 8.18 (s, 1H), 7.56 (d, J=8.4Hz, 1H), 7.24 (s, 1H), 2.70 (s, 3H). ^{13}C NMR (74.5MHz, DMSO-d^{6}) δ 172.4, 172.2, 169.7, 136.3, 133.9, 131.0, 129.1, 128.6, 123.0, 117.8, 117.3, 109.4.

Example 22: Synthesis of 3-(*N*-(*N,N*-dimethylcarbamoyl)-5-bromoindol-3-yl)-1*H*-pyrrole-2,5-dione (J-1-117)

Compound 20 (80 mg, 0.275 mmol), triethylamine (42 μL, 0.3 mmol), DMAP (5 mg), and *N,N*-dimethylcarbamoyl chloride (26 μL, 0.3 mmol) were stirred together in THF (5 mL) over night. Standard aqueous workup and recrystallization from ethyl acetate, provided compound 22 in 21% yield, as a yellow solid. The filtrate was approximately 95% pure.
m.p. 287.0-288.0 °C. ^{1}H NMR (200 MHz, DMSO-d^{6}) δ 10.98 (br s, 1H), 8.43 (s, 1H), 8.22 (s, 1H), 7.57 (d, J=8.7Hz, 1H), 7.48 (d, J=8.7Hz, 1H), 3.02 (s, 6H).

Example 23: Synthesis of 3-(*N*-(*p*-toluenesulfonyl)-5-bromoindol-3-yl)-1*H*-pyrrole-2,5-dione (J-1-118)

Compound 20 (50 mg, 0.172 mmol), DMAP (44 mg, 260 mmol), and *p*-toluenesulfonyl chloride (33 mg, 0.172 mmol) were refluxed in THF (5 mL) for 48 hours. Standard aqueous workup and purification by silica gel chromatography, eluting with 4:1 petroleum ether/ethyl acetate, provided compound 23 in 91% yield, as a yellow solid.
m.p. 262.0-263.8 °C. ^{1}H NMR (200 MHz, DMSO-d^{6}) δ 11.13 (s, 1H), 8.54 (s, 1H), 8.23 (s, 1H), 7.93 (d, J=8.2Hz, 2H), 7.93 (d, J=8.8Hz, 1H), 7.58 (dd, J=2.1, 8.8Hz, 1H), 7.40 (d, J=8.2HZ, 2H), 7.32 (s, 1H), 2.31 (s, 3H).^{13}C NMR (74.5MHz, DMSO-d^{6}) δ 172.3, 172.1, 146.5, 135.8, 133.2, 132.7, 131.0, 130.6, 130.0, 129.3, 128.7, 127.1, 123.8, 117.7, 115.2, 110.4, 21.1.

Example 24: Synthesis of 3-(*N*-(1-naphthylenesulfonyl)-5-bromoindol-3-yl)-1*H*-pyrrole-2,5-dione (J-1-160)

Compound 20 (146 mg, 0.50 mmol), triethylamine (77 μL, 0.55 mmol), DMAP (10 mg), and 1-naphthylenesulfonyl chloride (113mg, 0.5 mmol) were refluxed in THF (5 mL) for 48 hours.

Standard aqueous workup and purification by silica gel chromatography, eluting with 3:1 petroleum ether/ethyl acetate, provided compound 24 in 73% yield, as an off white solid. m.p. °C. ^{1}H NMR (200 MHz, DMSO-d^{6}) δ 11.14 (br s, 1H), 8.78 (s, 1H), 8.54 (d, J=7.4Hz, 1H), 8.50 (d, J=8.2Hz, 1H), 8.36 (d, J=8.2Hz, 1H), 8.20 (s, 1H), 8.08 (d, J=7.8Hz, 1H), 7.79-7.63 (m, 4H), 7.49 (d, J=9.0Hz, 1H), 7.30 (s, 1H). ^{13}C NMR (74.5MHz, DMSO-d^{6}) δ 172.4, 172.2, 169.7, 136.3, 133.9, 131.0, 129.1, 128.6, 123.0, 117.8, 117.3, 109.4.

Example 25: Synthesis of 3-(*N*-(2-naphthylenesulfonyl)-5-bromoindol-3-yl)-1*H*-pyrrole-2,5-dione (J-1-161)

Compound 20 (146 mg, 0.50 mmol), triethylamine (77 μL, 0.55 mmol), DMAP (10 mg), and 2-naphthylenesulfonyl chloride (113mg, 0.5 mmol) were refluxed in THF (5 mL) for 48 hours. Standard aqueous workup and purification by silica gel chromatography, eluting with 3:1 petroleum ether/ethyl acetate, provided compound 25 in 48% yield, as an off white solid. m.p. °C. ^{1}H NMR (200 MHz, DMSO-d^{6}) δ 11.14 (br s, 1H), 8.96 (s, 1H), 8.64 (s, 1H), 8.26-8.22 (m, 2H), 8.10 (d, J=9.0Hz, 1H), 8.05-7.98 (m, 1H), 7.99 (dd, J=2.0, 8.7Hz, 1H), 7.74-7.65 (m, 3H), 7.57 (dd, J=1.7, 9.0Hz, 1H), 7.31 (s, 1H). ^{13}C NMR (74.5MHz, DMSO-d^{6}) δ 172.4, 172.2, 135.8, 135.1, 132.9, 132.7, 131.5, 130.5, 130.3, 130.2, 129.8, 129.6, 129.3, 128.8, 128.3, 128.0, 123.8 (2 C's), 121.1, 117.8, 115.2, 110.5.

Example 26: Synthesis of 3-(*N*-dansyl-5-bromoindol-3-yl)-1*H*-pyrrole-2,5-dione (J-1-165)

Compound 20 (146 mg, 0.50 mmol), triethylamine (77 μL, 0.55 mmol), DMAP (10 mg), and dansyl chloride (202 mg, 0.75 mmol) were refluxed in THF (5 mL) for 48 hours. Standard aqueous workup and purification by silica gel chromatography, eluting with 3:1 petroleum ether/ethyl acetate, provided compound 26 in 42% yield, as an off white solid. m.p. °C. ^{1}H NMR (200 MHz, DMSO-d^{6}) δ 11.14 (br s, 1H), 8.78 (s, 1H), 8.57 (d, J=7.2Hz, 1H), 8.54 (d, J=7.2Hz, 1H), 8.24 (s, 1H), 8.11 (d, J=8.8Hz, 1H), 7.74 (J, J=8.4Hz, 2H), 7.66 (d, J=8.0Hz, 1H), 7.58 (d, J=8.6Hz, 1H), 7.53 (d, J=8.8Hz, 1H), 7.33 (s, 1H), 7.20 (d, J=7.7Hz, 1H), 2.74 (s, 6H). ^{13}C NMR (74.5MHz, DMSO-d^{6}) δ 171.8, 171.6, 151.6, 135.3, 132.4, 132.1, 130.8, 129.8, 129.2, 128.5, 128.4, 128.1, 127.9, 123.4, 123.3, 117.0, 115.9, 115.4, 114.3, 113.1, 109.1, 44.4.

Example 27: Synthesis of 3-(1-*H*-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-1-166)

Compound 27 was prepared in a manner similar manner to compound 20, using 5-benzyloxyindole (2.00 g, 8.96 mmol), oxalyl chloride (0.82 mL, 9.41 mmol), acetamide (1.70 g, 28.7 mmol), and a 1M solution of KO^tBu (45 mL, 44.8 mmol). Standard workup and purification first by silica gel chromatography, eluting with 3:1 petroleum ether/ethyl acetate, followed by recrystallization from MeOH, provided compound 27 as an orange solid in 53% yield.

m.p. °C. ^1H NMR (200 MHz, DMSO-d^6) δ 11.92 (s, 1H), 10.72 (s, 1H), 8.31 (d, J=3.0Hz, 1H), 7.53-7.31 (m, 7H), 6.95 (dd, J=3.0, 8.0Hz, 1H), 6.82 (s, 1H), 5.22 (s, 2H). ^{13}C NMR (74.5MHz, DMSO-d^6) δ 173.5, 173.3, 154.3, 139.4, 137.7, 131.6, 131.2, 128.4, 127.7, 126.2, 114.8, 113.6, 113.3, 105.3, 103.9, 69.9.

Example 28: Synthesis of 3-(*N*-acetyl-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-60)

Compound 27 (50 mg, 0.164 mmol), triethylamine (23 μL, 0.164 mmol), acetic anhydride (16 μL, 0.164 mmol), and DMAP (2 mg) were stirred together in THF (5 mL) over night. Standard aqueous workup and purification by silica gel chromatography, eluting with 3:1 petroleum ether/ethyl acetate, provided compound 28 in 75 % yield, as a yellow solid.

Example 29: Synthesis of 3-(*N*-benzoyl-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-61)

Compound 27 (50 mg, 0.164 mmol), triethylamine (23 μL, 0.164 mmol), benzoyl chloride (19 μL, 0.164 mmol), and DMAP (2 mg) were stirred together in THF (5 mL) over night. Standard aqueous workup and purification by silica gel chromatography, eluting with 4:1 petroleum ether/ethyl acetate, provided compound 29 in 51% yield, as a yellow solid.

^1H NMR (500 MHz, DMSO-d^6) δ 10.99 (s, 1H), 8.27 (s, 1H), 8.24 (d, J=9.0Hz, 1H), 7.80 (d, J=7.4Hz, 1H), 7.73 (t, J=7.4Hz, 1H), 7.63 (t, J=7.4Hz, 2H), 7.60 (d, J=2.2Hz, 1H), 7.51 (d, J=7.4Hz, 2H), 7.41 (t, J=7.4Hz, 2H), 7.33 (t, J=7.4Hz, 1H), 7.29 (s, 1H), 7.18 (dd, J=2.3, 9.0Hz, 1H), 5.28 (s, 2H). ^{13}C NMR (74.8MHz, DMSO-d^6) δ 172.7, 172.5, 168.0, 156.2, 137.2, 136.7, 133.3, 132.6, 131.8, 130.2, 129.3, 128.83, 128.79, 128.4, 127.83, 127.79, 122.3, 117.0, 155.2, 110.2, 105.0, 70.0.

Example 30: Synthesis of 3-(*N*-(2,4-dimethoxybenzoyl)-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-71)

Compound 27 (76 mg, 0.25 mmol), triethylamine (35 μL, 0.25 mmol), 2,4-dimethoxybenoyl chloride (30 μL, 0.3 mmol), and DMAP (2 mg) were stirred together in THF (5 mL) over night. Standard aqueous workup and recrystallization from methanol, provided compound 30 in 62% yield, as a yellow solid.

^{1}H NMR (500 MHz, DMSO-d^{6}) δ 10.97 (s, 1H), 8.24 (d, J=9.0Hz, 1H), 8.09 (s, 1H), 7.56 (d, J=1.4Hz, 1H), 7.52 (d, J=9.9Hz, 1H), 7.50 (d, J=8.6Hz, 1H), 7.40 (t, J=7.5Hz, 2H), 7.33 (t, J=7.5Hz, 1H), 7.25 (s, 1H), 7.14 (dd, J=2.4, 9.0Hz, 1H), 6.79 (d, J=2.2Hz, 1H), 6.73 (dd, J=2.2, 9.0Hz, 1H), 5.26 (s, 2H), 3.89 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (74.8MHz, DMSO-d^{6}) δ 172.6, 172.3, 166.4, 163.4, 157.9, 156.0, 137.2, 136.7, 131.9, 131.3, 129.6, 128.8, 128.4, 127.8, 127.7, 122.0, 116.6, 115.4, 115.0, 110.0, 106.1, 104.9, 98.84, 69.9, 55.9, 55.7.

Example 31: Synthesis of 3-(*N*-tosyl-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-1-172)

Compound 27 (100 mg, 0.314 mmol), triethylamine (48 μL, 0.346 mmol), DMAP (10 mg), and p-toluenesulfonyl chloride (66 mg, 0.346 mmol) were refluxed in THF (5 mL) for 48 hours. Standard aqueous workup and purification by silica gel chromatography, eluting with 3:1 petroleum ether/ethyl acetate, provided compound 31 in 86% yield, as an off white solid.

^{1}H NMR (200 MHz, DMSO-d^{6}) δ 11.11 (s, 1H), 8.52 (s, 1H), 7.90 (d, J=8.2Hz, 2H), 7.88 (d, J=9.4Hz, 1H), 7.52-7.31 (m, 8H), 7.27 (s, 1H), 7.12 (dd, J=2.2, 9.1Hz, 1H), 5.19 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (125.7MHz, DMSO-d^{6}) δ 172.5, 172.3, 156.1, 146.2, 137.0, 136.3, 133.3, 130.5, 129.7, 128.7, 128.4, 127.8, 127.7, 127.0, 122.8, 115.5, 114.3, 113.6, 111.0, 105.1, 70.0, 21.0.

Example 32: Synthesis of 3-(*N*-(4-nitrobenzenesulfonyl)-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-28)

Compound 27 (50 mg, 0.157 mmol), triethylamine (24 μL, 0.157 mmol), DMAP (2 mg), and 4-nitrobenzenesulfonyl chloride (38 mg, 0.173 mmol) were refluxed in THF (5 mL) for 48 hours. Standard aqueous workup and purification by silica gel chromatography, eluting with 4:1 to 1:1 petroleum ether/ethyl acetate, provided compound 32 in 27% yield, as a light yellow solid.

^{1}H NMR (200 MHz, DMSO-d^6) δ 11.16 (s, 1H), 8.53 (s, 1H), 8.33 (br s, 4H), 7.92 (d, J=9.0Hz, 1H), 7.53-7.41 (m, 4H), 7.36 (d, J=7.6Hz, 2H), 7.32 (s, 1H), 7.15 (dd, J=1.2, 9.0Hz, 1H), 5.20 (s, 2H). ^{13}C NMR (74.8MHz, DMSO-d^6) δ 172.5, 172.2, 156.4, 151.1, 141.1, 137.0, 136.0, 129.4, 128.9, 128.7, 128.4, 127.9, 127.8, 125.3, 123.5, 120.1, 115.8, 114.3, 112.0, 105.3, 70.0.

Example 33: Synthesis of 3-(*N*-benzyl-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-2-63)

Step 1: 5-Benzyloxyindole (500 mg, 2.24 mmol) was dissolved in benzene (15 mL) and treated with a 50% sodium hydroxide solution (5 mL) in the presence of tetrabutylammonium hydrogensulfate (76 mg, 0.22 mmol) for 30 minutes, followed by the addition of benzyl bromide (0.40 mL, 3.36 mmol). After stirring for 48 hours, standard aqueous workup provided 800 mg of crude material. Purification by silica gel chromatography eluting with 10:1 hexanes\ethyl acetate afforded clean product in 50 % yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (m, 15H), 6.59 (d, J=2.2Hz, 1H), 5.22 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 153.4, 153.1, 141.2, 137.8, 137.7, 137.6, 132.4, 131.8, 129.1, 128.8, 128.7, 128.4, 128.3, 127.6, 127.5, 127.5, 127.3, 126.7, 126.6, 125.8, 114.3, 112.8, 112.7, 112.5, 110.4, 104.3, 103.0, 101.3, 70.9, 50.2, 50.0, 31.6.

Step 2: Compound 33 was prepared from *N*-Benzyl-5-benzyloxyindole in a similar fashion as that described for compound 19. To a solution of *N*-Benzyl-5-benzyloxyindole in THF was added oxalyl chloride (83.5 μL, 0.96 mmol), stirred for 24 hours followed by addition of acetamide (0.15 g, 2.55 mmol), and 1M THF solution of KO^{t}Bu (4.1 mL, 4.07 mmol). The reaction mixture was stirred for 3 days at room temperature. Standard workup and purification using silica gel chromatography, eluting with 3:1 hexanes/ethyl acetate, provided compound 33 as a yellow solid in 21% overall yield.

^{1}H NMR (200 MHz, DMSO-d_6) δ 10.77 (s, 1H), 8.50 (s, 1H), 7.38 (m, 12H), 6.95 (dd, J=2.15; 8.97Hz, 1H), 6.86 (s, 1H), 5.51 (s, 2H), 5.20 (s, 2H). ^{13}C NMR (200 MHz, DMSO-d^6) δ 173.6, 173.3, 154.7, 138.9, 137.6, 137.3, 134.2, 131.6, 128.8, 128.5, 128.8, 127.2, 127.1, 115.3, 113.6, 112.4, 104.8, 104.3, 70.0, 49.7.

Example 34: Synthesis of 3-(*N*-(2,3-dimethoxybenzyl)-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-)

Example 35: Synthesis of 3-(*N*-(2-fluorobenzyl)-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-?)

Example 36: Synthesis of 3-(*N*-(3-fluorobenzyl)-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-?)

Example 37: Synthesis of 3-(*N*-(4-fluorobenzyl)-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-?)

Example 38: Synthesis of 3-(*N*-(methylenephthalimido)-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (CT-1-5)

Example 39: Synthesis of 3-(*N*-(methylene-2-naphthyl)-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (CT-1-21)

Example 40: Synthesis of 3-(*N*-(methylenecyclohexyl)-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (CT-1-)

Example 41: Synthesis of 3-(*N*-octyl-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-2-57)

Step 1: *N*-octyl-5-benzyloxyindole was prepared by general method A. 5-Benzyloxyindole (500 mg, 2.24 mmol) was dissolved in THF (20 mL) and treated with 1M KO^{t}Bu in THF (3.81 mL, 3.8 mmol). After stirring for 3 hours, 1-bromooctane (0.39 mL, 2.24 mmol) was added and the reaction mixture was stirred for an additional 24 hrs. Standard aqueous workup provided crude *N*-octyl-5-benzyloxyindole, which was purified by silica gel chromatography using pure hexanes to afford a clean solid.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (m, 7H), 7.35 (m, 2H), 6.78 (d, J=2.9Hz, 1H), 5.40 (s, 2H), 4.23 (t, J=7.0Hz, 2H), 2.05 (broad t, J=6.5Hz, 2H), 1.62 (broad s, 10H), 1.31 (t, J=6.2Hz, 3H)

^{13}C NMR (50 MHz, $CDCl_3$) δ 152.9, 137.7, 131.3, 128.7, 128.2, 128.0, 127.7, 127.6, 127.4, 127.2, 112.1, 109.8, 103.8, 100.2, 70.4, 46.1, 31.6, 30.0, 29.3, 29.0, 26.7, 22.5, 14.0.

Step 2: Compound 41 was prepared from *N*-octyl-5-benzyloxyindole in a similar fashion as that described for compound 19. To a solution of *N*-octyl-5-benzyloxyindole in THF was

added oxalyl chloride (0.12 mL, 1.4 mmol), stirred for 24 hours followed by addition of acetamide (0.22 g, 3.74 mmol), and 1M THF solution of KO^tBu (5.95 mL, 5.95 mmol). The reaction mixture was stirred for 3 days at room temperature. Standard workup and purification using silica gel chromatography, eluting with 5:1 hexanes/ethyl acetate, yielded an orange solid in 30% overall yield.

^1H NMR (200 MHz, DMSO-d^6) δ 10.73 (s, 1H), 8.33 (s, 1H), 7.41 (m, 7H), 7.01 (d, J=2.4Hz, 1H), 6.80 (s, 1H), 5.21 (s, 2H), 4.23 (t, J=2.77Hz, 2H), 1.72 (m, 2H), 1.21 (s, 10H), 0.83 (m, 3H)

^{13}C NMR (50 MHz, DMSO-d^6) δ 173.5, 173.3, 154.6, 139.1, 137.7, 133.8, 131.6, 128.4, 127.7, 126.9, 114.7, 113.4, 111.9, 104.4, 104.4, 70.1, 46.3, 31.2, 29.6, 28.6, 28.5, 26.2, 22.1, 13.9.

Example 42: Synthesis of 3-(*N*-(2-hydroxyethyl)-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-67)

Step 1: 5-Benzyloxyindole () and *n*-Bu_4NHSO_4 ( ) were partitioned between toluene () and 50% aqueous NaOH ( ). This solution was stirred vigerously for 30 minutes before neat ethyl bromoacetate () was added. After stirring for an additional 2 hours the mixture was diluted with diethyl ether and water. The aqueous layer was washed with diethyl ether before being acidified with 6N HCl. The resulting solid was filtered off, washed with water, and dried *in vacuo* to privide of *N*-(5-Benzyloxyindole) acetic acid.

Step 2: Crude *N*-(5-benzyloxyindole)acetic acid was dissolved in THF () and added dropwise to a THF suspension of $LiAlH_4$ (). After stirring at room temperature for 1 hour 2M HCl was added, followed by diethyl ether. The organic layer was subjected to standard aqueous workup to provide *N*-ethylhydroxy-5-benzyloxyindole in yield as a clear oil.

Step 3: *N*-Ethylhydroxy-5-benzyloxyindole (), acetic anhydride, triethylamine, and DMAP were stirred together in THF for 1 hour before standard aqueous workup provided *N*-ethylacetoxy-5-benzyloxyindole in yield as a clear oil.

Step 4: Compound 30 was prepared in a manner similar manner to compound 8, using *N*-ethylacetoxy-5-benzyloxyindole (2.00 g, 13.5 mmol), oxalyl chloride (1.18 mL, 13.5 mmol), acetamide (2.67 g, 40.5 mmol), and a 1M solution of KO^tBu (68.0 mL, 68.0 mmol). Standard workup and purification first by silica gel chromatography, eluting with 2:1 petroleum ether/ethyl acetate provided compound 42 as a deep red solid in 62% yield.

m.p. °C. ^{1}H NMR (200 MHz, DMSO-d^6) δ 10.72 (s, 1H), 8.36 (s, 1H), 7.55-7.31 (m, 7H), 6.98 (dd, J=2.0, 9.0Hz, 1H), 6.80 (s, 1H), 5.22 (s, 2H), 4.94 (t, J=5.1Hz, 1H), 4.28 (m, 2H), 3.70 (m, 2H).

Example 43: Synthesis of 3-(*N*-(*O*-acetoxyethyl)-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-74)

Example 44: Synthesis of *rac*-3-(*N*-(2,3-dihydroxypropyl)-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-)

Example 45: Synthesis of 3-(1*H*-5-methoxyindol-3-yl)-1*H*-pyrrole-2,5-diones (J-1-122)

Compound 44 was prepared in a manner similar manner to compound 19, using 5-methoxyindole (2.00 g, 13.5 mmol), oxalyl chloride (1.18 mL, 13.5 mmol), acetamide (2.67 g, 40.5 mmol), and a 1M solution of KO^{t}Bu (68.0 mL, 68.0 mmol). Standard workup and purification first by silica gel chromatography, eluting with 2:1 petroleum ether/ethyl acetate provided compound 33 as an light orange solid in 62% yield.

m.p. °C. ^{1}H NMR (200 MHz, DMSO-d^6) δ 11.95 (s, 1H), 10.71 (s, 1H), 8.31 (s, 1H), 7.40 (d, J=8.7Hz, 1H), 7.32 (d, J=2.2Hz, 1H), 6.87 (dd, J=2.2, 8.7Hz, 1H), 6.81 (s, 1H), 3.84 (s, 3H).

Example 46: Synthesis of 3-(*N*-tosyl-5-methoxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-1-175)

Compound 45 (70 mg, 0.289 mmol), triethylamine (48 μL, 0.347 mmol), DMAP (10 mg), and *p*-toluenesulfonyl chloride (66 mg, 0.347 mmol) were refluxed in THF (5 mL) for 48 hours. Standard aqueous workup and purification by silica gel chromatography, eluting with 2:1 petroleum ether/ethyl acetate, provided compound 46 in 43% yield, as a light yellow solid.

Example 47: Synthesis of 3-(*N*-(4-nitrobenzenesulfonyl)-5-methoxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-29)

Compound 45 (44 mg, 0.182 mmol), triethylamine (32 μL, 0.227 mmol), DMAP (2 mg), and 4-nitrobenzenesulfonyl chloride (50 mg, 0.227 mmol) were refluxed in THF (5 mL) for 48 hours.

Standard aqueous workup and purification by silica gel chromatography, eluting with 4:1 to 1:1 petroleum ether/ethyl acetate, provided compound 47 in 17% yield, as a light yellow solid. ^{1}H NMR (200 MHz, DMSO-d^{6}) δ 11.15 (s, 1H), 8.52 (s, 1H), 8.33 (br s, 4H), 7.91 (dd, J=1.1, 9.0Hz, 1H), 7.39 (s, 1H), 7.32 (s, 1H), 7.07 (d, J=9.1Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (74.8Hz, DMSO-d^{6}) δ 172.4, 172.2, 157.3, 151.1, 141.1, 136.0, 129.4, 128.9, 128.7, 128.2, 125.3, 123.6, 115.2, 114.3, 112.0, 104.2, 55.9.

Example 48: Synthesis of 3-(*N*-allyl-5-methoxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-40)

Step 1: *N*-Allyl-5-methoxyindole was prepared by general method A. 5-Methoxyindole (294 mg, 2.0 mmol) was dissolved in THF (10 mL) and treated with 1M KO^{t}Bu in THF (2.2 mL, 2.2 mmol). After stirring for 1 hour, allyl bromide (190 μL, 2.2 mmol) was added and the reaction mixture was stirred for an additional 2 hrs. Standard aqueous workup provided *N*-Allyl-5-methoxyindole as an off white solid, which was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (d, J=9.0Hz, 1H), 7.13 (d, J=2.5Hz, 1H), 7.09 (d, J=2.0Hz, 1H), 6.93 (dd, J=2.0, 9.0Hz, 1H), 6.51 (d, J=2.5Hz, 1H), 6.03 (tdd, J=5.4, 10.4, 19.7Hz, 1H), 5.23 (dd, J=1.1, 10.4Hz, 1H), 5.14 (dd, J=1.1, 16.9Hz, 1H), 4.90 (d, J=5.4Hz, 2H), 3.91 (s, 3H).

Step 2: Compound 48 was prepared from *N*-Allyl-5-methoxyindole in a similar fashion as that described for compound 20, using the crude *N*-Allyl-5-methoxyindole from above, oxalyl chloride (192 μL, 2.2 mmol), acetamide (360 mg, 6.0 mmol), and 1M THF solution of KO^{t}Bu (20 mL, 20.0 mmol). Standard workup and purification using silica gel chromatography, eluting with 4:1 to 1:1 petroleum ether/ethyl acetate, yielded a light yellow solid in 60% overall yield. ^{1}H NMR (200 MHz, DMSO-d^{6}) δ 10.75 (s, 1H), 8.34 (s, 1H), 7.45 (d, J=9.0Hz, 1H), 7.33 (d, J=2.0Hz, 1H), 6.91 (dd, J=2.0, 9.0Hz, 1H), 6.83 (s, 1H), 6.00 (tdd, J=5.4, 10.4, 19.7Hz, 1H), 5.19 (dd, J=1.1, 10.4Hz, 1H), 5.09 (dd, J=1.1, 16.9Hz, 1H), 4.90 (d, J=5.4Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (74.8Hz, DMSO-d^{6}) δ 173.4, 173.2, 155.5, 138.9, 133.7, 131.4, 126.9, 120.1, 117.6, 115.0, 112.8, 112.1, 104.5, 102.8, 55.7, 48.6.

Example 49: Synthesis of 3-(*N*-allyl-5-hydroxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-42)

Compound 48 (103 mg, 0.366 mmol) and BBr_3 (346 mL, 3.66 mmol) were refluxed together in CH_2Cl_2 for 16 hours. The resulting solution was treated with 2M HCl (5 mL) and extracted with ethyl acetate. A deep blue solid was filtered off, and the organic layer was

washed with water, dried over anhydrous Mg_2SO_3, filtered, and the solvent removed under reduced pressure. The resulting solid was purified by silica gel chromatography, eluting with 2:1 petroleum ether/ethyl acetate, to yield compound 49 as a pail yellow solid in 32% yield.

Example 50: Synthesis of 3-(*N*-tosyl-5-hydroxyindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-31)

Compound 47 (15 mg, 0.038 mmol) and BBr_3 (7.2 μL, 0.076 mmol) were refluxed together in CH_2Cl_2 for 16 hours. An additional 8 μL of BBr_3 was added and the reaction mixture was refluxed for an additional 24 hours. Standard aqueous/ethyl acetate workup and purification of the crude solid by silica gel chromatography, eluting with 2:1 petroleum ether/ethyl acetate, yielded compound 50 as a pail yellow solid in 57% yield.

^{13}C NMR (74.8Hz, DMSO-d^6) δ 172.3, 172.2, 154.9, 146.0, 136.7, 133.5, 130.4, 129.5, 128.9, 127.5, 126.9, 122.2, 114.9, 114.2, 110.7, 106.1, 21.0.

Example 51: Synthesis of 3-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (J-1-191)

Compound 51 was prepared in a manner similar manner to compound 20, using indole (4.00 g, 19.7 mmol), oxalyl chloride (1.47 mL, 19.7 mmol), acetamide (1.16 g, 19.7 mmol), and a 1M solution of KO^{t}Bu (59.1 mL, 59.1 mmol). Standard workup and purification by titration with acetone provided compound 51 as an orange solid 45% yield.

^1H NMR (200 MHz, DMSO-d^6) δ 12.01 (s, 1H), 10.76 (s, 1H), 8.36 (d, J=7.2Hz, 1H), 7.95 (d, J=6.8Hz, 1H), 7.52 (d, J=7.0Hz, 1H), 7.28-7.15 (m, 2H), 6.77 (s, 1H).

Example 52: Synthesis of 3-(*N*-(*p*-toluenesulfonyl)indol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-2)

Compound 51 (52 mg, 0.25 mmol), triethylamine (52 μL, 0.375 mmol), DMAP (10 mg), and *p*-toluenesulfonyl chloride (72 mg, 0.375 mmol) were refluxed in THF (5 mL) for 48 hours. Standard aqueous workup and purification by silica gel chromatography, eluting with 4:1 petroleum ether/ethyl acetate, provided compound 52 in 66% yield, as a light yellow solid.

^1H NMR (200 MHz, DMSO-d^6) δ 11.12 (s, 1H), 8.56 (s, 1H), 8.07 (d, J=7.7Hz, 1H), 8.02 (d, J=7.7Hz, 1H), 7.9 (d, J=8.7Hz, 2H), 7.42 (t, J=7.7Hz, 1H), 7.40 (d, J=8.3Hz, 2H), 7.37 (t, J=7.7Hz, 1H), 7.21 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (74.8Hz, DMSO-d^6) δ 172.4, 172.3, 146.3, 136.4, 133.9, 133.4, 130.6, 129.1, 127.6, 127.1, 126.0, 124.6, 123.0, 121.5, 113.4, 111.0, 21.1.

Example 53: Synthesis of 3-(*N*-(4-acetamindobenzenesulfonyl)indol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-3)

Compound 51 (52 mg, 0.25 mmol), triethylamine (52 μL, 0.375 mmol), DMAP (10 mg), and 4-acetamindobenzenesulfonyl chloride (88 mg, 0.375 mmol) were refluxed in THF (5 mL) for 48 hours. Standard aqueous workup and purification by silica gel chromatography, eluting with 2:1 to 1:1 petroleum ether/ethyl acetate, provided compound 53 in 33% yield, as a light yellow solid. ^{1}H NMR (200 MHz, DMSO-d^{6}) δ 11.11 (s, 1H), 10.44 (s, 1H), 8.56 (s, 1H), 8.15 (d, J=6.5Hz, 1H), 8.02 (d, J=9.0Hz, 2H), 7.95 (d, J=6.5Hz, 1H), 7.75 (d, J=9.0Hz, 2H), 7.46 (t, J=6.5Hz, 1H), 7.37 (t, J=6.5Hz, 1H), 7.20 (s, 1H), 2.03 (s, 3H). ^{13}C NMR (74.8Hz, DMSO-d^{6}) δ 172.5, 172.3, 169.3, 145.2, 136.5, 133.8, 129.2, 128.7, 125.9, 124.5, 122.8, 121.9, 121.6, 121.5, 119.0, 113.3, 110.8, 24.1.

Example 54: Synthesis of 3-(*N*-(2-nitrobenzenesulfonyl)indol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-6)

Compound 51 (52 mg, 0.25 mmol), triethylamine (52 μL, 0.375 mmol), DMAP (10 mg), and 2-nitrobenzenesulfonyl chloride (56 mg, 0.25 mmol) were refluxed in THF (5 mL) for 48 hours. Standard aqueous workup and purification by silica gel chromatography, eluting with 2:1 petroleum ether/ethyl acetate, provided compound 54 in 44% yield, as a light yellow solid.

Example 55: Synthesis of 3-(*N*-(4-nitrobenzenesulfonyl)indol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-7)

Compound 51 (52 mg, 0.25 mmol), triethylamine (52 μL, 0.375 mmol), DMAP (10 mg), and 2-nitrobenzenesulfonyl chloride (56 mg, 0.25 mmol) were refluxed in THF (5 mL) for 48 hours. Standard aqueous workup and purification by silica gel chromatography, eluting with 2:1 petroleum ether/ethyl acetate, provided compound 55 in 11% yield, as a light yellow solid. ^{1}H NMR (200 MHz, DMSO-d^{6}) δ 11.16 (s, 1H), 8.58 (s, 1H), 8.36 (br s, 4H), 8.09 (d, J=7.0Hz, 1H)8.03 (d, J=7.0Hz, 1H), 7.51 (t, J=7.0Hz, 1H), 7.41 (t, J=7.0Hz, 1H), 7.26 (s, 1H). ^{13}C NMR (74.8Hz, DMSO-d^{6}) δ 172.3, 172.1, 151.1, 141.1, 133.8, 130.9, 128.8, 128.7, 127.6, 126.4, 125.3, 125.0, 123.7, 121.7, 113.3, 111.9.

Example 56: Synthesis of 3-(*N*-(2-thiophenesulfonyl)indol-3-yl)-1*H*-pyrrole-2,5-dione

(J-3-8)

Compound 51 (52 mg, 0.25 mmol), triethylamine (52 μL, 0.375 mmol), DMAP (10 mg), and 2-thiophenesulfonyl chloride (66 mg, 0.375 mmol) were refluxed in THF (5 mL) for 48 hours. Standard aqueous workup and purification by silica gel chromatography, eluting with 2:1 petroleum ether/ethyl acetate, provided compound 56 in 58% yield, as an off white solid.
^{1}H NMR (200 MHz, DMSO-d^6) δ 11.12 (br s, 1H), 8.47 (s, 1H), 8.04-7.97 (m, 3H), 7.45 (t, J=7.5Hz, 1H), 7.38 (t. J=7.5Hz, 1H), 7.19-7.15 (m, 2H). ^{13}C NMR (74.8Hz, DMSO-d^6) δ 172.5, 172.3, 137.4, 136.3, 135.7 (2), 133.9, 128.8 (2), 127.7, 126.2, 125.0, 123.2, 121.7, 113.5, 111.6.

Example 57: Synthesis of 3-(*N*-octanesulfonylindol-3-yl)-1*H*-pyrrole-2,5-dione (J-3-11)
Compound 51 (52 mg, 0.25 mmol) was dissolved in THF (5 mL) and treated with a 1.0M THF solution of KO^{t}Bu (250 μL, 0.25 mmol). To the resulting deep red solution was added neat butanesulfonyl chloride (36 μL, 0.257 mmol) and this mixture was stirred for 16 hours. Standard aqueous workup and purification by silica gel chromatography, eluting with 3:1 petroleum ether/ethyl acetate, provided compound 57 in 10% yield, as red semi-solid.

Example 58: Synthesis of 3-(1*H*-5-chloroindol-3-yl)-1*H*-pyrrole-2,5-dione (PT-1-126)
Compound 51 was prepared in a manner similar manner to compound 8, using 5-chloroindole (1.00 g, 6.60 mmol), oxalyl chloride (633 μL, 7.26 mmol), acetamide (1.19 g, 19.8 mmol), and a 1M solution of KO^{t}Bu (38.0 mL, 33.0 mmol). Standard workup and purification by tituration with acetone provided compound 58 as a light orange solid in 5% yield.
^{1}H NMR (200 MHz, DMSO-d^6) δ 12.14 (br s, 1H), 10.78 (br s, 1H), 8.38 (s, 1H), 8.00 (s, 1H), 7.51 (d, J=8.6 Hz, 1H), 7.25 (d, J=1.6 Hz, 1H), 6.89 (s, 1H).

Example 59: Synthesis of 3-(1*H*-6-chloroindol-3-yl)-1*H*-pyrrole-2,5-dione (PT-1-128)
Compound 59 was prepared in a manner similar manner to compound 20, using 6-chloroindole (500 mg, 3.30 mmol), oxalyl chloride (317 μL, 3.62=3 mmol), acetamide (590 mg, 9.90 mmol), and a 1M solution of KO^{t}Bu (16.5 mL, 16.5 mmol). Standard workup and purification by tituration with acetone provided compound 59 as a light orange solid in 43% yield.

^{1}H NMR (200 MHz, DMSO-d^6) δ 12.07 (br s, 1H), 10.79 (r s, 1H), 8.37 (d, J=2.4 Hz, 1H), 7.99 (d, J=8.5Hz, 1H), 7.56 (s, 1H), 7.18 (d, J=8.5 Hz, 1H), 6.83 (s, 1H). ^{13}C NMR (57.3 MHz, DMSO-d^6) δ 173.2, 172.9, 138.9, 137.1, 131.7, 127.5, 124.3, 121.7, 121.4, 116.2, 112.2, 105.4.

Example 60: Synthesis of 3-(1*H*-7-chloroindol-3-yl)-1*H*-pyrrole-2,5-dione (PT-1-142)

Compound 60 was prepared in a manner similar manner to compound 20using 7-chloroindole (500 mg, 3.30 mmol), oxalyl chloride (317 μL, 3.62 mmol), acetamide (590 mg, 9.90 mmol), and a 1M solution of KO^{t}Bu (16.5 mL, 16.5 mmol). Standard workup and purification by tituration with acetone provided compound 60 as a light orange solid in 37% yield.

^{1}H NMR (200 MHz, DMSO-d^6) δ 12.39 (br s, 1H), 10.84 (br s, 1H), 8.32 (d, J=3.1Hz, 1H), 7.98 (d, J=8.0 Hz, 1H), 7.35 (d, J=7.6Hz, 1H), 7.20 (t, J=7.9Hz, 1H), 6.90 (s, 1H).

Example 61: Synthesis of 3-(1*H*-5-flouroindol-3-yl)-1*H*-pyrrole-2,5-dione (PT-1-130)

Compound 61 was prepared in a manner similar manner to compound 20, using 5-fluoroindole (500 mg, 3.70 mmol), oxalyl chloride (355 μL, 4.07 mmol), acetamide (655 mg, 11.1 mmol), and a 1M solution of KO^{t}Bu (18.5 mL, 18.5 mmol). Standard workup and purification by titration with acetone provided compound 61 as a light orange solid 36% yield.

^{1}H NMR (200 MHz, DMSO-d^6) δ 12.07 (br s, 1H), 10.74 (br s, 1H), 8.40 (d, J=2.7 Hz, 1H), 7.52 (dd, J=4.8Hz, 8.9Hz, 1H), 7.09 (m, 1H), 6.86 (s, 1H).

Example 62: Synthesis of 3-(1*H*-6-flouroindol-3-yl)-1*H*-pyrrole-2,5-dione (PT-1-132)

Compound 62 was prepared in a manner similar manner to compound 20, using 6-fluoroindole (500 mg, 3.70 mmol), oxalyl chloride (355 μL, 4.07 mmol), acetamide (655 mg, 11.1 mmol), and a 1M solution of KO^{t}Bu (18.5 mL, 18.5 mmol). Standard workup and purification by titration with acetone provided compound 62 as a light orange solid 15% yield.

^{1}H NMR (200MHz, DMSOD$_6$)δ12.02 (br s, 1H), 10.77 (br s, 1H), 8.33 (d, J=3.0Hz, 1H), 7.96 (dd, J=8.9Hz, 5,2Hz, 1H), 7.30 (dd, J=10.4Hz, 2.3Hz, 1H), 7.04 (dt, J=7.3Hz, 2.3Hz, 1H), 6.83 (s, 1H).

Example 63: Synthesis of 3-(1-*H*-5-benzyloxyindol-3-yl)-1*H*-pyrrole-2-one-5-thione (J-3-36)

Compound 63 was prepared in a manner similar manner to compound 20, using 5-benzyloxyindole (223 mg, 1.0 mmol), oxalyl chloride (96 μL, 1.1 mmol), thioacetamide (250 mg, 3.3 mmol), and a 1M solution of KO^{t}Bu (5.0 mL, 5.0 mmol). Standard workup and purification by tituration with acetone provided compound 63 as a red solid 19% yield.
^{1}H NMR (200 MHz, DMSO-d^6) δ 12.07 (s, 1H), 11.93 (s, 1H), 8.38 (d, J=2.8Hz, 1H), 7.53-7.31 (m, 7H), 7.01 (s, 1H), 6.97 (dd, J=2.0, 8.8Hz, 1H), 5.22 (s, 2H).

Example 64: High/Low Potassium Assay

CGNs were harvested from day 8/9 post-natal CD1 mice, plated on Poly-D-Lycine coated plates and incubated for 6 days at 37 °C, with 25 mM potassium, under 5% CO_2. Pretreated cells were treated with drug 24 hours prior to changing the media to one containing 5 mM potassium and drug. Cells were assayed 16 hours after the final media change using cell TITER96 (Promaga)..

Example	CONC.	CGN HK/LK % Survival 24 hour pretreatment	no pretreatment
K252a	10 um		
	1 um	toxic	
	250 nm	41.5	
CEP 1347	10 um		
	3 um	0T	
	1 um	71.72;47.1;56.25;60.79;87.46;91.32; 0T; 35.8T	49.85
	300 nm	37.37; 41.04	
	250 nm	58.95;41.63;	
	100 nm	0;25.89;39.72; 34.2	33.12
	30 nm	3.66; 3.14	
	10 nm	17.37; 0; 0	0
1	10 uM	47.89;37.05;63.0;39.5; 40.22	51.92
	3 uM	31.94	
	1 uM	28.17;3.90;48.0;30.98; 26.58	0
	300 nM	0	
	100 nM	0	0
2	10 uM	32.74	
	1 uM	35.1	
	0.1 uM	6.48	
3	10 uM	84.85;70.63;93.85;76.11T; 70.80; 80.56	71.33
	5 uM	50.14;	
	3 uM	36.85; 52.52	
	1 uM	40.56;21.51;57.93;18.64; 19.38; 14.28	28.64
	300 nM	0; 5.41	
	100 nM	24.69; 0; 4.56	18.16
8	10 uM	94.45; 104.14	
	3 uM	37.64	
	1 uM	24.82; 33.64	
	300 nm	29.15	
	100 nm	11.84;28.09	
9	10 uM	72.25; 54.98	
	3 uM	41.48	
	1 uM	31.2; 39.27	
	300 nm	27.52	
	100 nm	5.51; 30.47	
	1 uM	0	
20	10 uM	24.13; 14.9	
	1uM	0	
21	10 uM	7.38; 2.02	

	1 uM	0	
22	10 uM	0	
23	10 uM	51.83;63.91	
	1 uM	0	
	0.1 uM	0	
24	10 uM	toxic	
	5 uM	27.69	
	1 uM	25.69;2.75;8.0	
	0.1 uM	0	
25	10 uM	toxic	
	1 uM	16.56;0	
	0.1 uM	0	
26	10 uM	0	
	1 uM	28.07	
27	10 uM	46.09;71.88;38.79; 66.1; 60.63T	77.07
	3 uM	36.94; 16.3	
	1 uM	16.12;50.56;13.36; 24.26; 13.58	42.5
	300 nM	0; 13.76	
	100 nM	0; 1.02; 9.39	24.65
28	10 uM	70.5	
	3 uM	10.1	
	1 uM	4	
	300 nM	0	
	100 nM	0	
29		BnO/Bn	
30	10 uM	93.2T	
	1 uM	0	
31	10 uM	toxic	
	1 uM	2.02	
32	10 uM	T	
	1 uM	10.75	
	100 nM	0	
33		BnO/n-Bn	
34		BnO/MeO2Bn	
35		2-F	
36		3-F	
37		4-F	
38		1.48	
39	10 uM	43.99; 28.64	
	3 uM	18.09	
	1 uM	12.62	
	300 nM	9.34	
40		cy	
41		oct	
42	10 uM	21.1	
	1 uM	6.6	
43	10 uM	6.1	
	1 uM	5.6	
44		CH2CH(OH)CH2OH	
45	10 uM	31.68;25.27	
	1 uM	15.46	
	100 nM	0	
46	10 uM	43.22;34.22;11.98	26.52
	1 uM	15.63;0;0	14.37
	100 nM	0	10.34
47	10 uM	T	

	1 uM	8.82
48		MeO/allyl
49	10 uM	39.77; 35.35
	3 uM	21.41
	1 uM	6.77
	300 nM	3.29
50	10 uM	2.83T
	1 uM	
51	10 uM	34.74
52	10 uM	30.09T
	1 uM	
53	10 uM	10.35T
	1 uM	
54	10 uM	64.94; 55.60
	3 uM	18.18
	1 uM	0
	300 nM	0
	100 nM	0
55	10 uM	66.2; 36.61
	3 uM	8.57
	1 uM	0
	300 nM	0
	100 nM	0
56	10 uM	21.32T
	1 uM	
57	10 uM	0
60	10 uM	3.4
	1 uM	0

Example 65: β-Amyloid Aggregation Assay

CGNs were harvested from day 8/9 post-natal CD1 mice, plated on Poly-D-Lycine coated plates and incubated for 6 days at 37 °C under 5% CO_2. Pretreated cells were treated with drug 24 hours prior to A-β (25 uM) and drug addition. Cells were assayed 5 days after A-β addition using cell TITER96 (Promaga)..

Example	CONC.	CGN HK/LK % Survival 24 hour pretreatment	no etreatement
K252a	10 um		
	1 um		
	250 nm		
CEP 1347	3 um	0T	
	1 um	81.59T;79.01T; 54.02T; 0T	0T
	300 nm	0T	
	250 nm		
	100 nm	36.15; 0T	32.3
	30 nm	0	
	10 nm	3.69; 7.42	31.77
1	10 uM	19.81;51.92; 46.78; 4.27	61.68
	3 uM	0	
	1 uM	48.86; 33.03; 0	42.73
	300 nM	0	
	100 nM	54.35; 13.13	0
3	10 uM	74.74;79.64T; 72.38T; 63.67	95.48T
	5 uM		
	3 uM	0	
	1 uM	6.22;54.63; 5.71; 0	1.55
	300 nM	0	
	100 nM	10.67; 0	0
24	1 uM	0	
	0.1 uM	1.11	
25	10 uM		
	1 uM	26.11	
	0.1 uM	5.61	
26	10 uM	86.18;92.86; 116.47; 88.13	102.65
	3 uM	72.45	
	1 uM	55.66; 57.73; 0	0
	300 nM	0	
	100 nM	24.59; 0	25.2
36	10 uM	66.38; 98.85	29.26
	1 uM	0; 14.87	0
	100 nM	0	0
50	10 uM	471.7T	
54	10 uM	0	
	3 uM	0	
	1 uM	0	
	300 nM	6.37	

	100 nM	0
55	10 uM	6.29
	3 uM	0
	1 uM	0
	300 nM	4.8
	100 nM	8.38

Example 66: Ceramide and Glutamate Assays

CGNs were harvested from day 8/9 post-natal CD1 mice, plated on Poly-D-Lycine coated plates and incubated for 6 days at 37 °C under 5% CO_2. Pretreated cells were treated with drug 24 hours prior to glutamate (100 uM) and drug addition. Cells that were not pretreated with drug were treated with media containing drug and either ceramide (100 uM) or glutamate (100 uM) Cells were assayed 16 hours after final drug treatments using cell TITER96 (Promaga)..

Example	CONC.	CGN % Survival Ceramide	Glutamate (24-pre)	Glutamate (no-pre)
K252a	250 nm	0	4.25	
CEP 1347	1 um	3.86;0;0	22.76;0;0;0	0
	300 nm			
	250 nm	0	49.96	
	100 nm		0	0
	30 nm			
	10 nm		0	1.55
1	10 uM	10.73	6.64;31.33	11.94
	1 uM	11.36	16.81;17.06	1.35
	100 nM		0.01	9.79
3	10 uM	17.97	0;0	0
	1 uM	19.63	1.95;0	0
	100 nM		0	0
24	1 uM	5.13	0	
	0.1 uM	0	0	
25	10 uM			
	1 uM	0	0	
	0.1 uM	0	0	
26	10 uM			
	1 uM			
27	10 uM	5.11	19.56;45.26	18.48
	3 uM			
	1 uM	17.86	8.2;0	6.44
	300 nM			
	100 nM		0	6.78
46	10 uM	9.11	23.02;0	0
	1 uM	1.36	0;0	0
	100 nM		2.49	0

Example 66: Cisplatin Assays

CGNs were harvested from day 8/9 post-natal CD1 mice, plated on Poly-D-Lycine coated plates and incubated for 6 days at 37 °C under 5% CO_2. The cells were treated with media containing drug and cisplatin (25 mg/mL). Cells were assayed 48 hours after final drug treatments using cell TITER96 (Promaga)..

Example	**CONC.**	CGN % Survival
3	10 mM	74.86
27	10 mM	72.88

Example 67: Etoposide Assays

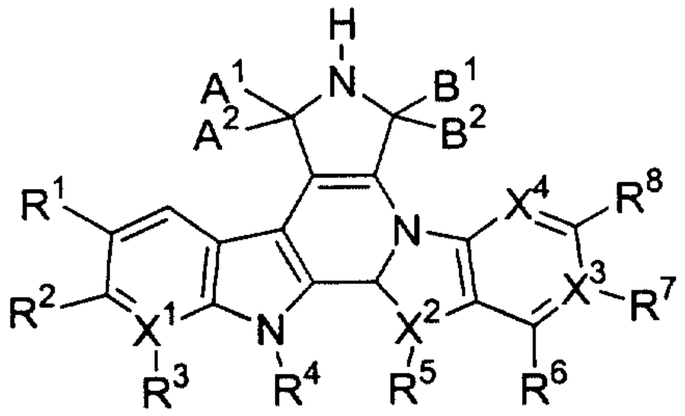
CGNs were harvested from day 8/9 post-natal CD1 mice, plated on Poly-D-Lycine coated plates and incubated for 6 days at 37 °C under 5% CO_2. The cells were treated with media containing drug and etoposide (50 uM). Cells were assayed 48 hours after final drug treatments using cell TITER96 (Promaga).

SHSY-5Y cells were grown in grouth media. Cells are placed at 50,000 cells per 96 well. Four days latter the cells were treated with drug for 48 hours prior to etoposide (32 uM) treatment. On day 6 media was changed to that containing etoposide and drug for 4 hours, at which poin the media was changed to media containing drug only. Cells are allowed to survive overnight and then assessed for viability with metabolic activity measured (WST-1 – Beohringer Mannheime).

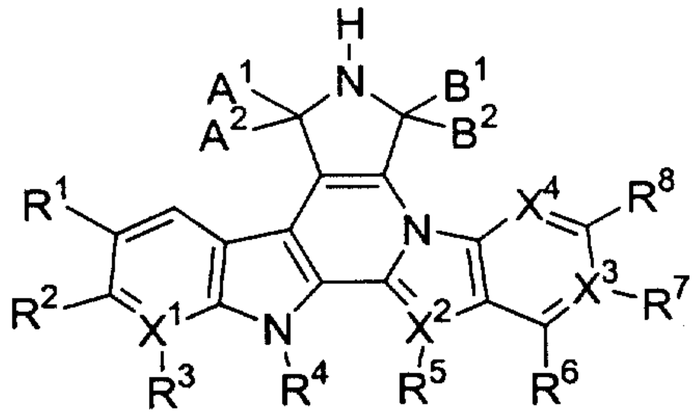
Example	CONC.	CGN % Survival	SHSY-5Y % Survival
K252a	1 um		13.9
	250 nm	2.91	
CEP 1347	10 um		
	3 um		
	1 um	5.75;15.5;18.47	12.5
	300 nm		
	250 nm	2.5	
1	10 uM	0	
	1 uM	0	
3	10 uM	18.09	
	1 uM	2.69	
24	1 uM	0	
	0.1 uM	0	
25	1 uM	0	
	0.1 uM	0	
26	10 uM	3.94	
	1 uM	0.36	
45	10 uM		4.65
46	10 uM	6.04	
	1 uM	1.73	

Claims:

1. Indolocarbazole K252a derivatives represented by one of the following formulae (I) and (II):



I



II

or a pharmaceutically acceptable salt thereof

wherein:

II is the fully oxidized derivative of I;

A^1 and A^2 are hydrogen, A^1 and A^2 together represent oxygen, or A^1 is hydroxyl and A^2 is hydrogen;

B^1 and B^2 are hydrogen, B^1 and B^2 together represent oxygen, or A^1 is hydroxyl and A^2 is hydrogen;

R^1, R^2, R^3 (when X^1 is C), R^6, R^7 (when X^3 is C), and R^8 is selected from, or a combination of, the groups consisting of:

a) hydrogen, lower alkyl, halogen, nitro, NRR (wherein R and R is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl; carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl);

b) -OR, wherein R is selected from the group consisting of;

   1) hydrogen, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

c) $-O(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of:

1) hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl;
2) OR;
3) SR;

d) -SR, wherein R is selected from the group consisting of;
1) hydrogen, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

e) $-S(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of:
1) hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl;
2) OR;
3) SR;

f) -CH=CH-R, wherein the stereochemisrty is either E or Z, and R is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively);

g) $-(CH_2)_jR$, wherein j is 2 to 6, and R is hydrogen, halogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively);

h) $-CH_2OR$, wherein R is hydrogen, substituted lowed alkyl, unsubstituted lower alkyl;

R^4 is selected from the group consisting of:

a) H, substituted lower alkyl, unsubstituted lower alkyl; substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

b) -$(CH_2)_jCH_2OR$, where j is 0 to 4 and where R and R is selected from the group consisting of:

1) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylcarbonyl, substituted arylcarbonyl or unsubstituted arylcarbonyl, CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, a sugar moiety as described in f) below;

c) -$CH_2CH(OR)CH_2OR$, where R and R is selected from the group consisting of;

1) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle;

d) $CO(CH_2)_jR$, wherein j is 1 to 6, and R is selected from the group consisting of;

1) hydrogen or a halogen;

2) NRR, werein R and R independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, or R and R are joined in a ring with the nitrogen atom to form a heterocyclic group;

3) substituted aryl, unsubstituted aryl, substituted heterocycle, unsubstituted heterocycle;

4) COR, wherein R is selected from the group consisting of;

i) OH;

ii) R is the same as R;

iii) NRR, wherein R and R are the same as R and R, respectively;

e) SO_2R, wherein R is selected from the group consisting of;

1) -$(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of;

a) H, halogen;

b) OR, wherein R is selected from the group consisting of;

i) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylcarbonyl, substituted arylcarbonyl or unsubstituted arylcarbonyl, CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, a sugar moiety as described in f) above;

b) NRR, werein R and R independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-substituted heterocycle, or R and R are joined in a ring with the nitrogen atom to form a heterocyclic group.

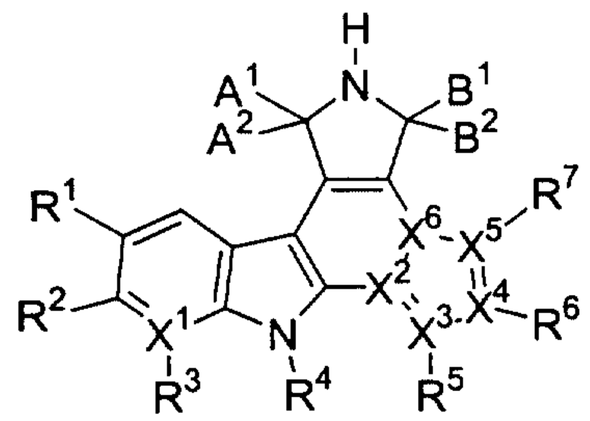
2) unsubstituted aryl, substituted aryl, unsubstituted heteroaryl, substituted heteroaryl;

f) a sugar moiety being of either the α- or β-antipoid, including, but not limited to the substitited or unsubstituted sugars glucose, fructose, galactose, maltose, ribose, and glucosamine;

when X^2 is C, R^5 is selected from the group consisting of:

X^1, X^2, and X^3 are either C or N, such that R^3 is a lone pair when X^1 is N, R^5 is a lone pair when X^2 is N, and R^7 is a lone pair when X^3 is N; and
X^4 is either CH or N.

2. Compounds represented by the following formula:



III

or a pharmaceutically acceptable salt thereof

wherein:

A^1 and A^2 are hydrogen, A^1 and A^2 together represent oxygen, or A^1 is hydroxyl and A^2 is hydrogen;

B^1 and B^2 are hydrogen, B^1 and B^2 together represent oxygen, or A^1 is hydroxyl and A^2 is hydrogen;

R^1, R^2, R^3 (when X^1 is C), R^5 (when X^3 is C), R^6 (when X^4 is C), and R^7 (when X^5 is C), is selected from, or a combination of, the groups consisting of:

a) hydrogen, lower alkyl, halogen, nitro, NRR (wherein R and R is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl);

b) -OR, wherein R is selected from the group consisting of;

   1) hydrogen, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

c) $-O(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of:

   1) hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl;

   2) OR;

   3) SR;

d) -SR, wherein R is selected from the group consisting of;

1) hydrogen, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

e) $-S(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of:

1) hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl;

2) OR;

3) SR;

f) -CH=CH-R, wherein the stereochemisrty is either E or Z, and R is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively);

g) $-(CH_2)_jR$, wherein j is 2 to 6, and R is hydrogen, halogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively);

h) $–CH_2OR$, wherein R is hydrogen, substituted lowed alkyl, unsubstituted lower alkyl;

R^4 is selected from the group consisting of:

a) H, substituted lower alkyl, unsubstituted lower alkyl;

b) $-(CH_2)_jCH_2OR$, where j is 0 to 4 and where R and R is selected from the group consisting of:

1) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylcarbonyl, substituted arylcarbonyl or unsubstituted arylcarbonyl, CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, a sugar moiety as described in f) below;

c) $-CH_2CH(OR)CH_2OR$, where R and R is selected from the group consisting of;

1) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle;

d) $CO(CH_2)_jR$, wherein j is 1 to 6, and R is selected from the group consisting of;

1) hydrogen or a halogen;

2) NRR, werein R and R independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, or R and R are joined in a ring with the nitrogen atom to form a heterocyclic group;

3) substituted aryl, unsubstituted aryl, substituted heterocycle, unsubstituted heterocycle;

4) COR, wherein R is selected from the group consisting of;

i) OH;

ii) R is the same as R;

iii) NRR, wherein R and R are the same as R and R, respectively;

e) SO_2R, wherein R is selected from the group consisting of;

1) $-(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of;

a) H, halogen;

b) OR, wherein R is selected from the group consisting of;

i) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylcarbonyl, substituted arylcarbonyl or unsubstituted arylcarbonyl, CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, a sugar moiety as described in f) above;

b) NRR, werein R and R independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-substituted heterocycle, or R and R are joined in a ring with the nitrogen atom to form a heterocyclic group.

2) unsubstituted aryl, substituted aryl, unsubstituted heteroaryl, substituted heteroaryl;

f) a sugar moiety being of either the α- or β-antipoid, including, but not limited to the substitited or unsubstituted sugars glucose, fructose, galactose, maltose, ribose, and glucosamine;

when X^2 is C, R^5 is selected from the group consisting of:

X^1, X^2, and X^3 are either C or N, such that R^3 is a lone pair when X^1 is N, R^5 is a lone pair when X^2 is N, and R^7 is a lone pair when X^3 is N;

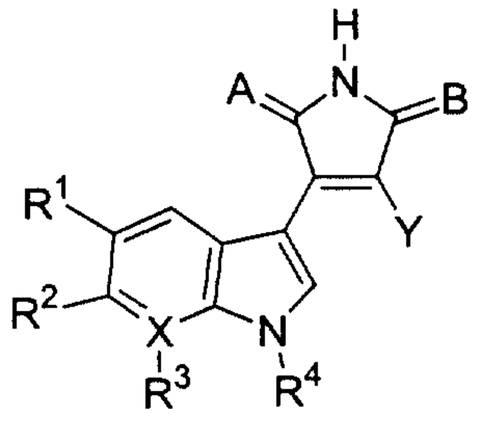
X^4 is selected from the group consisting of;

a) C;

b) N; and

c) NR, wherein R is hydrogen, halogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively).

3. A 3-(indol-3-yl)-1*H*-pyrrole-2,5-dione compound, represented by the following formula:



IV

or a pharmaceutically acceptable salt thereof

wherein:

A^1 and A^2 are hydrogen, A^1 and A^2 together represent oxygen, or A^1 is hydroxyl and A^2 is hydrogen;

B^1 and B^2 are hydrogen, B^1 and B^2 together represent oxygen, or A^1 is hydroxyl and A^2 is hydrogen;

R^1, R^2, R^3 (when X is C), is selected from, or a combination of, the groups consisting of:

a) hydrogen, lower alkyl, halogen, nitro, NRR (wherein R and R is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl);

b) -OR, wherein R is selected from the group consisting of;

1) hydrogen, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

c) $-O(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of:

1) hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl;

2) OR;

3) SR;

d) -SR, wherein R is selected from the group consisting of;

1) hydrogen, acyl, substituted lower alkylcarbonyl, unsubstituted lower alkylcarbonyl, substituted arylcarbonyl, unsubstituted arylcarbonyl;

e) $-S(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of:

1) hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl;

2) OR;

3) SR;

f) -CH=CH-R, wherein the stereochemisrty is either E or Z, and R is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively);

g) $-(CH_2)_jR$, wherein j is 2 to 6, and R is hydrogen, halogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, CO_2R (wherein R is the same as R), CONRR , OR (wherein R is the same as R), or NRR (wherein R and R are the same as R and R, respectively);

h) $-CH_2OR$, wherein R is hydrogen, substituted lowed alkyl, unsubstituted lower alkyl;

R^4 is selected from the group consisting of:

a) H, substituted lower alkyl, unsubstituted lower alkyl;

b) $-(CH_2)_jCH_2OR$, where j is 0 to 4 and where R and R is selected from the group consisting of:

1) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylcarbonyl, substituted arylcarbonyl or unsubstituted arylcarbonyl, CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, a sugar moiety as described in f) below;

c) $-CH_2CH(OR)CH_2OR$, where R and R is selected from the group consisting of;

1) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle;

d) $CO(CH_2)_jR$, wherein j is 1 to 6, and R is selected from the group consisting of;

1) hydrogen or a halogen;

2) NRR, werein R and R independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, or R and R are joined in a ring with the nitrogen atom to form a heterocyclic group;

3) substituted aryl, unsubstituted aryl, substituted heterocycle, unsubstituted heterocycle;

4) COR, wherein R is selected from the group consisting of;

i) OH;

ii) R is the same as R;

iii) NRR, wherein R and R are the same as R and R, respectively;

e) SO_2R, wherein R is selected from the group consisting of;

1) $-(CH_2)_jR$, wherein j is 1 to 8, and R is selected from the group consisting of;

a) H, halogen;

b) OR, wherein R is selected from the group consisting of;

i) hydrogen, lower substituted alkyl, lower unsubstituted alkyl, acyl, lower alkylcarbonyl, substituted arylcarbonyl or unsubstituted arylcarbonyl, CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-unsubstituted heterocycle, a sugar moiety as described in f) above;

b) NRR, werein R and R independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl), CH_2-substituted aryl, CH_2-unsubstituted aryl, CH_2-substituted heterocycle, CH_2-substituted heterocycle, or R and R are joined in a ring with the nitrogen atom to form a heterocyclic group.

2) unsubstituted aryl, substituted aryl; unsubstituted heteroaryl, substituted heteroaryl;

f) a sugar moiety being of either the α- or β-antipoid, including, but not limited to the substitited or unsubstituted sugars glucose, fructose, galactose, maltose, ribose, and glucosamine;

X is C or N, such that R^3 is a lone pair when X^1 is N; and

Y is hydrogen or halogen.

4. Use of a compound according to any one of claims 1 to 3 for prevention or treatment of condition selected from the group consisting of neurodegenerative diseases, inflammatory diseases, conditions resulting in loss of growth and cellular differentiation control, and cancer.

5. Treatment or prevention of a condition selected from the group consisting of neurodegenerative diseases, inflammatory diseases, conditions resulting in loss of growth and cellular differentiation control, and cancer by administration of an effective amound of the compound according to any one of claims 1 to 3 to a patient in need thereof.

6. Use of a compound according to any one of claims 1 to 3 for altering signal transduction.

7. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to any one of claims 1 to 3 in combination with a pharmaceutically acceptable carrier.

8. A pharmaceutical package comprising the pharmaceutical composition according to claim 7 in combination with directions for use.