SUBSTITUTED BISINDOLYLMALEIMIDES FOR THE INHIBITION OF CELL PROLIFERATION

The present invention is directed to certain substituted pyrroles that are anti-proliferative agents. These compounds and their pharmaceutically acceptable salts are useful in the treatment or control of cell proliferative disorders, in particular cancer. The invention is also directed to pharmaceutical compositions containing such compounds, and to methods for the treatment and/or prevention of cancer, particularly the treatment or control of solid tumors.

Background of the Invention

Uncontrolled cell proliferation is the hallmark of cancer. Cancerous tumor cells typically have some form of damage to the genes that directly or indirectly regulate the cell-division cycle. Much research has been expended in the study of antiproliferative agents. While many agents have been identified having desired antiproliferative activities, many of these agents have various drawbacks, including poor solubility, molecular complexity, etc., which may render them either unsuitable or inconvenient for therapeutic use in human patients. There continues to be a need for small molecule compounds that may be readily synthesized, are effective as cancer therapeutic agents and are suitable for continuous infusion delivery to patients. It is thus an object of this invention to provide such compounds as well as pharmaceutical compositions containing such compounds.

Definitions

As used herein, the following terms shall have the following definitions.

"Alkenyl" means a straight-chain or branched aliphatic unsaturated hydrocarbon having 1 to 15 carbon atoms, preferably 1 to 10 carbon atoms, most preferably 1 to 6 carbon atoms.

"Alkoxy" means an alkyl or alkenyl group that is attached to the remainder of the molecule by oxygen (e.g. RO-, such as methoxy, ethoxy, etc.).

"Aryl" means an aromatic ring having 5 to 10 atoms and consisting of 1 or 2 rings, which optionally may include one or more heteroatoms that are the same or different. For the purposes of this definition, aryl includes heteroaryl. Preferred heteroatoms include nitrogen, sulfur, or oxygen, singly or in any combination, in place of one or more of the carbons. Examples of aryl groups within this definition are phenyl, pyridine, imidazole, pyrrole, triazole, furan, pyrimidine.

"Cycloalkyl" means a non-aromatic, partially or completely saturated cyclic aliphatic hydrocarbon group containing 3 to 8 atoms. Examples of cycloalkyl groups include cyclopropyl, cyclopentyl and cyclohexyl.

"Effective amount" means an amount of at least one compound of Formula I or a pharmaceutically acceptable salt thereof that significantly inhibits proliferation and/or prevents differentiation of a human tumor cell, including human tumor cell lines.

"Hetero atom" means an atom selected from nitrogen, sulfur and oxygen. Hetero atoms are independently selected and may replace one or more carbon atoms.

"Heterocycle" means a 3- to 10- membered non-aromatic, partially or completely saturated hydrocarbon group that contains at least one hetero atom. Such ring systems include, morpholine, pyrrolidine, piperidine, piperazine

"IC_{50}" refers to the concentration of a particular compound according to the invention required to inhibit 50% of a specific measured activity. IC_{50} can be measured, *inter alia*, as is described in Example 15, *infra*.

"Lower alkyl" denotes a straight-chain or branched saturated aliphatic hydrocarbon having 1 to 6, preferably 1 to 4, carbon atoms. Lower alkyl groups may be substituted as specifically provided *infra*. In addition the alkyl chain may include one or more hetero atoms in lieu of one or more carbon atoms. Typical lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, 2-butyl, pentyl, hexyl, and the like.

"Pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid and nitric acid, and those derived from organic acids such as acetic acid, tartaric acid, salicylic acid, methanesulfonic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Sample base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide.

"Pharmaceutically acceptable," such as pharmaceutically acceptable carrier, excipient, etc., means pharmacologically acceptable and substantially non-toxic to the subject to which the particular compound is administered.

"Pharmaceutically active metabolite" means a metabolic product of a compound of formula I which is pharmaceutically acceptable and effective.

"Polyethylene glycol" or "PEG" groups represent structures of the general formula $R^9(OCH_2CH_2)_nOH$, where n is on average between 2 and 1500, preferably 15 to 150, with an average molecular weight of 500 to 5000 Daltons, and wherein R^9 is carboxy or lower alkyl, preferably methyl or ethyl.

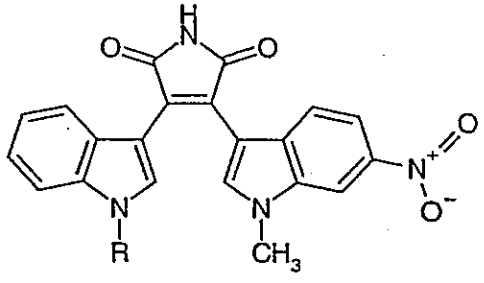
"Prodrug" refers to a compound that may be converted under physiological conditions or by solvolysis to a pharmaceutical active compound. A prodrug may be inactive when administered to a subject but is converted *in vivo* to an active compound.

"Substituted," as in substituted alkyl, means that the substitution can occur at one or more positions and, unless otherwise indicated, that the substituents at each substitution site are independently selected from the specified options.

"Substituted amino" means an amino group, which is mono- or di-substituted with another group, preferably lower alkyl (e.g. methyl, or ethyl).

Detailed Description of the Invention

Specifically, the invention relates to substituted pyrroles having the formula:



I

and pharmaceutically acceptable salts of the foregoing compounds, wherein:

R is selected from the group consisting of $-PO_3R^1R^2$, $-CHR^3OCOR^4$, $-CHR^3OCO_2R^4$, $-CHR^3OCONHR^4$ and $-COR^4$;

R^1 and R^2 are selected from the group consisting of H, Na and NH_4, and are the same unless either R^1 or R^2 is H, in which case the other can be different, or alternatively, R^1 and R^2 together represent Ca;

R^3 is selected from the group consisting of H or methyl;

R^4 is selected from a group consisting of

lower alkyl, which may be optionally substituted by one or more substituents selected from the group consisting of $-CO_2R^5$, $-NR^6R^7$, polyethylene glycol, $-OPO_3R^1R^2$, hydroxy, alkoxy, and aryl,

alkenyl, which may be optionally substituted by one or more substituents selected from the group consisting of $-CO_2R^5$, $-NR^6R^7$, polyethylene glycol, $-OPO_3R^1R^2$, hydroxy, alkoxy, and aryl,

cycloalkyl, which may be optionally substituted by one or more substituents selected from the group consisting of $-CO_2R^5$, $-NR^6R^7$, polyethylene glycol, $-OPO_3R^1R^2$, hydroxy, alkoxy, and aryl.

heterocycle, which when including N as a hetero atom the N optionally may be substituted with $-COR^8$, and

aryl which optionally may be substituted by one or more substituents selected from the group consisting of $-CO_2R^5$, hydroxy, alkoxy, polyethylene glycol, $-OPO_3R^1R^2$, and lower alkyl which itself may be substituted with hydroxy, carboxy, and substituted amino;

R^5 is selected from the group consisting of H, Na, or lower alkyl;

R^6 and R^7 are each independently selected from H, lower alkyl, and COR^8, or alternatively, the group-NR^6R^7 forms a 5 or 6 membered heterocyclic ring; and

R^8 is lower alkyl, which optionally may be substituted with a polyethylene glycol.

The compounds of this invention have antiproliferative activity, specifically, they inhibit cell division in G2/M phase of the cell cycle and are generally referred to as "G2/M phase cell-cycle" inhibitors. These compounds are soluble prodrugs of an active metabolite of an anticancer therapeutic agent within U. S. Patent 5,057,614 (Davis et al.), and are thus suitable for continuous infusion delivery.

The present invention is further directed to pharmaceutical compositions comprising a pharmaceutical effective amount of any one or more of the above-described compounds and a pharmaceutical acceptable carrier or excipient.

The present invention is further directed to the use of any one or more of the above-described compounds for the preparation of medicaments for the treatment of cell proliferative disorders, particular cancer, e. g. solid tumors, breast, colon, or lung cancer.

The present invention is also directed to a method for treating solid tumors, in particular breast or colon tumors, by administering to a human patient in need of such therapy an effective amount of a compound of formula I and/or its pharmaceutical acceptable salts.

In a preferred embodiment of the compounds of formula I, R is $-CHR^3OCOR^4$. Most preferably R^3 is H and R^4 is lower alkyl that is substituted with polyethylene glycol.

In another preferred embodiment of the compounds of formula I, R is $-COR^4$. More preferably, R^4 is selected from the group consisting of heterocycle and lower alkyl, most preferably lower alkyl that is substituted with $-NR^6R^7$.

In another preferred embodiment of the compounds of formula I, the polyethylene glycol has a molecular weight of from about 750 to about 5000 Daltons, most preferably about 2000 Daltons.

The following are examples of preferred compounds of formula I:

3-[2-(2-Methoxy-ethoxy)-ethoxy]-propionic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester;

O-[2-[[2,5-dihydro-3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-pyrrol-3-yl]-indol-1-yl]methoxycarbonyl]ethyl]-O'-methylpolyethylene glycol 2000;

2,3-Dimethoxy-benzoic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester;

3-Diethylaminomethyl-benzoic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester hydrochloride;

3-(1H-Indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-1-octadec-9-enoyl-pyrrole-2,5-dione;

{3-[4-(1-Methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-phosphonic acid;

3-(1-Acetyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione;

Trifluoro-acetic acid 3-(1-methyl-6-nitro-1H-indol-3-yl)-4-[1-(piperidine-4-carbonyl)-1H-indol-3-yl]-pyrrole-2,5-dione;

3-(1-Aminoacetyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione hydrochloride;

Acetic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester;

Pentanedioic acid mono-{3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl} ester;

2,3-Dimethoxy-benzoic acid 1-{3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-ethyl ester; and

3-Diethylaminomethyl-benzoic acid 1-{3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-ethyl ester hydrochloride.

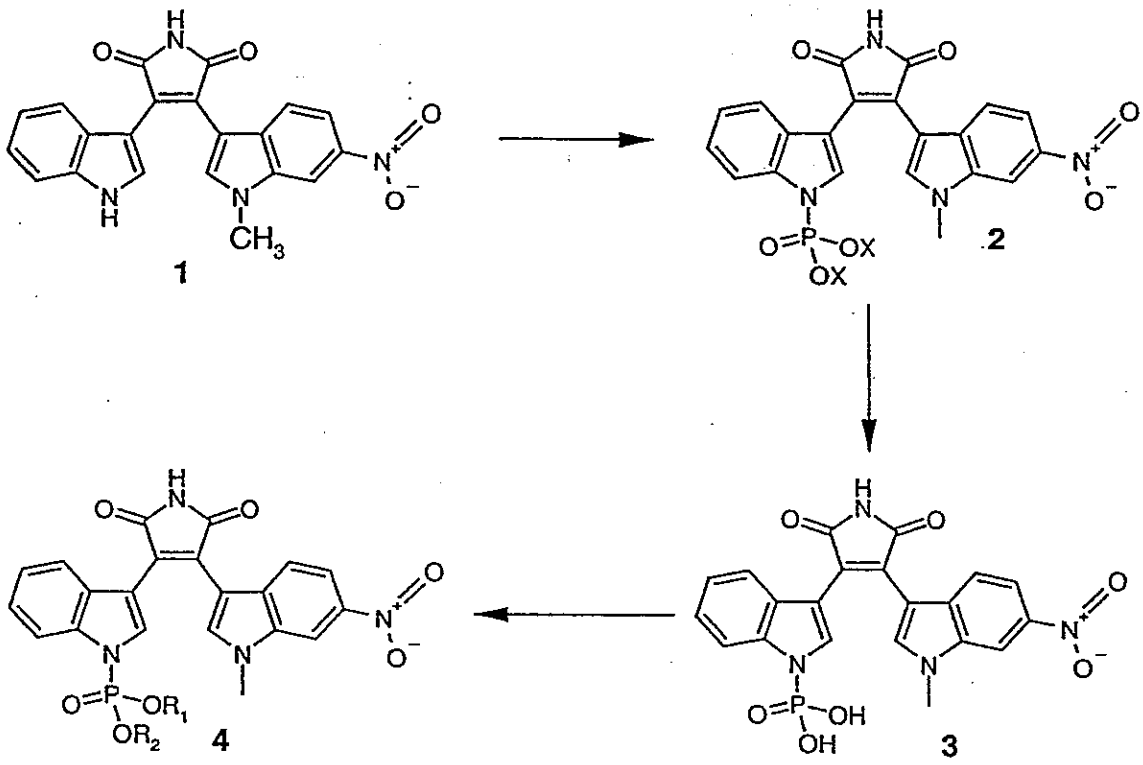
The compounds disclosed herein and covered by the above formulae may exhibit tautomerism or structural isomerism. It is intended that the invention encompasses any tautomeric or structural isomeric form of these compounds, or mixtures of such forms, and is not limited to any one tautomeric or structural isomeric form utilized within the formulae drawn above.

Synthesis of Compounds According to the Invention

The compounds of the invention may be prepared by processes known in the art. Suitable processes for synthesizing these compounds are provided in the examples. Generally, these compounds may be prepared as set forth in claim 18.

More specifically, compounds of formula I, in which R signifies $-PO_3R^1R^2$, and in which R^1 and R^2 are as described above, may be prepared as indicated in scheme I below.

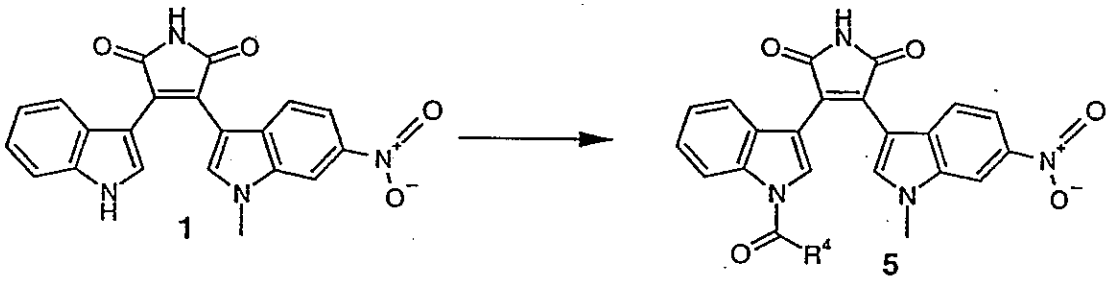
Scheme I



As indicated in scheme I, 3-(1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (**1**), (prepared as described in copending USSN 09/268,887, the relevant portions of which are herein incorporated by reference), was treated with a suitably protected chlorophosphonate in the presence of a strong base, such as lithium bis(trimethylsilyl)amide, in an appropriate solvent such as THF, to afford the protected phosphonic acid derivative **2**, in which X represents a suitable protecting group known to those skilled in the art, such as benzyl. Removal of the protecting groups may be achieved by any of the standard methods known to those skilled in the art to give the phosphonic acid **3**. In particular, when X represents a benzyl group, the protective groups are removed by using cyclohexadiene and palladium on carbon as a catalyst. Compound 3 can then be converted to its salt **4**, such as a monosodium salt, by standard methods also known to those skilled in the art.

Compounds of formula I, in which R signifies -COR4, may be prepared according to scheme II below.

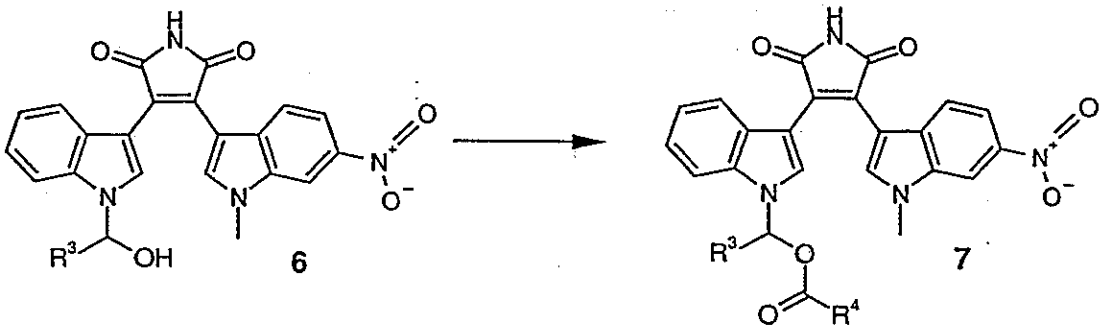
Scheme II



Typically, 3-(1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (compound **1**, prepared as described above in Scheme I) is deprotonated in a aprotic solvent such as THF at -60°C using a strong base such as lithium bis(trimethylsiliyl)amide. The resulting anion is then treated with a known acid chloride or an acid chloride prepared by known methods. Alternatively, compound 1 may be coupled to a known carboxylic acid, or a carboxylic acid prepared by known methods, using standard amide bond formation procedures, such as diisopropylcarbodiimide and HOBt. Compound **5** wherein R^4 contains a suitably protected carboxyl, hydroxyalkyl, amino or monoalkylamino, may be further modified by removing the protective group by known methods, and then optionally modifying the resulting carboxyl, hydroxy, or amino group to the desired amide or ester by methods known to those skilled in the art.

Compounds of the general formula I in which R signifies $-CHR^3OCOR^4$, can be prepared according to scheme III below.

Scheme III



As indicated in Scheme III above, the hydroxy alkyl derivative **6** is esterified using known procedures. Typically, compound **6** is treated with a known carboxylic acid or a carboxylic acid prepared by known methods, in a solvent such as methylene chloride in the presence of EDC and dimethylaminopyridine for several hours at room temperature. Alternatively, the hydroxy intermediate **6** may be treated with a known acid chloride or an acid chloride prepared from known methods. Alternatively, the hydroxy intermediate **6** may be treated with a known acid anhydride or an acid anhydride prepared from known methods.

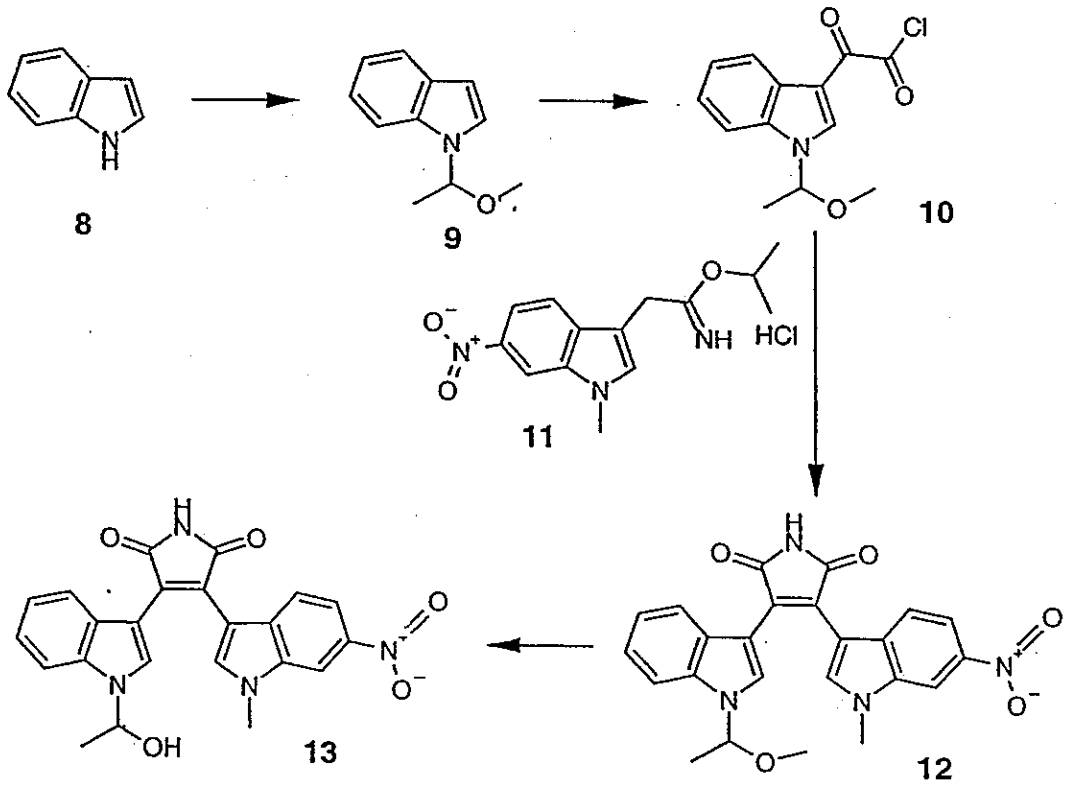
To prepare compound **7** wherein R^4 contains a heteroaromatic ring, the heteroatom, such as N, may be further modified by reaction with an alkyl iodide, such as $-CH_3I$, in a solvent such as acetonitrile.

Alternatively compound **7** where in R^4 contains a suitably protected carboxyl, hydroxyalkyl, amino or monoalkylamino, may be further modified by removing the protecting group by known methods, and then optionally modifying the resulting carboxyl, hydroxy, or amino group to the desired amide or ester by methods known to those skilled in the art.

The starting material 6 wherein R^3 signifies H, can be prepared also as described in US pat appl 09/268,887 (Compound II), the relevant portions of which are herein incorporated by reference.

Starting material 6 wherein R^3 signifies methyl may be prepared pursuant to Scheme IV below.

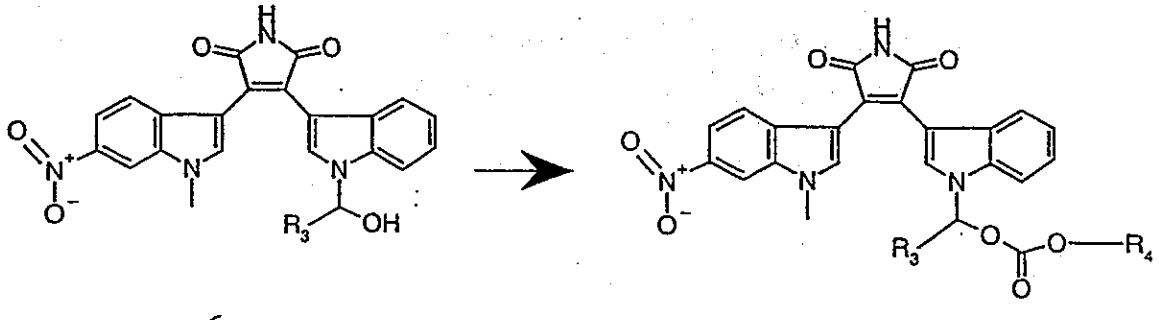
Scheme IV



Compound 8 is commercially available (for example from Aldrich).

Compounds of the general formula I in which R signifies $-CHR^3OCO_2R^4$, and in which R^3 and R^4 are as described above, may be prepared pursuant to scheme V below.

Scheme V

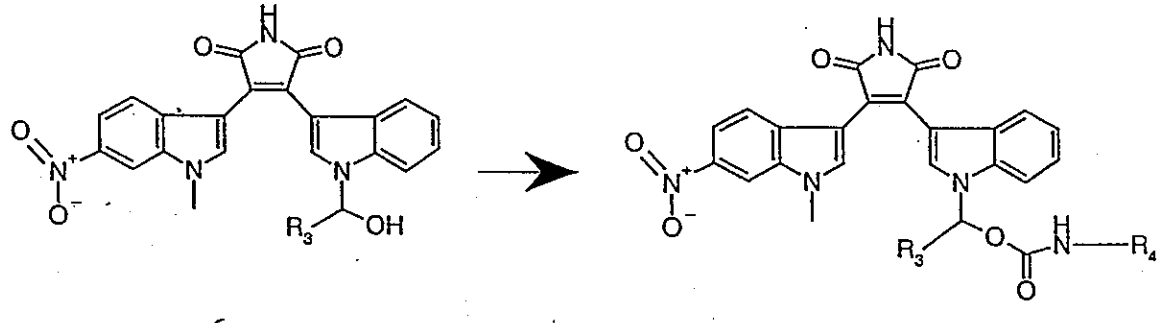


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Typically, the hydroxy alkyl derivative **6** is treated with a known chloroformate or a chloroformate prepared using known procedures, in a solvent such as dichloromethane at temperatures of –78 to 20, in the presence of dimethylaminopyridine to afford the desired carbonate **14**.

Compounds of the general formula I in which R signifies $-CHR^3OCONHR^4$, and in which R^3 and R^4 are as described above, may be prepared according to scheme VI below.

Scheme VI



6 15

Typically, hydroxymethyl intermediate 6 is deprotonated using a strong base such as lithium bis(trimethylsilyl)amide in a solvent such as THF at 0º C. The anion generated is then treated in the same solvent with bis(p-nitrophenyl)carbonate, followed by a known amine or an amine prepared using known procedures.

Acidic compounds of formula I may be converted into a pharmaceutically acceptable salt by treatment with a suitable base by processes known to those skilled in the art. Suitable salts are those derived not only from inorganic bases, for example, sodium, potassium or calcium salts, but also from organic bases such as ethylenediamine, monoethanolamine or diethanolamine. The conversion of a basic compound of formula I into a pharmaceutically acceptable salt can be carried out by treatment with a suitable acid in a known manner. Suitable salts are those derived not only from inorganic acids, for example, hydrochlorides, hydrobromides, phosphates or sulphates, but also from organic acids, for example, acetates, citrates, fumarates, tartrates, maleates, methanesulphonates or p-toluenesulphonates.

Compositions/Formulations

In an alternative embodiment, the present invention is directed to pharmaceutical compositions comprising at least one compound of formula I or a pharmaceutically acceptable salt thereof.

These pharmaceutical compositions can be administered orally, for example, in the form of tablets, coated tablets, dragees, hard or soft gelatin capsules, solutions, emulsions or suspensions. They can also be administered rectally, for example, in the form of suppositories. In particular, however, the compounds of the present invention are suitable for parenteral administration, for example, in the form of injection solutions.

The pharmaceutical compositions of the present invention comprising compounds of formula I, prodrugs of such compounds, or the salts thereof, may be manufactured in a manner that is known in the art, *e.g.* by means of conventional mixing, encapsulating, dissolving, granulating, emulsifying, entrapping, dragee-making, or lyophilizing processes. These pharmaceutical preparations can be formulated with therapeutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, steric acid or its salts can be used as such carriers

for tablets, coated tablets, dragees and hard gelatin capsules. Suitable carriers for soft gelatin capsules include vegetable oils, waxes and fats. Depending on the nature of the active substance, no carriers are generally required in the case of soft gelatin capsules. Suitable carriers for the manufacture of solutions and syrups are water, polyols, saccharose, invert sugar and glucose. Suitable carriers for injection are water, alcohols, polyols, glycerine, vegetable oils, phospholipids and surfactants. Suitable carriers for suppositories are natural or hardened oils, waxes, fats and semi-liquid polyols.

The pharmaceutical preparations can also contain preserving agents, solubilizing agents, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain other therapeutically valuable substances, including additional active ingredients other than those of formula I.

Dosages

As mentioned above, the compounds of the present invention are useful in the treatment or control of cell proliferative disorders, in particular oncological disorders. These compounds and formulations containing said compounds are particularly useful in the treatment or control of solid tumors, such as, for example, breast and colon tumors.

A therapeutically effective amount of a compound in accordance with this invention means an amount of compound that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is within the skill in the art.

The therapeutically effective amount or dosage of a compound according to this invention can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, in the case of oral or parenteral

administration to adult humans weighing approximately 70 Kg, a daily dosage of about 10 mg to about 10,000 mg, preferably from about 200 mg to about 1,000 mg, should be appropriate, although the upper limit may be exceeded when indicated. The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration, it may be given as continuous infusion.

Examples

The compounds of the present invention may be synthesized according to known techniques, such as, for example, the general schemes provided above. The following examples illustrate preferred methods for synthesizing the compounds and formulations of the present invention.

Example 1: 3-[2-(2-Methoxy-ethoxy)-ethoxy]-propionic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester

A suspension of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.HCl ("EDC•HCL"; Aldrich, 77 mg, 0.40 mmol) in dry THF (12 ml) was treated with DMAP (Aldrich) (55 mg, 0.45 mmol) for 2 min at 22°C. To this was added 3-(1-hydroxymethyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione(110 mg, 0.26 mmol) (prepared below). The mixture was stirred for 20 min and to this was added 2-(2-methoxy-ethoxy)-ethoxy]-propionic acid (CAS: 209542-49-4) (120 mg, 0.62 mmol). Stirring was continued at 22°C for 4 hr. All solvent was evaporated and the product was purified by silica gel chromatography to give 130 mg of 3-[2-(2-methoxy-ethoxy)-ethoxy]-propionic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester. (Yield 80 %)

3-(1-hydroxymethyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione was prepared as described in USSN 09/268,887 (Compound II), the relevant portions of which are herein incorporated by reference.

Example 2: O-[2-[[2,5-dihydro-3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-pyrrol-3-yl]-indol-1-yl]methoxycarbonyl]ethyl]-O'-methylpolyethylene glycol 2000

To a solution of 3-(1-hydroxymethyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (200 mg, 0.5 mmol) (prepared as described above in Example 1) in dichloromethane was added at –78°C, triethylamine (0.6 mmol) followed by O-(2-carboxyethyl)-O'-methyl polyethylene glycol 2000 acid chloride (0.6 mmol) (prepared by standard methods from mono-methyl polyethylene glycol 2000 propanoic acid). The solution was stirred at room temperature for 3 hours, and the solvent was evaporated. The residue was purified by silica gel flash chromatography to yield 1 gm of O-[2-[[2,5-dihydro-3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-pyrrol-3-yl]-indol-1-yl]methoxycarbonyl]ethyl]-O'-methylpolyethylene glycol 2000. (Yield 80%).

Example 3: Using the same procedure as in example 2 the following compounds were prepared:

a) 2,3-Dimethoxy-benzoic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester;

b) 3-Diethylaminomethyl-benzoic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester hydrochloride.

Example 4: 3-(1H-Indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-1-octadec-9-enoyl-pyrrole-2,5-dione

A solution of 3-(1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (250 mg, 0.65 mmol), prepared as described in USSN 09/268,887, was dissolved in THF (15 ml) and cooled to -60°C. To this solution was added lithium bis(trimethylsilyl)amide (0.7 mmol, 0.7 ml, 1.0 M in THF), followed by oleyl chloride (Aldrich) (0.300 g, 1.0 mmol) in THF (5 ml). The resulting mixture was stirred at 0°C for 1 hr. All solvent was evaporated and the crude material was pre-purified by silica gel chromatography. The resulting products were separated using silica gel

chromatography using a gradient of ethyl acetate and hexane. This gave 310 mg of 3-(1H-Indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-1-octadec-9-enoyl-pyrrole-2,5-dione. (Yield 70 %)

Example 5: {3-[4-(1-Methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-phosphonic acid

a) A solution of 3-(1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (210 mg, 0.55 mmol), prepared as described in USSN 09/268,887, in THF (150 ml) and cooled to -70°C. To this solution was added lithium bis(trimethylsilyl)amide (1.5 mmol, 1.5 ml, 2.5 eq, 1.0 M in THF). To this was added dibenzyl chlorophosphate (CAS: 538-37-4) (500mg, 1.6 mmol) in THF (5 ml). The cooling bath was removed and when the temperature of the solution reached -40°C, the solution was poured in water and extracted into ethyl acetate/hexane (1:4). The organics were washed with water, dried and evaporated. The residue was purified and separated into component products by silica gel chromatography using a gradient of ethyl acetate/hexane. This gave 150 mg of {3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-phosphonic acid dibenzyl ester. (Yield 43 %).

b) A solution of {3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-phosphonic acid dibenzyl ester (50 mg, 0.08 mmol) (from step a) above) in a mixture of THF/ethanol (3 ml/6 ml) was treated with 10% Pd/C (75 mg) and 1,4-cyclohexadiene (0.5 ml) and warmed to 35-40°C for 2 hr. The reaction was cooled, filtered through celite and evaporated to dryness. Crystals were obtained from THF/hexane to yielding 20 mg of {3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-phosphonic acid. (Yield 55 %)

Example 6: 3-(1-Acetyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione

A solution of 3-(1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (51 mg, 0.13 mmol), prepared as described in USSN 09/268,887, in THF (20 ml) and cooled to -70°C. To this solution was added lithium bis(trimethylsilyl)amide (0.5 mmol, 0.5 ml, 3.8 eq, 1.0 M in THF, followed by excess acetyl chloride (0.1 ml). The resulting solution was stirred until the temperature reached -45°C. The reaction was evaporated and purified by silica gel chromatography to give 33 mg of 3-(1-acetyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione. (Yield 65 %).

Example 7: Trifluoro-acetic acid 3-(1-methyl-6-nitro-1H-indol-3-yl)-4-[1-(piperidine-4-carbonyl)-1H-indol-3-yl]-pyrrole-2,5-dione

1.5 equivalents of N-(tert-butoxycarbonyl)-piperidine-4-carboxylic acid (Bachem, CA) were added to a solution of 3-(1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (prepared as described in USSN 09/268,887 (Compound 1), the relevant portions of which are herein incorporated by reference) in THF. 1.3 equivalents each of diisopropyl carbodiimide and N-Hydroxybenztriazole were added. This solution was stirred at RT for 6.5 hrs. A small amount of Cesium carbonate and 0.5 ml DMF were added. The reaction was stirred for 20 min. The reaction mixture was then diluted with CH_2Cl_2 and washed with saturated NH_4Cl and water. The product was purified by flash chromatography. (Yield 92%). The resulting BOC protected amine was dissolved in CH_2Cl_2 and treated with trifluoroacetic acid at RT for 1 hr. The solvent was evaporated and the residue was purified by HPLC yielding trifluoro-acetic acid; 3-(1-methyl-6-nitro-1H-indol-3-yl)-4-[1-(piperidine-4-carbonyl)-1H-indol-3-yl]-pyrrole-2,5-dione. (Yield 54%).

Example 8: 3-(1-Aminoacetyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione hydrochloride

1.05 equivalents of N-(tert-butoxycarbonyl)glycine (Bachem, CA) and 1 equivalent of 3-(1H-Indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (prepared as

above) were dissolved in THF. 1.3 equivalent each of N-hydroxybenzotriazole and diisopropylcarbodiimide were added and the reaction was stirred for 5 hrs. A small amount of Cesium carbonate and DMF were added. The reaction was stirred for 30 min. The reaction mixture was diluted with ethyl acetate and ether, washed with water and dried over sodium sulfate. The resulting 3-[N-butyloxycarbonyl-(1-aminoacetyl-1H-indol-3-yl)]-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione was purified on a Prep TLC plate. (Yield 53%). The BOC-protected product was dissolved in THF and 12N HCl was added dropwise. The reaction was stirred at RT for 2 hrs. The reaction was concentrated under a stream of N_2 and purified by HPLC, to afford 0.026 g 3-(1-aminoacetyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione. (Yield 95%).

Example 9: Acetic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester

A slurry of 3-(1-hydroxymethyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (120 mg, 0.288 mmol) (prepared as described in USSN 09/268,887 (Compound II)) in 3 mL of acetic anhydride (Aldrich) was stirred at room temperature for 19 hours, and at 100 ° C for 2.5 hours. The resulting solution was cooled, diluted with water, and extracted with EtOAc. The EtOAc layer was washed with water, brine, dried over magnesium sulfate, and evaporated. The residue was purified by flash chromatography using EtOAc/hexanes to give 77.1 mg of acetic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester. (Yield 53%).

Example 10: Pentanedioic acid mono-{3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl} ester

A solution of 3-(1-hydroxymethyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione(103 mg, 0.248 mmol), (prepared as described above in Example 1), glutaryl anhydride (35.1 mg, 0.308 mol) (Aldrich), and triethylamine (0.03 ml, 0.924 mmol) in 5 mL of EtOAc was heated at reflux for 6 hours. The solution was

cooled, diluted with EtOAc, washed with 0.5 N HCl, water, brine, dried over magnesium sulfate, and evaporated. The residue was purified by flash chromatography using EtOAc/acetone to give 35 mg of pentanedioic acid mono-{3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl} ester. (Yield 27 %).

Example 11: 2,3-Dimethoxy-benzoic acid 1-{3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-ethyl ester

a) To a suspension of NaH (1.92 gm of a 60% dispersion in oil) in 75 mL of DMF was added indole (4.68 gm, 40 mmol) (Aldrich). The mixture was stirred for 15 minutes at 0 °C, and 1-chloroethyl methylether (4 mL) was added dropwise. The resulting mixture was stirred at 0 °C for 1 hour and poured over ice/water, and extracted with toluene. The organic layer was dried over magnesium sulfate, and evaporated. The residue was purified by flash chromatography using EtOAc/hexanes to give 4 gm of 1-[1-methoxyethyl]indole. (Yield 58%).

b) To a solution of 1-(1-methoxyethyl)indole (4 gm, 23 mmol) (prepared as in step a) above) in anhydrous diethyl ether at 0 °C was added oxalyl chloride (4.2 mL, 48 mmol) over 5 minutes. The resulting slurry was stirred at 0 °C for 5 hours, and filtered to afford 1.9 gm of [1-(1-methoxy-ethyl)-1H-indol-3-yl]-oxo-acetyl chloride. (Yield 31%). The material was used without further purification.

c) To a slurry of [1-(1-methoxy-ethyl)-1H-indol-3-yl]-oxo-acetyl chloride (1.9 gm, 7.15 mmol) (from step b) above) and [1-methyl-6-nitro-1H-indol]-3-ethenimidic acid 1-methylethyl ester hydrochloride (2.3 gm, 7.3 mmol) (Compound **15** in Scheme 2 of USSN 09/268,887) in 75 mL of CH_2Cl_2 at 0 C, was added triethylamine (3.6 mL, 25.8 mmol) over 3 minutes. The mixture was stirred at 0 °C for 4 hours, and extracted with 0.5 N HCl. The aqueous layer was extracted with CH_2Cl_2, and the combined CH_2Cl_2 layers were washed with water, brine, dried over magnesium sulfate, and evaporated. The residue was dissolved in 70 mL of toluene and the

resulting solution was cooled to 0 C. p-toluenesulfonic acid hydrate (1.4 gm, 7.36 mmol) was added and the mixture was stirred at 0 °C for 1 hour. The slurry was washed with saturated $NaHCO_3$ and extracted with 2 X 50 mL of EtOAc. The combined EtOAC layers were dried over magnesium sulfate and evaporated to give 4.1 gm (Yield 100%) of 3-[1-(1-methoxy-ethyl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione as a red gummy solid which was used without purification.

d) To a solution of 3-[1-(1-methoxy-ethyl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (3.75 gm) (from step c) above) in 100 mL of THF was added 2 N HCl (75 mL). The solution was stirred at room temperature for 3 hours, and poured into EtOAc and brine. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined EtOAc layers were dried over magnesium sulfate, and evaporated. The residue was purified by flash chromatography using EtOAc/hexanes to give 1.1 gm (Yield 33%) of 3-[1-(1-hydroxy-ethyl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione.

e) To a solution of 3-[1-(1-hydroxy-ethyl)-1H-indol-3-yl]-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (165.3 mg, 0.678 mmol) (from step d) above), EDC•HCL (284.5 mg, 1.484 mmol), and dimethylaminopyridine (185.5 mg, 1.58 mmol) in 20 mL of CH_2Cl_2 was added 2,3-dimethoxybenzoic acid (287.4 mg, 0.668 mmol). The solution was stirred at room temperature for 0.5 hour, washed with saturated $NaHCO_3$, brine, dried over magnesium sulfate, and evaporated. The residue was purified by flash chromatography using EtOAc/hexanes to give 203 mg of 2,3-dimethoxy-benzoic acid 1-{3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-ethyl ester. (Yield 50%).

Example 12: 3-Diethylaminomethyl-benzoic acid 1-{3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-ethyl ester hydrochloride

3-Diethylaminomethyl-benzoic acid 1-{3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-ethyl ester hydrochloride was prepared according to the procedure of Example 11 e above using 3-diethylaminomethylbenzoic acid (*CAS*:137605-77-7) as a starting material. (Yield 50 %).

Example 13: Carbonic acid mono-methylpolyethyleneglycol 2000 ester, 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethylester

Monomethylpolyethyleneglycol (average MW=2000)(1 g, 0.5mmol) was treated with excess 20% phosgene in toluene solution at room temperature for 24 hours and evaporated. The resulting chloroformate in dichloromethane was added to a dry ice/acetone cooled mixture of 3-(1-hydroxymethyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (208 mg, 0.5 mmol) (prepared as described above in Example 1) and 4-dimethylaminopyridine (244 mg, 2mmol) in dichloromethane. The cooling bath was removed and the mixture stirred at room temperature for one hour. The reaction mixture was purified by flash chromatography using methanol/dichloromethane followed by crystallization of the product fractions from THF/ethyl ether to give 0.8 g of carbonic acid mono-methylpolyethyleneglycol 2000 ester, 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethylester, as an orange solid, mp 46-48. (Yield 65%).

Example 14: Mono-methylpolyethyleneglycol 2000-carbamic acid, 3-[4-(1-methyl-6-nitro-1H-indo-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]indol-1-ylmethyl ester

Lithium bis(trimethylsilyl)amide (0.25mL, 0.25 mmol, 1M in THF) was added dropwise to a solution of 3-(1-hydroxymethyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione (104 mg, 0.25 mmol) (prepared as described above in Example 1) in THF (5 mL) at 0º C. After 10 minutes bis(p-nitrophenyl)carbonate (84

mg, 0.275 mmol) was added and the solution was stirred at 0º C for 10 minutes. Methoxy-PEG2000-amine (0.6 g, 0.3 mmol) (Shearwater Polymers, Inc.) was added and the mixture was warmed to ~40º C to dissolve the solids. The resulting solution was stirred at room temperature for 2 hours and evaporated to remove solvents. The residue was chromatographed on silica gel using methanol/dichloromethane followed by crystallization of the product fractions from THF/ethyl ether to give 0.425 g of mono-methylpolyethyleneglycol 2000-carbamic acid, 3-[4-(1-methyl-6-nitro-1H-indo-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]indol-1-ylmethyl ester, as an orange solid, mp 49-51º C.(Yield 70%)

Example 15: Antiproliferative Activity

The antiproliferative activity of the compounds of the invention is demonstrated below. These effects indicate that the compounds of the present invention are useful in treating cancer, in particular solid tumors such as breast and colon tumors.

MDAMB-435 Cell-Based Assay

The epithelial breast carcinoma cell line (MDAMB-435) was purchased from ATCC (American Type Cell Culture Collection) and was grown in culture in medium as recommended by ATCC. For analysis of the effect of various compounds of formula I on the growth of these cells, the cells were plated at a concentration of 1500 cells/well in a 96 well tissue culture plate ("test plate). The day after the cells were plated, the compounds to be analyzed were dissolved in 100% DMSO (dimethyl sulfoxide) to yield at 10mM stock solution. Each compound was diluted in H_2O to 1mM and was added to triplicate wells in the first row of a 96 well master plate containing medium to yield a final concentration of 40µM. The compounds were then serially diluted in medium in the "master plate". The diluted compound(s) were then transferred to test plates containing cells. A row of vehicle "control cells"

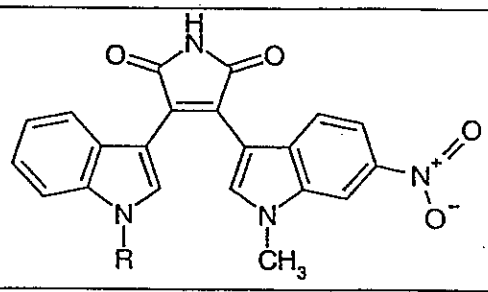
received DMSO. The final concentration of DMSO in each well was 0.1%. 5 days post drug addition, the plate was analyzed as described below.

MTT (3-(4-5 methyl thiazole-2-yl)-2,5-diphenyl tetrazolium bromide; thiazolyl blue) was added to each well to yield a final concentration of 1mg/ml. The plate was then incubated at 37°C for 2 1/2 - 3 hours. The MTT- containing medium was then removed and 50µl of 100% ethanol was added to each well to dissolve the formazan. The absorbencies were then read using an automated plate reader (Bio-tek microplate reader). IC_{50}measurements were calculated using the Reed and Munsch equation, *see* Am. J. Hygiene Vol. 27 pgs. 493-497,1938.

The results of the foregoing *in vitro* experiments are set forth in Table I below.

Each of the compounds in Table I had an $IC_{50} \leq 0.3$ µM.

TABLE I



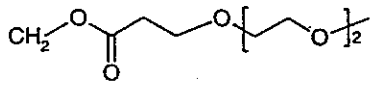
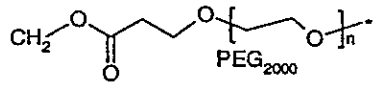
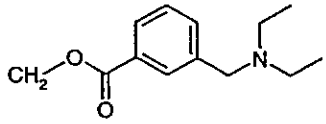
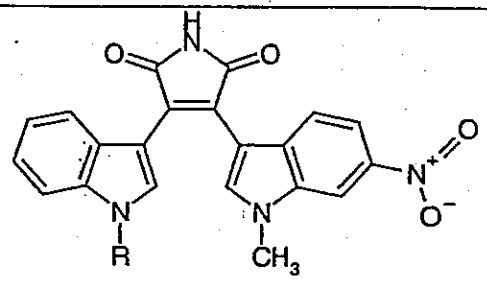
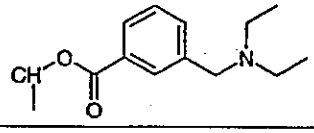
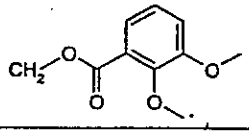
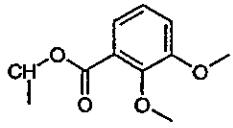
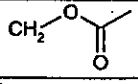
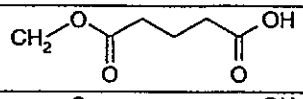
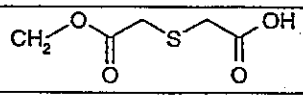
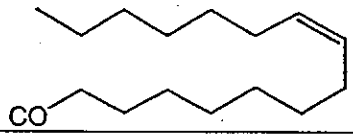
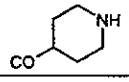
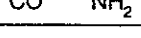
Example	R	IC_{50} (µM)	Scheme
1		0.02	III
2		0.04	III
3b		0.01	III

TABLE I (Continued)



Example	R	IC_{50} (μM)	Scheme
12		0.01	III/IV
3a		0.02	III
11		0.02	III/IV
9		0.02	III
10		0.02	III
		0.01	III
4		0.3	II
5	PO_3Na_2	0.2	I
6	$COCH_3$	0.01	II
7		0.01	II
8		0.01	II

These compounds are suitable for administration to patients by continuous infusion.

Example 16: Tablet Formulation

Item	Ingredients	Mg/Tablet					
1	Compound A *	5	25	100	250	500	750
2	Anhydrous Lactose	103	83	35	19	38	57
3	Croscarmellose Sodium	6	6	8	16	32	48
4	Povidone K30	5	5	6	12	24	36
5	Magnesium Stearate	1	1	1	3	6	9
	Total Weight	120	120	150	300	600	900

*Compound A represents a compound of the invention.

Manufacturing Procedure:

1. Mix items 1, 2 and 3 in a suitable mixer for 15 minutes.
2. Granulate the powder mix from step 1 with 20% Povidone K30 Solution (Item 4).
3. Dry the granulation from step 2 at 50°C.
4. Pass the granulation from step 3 through a suitable milling equipment.
5. Add the Item 5 to the milled granulation step 4 and mix for 3 minutes.
6. Compress the granulation from step 5 on a suitable press.

Example 17: Capsule Formulation

Item	Ingredients	mg/Capsule				
1	Compound A *	5	25	100	250	500
2	Anhydrous Lactose	159	123	148	--	--
3	Corn Starch	25	35	40	35	70
4	Talc	10	15	10	12	24
5	Magnesium Stearate	1	2	2	3	6
	Total Fill Weight	200	200	300	300	600

* Compound 1 represents a compound of the invention.

Manufacturing Procedure:

1. Mix items 1, 2 and 3 in a suitable mixer for 15 minutes.
2. Add items 4 & 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Example 18: Injection Solution/Emulsion Preparation

Item	Ingredient	mg/mL
1	Compound A *	1 mg
2	PEG 400	10-50 mg
3	Lecithin	20-50 mg
4	Soy Oil	1-5 mg
5	Glycerol	8-12 mg
6	Water q.s.	1 mL

* Compound A represents a compound of the invention.

Manufacturing Procedure:

1. Dissolve item 1 in item 2.
2. Add items 3, 4 and 5 to item 6 and mix until dispersed, then homogenize.
3. Add the solution from step 1 to the mixture from step 2 and homogenize until the dispersion is translucent.
4. Sterile filter through a 0.2 µm filter and fill into vials.

Example 19: Injection Solution/Emulsion Preparation

Item	Ingredient	mg/mL
1	Compound A *	1 mg
2	Glycofurol	10-50 mg
3	Lecithin	20-50 mg
4	Soy Oil	1-5 mg
5	Glycerol	8-12 mg
6	Water	q.s. 1 mL

* Compound A represents a compound of the invention.

Manufacturing Procedure:

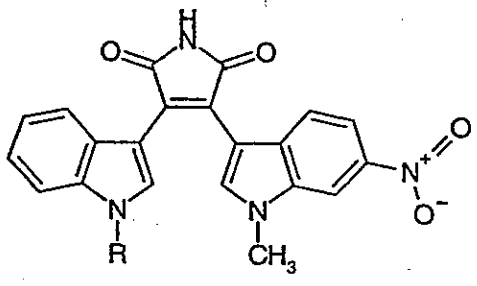
1. Dissolve item 1 in item 2.
2. Add items 3, 4 and 5 to item 6 and mix until dispersed, then homogenize.
3. Add the solution from step 1 to the mixture from step 2 and homogenize until the dispersion is translucent.
4. Sterile filter through a 0.2 µm filter and fill into vials.

While the invention has been illustrated by reference to specific and preferred embodiments, those skilled in the art will understand that variations and modifications may be made through routine experimentation and practice of the invention. Thus, the invention is intended not to be limited by the foregoing description, but to be defined by the appended claims and their equivalents.

CLAIMS

What Is Claimed Is:

1. A compound having the formula



I

and pharmaceutically acceptable salts of said compounds, wherein:

R is selected from the group consisting of $-PO_3R^1R^2$, $-CHR^3OCOR^4$, $-CHR^3OCO_2R^4$, $-CHR^3OCONHR^4$ and $-COR^4$;

R^1 and R^2 are selected from the group consisting of H, Na and NH_4, and are the same unless either R^1 or R^2 is H, in which case the other can be different, or alternatively, R^1 and R^2 together represent Ca;

R^3 is selected from the group consisting of H or methyl;

R^4 is selected from a group consisting of
lower alkyl, which may be optionally substituted by one or more substituents selected from the group consisting of $-CO_2R^5$, $-NR^6R^7$, polyethylene glycol, $-OPO_3R^1R^2$, hydroxy, alkoxy, and aryl,

alklenyl, which may be optionally substituted by one or more substituents selected from the group consisting of $-CO_2R^5$, $-NR^6R^7$, polyethylene glycol, $-OPO_3R^1R^2$, hydroxy, alkoxy, and aryl,

cycloalkyl, which may be optionally substituted by one or more substituents selected from the group consisting of $-CO_2R^5$, $-NR^6R^7$, polyethylene glycol, $-OPO_3R^1R^2$, hydroxy, alkoxy, and aryl.

heterocycle, which when including N as a heteroatom the N optionally may be substituted with $-COR^8$, and

aryl which optionally may be substituted by one or more substituents selected from the group consisting of $-CO_2R^5$, hydroxy, alkoxy, polyethylene glycol, $-OPO_3R^1R^2$, and alkyl which itself may be substituted with hydroxy, carboxy, and substituted amino;

R^5 is selected from the group consisting of H, Na, or lower alkyl;

R^6 and R^7 are each independently selected from H, lower alkyl, and $-COR^8$, or alternatively, the group $-NR^6R^7$ forms a 5 or 6 membered heterocyclic ring; and

R^8 is lower alkyl that optionally may be substituted with a polyethylene glycol.

2. The compound of claim 1 wherein R is $-CHR^3OCOR^4$.

3. The compound of claim 2 wherein R^3 is H.

4. The compound of claim 3 wherein R^4 is lower alkyl.

5. The compound of claim 4 wherein R^4 is lower alkyl substituted with polyethylene glycol.

6. The compound of claim 5 wherein the polyethylene glycol has a molecular weight of from about 750 to about 5000 Daltons.

7. The compound of claim 6 wherein the polyethylene glycol has a molecular weight of about 2000.

8. The compound of claim 1 wherein R is $-COR^4$.

9. The compound of claim 8 wherein R^4 is heterocycle.

10. The compound of claim 8 wherein R^4 is lower alkyl.

11. The compound of claim 8 wherein R^4 is lower alkyl which is substituted with $-NR^6R^7$.

12. The compound of claim 1 wherein the polyethylene glycol has a molecular weight of from about 750 to about 5000 Daltons.

13. The compound of claim 12 wherein the polyethylene glycol has a molecular weight of about 2000 Daltons.

14. A compound selected from the group consisting of:

3-[2-(2-Methoxy-ethoxy)-ethoxy]-propionic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester;

O-[2-[[2,5-dihydro-3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-pyrrol-3-yl]-indol-1-yl]methoxycarbonyl]ethyl]-O'-methylpolyethylene glycol 2000;

2,3-Dimethoxy-benzoic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester;

3-Diethylaminomethyl-benzoic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester hydrochloride;

3-(1H-Indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-1-octadec-9-enoyl-pyrrole-2,5-dione;

{3-[4-(1-Methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-phosphonic acid; and

3-(1-Acetyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione.

15. A compound selected from the group consisting of:

Trifluoro-acetic acid 3-(1-methyl-6-nitro-1H-indol-3-yl)-4-[1-(piperidine-4-carbonyl)-1H-indol-3-yl]-pyrrole-2,5-dione;

3-(1-Aminoacetyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-pyrrole-2,5-dione hydrochloride;

Acetic acid 3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl ester;

Pentanedioic acid mono-{3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-ylmethyl} ester;

2,3-Dimethoxy-benzoic acid 1-{3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-ethyl ester; and

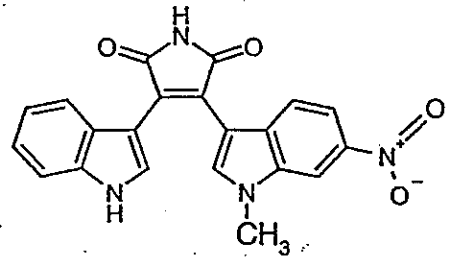
3-Diethylaminomethyl-benzoic acid 1-{3-[4-(1-methyl-6-nitro-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]-indol-1-yl}-ethyl ester hydrochloride.

16. A pharmaceutical composition comprising as an active ingredient an effective amount of a compound of any one of claims 1-15 and a pharmaceutically acceptable carrier or excipient.

17. The pharmaceutical composition of claim 16 which is suitable for parenteral administration.

18. Process of the preparation of the compounds as defined in any one of claims 1-15, which comprises

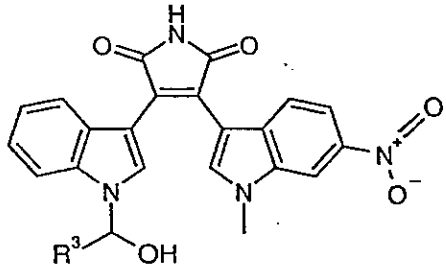
a) when R in formula I is $-PO_3R^1R^2$ or $-COR^4$ introducing this group into the starting compound of formula



by treatment with agents yielding said group,

or

b) when R in formula I is $-CHR^3OCOR^4$, $-CHR^3OCOOR^4$ or $-CHR^3OCONHR^4$ introducing this group into the starting compound of the general formula.



wherein R^3 is as in claim 1, by treatment with agents yielding said group, or

c) converting a compound of formula I into a pharmaceutically acceptable salt thereof.

19. Compounds according to any one of claims 1-15, whenever prepared by the process of claim 18 or by an obvious chemical equivalent thereof.

20. The use of a compound as defined in any one of claims 1-15 for the preparation of medicaments for the treatment of cell proliferative disorders.

21. The use of a compound as defined in any one of claims 1-15 for the preparation of medicaments for the treatment of cancer.

22. The use of claim 21 wherein the cancer is a solid tumor.

23. The use of claim 21 wherein the cancer is breast, colon, or lung cancer.

24. The novel compounds, processes and methods as well as the use of such compounds substantially as described hereinbefore.