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(54) Title: HETEROCYCLIC AGENTS

(57) Abstract

This inventin relates to heterocyclic antineoplastic agents, including certain substituted furano[3,2–e]–indole–7–carboxylic acid derivatives, as well as to processes for their preparation, pharmaceutical compositions comprising the heterocyclic agents and methods for their use.

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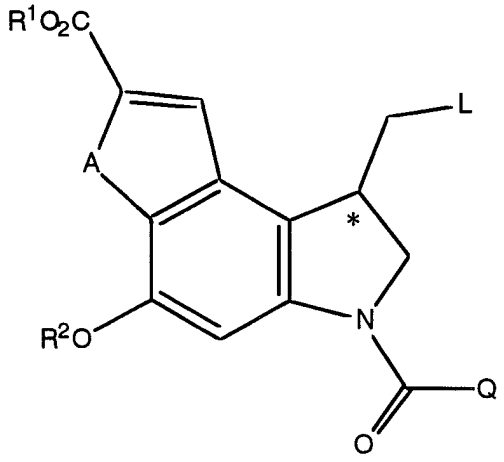
HETEROCYCLIC AGENTS

This invention relates to heterocyclic antineoplastic agents, as well as to processes for their preparation, pharmaceutical compositions comprising the heterocyclic agents and methods for their use. The heterocyclic agents are substituted furano[3,2-e]indole-7-carboxylic acid derivatives.

DNA interactive agents which interact in a base-specific and sequence-specific manner in the minor groove and bind covalently by alkylation show promise as antineoplastic agents. However, their development as therapeutic agents has been hampered by severe delayed lethality in experimental animals, particularly as related to hepatotoxicity. Reported agents include pyrrole[3,2-e]indole derivatives and furano[3,2-e]indole derivatives. See, for example, Annual Reports in Medicinal Chemistry, vol 25, p 134 (1990) and vol 28, p 176 (1993), as well as US patent 5,248,691 and Mohamadi, F., et al., J. Med. Chem. (1994), 37(2), 232-239. Despite the continuing promise of this class of compounds, there still exists a need for an agent which provides an improved separation between the antineoplastic effect and dose-limiting toxicity in other tissues.

The present invention is directed to the discovery of a new antineoplastic agent, as defined below, with improved properties for use in oncolytic therapy.

According to the invention, there is provided a compound of formula I



I

wherein

A is O or S;

L is a pharmaceutically acceptable leaving group;

-CO-Q is a group which binds in the minor groove of duplex DNA;

R^1 is (1-4C)alkyl; and

R^2 is hydrogen or a prodrug residue;

or (when said compound is acidic or basic) a pharmaceutically acceptable salt thereof.

This invention also relates to a pharmaceutical composition comprising the compound of formula I, or a pharmaceutically acceptable salt thereof, together with a suitable diluent or carrier.

In another embodiment this invention provides a method for treating a susceptible neoplasm, particularly a susceptible solid tumor, which comprises administering to an animal (particularly a mammal, more particularly a human or a companion mammal) in need thereof an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof. A companion mammal is, for example, a cat or a dog.

In this specification, the following definitions are used, unless otherwise described: Halo is fluoro, chloro,

bromo or iodo. Alkyl, alkoxy etc. denote both straight and branched groups; but reference to an individual residue such as "propyl" embraces only the straight chain ("normal") residue, a branched chain isomer such as "isopropyl" being referred to specifically. The compound of formula I contains a chiral center at the position indicated by "*" in formula I. Accordingly, it may exist in, and be isolated in optically active and racemic forms. If a compound of formula I contains an additional chiral element, such a compound of formula I may exist in, and be isolated in, the form of a diastereomeric mixture or as a single diastereomer. It is to be understood that the present invention encompasses a compound of formula I as a mixture of diastereomers, as well as in the form of an individual diastereomer, and that the present invention encompasses a compound of formula I as a mixture of enantiomers, as well as in the form of an individual enantiomer.

A compound of formula I, or a pharmaceutically acceptable salt thereof, may form a solvate. The compound, pharmaceutically acceptable salt or solvate may exhibit poly-morphism. It is to be understood, therefore, that the present invention encompasses any mixture of isomers, any racemic or optically active form, any pharmaceutically active salt, any solvate or any mixture thereof, which form possesses oncolytic properties, it being known in the art and described hereinbelow how to prepare optically active forms (for example, by resolution of the racemic form or by synthesis from optically active starting materials) and how to determine the oncolytic properties by standard tests including those described below.

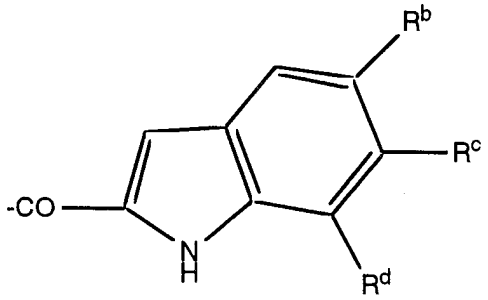
In general, it is preferred that the groups L, R^1, R^2 and Q not contain or introduce an element of chirality into the compound of formula I.

A particular value for A is O.

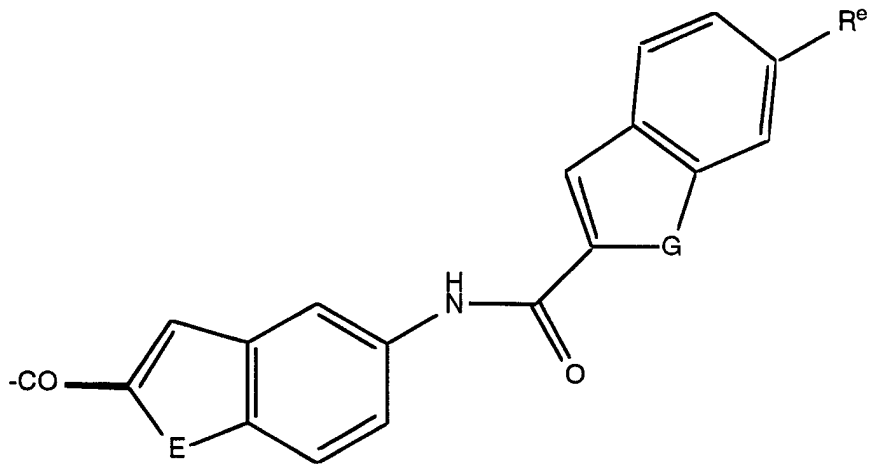
A pharmaceutically acceptable leaving group L is one which provides a compound of formula I which is sufficiently stable for formulation and administration and which provides

a nontoxic anion when the group L is released. Particular values for L include chloro, bromo, iodo, $-OSO_3H$ and $-OSO_2R^a$ in which R^a is (1-4C)alkyl, phenyl, phenyl bearing one or more methyl or halo substituents, and the like. A preferred value of L is chloro.

A particular compound of formula I is one wherein -CO-Q is

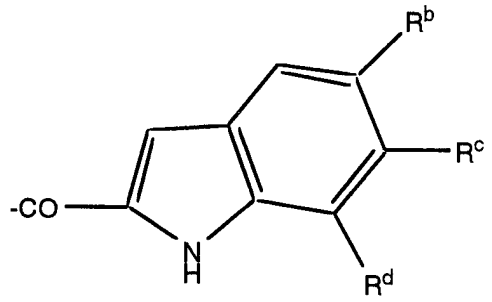


in which R^b, R^c, and R^d, independently, are methoxy or hydrogen, provided that at least one of them is methoxy; or wherein -CO-Q is



in which E and G are independently NH, O or S; and R^e is hydrogen, dimethylamino or diethylamino.

A preferred value for -CO-Q is

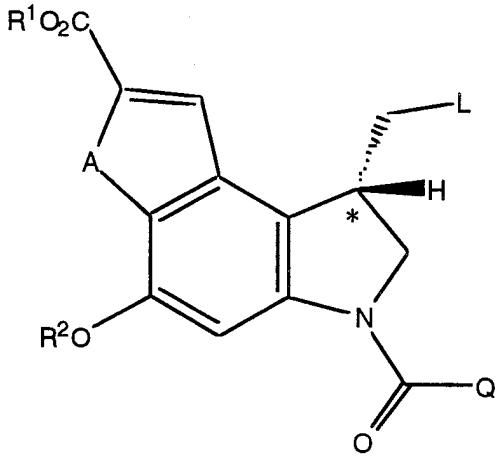


in which R^b, R^c, and R^d are each methoxy, or in which R^b is methoxy and R^c and R^d are each hydrogen.

A preferred value for R^1 is methyl.

One particular value of R^2 is hydrogen. When R^2 is a prodrug residue, it may be any conventional prodrug residue for a phenolic moiety, particularly an acyl residue of formula $-COR^f$, $-COOR^g$ or $-CONR^hR^i$ in which $HO-COR^f$ is a nontoxic carboxylic acid, $H-OR^g$ is a nontoxic alcohol, and $H-NR^hR^i$ is a nontoxic amine. A particular value for R^f includes $-(CH_2)_n-COOH$, $-(CH_2)_n-SO_3H$, $-(CH_2)_n-CONH-CH_2-SO_3H$, $-(CH_2)_n-NR^jR^k$, $-C(CH_3)_2CH_2NH_2$, $-CH_2C(CH_3)_2NH_2$, $-CH_2OCH_2COOH$, $-CH_2SCH_2COOH$, $-CH_2S(O_2)CH_2COOH$, or $-(CH_2)_n-CONH-(PEG)$ wherein n is 1, 2 or 3; R^j is hydrogen or (1-2C)alkyl; R^k is hydrogen, (1-2C)alkyl or $-CH(R^s)COOH$, wherein R^s denotes the side chain of a naturally occurring α-amino acid; or $-NR^jR^k$ is a morpholino, piperazino or 4-methylpiperazino group; and (PEG) denotes polyethylene glycol. A more particular value for R^f is 2-(diethylamino)ethyl or (4-methylpiperazino)-methyl. A particular value for $-OR^g$ is (1-3C)alkoxy, chloromethoxy, vinyloxy, benzyloxy, 2-[(1-4C)alkylsulfonyl]-ethyl or 2-(phenylsulfonyl)ethyl. A particular value for R^h or R^i is, independently, hydrogen or (1-2C)alkyl or $-NR^hR^i$ is anilino, morpholino, piperazino, 4-(1-piperidino)-1-piperidino or 4-methylpiperazino. A preferred value for R^2 when it is a prodrug residue is, for example, 4-methylpiperazinocarbonyl.

The preferred enantiomer of a compound of formula I is the one of the formula I-α



I-α

wherein A, L, Q, R^1 and R^2 have any of the values described above.

For any of the definitions herein, a particular value for a defined group, either alone or as part of another group (such as alkoxy or alkylsulfonyl, for example) for (1-2C)alkyl is methyl or ethyl; for (1-3C)alkyl is methyl, ethyl, propyl or isopropyl; for (1-4C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl; and for (1-5C)acyl is formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl or 3-methylbutanoyl.

A preferred compound of formula I is methyl 5-hydroxy-1-(chloromethyl)-1,2-dihydro-3-[5,6,7-trimethoxy-1H-indole-2-yl)carbonyl]-3H-furano[3,2-e]indole-7-carboxylate.

A more preferred compound of formula I is (+)-(1S) methyl 5-hydroxy-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1H-indole-2-yl)carbonyl]-3H-furano[3,2-e]indole-7-carboxylate.

Generally, an optical isomer of a compound of formula I, such as the enantiomer of formula I-α, or the above named (+)-(1S) species, is characterized as having an enantiomeric excess of at least 90%, and preferably an enantiomeric excess of at least 95%.

When a compound of formula I includes an acidic moiety, for example when L is $-OSO_3H$ or R^2 includes an acidic group, the acidic compound of formula I will form a salt with a pharmaceutically acceptable base. Such a pharmaceutically

acceptable salt may be made with a base which affords a pharmaceutically acceptable cation, which includes alkali metal salts (especially sodium and potassium), alkaline earth metal salts (especially calcium and magnesium), aluminum salts and ammonium salts, as well as salts made from physiologically acceptable organic bases such as triethylamine, morpholine, piperidine and triethanolamine. The potassium and sodium salt forms are particularly preferred.

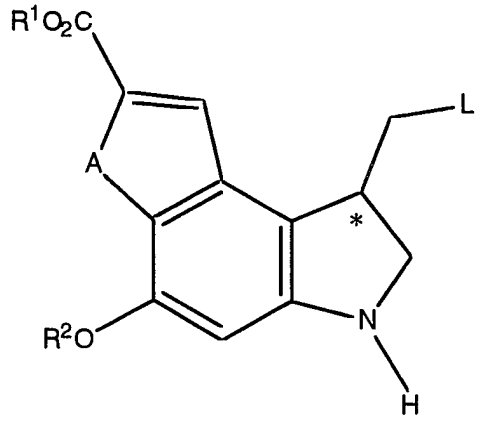
When a compound of formula I includes a basic moiety, for example when R^e is a substituted amino group or R^2 includes a basic moiety, the basic compound of formula I will form a pharmaceutically acceptable acid addition salt with a pharmaceutically acceptable acid. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid, citric acid and methanesulfonic acid.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

A compound of formula I may be made by a process which is analogous to one known in the chemical art for the production of structurally related heterocyclic compounds or by a novel process described herein. Novel processes and intermediates useful for the manufacture of a compound of formula I as defined above are provided as further features of the invention and are illustrated by the following procedures in which, unless otherwise specified, the meanings of the generic groups are as defined above. It will be recognized that it may be preferred or necessary to prepare a compound of formula I in which a functional group is protected using a conventional protecting group, then to

remove the protecting group to provide the compound of formula I.

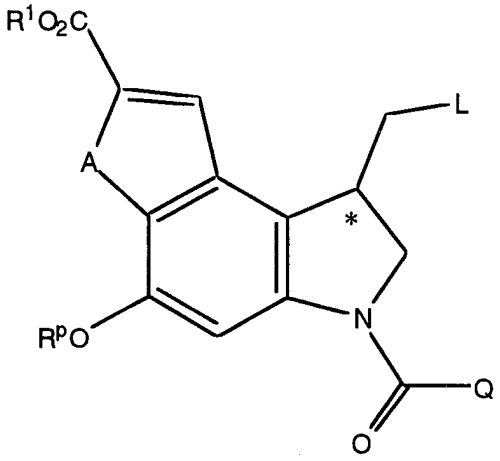
(A) Acylating an amine of formula II



II

with an acid of formula Q-COOH, or an activated derivative thereof. The acylation is carried out using a conventional procedure, for example using a coupling agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, for example as described in the examples below.

(B) For a compound of formula I in which R^2 is hydrogen, removing the protecting group R^p of a compound of formula Ip



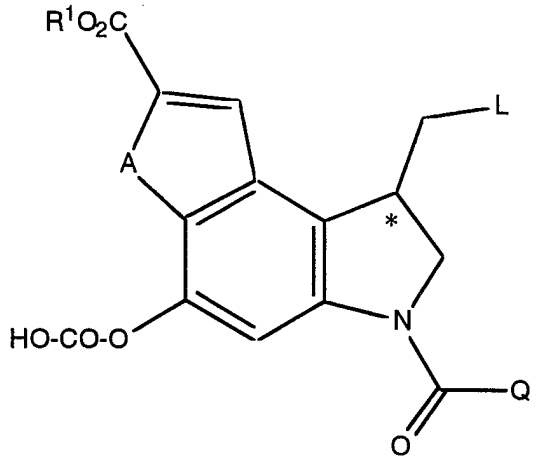
Ip

wherein R^p is a conventional protecting group for a phenolic hydroxy group, for example R^p is benzyl, by using a conventional method, such as hydrogenolysis of the benzyl

group using ammonium formate and palladium on carbon in aqueous tetrahydrofuran.

(C) For a compound of formula I in which R^2 is a prodrug residue, substitution of the hydrogen of a compound of formula I in which R^2 is hydrogen with the prodrug residue using a conventional method. For example, for a compound of formula I in which the prodrug residue is an acyl residue of formula $-COR^f$, $-COOR^g$ or $-CONR^hR^i$, acylating the compound of formula I in which R^2 is hydrogen with an acid of formula $HO-COR^f$, $HO-COOR^g$ or $HO-CONR^hR^i$, or an activated derivative thereof. A conveniently used activated derivative may be, for example, the acid chloride or an activated ester, such as the 4-nitrophenyl ester, or, when R^h is hydrogen, an isocyanate of formula R^i-NCO.

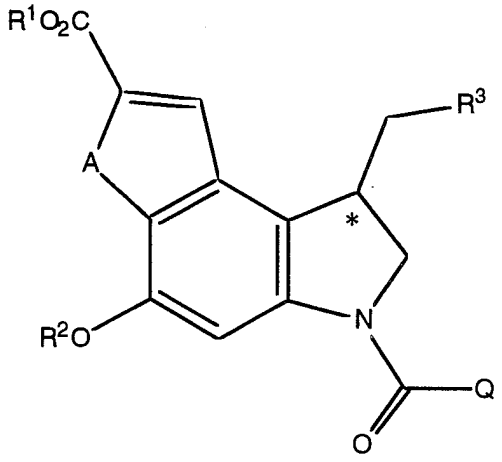
(D) For a compound of formula I in which R^2 is $-COOR^g$ or $-CONR^hR^i$, acylation of a corresponding alcohol of formula $H-OR^g$ or amine of formula $H-NR^hR^i$ with an activated derivative of a carbonic acid of formula Ic.



Ic

Conveniently, the activated derivative is the chlorocarbonate or an activated ester such as the 4-nitrophenyl ester, and is conveniently prepared from the corresponding compound of formula I in which R^2 is hydrogen using a conventional method.

(E) For a compound of formula I in which L is $-OSO_3H$ or $-OSO_2R^a$, formation of the sulfonic ester of a corresponding compound of formula III



III

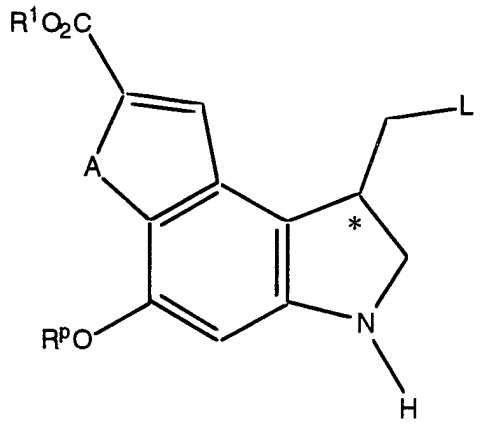
in which R^3 is hydroxy, using a conventional method.

Whereafter, for any of the above procedures, when a functional group is protected using a protecting group, removing the protecting group.

Whereafter, for any of the above procedures, when a pharmaceutically acceptable salt of a compound of formula I is required, it is obtained by reacting the acidic or basic form of such a compound of formula I with a base or an acid affording a physiologically acceptable counterion or by any other conventional procedure, such as, for example, exchanging the counterion of a salt.

The leaving group L of a compound of formula I (or formula Ip) may be converted into a different leaving group L by a conventional method of functional group interchange. It will be clear to one skilled in the art that a protecting group R^p also may serve as a value of R^2 wherein R^2 is a prodrug residue.

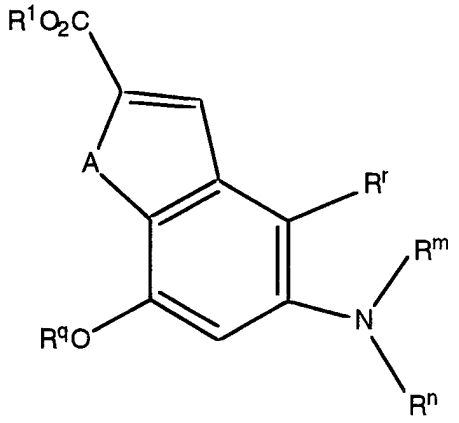
A protected compound of formula Ip may be prepared using a similar procedure to that described above in process (A), using an amine corresponding to that of formula II, but in which the phenolic hydroxy group is protected, which may be denoted as an amine of formula IIp



IIp

wherein R^p is a conventional protecting group for a phenolic hydroxy group, for example R^p is benzyl.

A convenient intermediate for the preparation of an amine of formula II or an amine of formula IIp is the corresponding ester of formula IV



IV

wherein R^m is hydrogen, R^n is a protecting group for an anilino nitrogen, R^q is a value of R^2 or R^p which is stable to the subsequent reaction conditions, and R^r is a group which will afford the corresponding aryl radical when subjected to a radical generating reagent or condition. The compound of formula IV provides another aspect of the invention and may be prepared using a process such as that outlined in the examples and which provides a further aspect of the invention. Thus, the process is illustrated in parts A-H of Example 1, beginning with 2-hydroxy-3-methoxy-5-

nitrobenzaldehyde for the preparation of a compound of formula IV in which A is O, R^1 is methyl, R^m is hydrogen, R^n is tert-butyloxycarbonyl (Boc), R^q is benzyl, and R^r is bromo.

Accordingly, there is provided a process for the preparation of a compound of formula IV wherein A, R^1, R^n, R^q and R^r are defined as above and R^m is hydrogen, from 2-hydroxy-3-methoxy-5-nitrobenzaldehyde which comprises

alkylating the phenolic hydroxy group with an ester of formula $X\text{-}CH_2\text{-}COOR^{1a}$ wherein R^{1a} is a carboxy-protecting residue [for example, R^{1a} is (1-4C)alkyl or benzyl and, more particularly, R^{1a} is methyl or ethyl] and X is a leaving group [for example, X is bromo or iodo] using a base and an inert solvent [for example, forming the potassium salt using potassium carbonate in methanol followed by alkylating with ethyl bromoacetate in dimethylformamide];

cyclizing the resulting ester to a benzofuran using a basic catalyst in an inert solvent [for example, cyclizing the ester using 1,8-diazabicyclo[5.4.0]undec-7-ene in refluxing ethanol] to afford the 7-hydroxy-5-nitrobenzofuran-2-carboxylic acid ester;

removing the O-protecting groups R^{1a} and O-methyl to afford 7-hydroxy-5-nitrobenzofuran-2-carboxylic acid [for example, by heating with molten pyridine hydrochloride];

esterifying the acid with the alcohol R^1OH [for example, refluxing with methanol and an acid catalyst such as dry hydrogen chloride];

reducing the nitro group to an amino group [for example, using a hydrogen atmosphere at about 4.1 bar over a 5% palladium-on-alumina catalyst in tetrahydrofuran/methanol];

substituting the amino group with the group R^n [for example, acylating the amino group with the "Boc" group using di-tert-butyl dicarbonate in tetrahydrofuran];

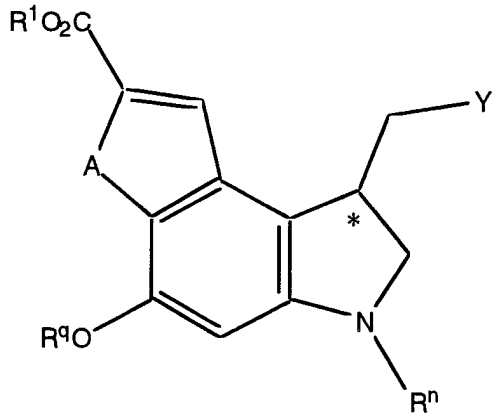
substituting the phenolic hydroxy group with the group R^q [for example, using an alcohol of formula R^1OH in the

presence of triphenyl phosphine and diethyl azodicarboxylate]; and (when R^r is not hydrogen)

substituting the 6-position with the group R^r [for example, for a compound of formula IV in which R^r is bromo, brominating the ring with a bromination reagent, such as for example, N-bromosuccinimide with catalytic 36 N sulfuric acid in dry tetrahydrofuran].

A preferred process for preparing an amine of formula II or of formula IIp from a corresponding ester of formula IV in which R^m is hydrogen comprises using the novel process for preparing a 3-substituted indoline which is further discussed below and is illustrated in parts I-K of Example 1 for a compound of formula IIp in which A is O, L is chloro, R^1 is methyl and R^p is benzyl (preferably isolated as its hydrochloride salt). Thus, a first step is alkylating the amine of a compound of formula IV in which R^m is hydrogen with an olefin of formula $X\text{-}CH_2CH{=}CHY$ in which X is a leaving group, such as chloro, bromo, iodo or a sulfonyloxy group such as methylsulfonyloxy, and Y denotes a group which has one of the values defined for L and which is stable to the subsequent cyclization conditions, for example Y is chloro, bromo or iodo, to afford a substituted vinyl compound of formula IV in which R^m is $-CH_2\text{-}CH{=}CHY$. Conveniently, X and Y are each chloro.

Cyclizing the substituted vinyl compound of formula IV is effected by subjecting it to a radical generating reagent or condition in an inert solvent in the presence of a radical reducing agent to afford a corresponding substituted indoline of formula V.



V

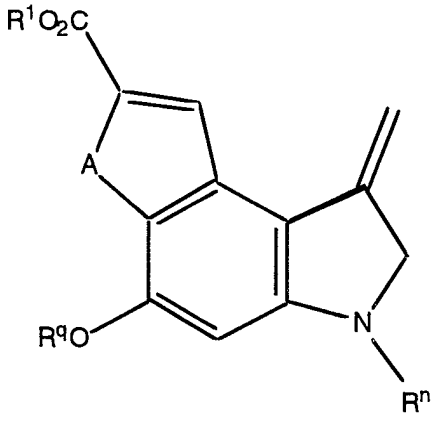
The cyclization conveniently is effected, for example, by subjecting a substituted vinyl compound of formula IV in which R^r is bromo to azobisisobutyronitrile (AIBN) under reflux in benzene in the presence of tributyltin hydride.

In addition to its utility as a synthetic intermediate, a compound of formula II or formula V also may be useful as an antineoplastic agent.

Removing the N-protecting group R^n of a compound of formula V in which R^q denotes a value of R^2 using a conventional method to afford a corresponding compound of formula II is a final step. Similarly, removing the N-protecting group R^n of a compound of formula V in which R^q denotes a value of R^p using a conventional method to afford corresponding compound of formula IIp is a final step. When R^n is a Boc group, it conveniently is removed using dry hydrogen chloride in an organic solvent such as dioxane, as described at Example 1-K, and the amine is preferably isolated as the hydrochloride salt.

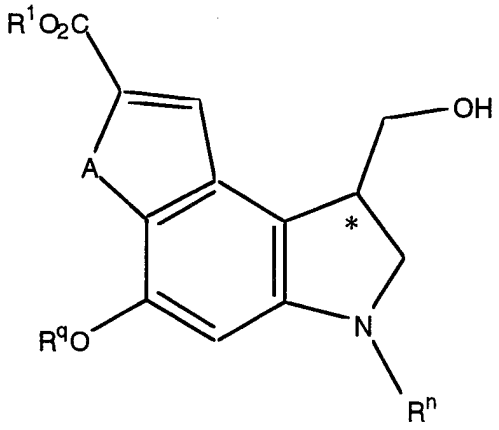
Alternatively, an ester of formula IV in which R^m is hydrogen may be converted into an amine of formula II or formula IIp by using a procedure which is analogous to a known procedure, for example as described in US 5,248,691. Thus, for example, for a compound of formula V wherein A is O, R^1 is methyl, R^n is Boc, and R^q is benzyl, alkylating the anilino nitrogen of a corresponding compound of formula IV in which R^m is hydrogen and R^r is bromo using propargyl bromide (for example, using sodium hydride in

dimethylformamide) affords the corresponding N-propargyl compound of formula IV in which R^m is propargyl. Cyclization of the N-propargyl compound using free radical cyclization conditions in the presence of a radical reducing agent, for example using AIBN under reflux in benzene in the presence of tributyltin hydride, affords the corresponding olefin of formula VI.



VI

Hydroboration of the olefin of formula VI (for example using dimethyl sulfide-borane in tetrahydrofuran followed by oxidation using hydrogen peroxide in aqueous sodium hydroxide) affords the corresponding alcohol of formula VII.



VII

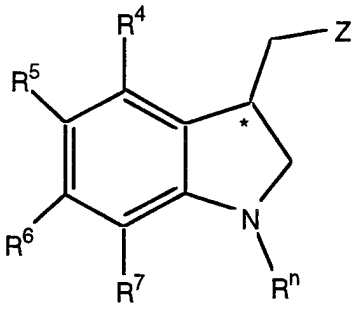
Resolution of the alcohol of formula VII conveniently may be effected by preparing the ester with a chiral acid, such as for example the (R)-(-)-O-acetylmandelate ester,

chromatographically separating the resulting diastereomers, and liberating the resolved alcohol of formula VII.

When R^q is a value of R^2, conversion of the alcohol of formula VII into an amine of formula II may be effected conveniently by converting the hydroxy group into the required value of L by using a conventional method (for example using triphenylphosphine and carbon tetrachloride in dichloromethane to afford the corresponding compound of formula V in which Y is chloro), followed by removing the N-protecting group R^n to afford the amine, conveniently isolated as its acid addition salt, such as the hydrochloride. If R^q is a value of R^p, a similar procedure affords an amine of formula IIp. Alternatively, if R^q is a value of R^p, the O-protecting group R^p may be removed and the required O-substituent R^2 obtained using conventional methods before removal of the N-protecting group R^n to afford the amine of formula II.

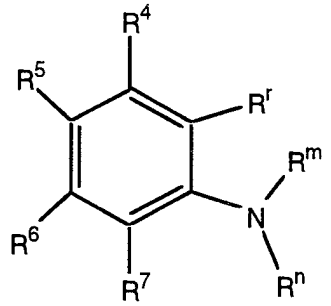
An amide of formula III in which R^3 is hydroxy may be obtained by using a process similar to that described above at (A), using an amine corresponding to the amine of formula II, but in which the value (R^3) corresponding to L is a hydroxy group or a protected hydroxy group (followed by deprotection). The amine conveniently is obtained from a corresponding primary alcohol of formula VII, which also may be obtained from a protected amine of formula V by converting the leaving group Y into hydroxy using a conventional method.

As noted above, a preferred process for preparing a compound of the invention is the novel one illustrated in parts I-K of Example 1 for a compound of formula IIp in which A is O, L is chloro, R^1 is methyl and R^p is benzyl. Thus, in general terms, another aspect of the invention is a process for the preparation of an indoline of formula VIII



VIII

wherein each of R^4, R^5, R^6, R^7, R^n and Z is a group which is stable to the reaction conditions of the process (or, further, in which R^n is hydrogen) from a corresponding aniline of formula IX



IX

wherein R^m is hydrogen, R^r is a group which will afford the corresponding aryl radical when subjected to a radical generating reagent or condition (and, further, for the preparation of a compound of formula VIII in which R^n is hydrogen, R^n is a protecting group for an anilino nitrogen) which comprises

alkylating the compound of formula IX in which R^m is hydrogen with an olefin of formula X-CH_2CH=CHZ in which X is a leaving group, and Z is a group which is stable to the subsequent cyclization conditions to afford a substituted vinyl compound of formula IX in which R^m is -CH_2-CH=CHZ; and

subjecting the substituted vinyl compound of formula IX to a radical generating reagent or condition in an inert solvent in the presence of a radical reducing agent to afford the corresponding substituted indoline of formula VIII (and,

further, for a compound of formula VIII in which R^n is hydrogen, removing the N-protecting group R^n using a conventional method).

This novel process for the preparation of a 3-substituted indoline has the advantage that the substituent Y or Z is introduced directly, with no requirement of modification of a different group to obtain it. Moreover, the novel process avoids the intermediacy of the olefin such as that of formula VI, which readily may isomerize into the corresponding 3-methylindole derivative.

As noted above, the values of the residues R^4, R^5, R^6, R^7, R^n and Y are limited only by stability to the reaction conditions. A pair of neighboring residues together may form a fused ring, for example as exemplified by compounds of formula IV and formula V.

For a residue R^4, R^5, R^6 or R^7, for example, a particular value for a residue is one independently selected from hydrogen, (1-4C)alkyl, hydroxy, (1-4C)alkoxy, benzyloxy, (1-5C)acyloxy, benzoyloxy, (1-4C)alkoxycarbonyloxy, phenoxycarbonyloxy, (1-5C)acyl, benzoyl, cyano, (1-5C)acylamino, benzoylamino, (1-4C)alkoxycarbonylamino or benzyloxycarbonylamino or a pair of neighboring residues together (such as, for example, R^4 and R^5) may form a fused ring, for example, a furano-, thiopheno-, pyrrolo- or benz-ring (for example, where the heteroatom, if present, is at the R^5-position), which fused ring may further bear one or more substituents [for example a methyl or a (1-4C)alkoxycarbonyl]. A particular value for R^n is, for example, tert-butyloxycarbonyl, formyl, acetyl, trichloroacetyl, 2,2,2-trichloroethoxycarbonyl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, 2-(p-tolylsulfonyl)ethoxycarbonyl, phenylsulfonyl, allyl, benzyl, triphenylmethyl or a value listed above for -CO-Q. Although hydrogen also is a value for R^r, a more particular value for R^r is, for example, halo (particularly, bromo or iodo), hydroxy, phenylsulfanyl, phenyselanyl, amino, nitro,

diazonium (with a conventional counter anion), an azo group of formula -N=N-R^t (wherein R^t forms a symmetrically substituted azo compound or R^t is, for example, phenyl, triphenylmethyl, hydroxy or acetoxy), or carboxy. A particular value for X is, for example, chloro, bromo, iodo or a sulfonyloxy group such as methylsulfonyloxy. A particular value of Z includes one defined above for Y, such as chloro, bromo or iodo, as well as methylsulfonyloxy, p-tolylsulfonyloxy, -$S(O)_mR^u$ wherein m is 0, 1 or 2 and R^u is, for example, methyl or phenyl.

Typical values for the novel process include those in which R^4 and R^5 together form a furano-, thiopheno- or pyrrolo-ring where the heteroatom is at the R^5-position; R^6 is (1-4C)alkoxy or benzyloxy; R^7 is hydrogen, (1-4C)alkoxy or benzyloxy; R^r is bromo or iodo; R^n is tert-butyloxycarbonyl; and Z is chloro or bromo.

As a particular aspect of the novel process, there is provided a process for the preparation of an indoline of formula V, wherein A, R^1, R^n, R^q and Y have any of the values defined above, from a corresponding aniline of formula IV, wherein R^m is hydrogen and R^r is a group which will afford the corresponding aryl radical when subjected to a radical generating reagent or condition, which comprises

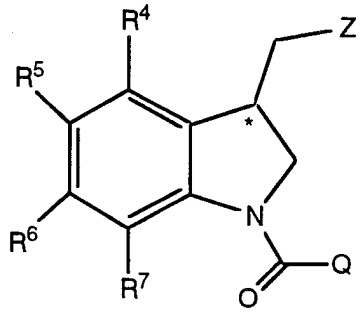
alkylating the compound of formula IV in which R^m is hydrogen with an olefin of formula X-CH_2CH=CHY in which X is a leaving group to afford a substituted vinyl compound of formula IV in which R^m is -CH_2-CH=CHY; and

subjecting the substituted vinyl compound of formula IV to a radical generating reagent or condition in an inert solvent in the presence of a radical reducing agent to afford the corresponding substituted indoline of formula V.

Values for the residue R^r and the corresponding radical generating reagent or condition, inert solvent and radical reducing agent include those known in the art. The inert solvent will depend upon the mode of generation of the radical and the solubility of the compound. Values for R^r and the corresponding conditions for radical generation and

reductive trapping are provided, for example, in Giese, B. Radicals in Organic Syntheses: Formation of Carbon-Carbon Bonds; Pergamon Press (1986). Thus, when R^r is, for example, halo, phenylsulfanyl, phenyselanyl, nitro, or the ester derived from treatment of a compound in which R^r is hydroxy with carbon disulfide and methyl iodide, the cyclization may be effected using, for example, a conventional azo-type radical initiator, such as AIBN, a trialkyltin hydride, for example tributyltin hydride, and benzene as a solvent at reflux. Conveniently, R^r is bromo or iodo and the radical generating reagent or condition is AIBN and tributyltin hydride in benzene at reflux.

As a further aspect of the novel process there is provided a process for the preparation of a compound of formula X,



X

wherein each of -CO-Q, R^4, R^5, R^6, R^7 and Z has any of the values defined above, from a corresponding aniline of formula IX in which R^n is a nitrogen protecting group which comprises

converting the aniline of formula IX into the corresponding substituted indoline of formula VIII using the process described above,

removing the N-protecting group R^n using a conventional method, and, further,

acylating the resulting indoline of formula VIII wherein R^n is hydrogen with an acid of formula Q-COOH, or an activated derivative thereof. The acylation is carried out

using a conventional procedure, for example using a coupling agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

It may be desired to use a protecting group during all or portions of the above-described processes; the protecting group then may be removed when the final compound or a required starting material is to be formed. As will be clear to one skilled in the art, the order of steps in the sequences leading to the starting materials and products of the invention may be altered if appropriate consideration relating to coupling methods, racemization, deprotection methods, etc., are followed.

The utility of a compound of the invention or a pharmaceutically acceptable salt thereof (hereinafter, collectively referred to as a "Compound") may be demonstrated by standard tests and clinical studies, including those described below.

In Vitro Pharmacology

The cytotoxicities of the compounds of Examples 1, 2 and 3 were determined by incubation (48 hours) of drug with a human squamous cell lung carcinoma (T222) and percent inhibition determined by measurement of [^{3}H]leucine uptake. T222 (Masui, et al. Cancer, 44(3): 1002-1007, 1984) human squamous carcinoma cells were grown in DMEM medium supplemented with 10% fetal bovine serum and 50 µg/mL gentamicin using standard tissue culture techniques. 1 X 10^4 target cells were distributed in each well of 96 well tissue culture plates and incubated in leucine deficient medium (leucine free DMEM plus 13 µg/mL L-leucine, 29.2 µg/mL L-glutamine, 50 µg/mL gentamicin and 10% dialyzed fetal calf serum) for 16 hours at 37°C in 5% CO_2. The medium was then removed aseptically and compound dilutions were added in 200 µl of leucine deficient medium. Following an additional 48 hour incubation, 4 µCi ^{3}H-leucine (NEN, Boston, MA) were added to each well and the plates were returned to the incubator for 24 hours. Radioactivity incorporated into macromolecules was determined using an

automated cell harvester and liquid scintillation techniques. Data were evaluated as percent reduction in incorporation of radioactivity relative to controls incubated in medium without compound to yield an 50% cytotoxic concentration (IC_{50}). The respective IC_{50}'s of the compounds of Examples 1, 2 and 3 in this assay were 0.39, 0.39 and 19.4 nM (indicating the enantiomer of Example 2 is the more active isomer). Potent cytotoxic activity was observed in similar protocols using other neoplastic cell lines [HCT-116, CCRF-CEM, GC3/C1, HL601S, HL60/ADR/REV, HL60/ADR(MRP+), HL60/VCR(Pgp+)], as well.

In Vivo Pharmacology

Inhibition of growth of nude mouse xenografts was demonstrated using several neoplastic tumors. For example, for T222 tumors, prior to each xenograft experiment, cells were collected by treatment with Trypsin/EDTA (Gibco, Life Technologies, Grand Island, NY) and washed with supplemented DMEM and finally suspended in Hanks balanced salt solution. 1×10^7 cells were injected s.c. into the flank of young adult female nude mice (Charles River Breeding Laboratories, Boston, MA). The mice were treated by i.v. injection in the tail vein at various time points. Tumor measurements were taken in two dimensions and converted to an estimate of mass using the formula [(length) ($width^2$)/2] as described by Geran, et al., Cancer Chemother. Rep., 3:1-103, 1972. Control groups contained 10 mice, with test groups containing 5 mice each. The Student test was used to evaluate differences between mean tumor masses. When dosed intravenously on days 3, 5 and 7 in the tail vein, the compound of Example 2 inhibited the growth of tumors in mice bearing a T222 burden (injected subcutaneously at day 0) as summarized in Table I for results at day 38.

Table I.
Efficacy in mice bearing a T222 tumor burden

Dose (mg/kg)	Percent Inhibition of Tumor Growth	Number of Deaths/ Number of Mice
0.8	46%	0/5
1.6	40%	0/5
3.2	84%	0/5
6.4	94%	1/5
12.8	TOXIC	

Dose dependent antitumor efficacy for the compound of Example 2 also was demonstrated in other xenograft protocols, including with GC3 colon tumor and MX-1 mammary tumor xenografts. While observed lethality was variable and delayed, a total dose of 5 mg/kg resulted in little lethality.

The compounds of formula I are antineoplastic agents and the invention provides a method of treating susceptible neoplasms. In particular, the present compounds are useful in treating solid tumors including carcinomas such as ovarian, non-small cell lung, gastric, pancreatic, prostate, renal cell, breast, colorectal, small cell lung, melanoma and head and neck; and sarcomas such as Kaposi's sarcoma and rhabdomyosarcoma.

Typically, a compound of formula I is administered using a parenteral route, such as an injection, for example, as an intravenous infusion; however, it may be preferred to administer the compound of formula I by another route, such as orally. The compound may be administered individually or in combination with one or more other agents, either simultaneously or in a sequence. The clinician will determine the exact dose depending upon the size and age of the patient, the neoplasm being treated and the treatment regime. For intravenous infusion, the compound may be given as a bolus or as a constant intravenous infusion. An

intravenous dose, for example, may be in the range of 0.05 to 20 mg/m^2 as a bolus once a week or in the range of 0.01 to 4 mg/m^2/day for 5 days. An oral dose may be, for example, from 0.01 to 50 mg/kg/day, possibly in divided doses.

The pharmaceutical composition comprising a compound of formula I will be appropriate for the elected mode of administration, and may be prepared using a conventional method.

For the pharmaceutical composition any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both (for example in polyethylene glycol 400/absolute ethanol/polyoxyethylenesor-bitan monooleate, 6:3:1, v/v/v). Useful carriers for a solution, suspension or emulsion

include polysorbate 80, polyoxyethylated castor oil, and a mixture of soybean oil, glycerol and egg lecithin. The active ingredient can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

Preferably the pharmaceutical formulation is in unit dosage form. The unit dosage form can be an ampoule containing the active ingredient in a form suitable for dissolution or dilution prior to administration or can be a prefilled syringe or bag containing a solution of the active ingredient. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration.

The pharmaceutical composition according to the invention may be made for oral, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation, either through the mouth or nose.

The following pharmaceutical formulations are illustrative only and are not intended to limit the scope of the invention in any way. "Active ingredient," refers to a compound of formula I or a pharmaceutically acceptable salt or solvate thereof.

Formulation 1: Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	50

Starch, dried	40
Magnesium stearate	2
Total	92 mg

Formulation 2: A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Active ingredient	50
Cellulose, microcrystalline	80
Silicon dioxide, fumed	2
Stearic acid	1
Total	133 mg

The components are blended and compressed to form tablets each weighing 133 mg.

Formulation 3: Tablets, each containing 60 mg of active ingredient, are made as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10 % solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50 °C and passed through a No. 18 mesh U.S.

Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 4: Capsules, each containing 80 mg of active ingredient, are made as follows:

Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 5: Suppositories, each containing 225 mg of active ingredient, are made as follows:

Active ingredient	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 6: Suspensions, each containing 50 mg of active ingredient per 5 ml dose, are made as follows:

Active ingredient	50 mg

Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mL
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to total	5 mL

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 7: An intravenous formulation may be prepared as follows:

Active ingredient	100 mg
Isotonic saline	1,000 mL

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 mL/min.

The following Examples are provided to further describe the invention and are not to be construed as limitations thereof. In general, unless otherwise indicated, evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-400 pascals, 4.5-30 mm Hg) with a bath temperature of up to 60 °C; pH adjustments and work-up are with aqueous acid or base solutions; and NMR data are given in the form of delta (δ) values as parts per million down field from tetramethylsilane (TMS) as an internal standard.

Conventional symbols and abbreviations are used in this specification including the following:

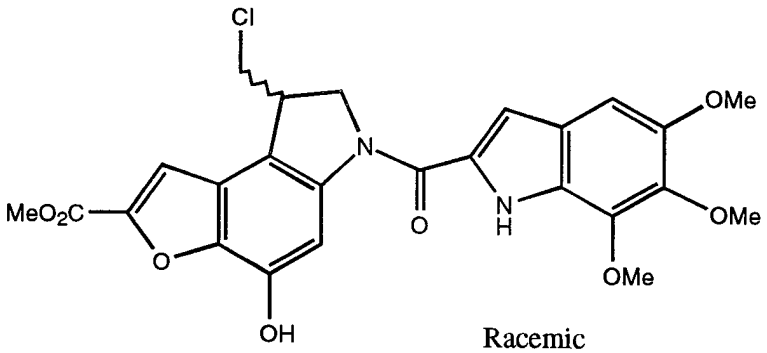
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	tert-butyloxycarbonyl
conc.	concentrated
DMSO	dimethylsulfoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (used as the hydrochloride)
Et	ethyl
EtOH	ethanol
Me	methyl
Pd/C	palladium-on-carbon
Ph	phenyl

and for spectroscopic methods:

IR	infrared spectrum
MS(FD)	mass spectrum (field desorption ionization)
NMR	(proton) nuclear magnetic resonance spectrum
UV	ultraviolet spectrum.

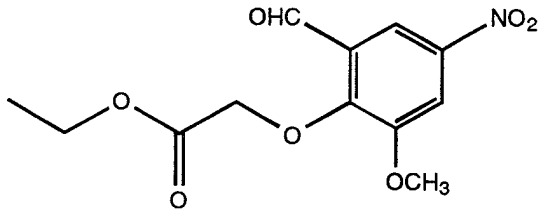
Example 1

Preparation of Methyl 5-Hydroxy-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1H-indole-2-yl)carbonyl]-3H-furano[3,2-e]indole-7-carboxylate



Racemic

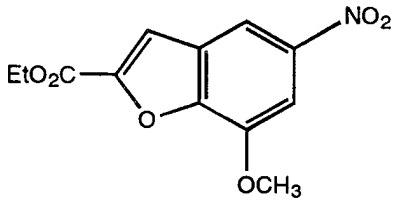
A. Ethyl 2-(6-Formyl-2-methoxy-4-nitrophenoxy)acetate



To a rapidly stirring solution of 2-hydroxy-3-methoxy-5-nitrobenzaldehyde (100 g, 0.507 mol) in dry methanol (1.5 L) was added powdered potassium carbonate (85%, 37.1 g, 0.562 mol) and the mixture refluxed for 45 min. The methanol was evaporated, and the solid residue suspended in dimethylformamide (1.5 L). The mixture was cooled to 0 °C and ethyl bromoacetate (103 mL, 0.925 mol) added. The solution was warmed to room temperature and stirred for 36 h. The solvent was evaporated, the solid residue diluted with water (3 L), and the product extracted with ethyl acetate (8 x 1 L). The organic extracts were washed with water, then brine, dried (Na_2SO_4) and evaporated to give the ester product as a tan solid (136.5 g, 95%).

^{1}H NMR (DMSO-d_6) δ 10.48 (s, 1, CHO), 8.09 (d, J = 2.94 Hz, ArH), 8.06 (d, J = 2.57 Hz, ArH), 5.06 (s, CH_2OAr), 4.14 (q, J = 6.99 Hz, CH_2O), 4.00 (s, OCH_3), 1.19 (t, J = 6.99 Hz, CH_3); IR (KBr) υ 3100, 3080, 3000, 2950, 2910, 1755, 1698, 1585, 1526, 1479, 1352, 1203, 1053, 744 cm^{-1}; UV (EtOH) λ_{max} 209 (ε = 10739), 245 (ε = 12353), 294.5 (ε = 5178) nm; MS (FD) 284 (M^+, 100); Anal. calcd. for $C_{12}H_{13}NO_7$ requires: C, 50.89; H, 4.63; N, 4.95%; Found: C, 50.82; H, 4.50; N, 4.76%.

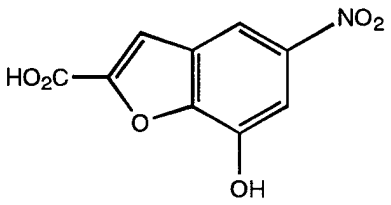
B. Ethyl 7-Methoxy-5-nitrobenzofuran-2-carboxylate



1,8-Diazabicyclo[5.4.0]undec-7-ene (80 mL, 0.535 mol) was added to a solution of ethyl 2-(6-formyl-2-methoxy-4-nitrophenoxy)acetate (136.4 g, 0.482 mol) in ethanol (2.5 L) and the solution heated at reflux for 4 hours. The reaction mixture was cooled to room temperature and the resulting solid filtered, washed with cold ethanol (600 mL), and dried (*in vacuo* at 40 °C) to provide the benzofuran derivative as a yellow solid (56.1 g, 44%).

^{1}H NMR (DMSO-d_6) δ 8.38 (d, J = 1.84 Hz, ArH), 7.93 (s, ArH), 7.90 (d, J = 2.21 Hz, ArH), 4.40 (q, J = 6.99 Hz, CH_2O), 4.10 (s, OCH_3), 1.36 (t, J = 6.99 Hz, CH_3); IR (KBr) υ 3500, 3200, 3000, 2950, 1718, 1529, 1345, 1322, 1297, 1188, 1096, 979, 944, 882, 739 cm^{-1}; UV (EtOH) λ_{max} 213 (ε = 14538), 264.5 (ε = 28797) nm; MS (FD) 265 (M^+, 100); Anal. calcd. for $C_{12}H_{11}NO_6$ requires: C, 54.34; H, 4.18; N, 5.28%; Found: C, 54.08; H, 4.10; N, 5.29%.

C. 7-Hydroxy-5-nitrobenzofuran-2-carboxylic Acid

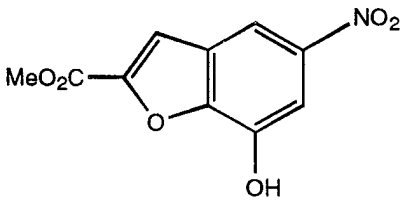


Ethyl 7-methoxy-5-nitrobenzofuran-2-carboxylate (55.9 g, 0.211 mol) was combined with pyridine hydrochloride (243 g, 2.11 mol) in a flask equipped with a paddle stirrer. The two solids were heated at 170 °C with vigourous stirring for 18 h. The mixture was allowed to cool to about 50 °C and then poured into ice water (2 L). The undissolved solid was filtered and washed with water (1 L). The crude solid was re-dissolved in 1N sodium hydroxide (1.5 L) washed with ethyl acetate (2 x 500 mL). The pH of the aqueous solution was then adjusted to 3 using conc. HCl and the precipitated

product was filtered, washed with water, and dried (*in vacuo* at 50 °C) to give the phenol derivative as a pale yellow solid (44 g, 88%).

^{1}H NMR (DMSO-d_6) δ 13.93 (s, CO_2H), 11.41 (s, OH), 8.21 (d, J = 2.21 Hz, ArH), 7.81 (s, ArH), 7.71 (d, J = 2.21 Hz, ArH); IR (KBr) υ 3274, 3093, 2542, 1694, 1584, 1530, 1347, 1286, 1225, 1193, 790 cm^{-1}; UV (EtOH) λ_{max} 208 (ε = 15442), 263.5 (ε = 18538) nm; MS (FD) 223 (M^+, 100); Anal. calcd. for $C_9H_5NO_6$ requires: C, 48.44; H, 2.26; N, 6.28%; Found: C, 48.74; H, 2.41; N, 6.28%.

D. Methyl 7-Hydroxy-5-nitrobenzofuran-2-carboxylate

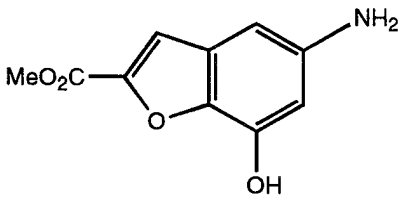


Acetyl chloride (13 mL, 186 mmol) was added dropwise to dry methanol (1.5 L) at 0 °C and then stirred at room temperature for 0.5 h. 7-Hydroxy-5-nitrobenzofuran-2-carboxylic acid (39.6 g, 177 mmol) was added to the resulting acidic methanol and the mixture heated at reflux under a nitrogen atmosphere for 18 h. The reaction mixture was cooled to room temperature and the resulting precipitated solid filtered, washed with cold methanol (500 mL) and dried to give the methyl ester as a light tan solid (41.2 g, 98%).

^{1}H NMR (DMSO-d_6) δ 11.48 (s, OH), 8.23 (d, J = 2.21 Hz, ArH), 7.91 (s, ArH), 7.73 (s, ArH), 3.93 (s, OCH_3); IR (KBr) υ 3281, 1688, 1582, 1523, 1442, 1356, 1328, 1256, 1102, 969, 901, 810, 744 cm^{-1}; UV (EtOH) λ_{max} 213 (ε = 16556), 267.5 (ε = 26855) nm; MS (FD) 238 (M^+, 100) Anal. calcd. for $C_{10}H_7NO_6$

requires: C, 50.64; H, 2.97; N, 5.91%; Found: C, 50.85; H, 3.01; N, 5.88%.

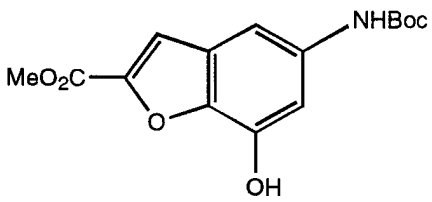
E. Methyl 5-Amino-7-hydroxybenzofuran-2-carboxylate



To a solution of methyl 7-hydroxy-5-nitrobenzofuran-2-carboxylate (42 g, 177 mmol) in tetrahydofuran: methanol (1:1, 1.5 L) was added 5% palladium / Al_2O_3 (5 g) and the mixture stirred under hydrogen at 4.1 bar for 4 h. The reaction mixture was filtered through diatomaceous earth and the filtrate evaporated to give a solid, which was purified by flash chromatography (gradient: 0-5% methanol: methylene chloride) to give the aniline derivative as a tan solid (35.6 g, 97%).

^{1}H NMR (DMSO-d_6) δ 9.93 (s,OH), 7.44 (s, ArH), 6.29 (d, J = 2 Hz, ArH), 6.24 (d, J = 1.75 Hz, ArH), 4.92 (s, NH_2), 3.85 (s, OCH_3); IR (KBr) υ 3416, 3335, 2947, 1713, 1610, 1568, 1454, 1434, 1356, 1204, 1155 cm^{-1}; MS (FD) 207 (M^+, 100); Anal., calcd. for $C_{10}H_9NO_4$ requires: C, 57.97; H, 4.38; N, 6.76%; Found: C, 57.72; H, 4.28; N, 6.63%.

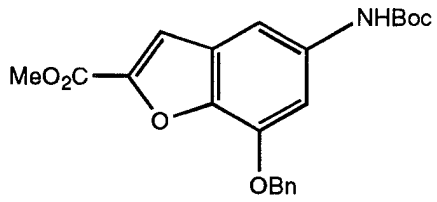
F. Methyl 5-[N-(tert-Butyloxycarbonyl)amino]-7-hydroxybenzofuran-2-carboxylate



Methyl 5-amino-7-hydroxybenzofuran-2-carboxylate (35.6 g, 172 mmol) was dissolved in tetrahydrofuran (750 mL) and di-tert-butyl dicarbonate (48 g, 222 mmol) added under a stream of nitrogen. The mixture was stirred at room temperature for 24 h and the solvent evaporated to give a solid residue. Crude product was dissolved in ethyl acetate (1.5 L), washed with 1 N aq. HCl (2 x 200 mL), water (2 x 600 mL), and brine (1 x 600 mL), and then dried (Na_2SO_4). The solution was passed through a plug of silica gel and evaporated to give the protected amine as a white powder (49.4 g, 93%).

^{1}H NMR (DMSO-d_6) δ 10.34 (s, OH), 9.34 (s, NH), 7.65 (s, ArH), 7.37 (d, J = 1.47 Hz, ArH), 7.10 (d, J = 1.84 Hz, ArH), 3.88 (s, OCH_3), 1.48 (s, 9 H, NBoc); IR (KBr) υ 3291, 1698, 1606, 1584, 1534, 1453, 1340, 1249, 1164, 1109, 1062, 976, 852, 763, 739 cm^{-1}; UV (EtOH) λ_{max} 211 (ε = 25983), 244.5 (ε = 31990), 287.5 (ε = 19236) nm; MS (FD) 308 (M^+, 100); Anal. calcd. for $C_{15}H_{17}NO_6$ requires: C, 58.63; H, 5.58; N, 4.56%; Found: C, 58.88; H, 5.63; N, 4.60%.

G. Methyl 5-[N-(tert-Butyloxycarbonyl)amino]-7-(benzyloxy)benzofuran-2-carboxylate

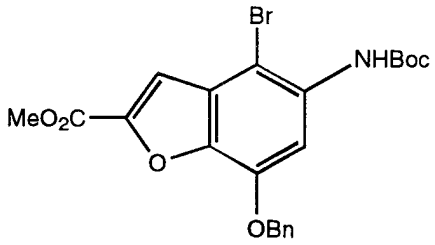


To a solution of methyl 5-[N-(tert-butyloxycarbonyl)amino]-7-hydroxybenzofuran-2-carboxylate (48.9 g, 159 mmol) in methylene chloride (1.5 L) was added benzyl alcohol (30 mL, 291 mmmol) and triphenylphosphine (75.1 g, 286 mmol) at room temperture and under a dry nitrogen atmosphere. The solution was cooled to 0 °C and diethyl azodicarboxylate (50 g, 287 mmol) added dropwise. The reaction mixture was stirred at room temperature for 18 h and then evaporated to

provide a solid, which was purified by flash chromatography (gradient: 5-20% ethyl acetate / hexanes) to furnish the benzyl ether as a white solid (57 g, 90%).

^{1}H NMR (DMSO-d_6) δ 9.43 (s, NH), 7.71 (s, ArH), 7.55 (s, 2 ArH), 7.53 (d, J = 1.75 Hz, ArH), 7.51 - 7.39 (m, 3 ArH), 7.29 (d, J = 1.75 Hz, ArH), 5.22 (s, CH_2Ph), 3.87 (s, OCH_3), 1.48 (s,9H, NBoc); IR (KBr) υ3440, 2982, 2954, 2934, 1725, 1606, 1582, 1528, 1320, 1158 cm^{-1}; MS (FD) 397 (M^+, 100); Anal. calcd. for $C_{22}H_{23}NO_6$ requires: C, 66.48; H, 5.83; N, 3.52%; Found: C, 66.25; H, 5.86; N, 3.69%.

H. Methyl 5-[N-tert-Butyloxycarbonyl)amino]-7-(benzyloxy)-4-bromobenzofuran-2-carboxylate

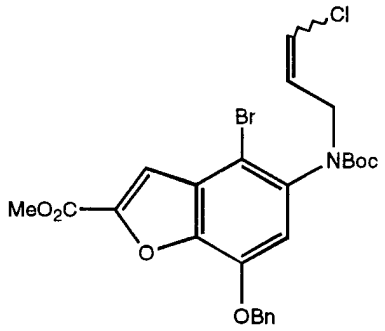


To a solution of methyl 5-[N-(tert-butyloxycarbonyl)amino]-7-(benzyloxy)benzofuran-2-carboxylate (30 g, 75.5 mmol) in dry tetrahydrofuran (250 mL) was added two drops of conc. H_2SO_4 followed by N-bromosuccinamide (14.8 g, 83 mmol) at -60 °C under a stream of nitrogen. The mixture warmed to 0 °C over 3 h and then quenched with 0.1 N aq. sodium bisulfite (5 mL). The organic solvent was evaporated and the residue diluted with ethyl acetate (300 mL), washed with water (2 x 150 mL) and brine (2 x 150 mL), dried (Na_2SO_4) and evaporated to give the aryl bromide as a light yellow solid (34.3 g, 95%).

^{1}H NMR ($CDCl_3$) δ 8.07 (s, NH), 7.54-7.49 (m, 3 ArH), 7.42-7.34 (m, 3 ArH), 6.94 (s, ArH), 5.31 (s, OCH_2), 3.97 (s, 3 OMe), 1.55 (s, 9 H, NBoc); IR ($CHCl_3$) υ3700, 3440, 3000, 2983, 1723, 1453, 1233, 1157 cm^{-1}; UV (EtOH) λ_{max} 212.5 (ε =

27223), 246 (ε = 28581), 287 (ε = 14281) nm; MS (FD) 475 (M^+, 100); Anal. calcd. for $C_{22}H_{22}BrNO_6$ requires: C, 55.48; H, 4.65; N, 2.94; Br, 16.78%; Found: C, 55.20; H, 4.70; N, 3.20; Br, 16.50%.

I. Methyl 5-[N-(tert-Butyloxycarbonyl)-N-(3-chloro-2-propen-1-yl)amino]-7-(benzyloxy)-4-bromobenzofuran-2-carboxylate



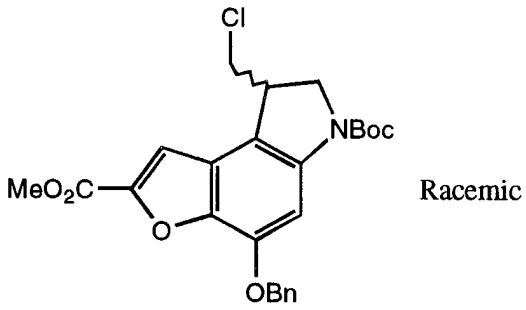
E:Z Mixture

Methyl 5-[N-tert-butyloxycarbonyl)amino]-7-(benzyloxy)-4-bromobenzofuran-2-carboxylate (1.43 g, 3 mmol) was added portionwise to a suspension of sodium hydride (60% in mineral oil; 156 mg, 3.90 mmol) in dry dimethylformamide (8.0 mL) at room temperature and under nitrogen. The resulting dark yellow mixture was stirred at room temperature for 40 min, cooled to 0 °C, and then neat 1,3-dichloropropene (846 µl, 9 mmol) added. The reaction mixture was allowed to warm to room temperature and strirred for a further 15 h. The reaction was quenched with brine (4 mL) and extracted with ethyl acetate (3 x 150 mL). Combined, dried ($MgSO_4$) organics were evaporated and the resulting crude brown oil chromatographed (gradient: hexanes-20% ethyl acetate/hexanes) to give the product as a yellow oil (1.36 g, 82%).

^1H NMR ($CDCl_3$) δ 7.58-7.20 (m, 6ArH), 6.85-6.71 (m, ArH), 5.99-5.85 (m, 2H, CH:CH), 5.32 (br s, 2H, OCH_2), 4.46 (dd, J= 6.2 and 15.5 Hz, NCHH), 4.35-4.20 (m, NCHH), 3.98 (s, OMe), 1.5 (br s, 3H,

NBoc), 1.28 (br s, 6H, NBoc); IR ($CHCl_3$) υ 2981, 1729, 1698, 1368, 1165 cm^{-1}; UV (EtOH) λ_{max} 203 (ε = 32586), 245.5 (ε = 30885), 286.5 (ε = 17684) nm; MS (FD) 551 (M+, 100); Anal. calcd. for $C_{25}H_{25}BrClNO_6$ requires: C, 54.51; H, 4.57; N, 2.58; Cl, 6.44; Br, 14.5%; Found: C, 54.31; H, 4.60; N, 2.68; Cl, 6.72; Br, 14.42%.

J. Methyl 5-(Benzyloxy)-3-(tert-butyloxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3H-furano[3,2-e]indole-7-carboxylate



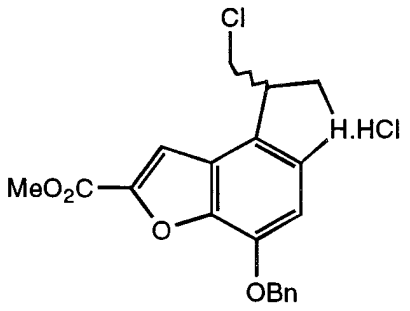
Racemic

To a deoxygenated solution of methyl 5-[N-(tert-butyloxy-carbonyl)-N-(3-chloro-2-propen-1-yl)amino]-7-(benzyloxy)-4-bromobenzofuran-2-carboxylate (12.30 g, 22.34 mmol) in dry benzene (1.49 L) was added tributyltin hydride (6.52 ml, 24.57 mmol) and catalytic AIBN (183 mg) at room temperature and under a dry nitrogen atmosphere. The solution was heated at reflux for 3.5 h, evaporated and the resulting oily residue trituated with hexanes to provide a solid which was filtered and washed with copious hexanes to yield the racemic tricyclic product as an off-white solid (7.79 g, 72%).

^1H NMR ($CDCl_3$) δ 7.85 (br s, ArH), 7.54-7.30 (m, 6 ArH), 5.28 (s, OCH_2), 4.17 (apparent t, J=10.4 Hz, NCHH), 4.08-3.98 (m, NCHH), 3.95 (s, OCH_3), 3.91-3.71 (m, 2H, CH_2Cl), 3.56 (apparent t, J= 10.3 Hz, CH), 1.56 (s, 9H, NBoc); IR ($CHCl_3$) υ 2956, 1725, 1695, 1497, 1158 cm^{-1}; UV (EtOH) λ_{max} 219 (ε = 27621), 254.5 (ε = 38111), 285 (ε = 14659), 346 (ε =

2729) nm; MS (FD) 471 (M+,100); Anal. calcd. for $C_{25}H_{26}ClNO_6$ requires: C, 63.63; H, 5.55; N, 2.97; Cl,7.51%; Found: C, 63.35; H, 5.51; N, 2.74; Cl, 7.30%.

K. Methyl 5-(Benzyloxy)-1-(chloromethyl)-1,2-dihydro-3H-furano[3,2-e]indole-7-carboxylate

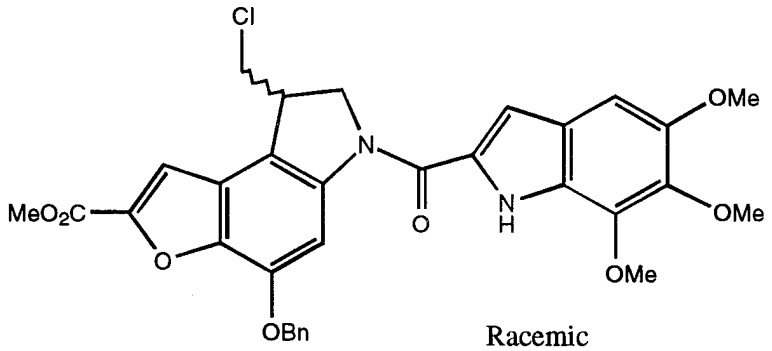


Racemic

A solution of the above urethane (1.00 g, 2.12 mmol) in dry 4 N HCl in dioxane (40 mL) was stirred under N_2 at 0 °C for 8 h and then the solvent evaporated at 0 °C to provide amine salt as an unstable brown solid (1.02 g, quantitative yield). The product was used immediately in the next step without further purification.

^{1}H NMR (DMSO-d_6) δ 7.73 (s, ArH), 7.47-7.29 (m, 6 ArH), 7.11 (s, NH), 5.33 (s, OCH_2), 4.26-4.23 (m, NCHH), 4.09-3.97 (m, NCHH), 3.95 (s, OCH_3), 3.95-3.91 (m, CHHCl), 3.84 (dd, J=4.4 and 12.1 Hz, CHHCl), 3.29-3.27 (m, CH); IR (KBr) υ 3423, 2853, 2471, 1703, 1577, 1332, 1206, 1105 cm^{-1}; UV (EtOH) λ_{max} 213 (ε = 23618), 244 (ε = 16705), 287.5 (ε = 11177), 352 (ε = 2569) nm; MS (FD) 371 (free amine) (M^+, 100); Anal. calcd. for $C_{20}H_{19}Cl_2NO_4$ requires: C, 58.84; H, 4.69; N, 3.43; Cl, 17.37%; Found: C, 58.54; H, 4.89; N, 3.09; Cl, 15.80%.

L. Methyl 5-(Benzyloxy)-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1H-indole-2-yl)carbonyl]-3H-furano[3,2-e]indole-7-carboxylate

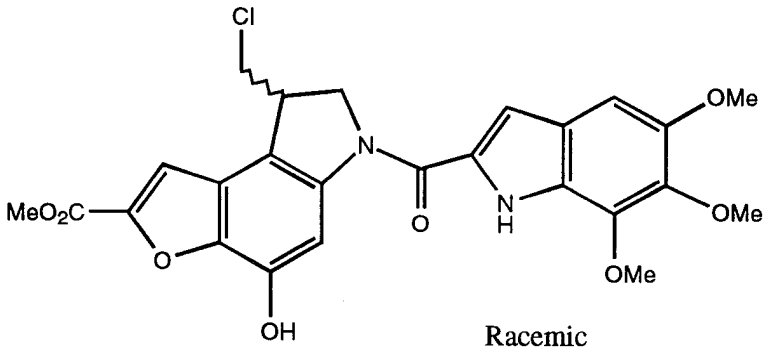


Racemic

The above crude amine salt (142.8 mg, 0.35 mmol), 5,6,7-trimethoxy-1H-indole-2-carboxylic acid (97 mg, 0.385 mmol), EDCI (147 mg, 1.75 mmol) and sodium bicarbonate (147 mg, 1.75 mmol) were suspended in dry dimethylformamide (3.50 mL) and stirred at room temperature under nitrogen for 19 h. The solvent was evaporated to 1/2 the original volume and ethyl acetate (6 mL) added. The organics were washed with 0.1 N aq. HCl (2 x 10 mL), H_2O (10 mL), sat. $NaHCO_3$ (10 mL), brine (10 mL) and then dried ($MgSO_4$). Evaporation, followed by chromatography of the crude solid, provided the amide as a pale yellow solid (142 mg, 67%).

^1H NMR (DMSO-d_6) δ 11.43 (br s, NH), 8.10 (br s, ArH), 8.02 (s, ArH), 7.51-7.32 (m, 5 ArH), 6.99 (s, ArH), 6.92 (s, ArH), 5.24 (br s, OCH_2), 4.69 (t, J=10.3 Hz, NCHH), 4.35 (dd, J= 4.6 and 10.9 Hz, NCHH), 4.11-3.93 (m, CH_2Cl), 3.87 (s, OCH_3), 3.86 (s, OCH_3), 3.76 (s, OCH_3), 3.74 (s, OCH_3), 3.43-3.28 (buried m, CH); IR (KBr) υ 1731, 1618, 1492, 1306, 1202, 1115, 752, 705 cm^{-1}; UV (EtOH) λ_{max} 208.5 (ε = 20887), 297.5 (ε = 12100), 325.5 (ε = 14129) nm; MS (FD) 604 (M+, 100); Anal. calcd. for $C_{32}H_{29}ClN_2O_8$ requires: C, 63.52; H, 4.83; N, 4.63; Cl, 5.86%; Found: C, 63.12; H, 4.86; N, 4.76; Cl, 6.20%.

M. Methyl 5-Hydroxy-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1H-indole-2-yl)carbonyl]-3H-furano[3,2-e]indole-7-carboxylate



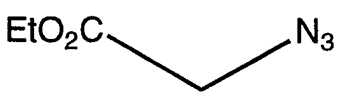
Racemic

To a solution of the above benzyl ether (323 mg, 0.534 mmol) in tetrahydrofuran (15.0 mL) was added 10% aq. ammonium formate (1.21 mL). The solution was cooled to 0 °C and 10% Pd/C (122 mg) added. The mixture was stirred at 0 °C for 3 h, filtered through a pad of diatomaceous earth and evaporated to provide the title product as a yellow solid (275 mg, quantative yield).

^{1}H NMR (DMSO-d_6) δ 11.39 (d, J=1.1 Hz, NH), 10.52 (s, OH), 7.96 (s, ArH), 7.94 (s, ArH), 6.98 (s, ArH), 6.92 (s, ArH), 4.67 (apparent t, J=10.3 Hz, NCHH), 4.33 (dd, J=4.1 and 11.4 Hz, NCHH), 4.08-4.04 (m, CHHCl), 3.99-3.91 (m, CHHCl), 3.88 (s, OCH_3), 3.87 (s, OCH_3), 3.77 (s, OCH_3), 3.75 (s, OCH_3), 3.34-3.26 (buried m, CH); IR (KBr) υ 3443, 1713, 1586, 1493, 1311, 1109, 916, 769 cm^{-1}; UV (EtOH, sparingly soluble) λ_{max} 208.5 (ε = 27879), 303 (ε = 22550), 325 (ε = 23229) nm; MS (FAB) 515.1 (M^+, 1.2); Anal. calcd. for $C_{25}H_{23}ClN_2O_8$ requires: C, 58.31; H, 4.50; N, 5.44; Cl, 6.89%; Found: C, 58.06; H, 4.34; N, 5.47; Cl, 6.88%.

The 5,6,7-trimethoxy-1H-indole-2-carboxylic acid used in part L above was prepared as follows.

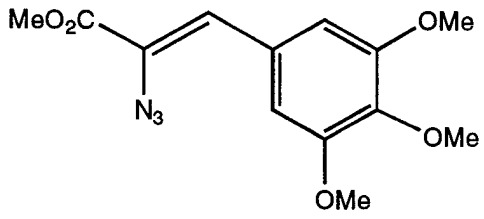
N. Ethyl azidoacetate



Ethyl chloroacetate (92.8 g,0.757 mol) and sodium azide (60 g, 0.923 mol) were suspended in 80% aqueous ethanol (600 mL) and the mixture heated at reflux for 4 h. The reaction was quenched with brine (4.5 L) and extracted with diethyl ether (5 x 500 mL). Combined organics were dried ($MgSO_4$) and evaporated to give the azide as an oil (41.0 g, 42%).

^1H NMR ($CDCl_3$) δ 4.21 (q, J=7.1 Hz, OCH_2), 3.82 (s, N_3CH_2), 1.26 (t, J=7.1 Hz, CH_3); IR (KBr) υ 3040, 2911, 2110, 1745, 1373, 1347, 1293, 1027 cm^{-1}; MS (FD) 129.1 (M^+); Anal. calcd. for $C_4H_7N_3O_2$ requires: C, 37.21; H, 5.47; N, 32.54%; Found: C, 36.98; H, 5.46; N, 32.41%.

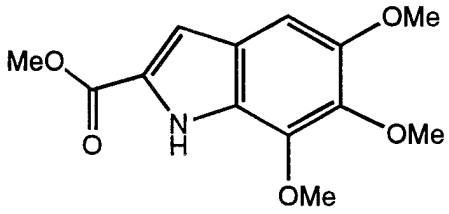
O. Methyl (Z)-2-Azido-3-(3,4,5-trimethoxyphenyl)acrylate



A solution of 3,4,5-trimethoxybenzaldehyde (7.84 g, 0.04 mol) and ethyl azidoacetate (21 g, 0.16 mol) in dry methanol (100 mL) was added dropwise to a solution of sodium methoxide (8.64 g, 0.16 mol) in methanol (400 mL) at -10 °C. The resulting solution was warmed to room temperature and then heated at 45 °C for 30 min resulting in the evolution of nitrogen (take care). The reaction was cooled to room temperature, quenched with brine (250 mL) and evaporated to a solid, which was diluted with H_2O (300 mL) and extracted with ethyl acetate (4 x 100 mL). Combined, dried ($MgSO_4$) organics were evaporated to give the product as a yellow solid (6.30 g, 51%) which was unstable and was immediately used in the next step.

^1H NMR ($CDCl_3$) δ 7.09 (s, 2ArH), 6.84 (s, :CH), 3.94 (s, OCH_3), 3.92 (s, OCH_3), 3.91 (s, OCH_3), 3.89 (s, OCH_3) ppm.

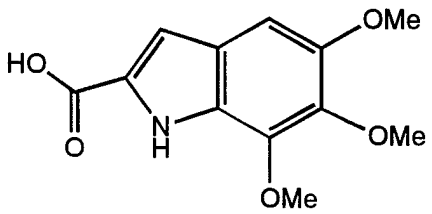
P. Methyl 5,6,7-Trimethoxy-1H-indole-2-carboxylate



The above crude azide (6.0 g, 0.0195 mol) was dissolved in toluene (520 mL) and heated at reflux for 1.5 h. The resulting orange solution was evaporated and the residue chromatographed (gradient: hexanes-25% ethyl acetate/hexanes) to provide the indole derivative as a yellow solid (2.75 g, 53%).

^{1}H NMR ($CDCl_3$) δ 8.94 (br s, NH), 7.10 (d, J=2.2 Hz, ArH), 6.81 (s, ArH), 4.06 (s, OCH_3), 3.94 (s, OCH_3), 3.92 (s, OCH_3), 3.89 (s, OCH_3); IR (KBr) υ 3318, 3284, 2944, 2838, 1718, 1710, 1579, 1438, 1253, 1230, 1091, 844 cm^{-1}; UV (EtOH) λ_{max} 300 (ε = 19212) nm; MS (FD) 265.1 (M^+, 100); Anal. calcd. for $C_{13}H_{15}NO_5$ requires: C, 58.86; H, 5.70; N, 5.28%; Found: C, 59.10; H, 5.81; N, 5.17%.

Q. 5,6,7-Trimethoxy-1H-indole-2-carboxylic Acid



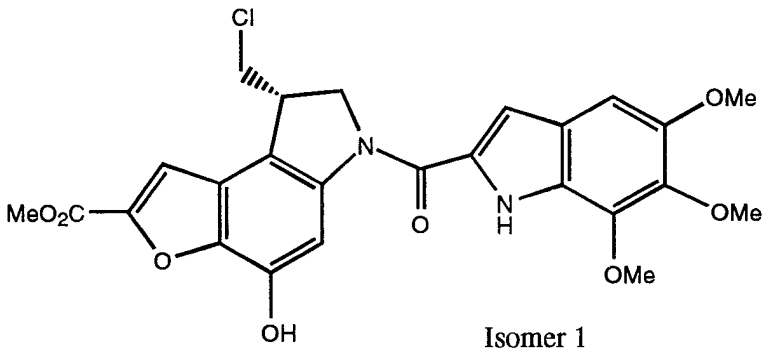
To a solution of the above methyl ester (2.60 g, 9.81 mmol) in methanol (20 mL) was added 2 N aq. NaOH (11 mL) at room temperature. The solution was stirred for 18.75 h at room temperature, evaporated, redissoved in 2 N aq. NaOH (50 mL), sonicated for 20 min and filtered. The aqueous filtrate was washed with ethyl acetate (3 x 30 mL) and acidified to pH 3

with 1 N aq. HCl to produce a precipitate, which was filtered, washed with H_2O and dried in vacuo (50 °C) to give the carboxylic acid as a white crystalline solid (1.88 g, 76%).

^1H NMR ($CDCl_3$) δ 12.69 (br s, CO_2H), 11.54 (s, NH), 6.96 (s, ArH), 6.87 (s, ArH), 3.85 (s, OCH_3), 3.75 (s, OCH_3), 3.73 (s, OCH_3); IR (KBr) υ 3282, 2933, 2837, 1655, 1539, 1506, 1262, 1230, 1110, 1090, 993, 841cm^{-1}; UV (EtOH) λ_{max} 208 (ε = 27060), 298 (ε = 18225) nm; MS (FD) 251.1 (M^+, 100); Anal. calcd. for $C_{12}H_{13}NO_5$ requires: C, 57.37; H, 5.22; N, 5.58%; Found: C, 57.37; H, 5.47; N, 5.29%.

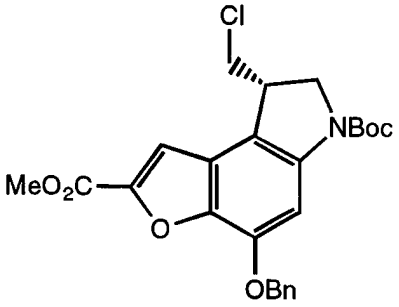
Example 2

Preparation of (+)-(1S) Methyl 5-Hydroxy-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1H-indole-2-yl)carbonyl]-3H-furano[3,2-e]indole-7-carboxylate



Isomer 1

A. (+)-(1S) Methyl 5-(Benzyloxy)-3-(tert-butyloxy-carbonyl)-1-(chloromethyl)-1,2-dihydro-3H-furano[3,2-e]indole-7-carboxylate



Isomer 1

Separation of enantiomers on a chiral column:

The preparative chromatographic system consisted of a semi-automated integrated system Model LC80.600.VE.70 from Prochrom, Inc.[Indianapolis, IN, USA]. The column pumping system was a diaphragm Lewa model EKM2 and the sample pump was a Lewa model FC1. The system had a 10 port fraction collector and Rainin Dynamax model UV-1 variable UV-VIS detector with full flow cell. The preparative column was an 8 cm x 70 cm Dynamic Axial Compression (DAC) configuration. The maximum bed length was 40 cm with a maximum working pressure of 70 bar [1000 psi]. The hydraulic pump used to compress the column bed was a Haskel model MS-36.

Six hundred grams of 20 micron Chiralpak AD (Amylose) [Chiralcel OD, OJ, Chiralpak AD analytical columns and bulk Chiralpak AD packing were purchased from Chiral Technologies, Inc. (Exton, PA, USA)] was slurred in 1200 mL of propanol and transferred to the 8 cm Prochrom column. Compression of the bed was done at a pressure of 85 bar. The resulting configuration was 8 cm x 24 cm with a CV (column volume) of 964 mL. Operating conditions for the preparative separation were a flow rate of 225 mL/min and a column pressure of 11 bar.

The enantiomers of methyl 5-(benzyloxy)-3-(tert-butyloxy-carbonyl)-1-(chloromethyl)-1,2-dihydro-3H-furano[3,2-e]in-dole-7-carboxylate, prepared as described in Example 1-J, were separated on the Chiralpak AD column with propanol/hexane (51:49). Solubility of the compound in the chromatographic eluent was approximately 1.5 mg/mL. Typically, three hundred sixty mg of the compound was dissolved in 300 mL of eluent and charged on the column using the sample pump. Three hundred mL corresponded to a loading of 31% of one CV without loss in resolution. The optimized run time was 13 min. Ten plus grams of the

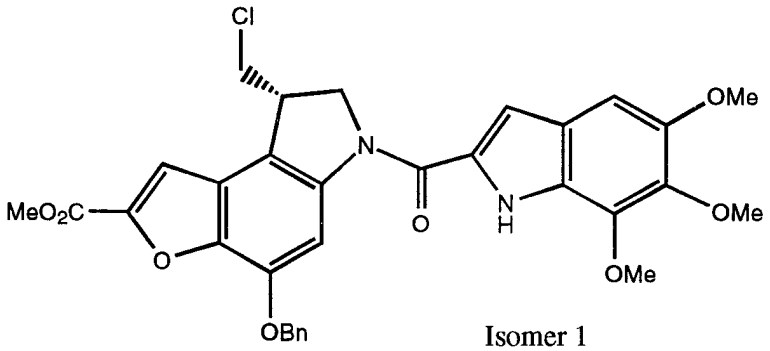
racemate was separated in 35 runs on the 8 cm column. The 5.1 gm (Isomer 1) and 5.0 gm (Isomer 2) of enantiomers isolated from the preparatory chromatography represented a 98% recovery from the racemate. Enantiomeric excess of the separated isomers was 97.6% (Isomer 1) and 95.5% (Isomer 2), respectively.

The analytical chromatograph consisted of an integrated Shimadzu Scientific Instruments system [Columbia, MD, USA] with gradient pump model LC-10AD, variable wavelength detector model SPD-10A, autosampler model SIL-10A, fraction collector model FRC-10A, and system controller model SCL-10A. The enantiomers were separated on a 10 micron 4.6 x 250 mm Chiralcel OD-R column using acetonitrile and perchlorate buffer.

Isomer 1 from the preparative separation was characterized as follows:

^{1}H NMR ($CDCl_3$) δ7.90 (br s, ArH), 7.55-7.33 (m, 7 ArH), 5.29 (s, OCH_2), 4.18 (apparent dd, J=10 and 11.3 Hz, NCHH), 4.08-3.93 (m, NHH), 3.96 (s, OCH_3), 3.87-3.80 (m, 2H, CH_2Cl), 3.60 (apparent t, J= 10.4 Hz, CH), 1.57 (s, 9H, NBoc); IR (KBr) υ 2990, 1737, 1696, 1152, 1137, 767, 696 cm^{-1}; UV (EtOH) λ_{max} 219 (ε = 27870), 254.5 (ε = 39132), 284.5 (ε = 14997), 346 (ε = 2901) nm; MS (FD) 470.9 (M^+, 100); $[\alpha]_D$ -8.47° (c 3.54, CH_2Cl_2); Anal. calcd. for $C_{25}H_{26}ClNO_6$ requires: C, 63.63; H, 5.55; N, 2.97; Cl, 7.51%; Found: C, 63.56; H, 5.53; N, 2.67; Cl, 7.72%.

B. (+)-(1S) Methyl 5-(Benzyloxy)-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1H-indole-2-yl)carbonyl]-3H-furano[3,2-e]indole-7-carboxylate

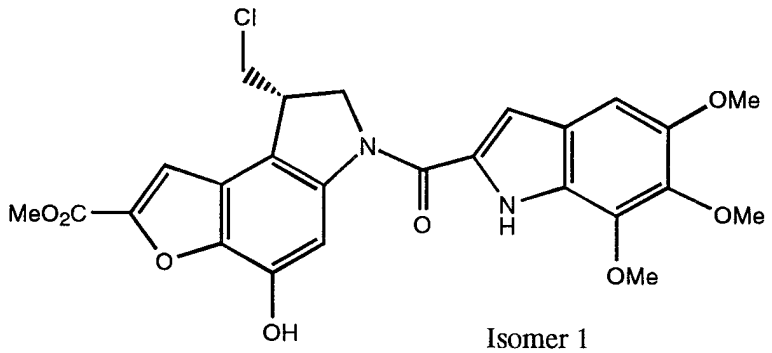


Isomer 1

A solution of the above urethane (200 mg, 0.424 mmol) in dry 4 N HCl in dioxane (10 mL) was stirred under N_2 at 0 °C for 5 h and then the solvent evaporated at 0 °C to provide the amine salt as an unstable green solid. The amine was used immediately, without further purification, in the next step. Amine salt (0.424 mmol), 5,6,7-trimethoxy-1H-indole-2-carboxylic acid (128 mg, 0.509 mmol), EDCI (244 mg, 1.272 mmol) and sodium bicarbonate (178 mg, 2.12 mmol) were suspended in dry dimethylformamide (4.0 mL) and stirred at room temperature under nitrogen for 18 h. The solvent was evaporated to 1/2 the original volume and ethyl acetate (6 mL) added. The organics were washed with 0.1 N aq. HCl (2 x 10 mL), H_2O (10 mL), sat. $NaHCO_3$ (10 mL), brine (10 mL) and then dried ($MgSO_4$). Evaporation followed by chromatograhy of the crude solid provided the amide as a yellow solid (127 mg, 50%).

^1H NMR (DMSO-d_6) δ 11.43 (br s, NH), 8.10 (br s, ArH), 8.02 (s, ArH), 7.51-7.32 (m, 5 ArH), 6.99 (s, ArH), 6.91 (s, ArH), 5.23 (br s, OCH_2), 4.69 (t, J=9.7Hz, NCHH), 4.35 (dd, J= 4.1 and 11.2 Hz, NCHH), 4.18-3.92 (m, CH_2Cl), 3.87 (s, OCH_3), 3.86 (s, OCH_3), 3.76 (s, OCH_3), 3.74 (s, OCH_3), 3.34-3.22 (buried m, CH); IR (KBr) υ 3459, 2936, 1732, 1622, 1494, 1308, 1203, 744, 697 cm^{-1}; UV (EtOH) λ_{max} 208.5 (ε = 35611), 297 (ε = 22216), 326 (ε = 24475) nm; MS (FD) 604 (M+, 100); $[\alpha]_D$ +16.67° (c 3.6, CH_2Cl_2); Anal. calcd. for $C_{32}H_{29}ClN_2O_8$ requires: C, 63.53; H, 4.83; N, 4.63; Cl, 5.86%; Found: C, 62.75; H, 5.19; N, 4.35; Cl, 5.46%.

C. (+)-(1S) Methyl 5-Hydroxy-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1H-indole-2-yl)carbonyl]-3H-furano[3,2-e]indole-7-carboxylate



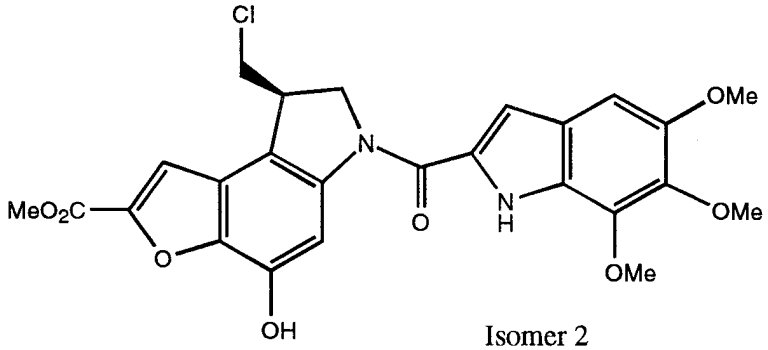
Isomer 1

To a solution of the above benzyl ether (149 mg, 0.247 mmol) in tetrahydrofuran (5.80 mL) was added 10% aq. ammonium formate (560 µL). The solution was cooled to 0 °C and 10% Pd/C (56 mg) added. The mixture was stirred at 0 °C for 5 h, filtered through a pad of diatomaceous earth and evaporated to provide the title product as a yellow solid (122 mg, 96%).

^{1}H NMR (DMSO-d_6) δ 11.39 (d, J=1.14 Hz, NH), 10.52 (s, OH), 7.96 (s, ArH), 7.92 (s, OH), 6.97 (d, J=1.7 Hz, ArH), 6.92 (s, ArH), 4.66 (apparent t, J=10 Hz, NCHH), 4.34 (dd, J=3.54 and 10.6 Hz, NCHH), 4.08-4.02 (m, CHHCl), 3.98-3.94 (m, CHHCl), 3.88 (s, OCH_3), 3.87 (s, OCH_3), 3.77 (s, OCH_3), 3.75 (s, OCH_3), 3.34-3.26 (buried m, CH); IR (KBr) υ 3449, 1726, 1589, 1492, 1453, 1310, 1198, 1106 cm^{-1}; UV (EtOH, sparingly soluble) λ_{max}302 (ε = 13513), 323 (ε = 14163) nm; MS (FD) 514 (M^+, 100); $[\alpha]_D$ + 19.94° (c 10.03, dimethylformamide); Anal. calcd. for $C_{25}H_{23}ClN_2O_8$ requires: C, 58.31; H, 4.50; N, 5.44; Cl, 6.89%; Found: C, 58.59; H, 4.66; N, 5.48; Cl, 6.57%.

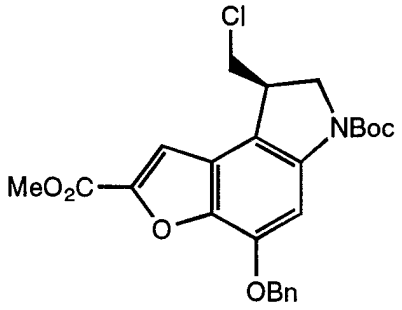
Example 3

Preparation of (-)-(1R) Methyl 5-Hydroxy-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1H-indole-2-yl)carbonyl]-3H-furano[3,2-e]indole-7-carboxylate



Isomer 2

A. (-)-(1R) Methyl 5-(Benzyloxy)-3-(tert-butyloxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3H-furano[3,2-e]indole-7-carboxylate



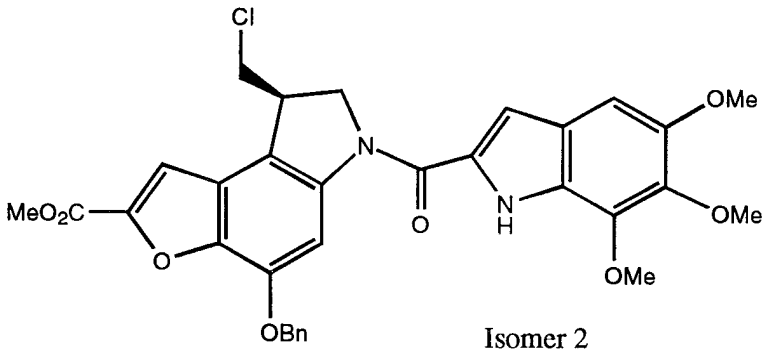
Isomer 2

Isomer 2 of the separation described in Example 2-A was characterized as follows:

^{1}H NMR ($CDCl_3$) δ7.90 (br s, ArH), 7.55-7.28 (m, 5 ArH), 5.29 (s, OCH_2), 4.18 (dd, J=10 and 11.6 Hz, NCHH), 4.08-3.98 (m, NCHH), 3.96 (s, OCH_3), 3.88-3.80 (m, 2H, CH_2Cl), 3.60 (apparent t, J=10.4 Hz, CH), 1.57 (s, 9H, NBoc); IR (KBr) υ 2990, 1736, 1697, 1499, 1424, 1349, 1208, 1152, 1137, 762, 697 cm^{-1}; UV (EtOH) λ_{max} 219.5 (ε = 26377), 254.5 (ε = 37628), 284.5 (ε = 14440), 346.5 (ε = 2823) nm; MS (FD) 470.9 (M+, 100); $[\alpha]_D$ +14.29° (c 3.50, CH_2Cl_2); Anal. calcd.

for $C_{25}H_{26}ClNO_6$ requires: C, 63.63; H, 5.55; N, 2.97; Cl, 7.51%; Found: C, 63.91; H, 5.58; N, 3.31; Cl, 7.59%.

B. (-)-(1R) Methyl 5-(Benzyloxy)-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1H-indole-2-yl)carbonyl]-3H-furano[3,2-e]indole-7-carboxylate



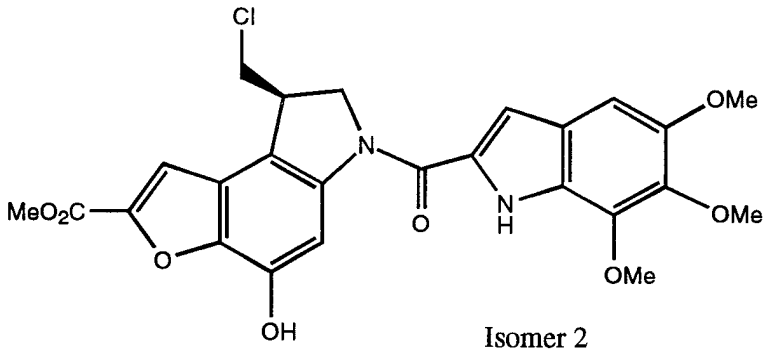
Isomer 2

A solution of the above urethane (250 mg, 0.530 mmol) in dry 4 N HCl in dioxane (10 mL) was stirred under N_2 at 0 °C for 6.5 h and then the solvent evaporated at 0 °C to provide the amine salt as an unstable green solid. The amine was used immediately, without further purification, in the next step. Amine salt (0.530 mmol), 5,6,7-trimethoxy-1H-indole-2-carboxylic acid (160 mg, 0.636 mmol), EDCI (306 mg, 1.59 mmol) and sodium bicarbonate (223 mg, 2.65 mmol) were suspended in dry dimethylformamide (6.0 mL) and stirred at room temperature under nitrogen for 17 h. The solvent was evaporated to 1/2 the original volume and ethyl acetate (6 mL) added. The organics were washed with 0.1 N aq. HCl (2 x 10 mL), H_2O (10 mL), sat. $NaHCO_3$ (10 mL), brine (10 mL) and then dried ($MgSO_4$). Evaporation, followed by chromatography of the crude solid, provided the amide as a yellow solid (161 mg, 50%).

^1H NMR (DMSO-d_6) δ 11.43 (br s, NH), 8.10 (br s, ArH), 8.02 (s, ArH), 7.48-7.32 (m, 5 ArH), 6.98 (s, ArH), 6.91 (s, ArH), 5.23 (br s, OCH_2), 4.69 (t, J=10Hz, NC<u>H</u>H), 4.35 (dd, J=3.9 and 10.7 Hz, NCH<u>H</u>), 4.13-3.91 (m, CH_2Cl), 3.87 (s,

OCH_3), 3.86 (s, OCH_3), 3.76 (s, OCH_3), 3.74 (s, OCH_3), 3.36-3.26 (buried m, CH); IR (KBr) υ 2937, 1731, 1622, 1494, 1416, 1309, 1204, 1109, 744, 697 cm^{-1}; UV (EtOH) λ_{max} 209 (ε = 44076), 297.5 (ε = 26058), 326 (ε = 30391) nm; MS (FD) 603.7 (M+, 100); $[\alpha]_D$ -8.42° (c 3.56, CH_2Cl_2); Anal. calcd. for $C_{32}H_{29}ClN_2O_8$: requires: C, 63.53; H, 4.83; N, 4.63; Cl, 5.86%; Found: C, 63.74; H, 4.81; N, 4.40; Cl, 6.01%.

C. (-)-(1R) Methyl 5-Hydroxy-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1H-indole-2-yl)carbonyl]-3H-furano[3,2-e]indole-7-carboxylate



Isomer 2

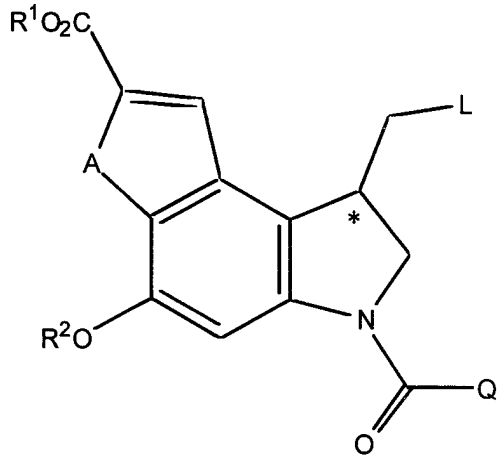
To a solution of the above benzyl ether (130 mg, 0.215 mmol) in tetrahydrofuran (10 mL) was added 10% aq. ammonium formate (585 μL). The solution was cooled to 0 °C and 10% Pd/C (60 mg) added. The mixture was stirred at 0 °C for 3.5 h, filtered through a pad of diatomaceous earth and evaporated to provide the title product as a yellow solid (109 mg, 99%).

^1H NMR (DMSO-d_6) δ 11.40 (s, NH), 10.51 (s, OH), 7.96 (s, ArH), 7.94 (s, OH), 6.98 (d, J=1.7 Hz, ArH), 6.92 (s, ArH), 4.67 (apparent t, J=10 Hz, NCHH), 4.32 (dd, J=4.2 and 11.4 Hz, NCHH), 4.08-4.05 (m, CHHCl), 3.98-3.92 (m, CHHCl), 3.89 (s, OCH_3), 3.87 (s, OCH_3), 3.77 (s, OCH_3), 3.75 (s, OCH_3), 3.36-3.27 (buried m, CH); IR (KBr) υ 3450, 1725, 1586, 1492, 1429, 1310, 1107, 746 cm^{-1}; UV (EtOH, sparingly soluble) λ_{max} 208, 303, 328 nm; MS (FD) 514 (M^+,100), 478 ([M-Cl^+], 25);

$[\alpha]_D^{589}$-28.64° (c 4.19, dimethylformamide); Anal. calcd. for $C_{25}H_{23}ClN_2O_8$ requires: C, 58.31; H, 4.50; N, 5.44; Cl, 6.89%; Found: C, 58.55; H, 4.67; N, 5.14; Cl, 6.92%.

What is claimed is:

1. A compound of formula I



I

wherein

A is O or S;

L is a pharmaceutically acceptable leaving group;

-CO-Q is a group which binds in the minor groove of duplex DNA;

R^1 is (1-4C)alkyl; and

R^2 is hydrogen or a prodrug residue;

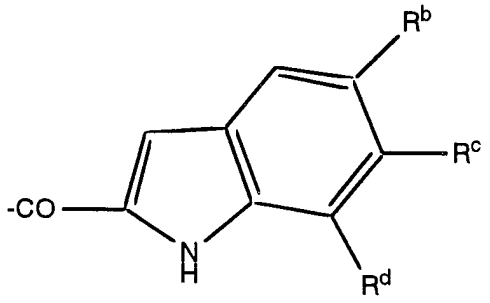
or (when said compound is acidic or basic) a pharmaceutically acceptable salt thereof.

2. The compound as claimed in Claim 1 wherein A is O.

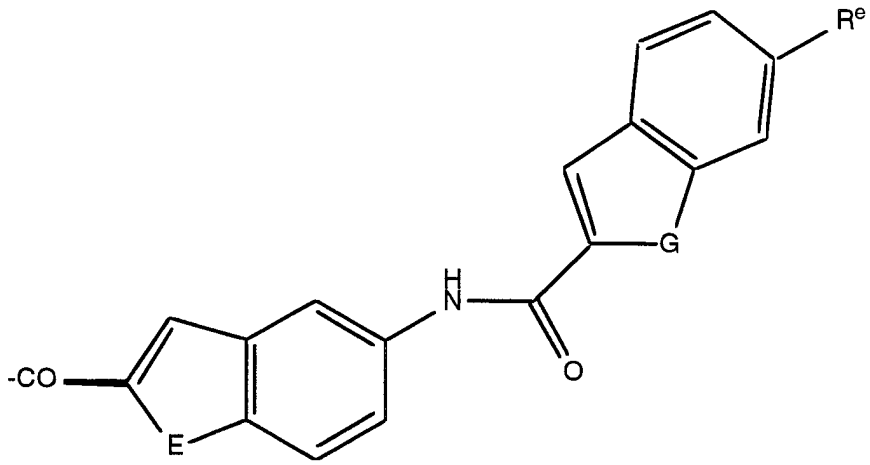
3. The compound as claimed in Claim 1 or 2 wherein L is chloro, bromo, iodo, $-OSO_3H$ or $-OSO_2R^a$ in which R^a is (1-4C)alkyl, phenyl or phenyl bearing one or more methyl or halo substituents.

4. The compound as claimed in Claim 3 wherein L is chloro.

5. The compound as claimed in any of Claims 1-4 wherein -CO-Q is

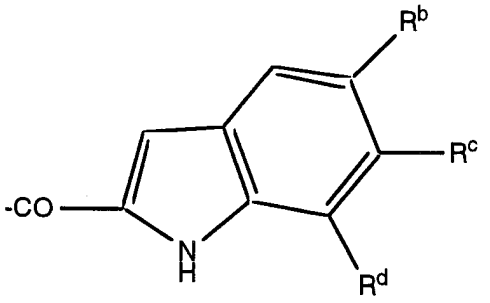


in which R^b, R^c, and R^d, independently, are methoxy or hydrogen, provided that at least one of them is methoxy; or wherein -CO-Q is



in which E and G are independently NH, O or S; and R^e is hydrogen, dimethylamino or diethylamino.

6. The compound as claimed in Claim 5 wherein -CO-Q is



in which R^b, R^c, and R^d are each methoxy, or in which R^b is methoxy and R^c and R^d are each hydrogen.

7. The compound as claimed in any one of Claims 1-6 wherein R^1 is methyl.

8. The compound as claimed in any one of Claims 1-7 wherein R^2 is hydrogen.

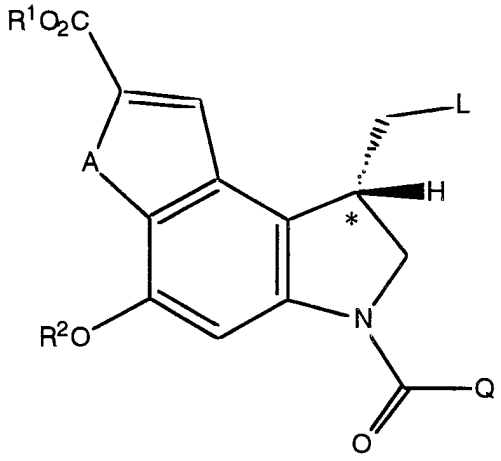
9. The compound as claimed in any one of Claims 1-7 wherein R^2 is a prodrug residue for a phenolic moiety selected from an acyl residue of formula $-COR^f$, $-COOR^g$ or $-CONR^hR^i$ in which $HO-COR^f$ is a nontoxic carboxylic acid, $H-OR^g$ is a nontoxic alcohol, and $H-NR^hR^i$ is a nontoxic amine.

10. The compound as claimed in Claim 9 wherein R^f is $-(CH_2)_n-COOH$, $-(CH_2)_n-SO_3H$, $-(CH_2)_n-CONH-CH_2-SO_3H$, $-(CH_2)_n-NR^jR^k$, $-C(CH_3)_2CH_2NH_2$, $-CH_2C(CH_3)_2NH_2$, $-CH_2OCH_2COOH$, $-CH_2SCH_2COOH$, $-CH_2S(O_2)CH_2COOH$, or $-(CH_2)_n-CONH-(PEG)$ wherein n is 1, 2 or 3; R^j is hydrogen or (1-2C)alkyl; R^k is hydrogen, (1-2C)alkyl or $-CH(R^s)COOH$, wherein R^s denotes the side chain of a naturally occurring α-amino acid; or $-NR^jR^k$ is a morpholino, piperazino or 4-methylpiperazino group; and (PEG) denotes polyethylene glycol; $-OR^g$ is (1-3C)alkoxy, chloromethoxy, vinyloxy, benzyloxy, 2-[(1-4C)alkylsulfonyl]-ethyl or 2-(phenylsulfonyl)ethyl; R^h or R^i is, independently, hydrogen or (1-2C)alkyl; or $-NR^hR^i$ is anilino, morpholino, piperazino, 4-(1-piperidino)-1-piperidino or 4-methylpiperazino.

11. The compound as claimed in Claim 10 wherein Rf is 2-(diethylamino)ethyl or (4-methylpiperazino)-methyl.

12. The compound as claimed in Claim 9 wherein R^2 is 4-methylpiperazinocarbonyl.

13. The compound as claimed in any of Claims 1-12 which is the enantiomer of a compound of formula I which is of the formula I-α



I-α

wherein A, L, Q, R^1 and R^2 have any of the values claimed in Claims 1-12.

14. The compound as claimed in any of Claims 1-13 wherein, either alone or as part of another group, (1-2C)alkyl is methyl or ethyl; (1-3C)alkyl is methyl, ethyl, propyl or isopropyl; and (1-4C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl.

15. The compound of Claim 1 which is methyl 5-hydroxy-1-(chloromethyl)-1,2-dihydro-3-[5,6,7-trimethoxy-1H-indole-2-yl)carbonyl]-3H-furano[3,2-e]indole-7-carboxylate.

16. The compound of Claim 1 which is (+)-(1S) methyl 5-hydroxy-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1H-indole-2-yl)carbonyl]-3H-furano[3,2-e]indole-7-carboxylate.

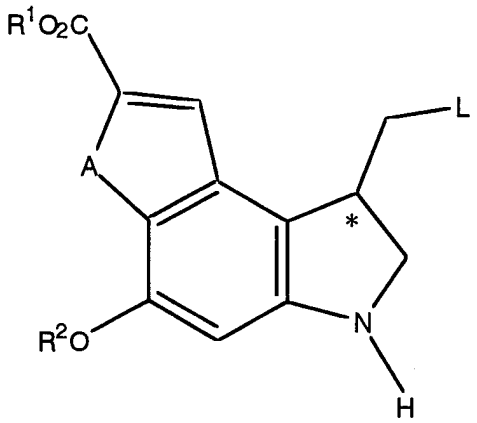
17. A pharmaceutically acceptable salt of an acidic or basic compound of formula I as claimed in Claim 1 which is selected from a salt made with a base which affords a pharmaceutically acceptable cation when the compound of formula I includes an acidic moiety, and an acid addition salt with a pharmaceutically acceptable acid when the compound of formula I includes a basic moiety.

18. A pharmaceutical composition comprising the compound of formula I, or a pharmaceutically acceptable salt thereof, as claimed in any of Claims 1-17, together with a suitable diluent or carrier.

19. A method for treating a susceptible neoplasm which comprises administering to an animal in need thereof an effective amount of the compound of formula I, or a pharmaceutically acceptable salt thereof, as claimed in any of Claims 1-17.

20. A process for preparing the compound of formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1-17 which comprises:

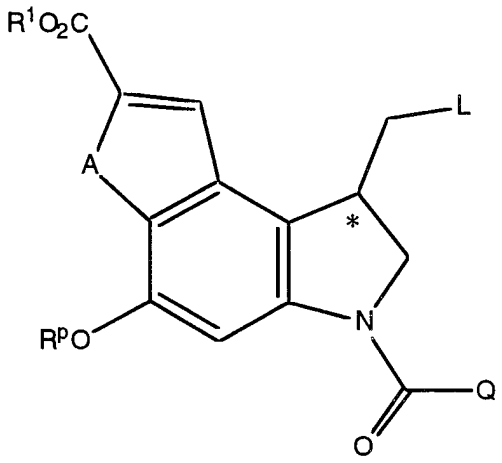
(A) acylating an amine of formula II



II

with an acid of formula Q-COOH, or an activated derivative thereof;

(B) for a compound of formula I in which R^2 is hydrogen, removing the protecting group R^p of a compound of formula Ip

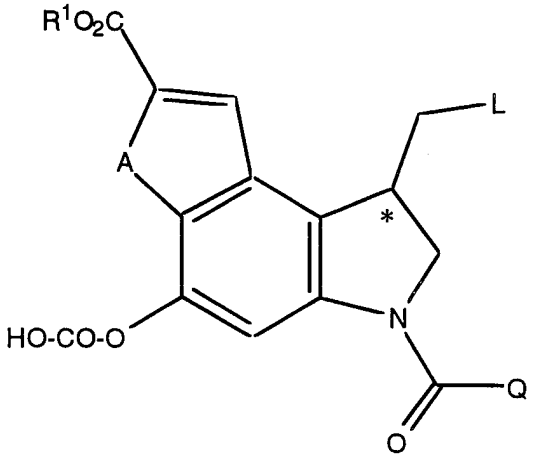


Ip

wherein R^p is a conventional protecting group for a phenolic hydroxy group, using a conventional method;

(C) for a compound of formula I in which R^2 is a prodrug residue, substitution of the hydrogen of a compound of formula I in which R^2 is hydrogen with the prodrug residue using a conventional method;

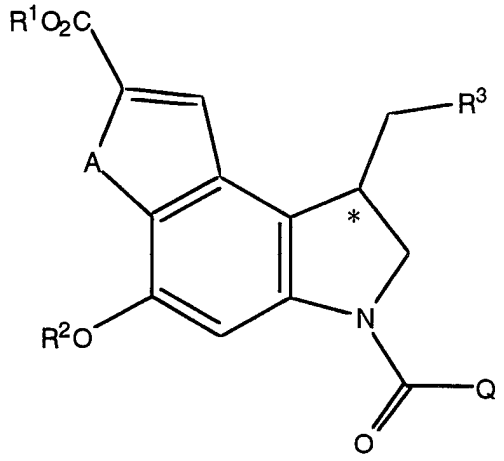
(D) for a compound of formula I in which R^2 is $-COOR^g$ or $-CONR^hR^i$, acylation of a corresponding alcohol of formula $H-OR^g$ or amine of formula $H-NR^hR^i$ with an activated derivative of a carbonic acid of formula Ic;



Ic

or

(E) For a compound of formula I in which L is $-OSO_3H$ or $-OSO_2R^a$, formation of the sulfonic ester of a corresponding compound of formula III



III

in which R^3 is hydroxy, using a conventional method;

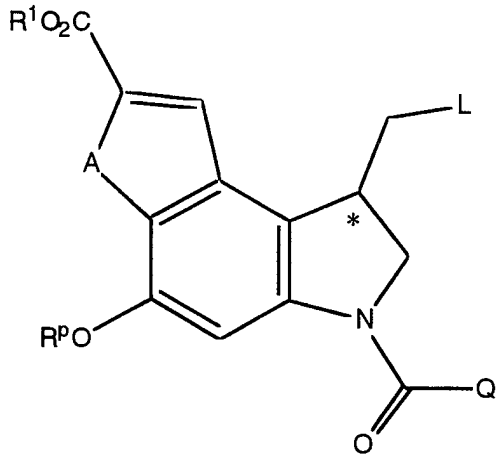
whereafter, for any of the above procedures, when a functional group is protected using a protecting group, removing the protecting group;

whereafter, for any of the above procedures, when a pharmaceutically acceptable salt of a compound of formula I is required, it is obtained by reacting the acidic or basic

form of such a compound of formula I with a base or an acid affording a physiologically acceptable counterion or by any other conventional procedure;

and wherein, unless otherwise specified, the groups A, L, -CO-Q, R^1 and R^2 and their components have any of the values defined in any of Claims 1-16.

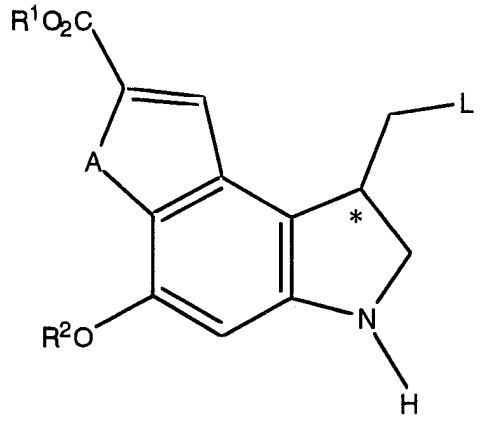
21. A compound of formula Ip



Ip

wherein R^P is a conventional protecting group for a phenolic hydroxy group and A, L, -CO-Q and R^1 have any of the values defined in any one of Claims 1-7, 13 or 14.

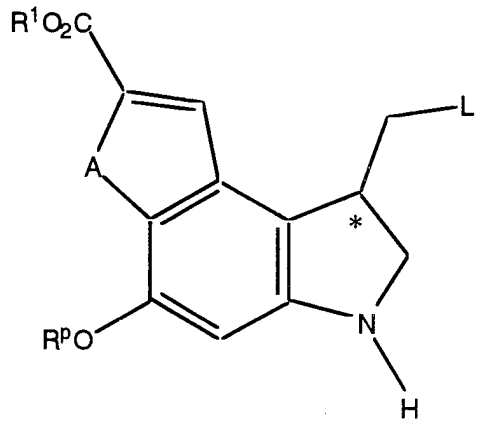
22. An amine of formula II



II

or an acid addition salt thereof, wherein A, L, R^1 and R^2 have any of the values defined in any of Claims 1-4 or 7-14.

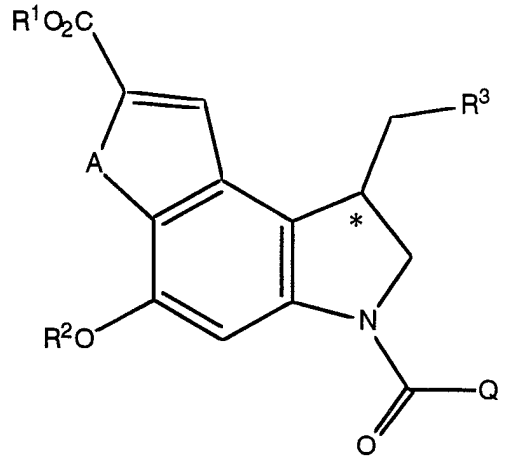
23. An amine of formula IIp,



IIp

or an acid addition salt thereof, wherein R^P is a protecting group for a phenolic hydroxy group and A, L and R^1 have any of the values defined in any one of Claims 1-4, 7, 13 or 14.

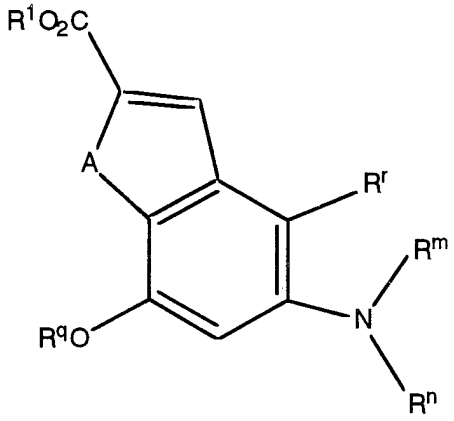
24. A compound of formula III



III

in which R^3 is hydroxy and A, -CO-Q, R^1 and R^2 have any of the values defined in any one of Claims 1, 2, or 5-14.

25. An ester of formula IV



IV

wherein R^m is hydrogen; R^n is a protecting group for an anilino nitrogen; R^q is a value of R^2 or R^p which is stable to the subsequent reaction conditions; R^r is a group which will afford the corresponding aryl radical when subjected to a radical generating reagent or condition; R^p is a protecting group for a phenolic hydroxy group; and A, R^1 and R^2 have any of the values defined in any one of Claims 1, 2 or 7-12.

26. A compound as claimed in Claim 25 in which A is O, R^1 is methyl, R^m is hydrogen, R^n is tert-butyloxycarbonyl (Boc), R^q is benzyl, and R^r is bromo.

27. A process for the preparation of a compound of formula IV wherein formula IV, A, R^1, R^m, R^n, R^q and R^r are defined as in Claim 25 or 26 from 2-hydroxy-3-methoxy-5-nitrobenzaldehyde which comprises

alkylating the phenolic hydroxy group with an ester of formula $X\text{-}CH_2\text{-}COOR^{1a}$ wherein R^{1a} is a carboxy-protecting residue and X is a leaving group using a base and an inert solvent;

cyclizing the resulting ester to a benzofuran using a basic catalyst in an inert solvent to afford the 7-hydroxy-5-nitrobenzofuran-2-carboxylic acid ester;

removing the O-protecting groups R^{1a} and O-methyl to afford 7-hydroxy-5-nitrobenzofuran-2-carboxylic acid;

esterifying the acid with the alcohol R^1OH;

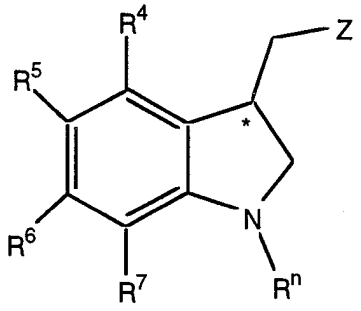
reducing the nitro group to an amino group;

substituting the amino group with the group R^n;

substituting the phenolic hydroxy group with the group R^q; and (when R^r is not hydrogen);

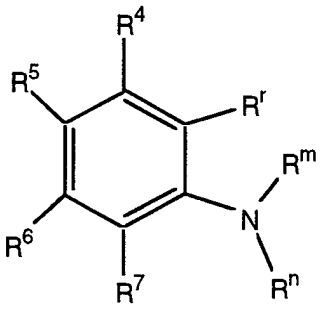
substituting the 6-position with the group R^r.

28. A process for the preparation of an indoline of formula VIII,



VIII

wherein each of R^4, R^5, R^6, R^7, R^n and Z is a group which is stable to the reaction conditions of the process, from a corresponding aniline of formula IX



IX

wherein R^m is hydrogen, R^r is a group which will afford the corresponding aryl radical when subjected to a radical generating reagent or condition which comprises

alkylating the compound of formula IX in which R^m is hydrogen with an olefin of formula X-CH_2CH=CHZ in which X is a leaving group, and Z is a group which is stable to the subsequent cyclization conditions to afford a substituted vinyl compound of formula IX in which R^m is -CH_2-CH=CHZ; and

subjecting the substituted vinyl compound of formula IX to a radical generating reagent or condition in an inert solvent in the presence of a radical reducing agent to afford the corresponding substituted indoline of formula VIII.

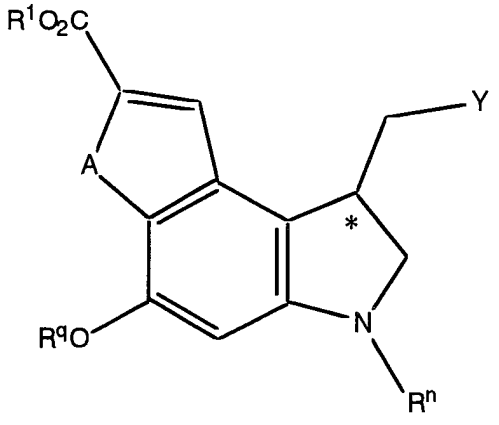
29. The process of Claim 28 for the preparation of an indoline of formula VIII, further in which R^n is hydrogen, from a corresponding aniline of formula IX in which R^n is a protecting group for an anilino nitrogen, which further comprises removing the N-protecting group R^n using a conventional method.

30. The process of Claim 28 or 29 wherein R^4, R^5, R^6 or R^7, is independently selected from hydrogen, (1-4C)alkyl, hydroxy, (1-4C)alkoxy, benzyloxy, (1-5C)acyloxy, benzoyloxy, (1-4C)alkoxycarbonyloxy, phenoxycarbonyloxy, (1-5C)acyl, benzoyl, cyano, (1-5C)acylamino, benzoylamino, (1-4C)alkoxycarbonylamino or

benzyloxycarbonylamino or a pair of neighboring residues together may form a fused a furano-, thiopheno-, pyrrolo- or benz-ring which fused ring may further bear one or more substituents; R^n is, tert-butyloxycarbonyl, formyl, acetyl, trichloroacetyl, 2,2,2-trichloroethoxycarbonyl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, 2-(p-tolylsulfonyl)ethoxycarbonyl, phenylsulfonyl, allyl, benzyl, triphenylmethyl or -CO-Q wherein -CO-Q has any of the values claimed in Claims 1, 5 or 6; R^r is halo, hydroxy, phenylsulfanyl, phenyselanyl, amino, nitro, diazonium (with a conventional counter anion), an azo group of formula $-N=N-R^t$ (wherein R^t forms a symmetrically substituted azo compound or R^t is phenyl, triphenylmethyl, hydroxy or acetoxy), or carboxy; X is chloro, bromo, iodo or methylsulfonyloxy; Z is chloro, bromo, iodo, methylsulfonyloxy, p-tolylsulfonyloxy, or $-S(O)_mR^u$ wherein m is 0, 1 or 2 and R^u is methyl or phenyl.

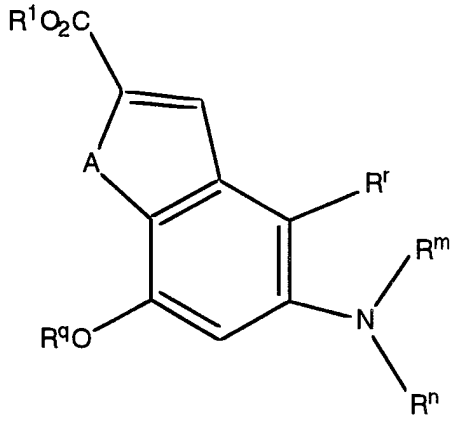
31. The process of Claim 30 wherein R^4 and R^5 together form a furano-, thiopheno- or pyrrolo-ring where the heteroatom is at the R^5-position; R^6 is (1-4C)alkoxy or benzyloxy; R^7 is hydrogen, (1-4C)alkoxy or benzyloxy; R^r is bromo or iodo; R^n is tert-butyloxycarbonyl; and Z is chloro or bromo.

32. A process for the preparation of an indoline of formula V,



V

from a corresponding aniline of formula IV,



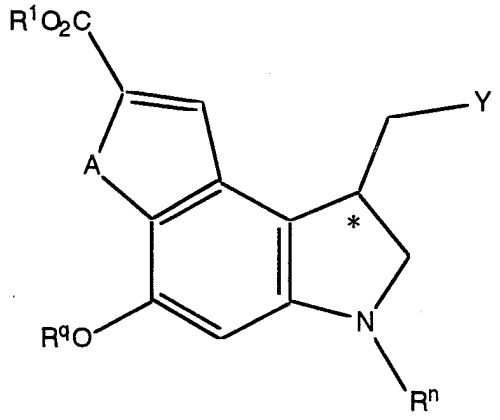
IV

wherein A is O or S, R^1 is (1-4C)alkyl, R^m is hydrogen, R^n is a protecting group for an anilino nitrogen, R^q is a protecting group for a phenolic hydroxy group or a prodrug residue which is stable to the subsequent reaction conditions, R^r is a group which will afford the corresponding aryl radical when subjected to a radical generating reagent or condition, and Y is a pharmaceutically acceptable leaving group which is stable to the subsequent reaction conditions which comprises

alkylating the compound of formula IV in which R^m is hydrogen with an olefin of formula $X\text{-}CH_2CH{=}CHY$ in which X is a leaving group to afford a substituted vinyl compound of formula IV in which R^m is $-CH_2\text{-}CH{=}CHY$; and

subjecting the substituted vinyl compound of formula IV to a radical generating reagent or condition in an inert solvent in the presence of a radical reducing agent to afford the corresponding substituted indoline of formula V.

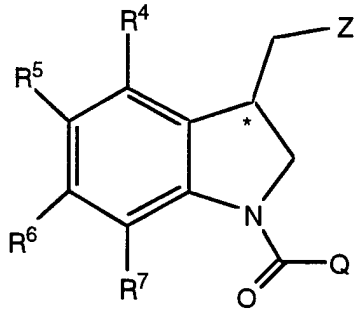
33. An indoline of formula V,



V

wherein A is O or S, R^1 is (1-4C)alkyl, R^n is a protecting group for an anilino nitrogen, R^q is a protecting group for a phenolic hydroxy group or a prodrug residue, and Y is a pharmaceutically acceptable leaving group.

34. The process of Claim 28, 29 or 30 further comprising a process for the preparation of a compound of formula X,



X

wherein -CO-Q has any of the values claimed in Claims 1, 5 or 6, from a corresponding aniline of formula IX in which R^n is a nitrogen protecting group, which comprises

converting the aniline of formula IX into the corresponding substituted indoline of formula,

removing the N-protecting group R^n using a conventional method, and, further,

acylating the resulting indoline of formula VIII wherein R^n is hydrogen with an acid of formula Q-COOH, or an activated derivative thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/03612

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :514/232.8, 255, 321, 411; 544/142, 373; 546/276.7; 548/430
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/232.8, 255, 321, 411; 544/142, 373; 546/276.7; 548/430

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

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

cas online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,248,691 A (**MOHAMADI**) 28 September 1993, see entire document.	1-34

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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

Date of the actual completion of the international search 21 APRIL 1998	Date of mailing of the international search report 15 JUL 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer AMELIA A. OWENS Telephone No. (703) 308-3230

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/03612

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/40, 31/445, 31/495, 31/535; C07D 401/00, 403/00, 413/00, 491/02