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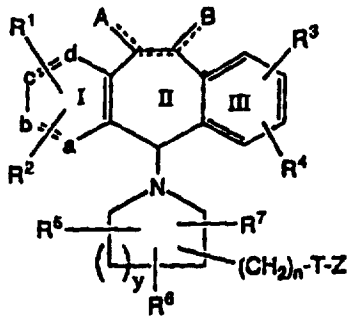
(54) Title: SUBSTITUTED BENZOCYCLOHEPTAPYRIDINE USEFUL AS INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE



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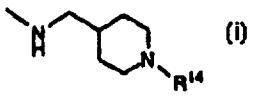

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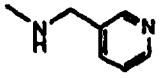

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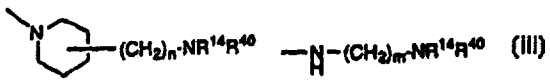

(iii)

(57) Abstract

Novel tricyclic compounds of formula (1.0) or a pharmaceutically acceptable salt or solvate thereof, wherein: one of a, b, c and d represents N or NR^9 wherein R^9 is O^-, $-CH_3$ or $-(CH_2)_nCO_2H$ wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR^1 or CR^2; or each of a, b, c, and d are independently selected from CR^1 or CR^2; each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2), -SCN, $-N(R^{10})_2$, $-NR^{10}R^{11}$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$, $-SR^{11}N(R^{75})_2$; y is 0 (zero) or 1; n is 0, 1, 2, 3, 4, 5 or 6; T is -CO-; -SO-; $-SO_2$-; or $-CR^{30}R^{31}$; Z represents alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, $-OR^{40}$, $-SR^{40}$, 1C-$R^{40}R^{42}$, (i), (ii), $-NR^{40}R^{42}$, (iii). Pharmaceutical compositions are disclosed which are inhibitors of the enzyme, farnesyl protein transferase. Also disclosed is a method of inhibiting Ras function and therefore inhibiting the abnormal growth of cells. The method comprises administering the novel tricyclic compound to a biological system. In particular, the method inhibits the abnormal growth of cells in a mammal such as a human.

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SUBSTITUTED BENZOCYCLOHEPTAPYRIDINE USEFUL AS INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND

Patent application WO 95/00497 published 5 January 1995 under the Patent Cooperation Treaty (PCT) describes compounds which inhibit the enzyme, farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of Ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

In view of the current interest in inhibitors of farnesyl protein transferase, a welcome contribution to the art would be additional compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

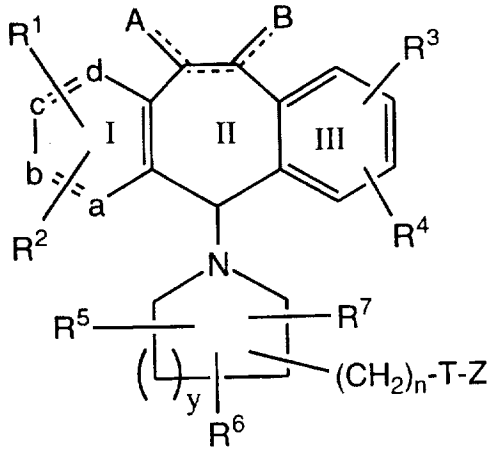
SUMMARY OF THE INVENTION

Inhibition of farnesyl protein transferase by tricyclic compounds of this invention has not been reported previously. Thus, this invention provides a method for inhibiting farnesyl protein transferase using tricyclic compounds of this invention which: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, in vitro; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a

geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras. Several compounds of this invention have been demonstrated to have anti-tumor activity in animal models.

This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

Compounds useful in the claimed methods are represented by Formula 1.0:



(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or NR^9 wherein R^9 is O^-, $-CH_3$ or $-(CH_2)_nCO_2H$ wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2; each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$ (e.g., $-OCH_3$), $-COR^{10}$, $-SR^{10}$ (e.g., $-SCH_3$ and $-SCH_2C_6H_5$), $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2, e.g., $-SOCH_3$ and $-SO_2CH_3$), -SCN, $-N(R^{10})_2$, $-NR^{10}R^{11}$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$ (e.g., $-SCH_2CO_2CH_3$), $-SR^{11}N(R^{75})_2$ wherein each R^{75}

is independently selected from H and -C(O)OR^{11} (e.g., -$S(CH_2)_2NHC(O)O$-t-butyl and -$S(CH_2)_2NH_2$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl substituted tetrazol5-ylthio such as 1-methyl-tetrazol-5-ylthio), alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, -OR^{10} or -CO_2R^{10};

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III);

R^5 and R^6 (y=0) or R^5, R^6 and R^7 (y=1) each independently represents H, -CF_3, -COR^{10}, alkyl or aryl, said alkyl or aryl optionally being substituted with -OR^{10}, -SR^{10}, -$S(O)_tR^{11}$, -$NR^{10}COOR^{11}$, -$N(R^{10})_2$, -NO_2, -COR^{10}, -$OCOR^{10}$, -OCO_2R^{11}, -CO_2R^{10}, OPO_3R^{10} or one of R^5, R^6 and R^7 can be taken in combination with R^{40} as defined below to represent -$(CH_2)_r$- wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, -CF_3 or aryl, or R^5 is combined with R^6 or R^7 to represent =O or =S;

R^{10} independently represents H, alkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, aryl, aralkyl or -$NR^{40}R^{42}$ wherein R^{40} and R^{42} independently represent H, aryl, alkyl, aralkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl;

R^{11} represents alkyl or aryl;

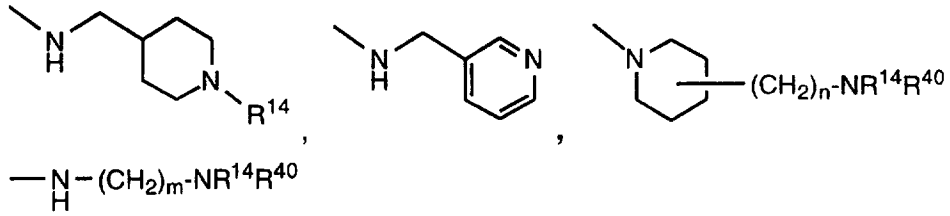
the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent -NO_2, -R^{10}, halo, -OR^{11}, -OCO_2R^{11} or -$OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, -$(OR^{11})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and -$OC(O)R^{10}$, H and -OR^{10}, oxy, aryl and H, =NOR^{10} or -O-$(CH_2)_p$-O- wherein p is 2, 3 or 4; and

y is 0 (zero) or 1;

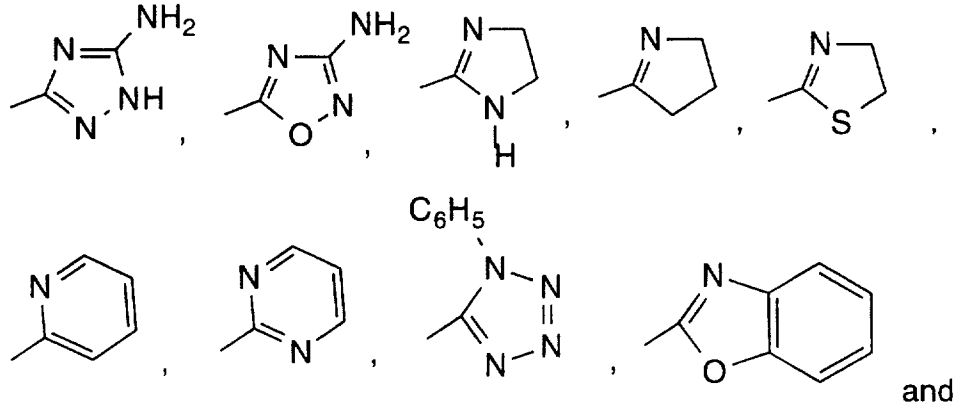
n is 0, 1, 2, 3, 4, 5 or 6;

T is -CO-; -SO-; -SO_2-; or -$CR^{30}R^{31}$- wherein R^{30} and R^{31} independently represent H, alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

Z represents alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, $-OR^{40}$, $-SR^{40}$, $-CR^{40}R^{42}$ or $-NR^{40}R^{42}$ wherein R^{40} and R^{42} are defined hereinbefore



wherein n, R^{40} and R^{42} are defined hereinbefore,
m is 2, 3 4, 5, 6, 7 or 8;
and R^{14} represents H, C_{1-6} alkyl, aralkyl, acyl, carboxamido, cyano, alkoxycarbonyl, aralkyloxycarbonyl, D- and L-amino acids covalently bonded through the carboxyl group, imido, imidamido, sulfamoyl, sulfonyl, dialkylphosphinyl, N-glycosyl,



and

$-C(NHCH_3)=CHNO_2$,
with the proviso that when T is -SO-, Z is not $-NR^{40}R^{42}$.

In the compounds of Formula (1.0), preferably a is N and b, c and d are carbon. Preferably A and B each represent H_2 and the optional double bond is absent. Also preferred is that R^1 and R^4 are H, and R^2 and R^3 are halo, preferably independently Br or Cl. For example, R^2 is Br and R^3 is Cl. These compounds include compounds wherein R^2 is in the 3-position and R^3 is in the 8-position, e.g., 3-Br and 8-Cl.

Also, compounds of Formula (1.0) preferably include compounds wherein R^1 is H, and R^2, R^3 and R^4 are halo, preferably independently selected from Br or Cl. These compounds include compounds wherein R^2 is in the 3-position, R^3 is in the 7-position and R^4 is in the 8-position, e.g., 3-Br, 7-Br, 8-Cl. Also included are compounds wherein R^2 is in the

3-position, R^3 is in the 8-position and R^4 is in the 10-position, e.g. 3-Br, 8-Cl and 10-Br.

Preferably n is zero. Also preferred is that the moiety $-(CH_2)_n$-T-Z is bonded at the 2-position on the pyrrolidine or azetidine ring. Also preferred is that T is -CO- and Z is $-NR^{40}R^{42}$, more preferably where one of R^{40} or R^{42} is H. Also preferred is that R^{40} is H and R^{42} is 3-pyridylmethyl.

In another embodiment, the present invention is directed toward a pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound (1.0) in combination with a pharmaceutically acceptable carrier.

In another embodiment, the present invention is directed toward a method for inhibiting the abnormal growth of cells, including transformed cells, comprising administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs, and (4) benign or malignant cells that are activated by mechanisms other than the Ras protein. Without wishing to be bound by theory, it is believed that these compounds may function either through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer, or through inhibition of ras farnesyl protein transferase, thus making them useful for their antiproliferative activity against ras transformed cells.

The cells to be inhibited can be tumor cells expressing an activated ras oncogene. For example, the types of cells that may be inhibited include pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells. Also, the inhibition of the abnormal growth of cells by the treatment with compound (1.0) may be by inhibiting ras farnesyl protein transferase. The inhibition may be of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

Alternatively, compounds (1.0) may inhibit tumor cells activated by a protein other than the Ras protein.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma and epidermal carcinoma.

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition being accomplished by the administration of an effective amount of the carbonyl piperazinyl and piperidinyl compounds (1.0) described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited by the carbonyl piperazinyl and piperidinyl compounds (1.0) described herein.

In another embodiment, the present invention is directed toward a method for inhibiting ras farnesyl protein transferase and the farnesylation of the oncogene protein Ras by administering an effective amount of compound (1.0) to mammals, especially humans. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

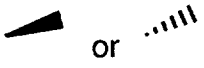
DETAILED DESCRIPTION OF THE INVENTION

The following solvents and reagents are referred to herein by the abbreviations indicated:

tetrahydrofuran (THF);

ethanol (EtOH);
methanol (MeOH);
ethyl acetate (EtOAc);
N,N-dimethylformamide (DMF);
trifluoroacetic acid (TFA);
1-hydroxybenzotriazole (HOBT);
1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC);
dimethylsulfoxide (DMSO);
acetic acid (HOAc or AcOH)
4-methylmopholine (NMM);
dimethylaminopyridine (DMAP); and
dimethoxyethane (DME).
t-butoxycarbonyl (BOC)
acetyl(OAc)

As used herein, the following terms are used as defined below unless otherwise indicated:

 - indicates a pure isomer;

 - when attached to a carbon atom labeled with an asterisk (*), indicates a separated isomer whose stereochemistry is not established;

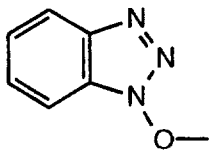
 - indicates a racemic mixture;

M^+ -represents the molecular ion of the molecule in the mass spectrum;

MH^+ -represents the molecular ion plus hydrogen of the molecule in the mass spectrum;

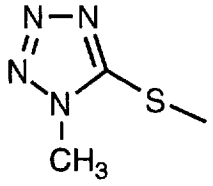
PMR or NMR refers to proton magnetic resonance spectroscopy or nuclear magnetic resonance spectroscopy, whose terms are interchangeable;

Bu-represents butyl;
Et-represents ethyl;
Me-represents methyl;
Ph-represents phenyl;
benzotriazol-1-yloxy represents



;

1-methyl-tetrazol-5-ylthio represents



;

acyl-a moiety of the formula -COR^{15} wherein R^{15} represents H, C_{1-6} alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl and heterocycloalkylalkyl;

alkyl-(including the alkyl portions of alkoxy, alkylamino and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms (i.e. C_{1-6} alkyl); for example methyl, ethyl, propyl, iso-propyl, n-butyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; wherein said alkyl and said C_{1-6} alkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino (-NH_2), alkylamino, cyano (-CN), -CF_3, dialkylamino, hydroxy, oxy (=O), phenoxy, -OCF_3, heterocycloalkyl, -SO_2NH_2, -$NHSO_2R^{10}$, -SO_2NHR^{10}, -SO_2R^{10}, -SOR^{10}, -SR^{10}, -$NHSO_2$, -NO_2, -$NCOR^{10}$ or -$COOR^{10}$.

alkoxy-an alkyl moiety of one to 20 carbon atoms covalently bonded to an adjacent structural element through an oxygen atom, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the like; wherein said alkoxy group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF_3, dialkylamino, hydroxy, oxy, phenoxy, -OCF_3, heterocycloalkyl, -SO_2NH_2, -$NHSO_2R^{10}$, -SO_2NHR^{10}, -SO_2R^{10}, -SOR^{10}, -SR^{10}, -$NHSO_2$, -NO_2, -$CONR^{10}$, -$NCOR^{10}$ or -$COOR^{10}$;

alkoxycarbonyl - represents a alkoxy moiety, as defined above, covalantly bonded to a carbonyl moiety (-CO-) through an oxygen atom, for example, -$COOCH_3$, -$COOCH_2CH_3$ and -$COOC(CH_3)_3$;

alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 3 to 6 carbon atoms; wherein said alkenyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF_3, dialkylamino, hydroxy, oxy, phenoxy, -OCF_3, heterocycloalkyl, -SO_2NH_2,

$-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$;

alkynyl-represents straight and branched carbon chains having at least one carbon to carbon triple bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms; wherein said alkynyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$;

amino acid- refers to organic compounds having both an amino group ($-NH_2$) and a carboxyl group (-COOH). Representative amino acids include glycine, serine, alanine, phenylalanine, tyrosine, S-methyl methionine and histidine;

aryl (including the aryl portion of aralkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is phenyl), wherein said aryl group optionally can be fused with aryl, cycloalkyl, heteroaryl or heterocycloalkyl rings; and wherein any of the available substitutable carbon and nitrogen atoms in said aryl group and/or said fused ring(s) may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$;

aralkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms of the alkyl moiety have been substituted with one or more aryl groups; wherein said aralkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$; Representative aralkyl groups include benzyl and diphenylmethyl;

aralkyloxy - represents an aralkyl group, as defined above, covalently bonded to an adjacent structural element through an oxygen atom, for example, phenylmethyloxy and phenylethyloxy;

aralkyloxycarbonyl - represents an aralkyloxy group, as defined above, covalantly bonded to a carbonyl moiety (-CO-) through an oxygen atom, for example, -$COOCH_2C_6H_5$ and -$COOCH_2CH_2C_6H_5$;

carboxamido - represents a moiety of the formula -$CONH_2$ or -$CONR^{40}R^{42}$;

cycloalkyl-represents saturated carbocyclic rings branched or unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms; wherein said cycloalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF_3, dialkylamino, hydroxy, oxy, phenoxy, -OCF_3, heterocycloalkyl, -SO_2NH_2, -$NHSO_2R^{10}$, -SO_2NHR^{10}, -SO_2R^{10}, -SOR^{10}, -SR^{10}, -$NHSO_2$, -NO_2, -$CONR^{10}$, -$NCOR^{10}$ or -$COOR^{10}$;

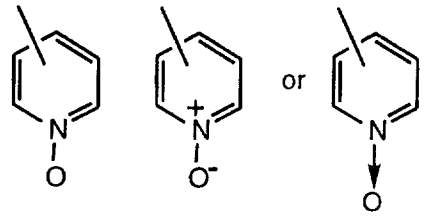
cycloalkylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms of the alkyl moiety have been substituted with one or more cycloalkyl groups; wherein said cycloalkylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF_3, dialkylamino, hydroxy, oxy, phenoxy, -OCF_3, heterocycloalkyl, -SO_2NH_2, -$NHSO_2R^{10}$, -SO_2NHR^{10}, -SO_2R^{10}, -SOR^{10}, -SR^{10}, -$NHSO_2$, -NO_2, -$CONR^{10}$, -$NCOR^{10}$ or -$COOR^{10}$;

halo-represents fluoro, chloro, bromo and iodo;

heteroalkyl-represents straight and branched carbon chains containing from one to twenty carbon atoms, preferably one to six carbon atoms interrupted by 1 to 3 heteroatoms selected from -O-, -S- and -N-; wherein any of the available substitutable carbon and nitrogen atoms in said heteroalkyl chain may be optionally and independendently substituted with one, two, three or more of the following: halo, C_1-C_6 alkyl, aryl, cyano, hydroxy, alkoxy, oxy, phenoxy, -CF_3, -OCF_3, amino, alkylamino, dialkylamino, heterocycloalkyl, -SO_2NH_2, -$NHSO_2R^{10}$, -SO_2NHR^{10}, -SO_2R^{10}, -SOR^{10}, -SR^{10}, or -$NHSO_2$, -NO_2, -$CONR^{10}$, -$NCOR^{10}$ or -$COOR^{10}$;

heteroaryl-represents cyclic groups having at least one heteroatom selected from O, S and N, said heteroatom(s) interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups containing from 2 to 14 carbon atoms,wherein said heteroaryl group optionally can be fused with one or more aryl, cycloalkyl, heteroaryl or

heterocycloalkyl rings; and wherein any of the available substitutable carbon or nitrogen atoms in said heteroaryl group and/or said fused ring(s) may be optionally and independendently substituted with one, two, three or more of the following: halo, C_1-C_6 alkyl, aryl, cyano, hydroxy, alkoxy, oxy, phenoxy, $-CF_3$, $-OCF_3$, amino, alkylamino, dialkylamino, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, or $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$. Representative heteroaryl groups can include, for example, furanyl, imidazoyl, pyrimidinyl, triazolyl, 2-, 3- or 4-pyridyl or 2-, 3- or 4-pyridyl N-oxide wherein pyridyl N-oxide can be represented as:

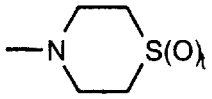


,

heteroarylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by one or more heteroaryl groups; wherein said heteroarylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$; as exemplified by 2-, 3- or 4-pyridylmethyl or 2-, 3- or 4-pyridylmethyl N-oxide;

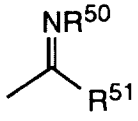
heterocycloalkyl-represents a saturated, branched or unbranched carbocylic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 heteroatoms selected from -O-, -S- and -N- , wherein optionally, said ring may contain one or two unsaturated bonds which do not impart aromatic character to the ring; and wherein any of the available substitutable carbon and nitrogen atoms in the ring may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$

Representative heterocycloalkyl groups can include 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 1-, 2-, 3- or 4-piperidinyl, 2- or

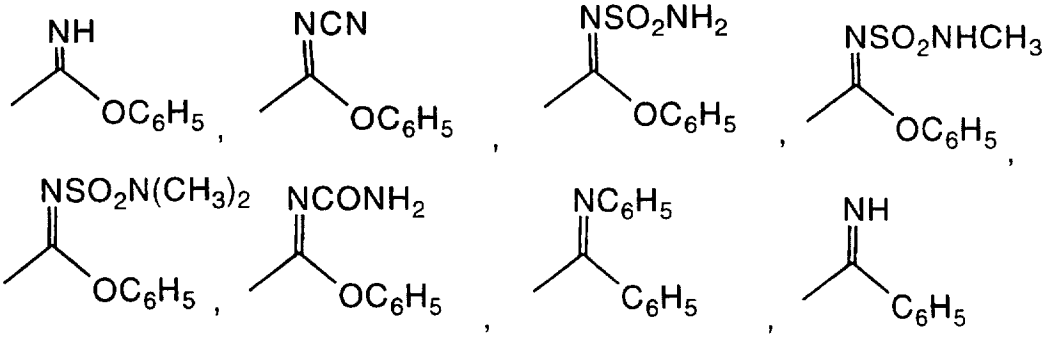


3-pyrrolidinyl, 1-, 2- or 3-piperizinyl, 2- or 4-dioxanyl, wherein t is 0, 1 or 2; morpholinyl,heterocycloalkylalkyl- represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by one or more heterocycloalkyl groups; wherein optionally, said ring may contain one or two unsaturated bonds which do not impart aromatic character to the ring; and wherein said heterocycloalkylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, $-CF_3$, dialkylamino, hydroxy, oxy, phenoxy, $-OCF_3$, heterocycloalkyl, $-SO_2NH_2$, $-NHSO_2R^{10}$, $-SO_2NHR^{10}$, $-SO_2R^{10}$, $-SOR^{10}$, $-SR^{10}$, $-NHSO_2$, $-NO_2$, $-CONR^{10}$, $-NCOR^{10}$ or $-COOR^{10}$;

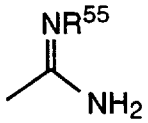
imido - represents a moiety of the formula



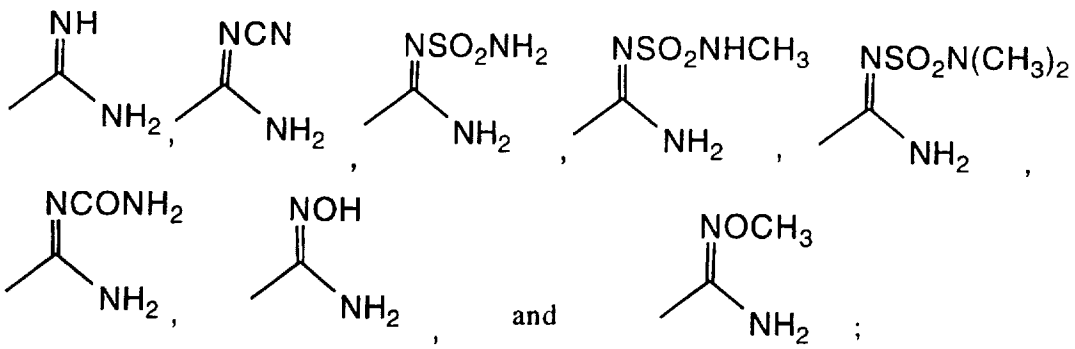
wherein and R^{50} represents H, cyano, aryl, $-SO_2NH_2$, $-SO_2NR^{40}R^{42}$ and carboxamido and R^{51} represents aryl and aryloxy. Representative imido groups can include, for example,



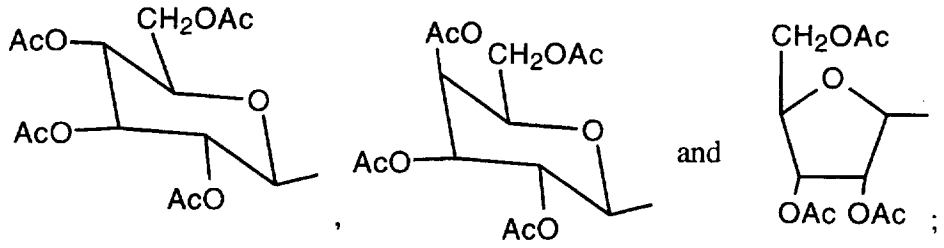
imidamido - represents a moiety of the formula



wherein and R^{55} represents H, cyano, $-SO_2NH_2$, $-SO_2NR^{40}R^{42}$, carboxamido, hydroxy and alkoxy. Representative imidamido groups can include, for example,



N-glycosyl- represents a pyranosyl or furanosyl monosaccaride. Representative N-glycosyl groups include (N → 1)-tetra-O-acetyl-D-glucosyl, (N → 1)-tetra-O-acetyl-D-galactosyl and (N → 1) -tri-O-acetyl-D-ribosyl, e.g.



D-glycosyl D-galactosyl D-ribosyl

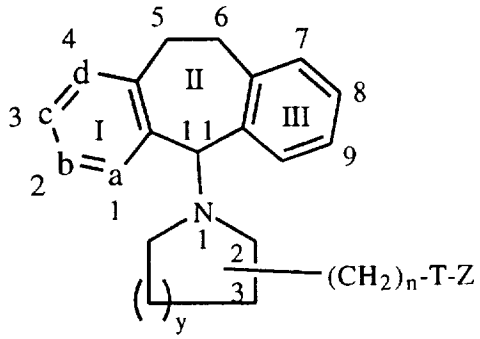
1-amino-2-nitroethenyl represents the formula: $-C(NHCH_3)=CHNO_2$;

dialkylphosphinyl - represents a phosphine (-PO) moiety covalently bonded to two alkyl groups. A representative dialkylphosphinyl group is $-PO(CH_3)_2$.

sulfamoyl - represents a moiety of the formula $-SO_2R^{60}$ wherein R^{60} represents amino, alkylamino and dialkylamino. Representative sulfamoyl groups can include, for example, $-SO_2NH_2$, $-SO_2NHCH_3$, $-SO_2N(CH_3)_2$.

sulfonyl - represents a moiety of the formula $-SO_2R^{60}$ wherein R^{60} represents alkyl, aryl and arylalkyl. Representative sulfonyl groups can include, for example, $-SO_2CH_3$, $-SO_2C_6H_5$, $-SO_2C_6H_4CH_3$, and $-SO_2CH_2C_6H_5$.

Reference to the position of the substituents R^1, R^2, R^3, and R^4 is based on the numbered ring structure:



Certain compounds of the invention may exist in different stereoisomeric forms (e.g., enantiomers and diastereoisomers). The invention contemplates all such stereoisomers both in pure form and in mixture, including racemic mixtures. For example, the carbon atom at the C-11 position can be in the S or R stereoconfiguration. Also, the carbon atom at the C-2 and C-3 positions of the pyrrolidine (y=1) or at the C-2 position of the azetidine moiety (y=0) bonded at C-11 can also be in the S or R stereoconfiguration.

Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

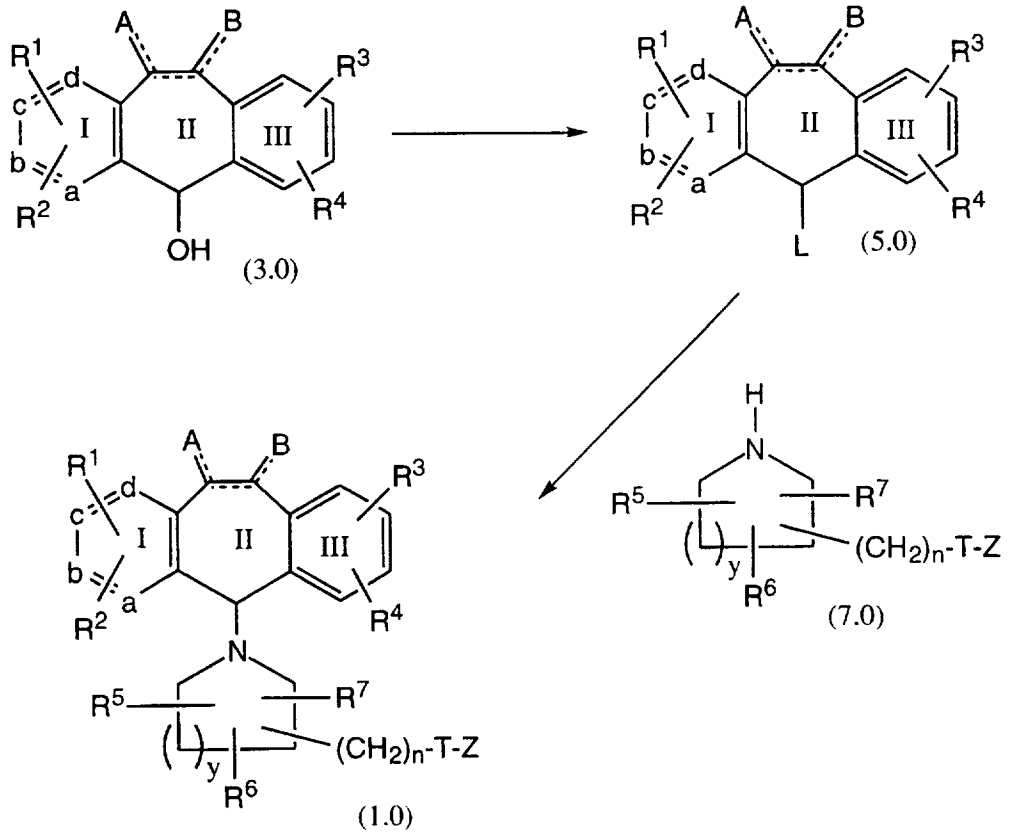
Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in

polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention..

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of the present invention can be prepared according to the following Scheme 1:

Scheme 1



wherein L represents a leaving group such as halo, preferably chloro or a leaving group such as o-tosyl and o-mesyl; the dotted line represents a single or double bond; and a, b, c, d, A, B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, m, n, T and Z are as defined hereinbefore.

Referring to the Scheme I, compounds of formula (5.0) can be prepared by reacting the compounds of formula (3.0) with a halogenating agent or a sulfonylating agent in the presence of a suitable base, and optional aprotic solvent, in amounts and under conditions effective to give compounds (5.0). Suitable bases include organic bases such as pyridine and triethylamine; or inorganic bases of alkali and alkaline earth metals including carbonates such as sodium, lithium, potassium and cesium carbonates, hydroxides such as sodium and potassium hydroxides; hydrides such as sodium or potassium hydride; and sodium t-butoxide, preferably sodium hydride. Suitable aprotic solvents include ethers, DMF, DMSO, THF, DME and mixtures thereof, preferably DMF. Preferably the

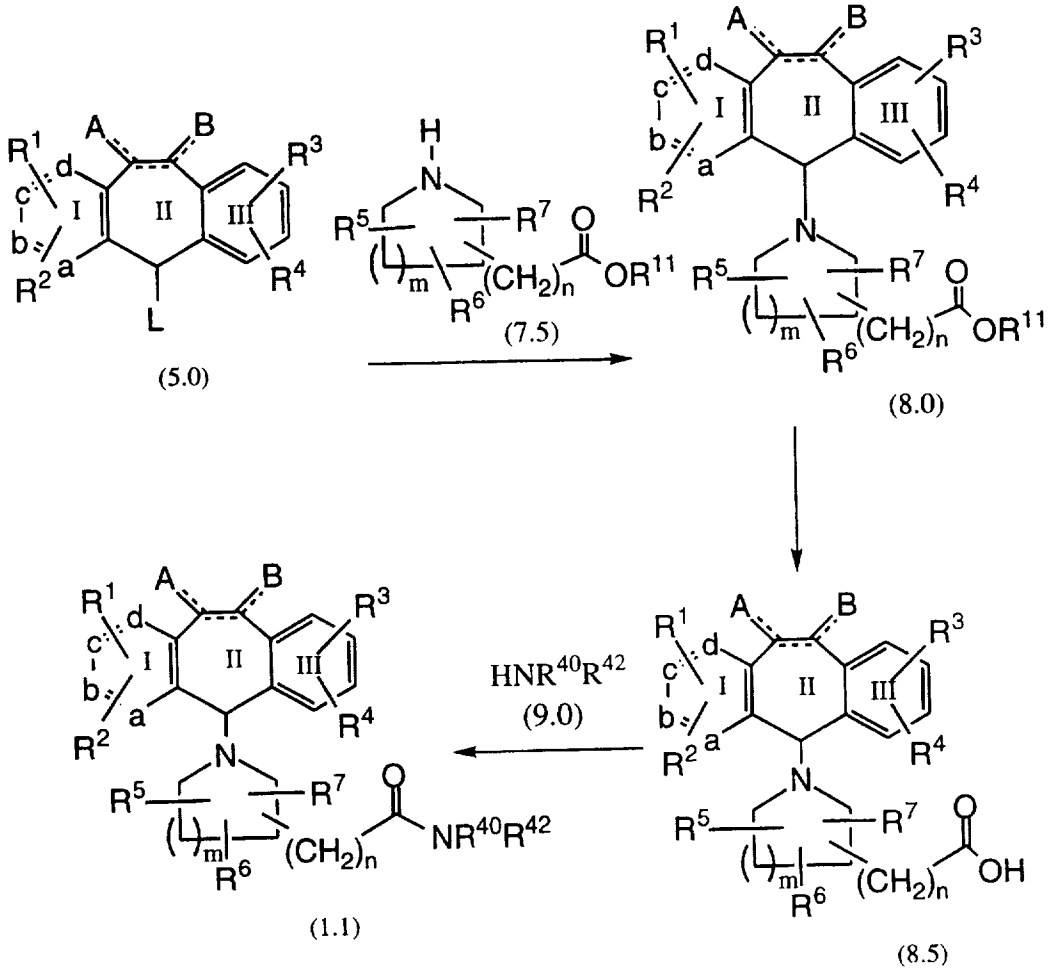
halogenating agent is a chlorinating agent, such as thionyl chloride. The sulfonylating can be sulfonyl chloride, methane sulfonyl chloride or toluene sulfonyl chloride. The amounts of the halogenating agent or the sulfonylating agent can range from about one to about 10 moles per mole of compound (3.0). Temperatures can range from 0° to 50°C, or reflux of the reaction mixture.

The desired tricylic piperidinyl compounds of formula (1.0) can be prepared by reacting the compounds of formula (5.0) with a suitably substituted pyrrolidine or azetidine compound of formula (7.0) in the presence of a suitable base and optional aprotic solvent, such as those described above, to give compounds (1.0). The amounts of the substituted pyrrolidine or azetidine compound of formula (7.0) to compound (5.0) can range from about one to about 10 moles per mole of compound (5.0) Temperatures can range from about room temperature to about 80°C.

The tricylic compounds of fomula (1.0) can be isolated from the reaction mixture using conventional procedures, such as, for example, extraction of the reaction mixture from water with organic solvents, evaporation of the organic solvents, followed by chromatography on silica gel or other suitable chromatographic media.

The compound of formula (1.0) wherein T = -CO- and Z = $-NR^{40}R^{42}$ wherein R^{40} and R^{42} are defined hereinbefore (i.e. an amide) can be prepared in accordance with Scheme 2.

Scheme 2



wherein L represents a leaving group, preferably chloro; the dotted line represents a single or double bond; and a, b, c, d, A, B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{11}, R^{40}, R^{42}, m and n are as defined hereinbefore.

Referring to the Scheme 2, compounds of formula (8.0) can be prepared by reacting the compounds of formula (5.0) with a piperdinyl carboxylic acid ester of formula (7.5) in the presence of a base and optional aprotic solvent, in amounts and under conditions effective to give compounds (8.0). Suitable bases and aprotic solvents are described hereinbefore. The amounts of compound (7.5) can range from about 1 to about 10 moles per mole of compound (5.0). Temperatures can range from room temperature to about 80°C. Compound (8.0) can be isolated as described hereinbefore.

Carboxylic acid compounds of formula (8.5) can be prepared by hydrolyzing carboxylic acid ester (8.0) with an excess amount of acid or base. Suitable acids include inorganic acids, organic acids or a mixture thereof. Inorganic acids include hydrogen chloride, hydrogen bromide,

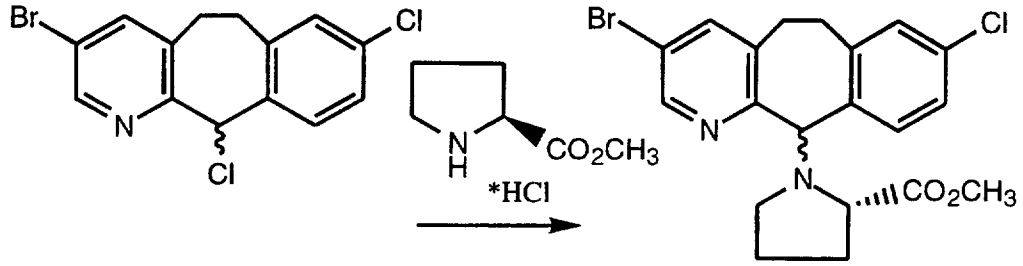
sulfuric acid, nitric acid, phosphoric acid, perchloric acid and the like. Organic acids include acetic, citric, formic, maleic, tartaric, methanesulfonic acid and arylsulfonic acids. Suitable bases, such as sodium hydroxide, or lithium hydroxide in an aqueous alcohol, have been described hereinbefore. The temperature can range from about 0°C to about 100°C.

The desired amide compounds of formula (1.1) can be prepared by reacting the compounds of formula (8.5) with a suitable amine of formula (9.0) in the presence of a base and a suitable aprotic solvent effective to give amide compound (1.1). Suitable bases and aprotic solvents are described hereinbefore. The amounts of amine (9.0) can range from about 1 to about 10 moles per mole of carboxylic acid (8.5). Temperatures can range from 0° to 100°C. Compound (1.1) can be isolated as described hereinbefore.

Compounds of the present invention and preparative starting materials therof, are exemplified by the following examples, which should not be construed as limiting the scope of the disclosure.

Example 1.

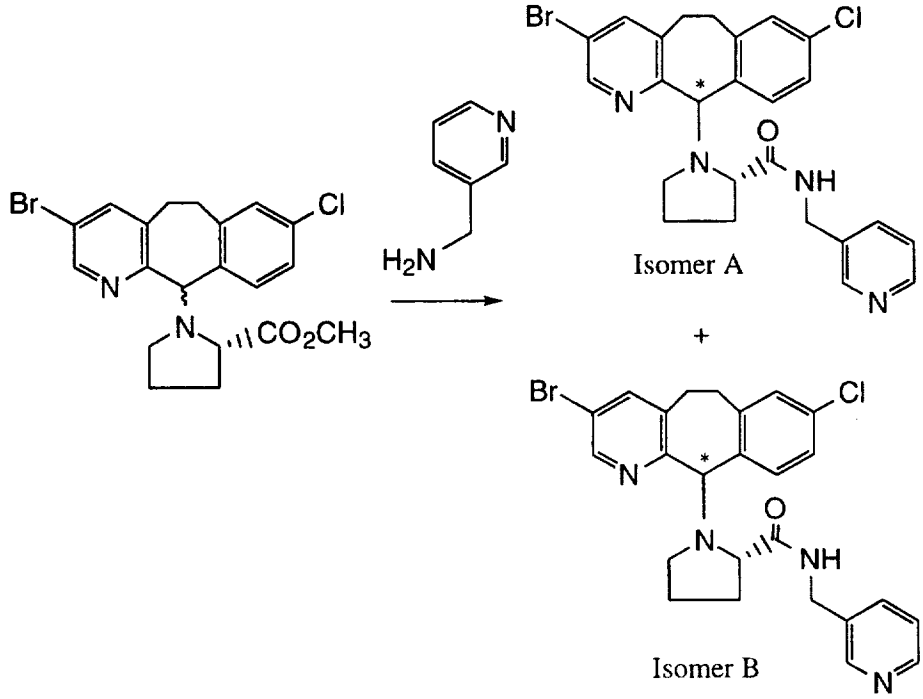
Step A. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-yl)-N-2-pyrrolidine methyl ester



A mixture of 3-bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (1.05 g, 3.06 mmole) , proline methyl ester hydrochloride (1.52 g 9.18 mmole) and N-methyl morpholine (1.85 g, 18.32 mmole) in DMF (15 mL) is heated at 85°C overnight. The reaction mixture is evaporated to dryness, extracted with CH_2Cl_2 (100 mL), washed with water (2 x100 mL), the organic extract is dried over $MgSO_4$ and the solvent evaporated to give an oily residue. The oily residue is flash chromatographed on a silica gel column eluting with hexane-15% ethyl acetate to give 0.78 g of the title compound, a foam. Partial PMR

($CDCl_3$, 200 MHz), 8.3 (s, 1H), 7.5 (d, 1H), 7-7.2 (m, 3H), 4.5 (s, 1H), 3.2 (s, 3H).

Step B. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-yl)-N-(3-pyridinylmethyl)2-pyrrolidine carboxamide



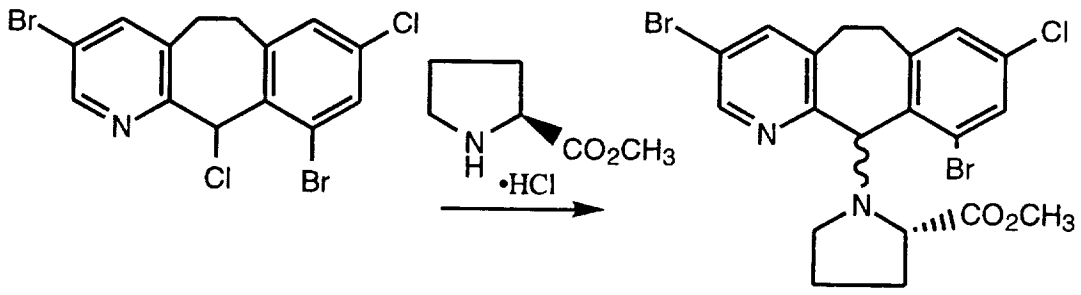
The title compound of Example 1, Step A (0.43 g, 9.1 mmole) and 3-aminomethylpyridine (0.196 g, 18.12 mmole) are heated at 130°C overnight. The residue is chromatographed on a silica gel column eluting with CH_2Cl_2-3% (CH_3OH-10% conc NH_4OH). and separated to give the title compounds:

Isomer A, 0.062 g , Mass Spec. MH^+ 513 (FAB); partial PMR (CDCl3, 200MHz), 8.45 (d, 1H), 8.4 (s, 1H), 8.3 (s, 1H), 7-7.4 (m, 6H), 4.68 (s, 1H)
FPT IC_{50} = 0.059 µM

Isomer B, 0.042 g, Mass spec. MH^+513, partial PMR (CDCl3, 200 MHz), 8.55 (d, 1H), 8.4 (s, 1H), 8.35 (s, 1H), 6.8-7.6 (m, 6H).
FPT IC_{50} = 0.14 µM

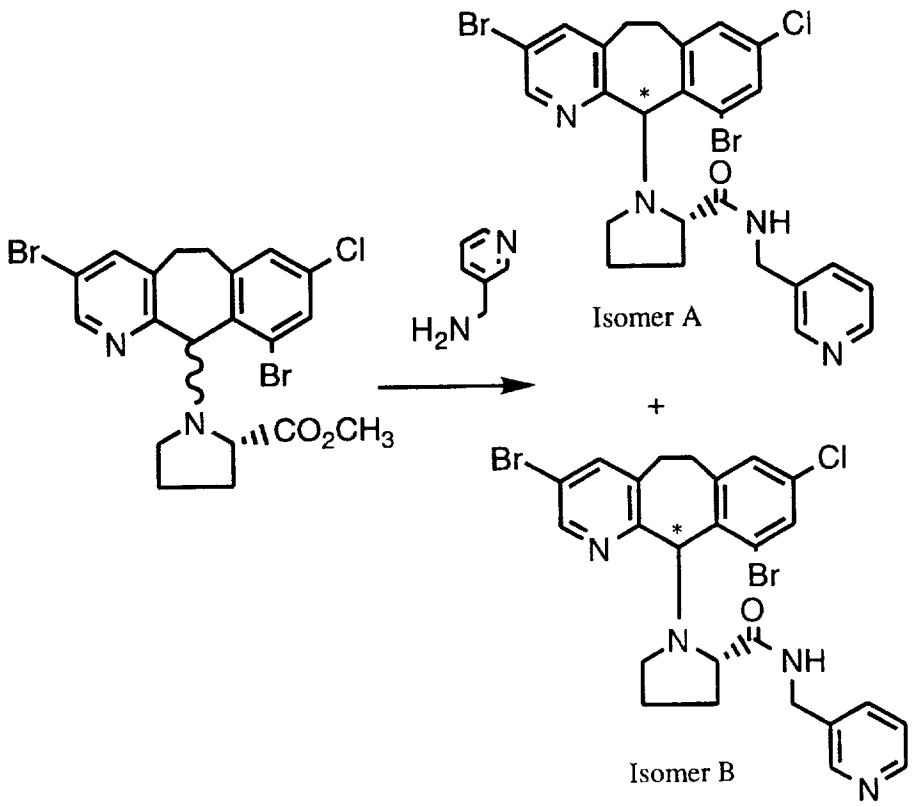
Example 2.

Step A. 1-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-yl)-N-2-pyrrolidine methyl ester



A mixture of 3,10-dibromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (0.5 g, 1.18 mmole) , proline methyl ester hydrochloride (0.59 g 3.55 mmole) and N-methyl morpholine (0.72 g, 7.11 mmole) in DMF (10 ML) is heated at 85°C for one hour. The reaction mixture is evaporated to dryness, extracted with CH_2Cl_2 (100 mL) and washed with water (2 x100 mL). The organic extract is dried over $MgSO_4$ and the solvent evaporated, leaving an oily residue which is flash chromatographed on a silica gel column eluting with hexane-15% ethyl acetate to give 0.43 g of the title compound as a foam. Partial PMR ($CDCl_3$, 200 MHz), 8.4 (d, 1H), 7.45 (d, 1H), 7.4 (d, 1H), 7.12 (d, 1H),5.56 (s, 1H), 5.01 (m, 1H), 3.55 (m, 1H), 3.23 (s, 3H).

Step B. 1-(3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-yl)-N-(3-pyridinylmethyl)-2-pyrrolidine carboxamide



The compound of Example 2, Step A (0.36 g) is dissolved in ethanol (10 mL) and heated at 80 °C with 1N LiOH (aqueous, 4 mL) overnight.. The pH is adjusted to 4 with 1N HCl and the solution evaporated to dryness. The product is dissolved in DMF (10 mL) and NMM (0.32 mL), and HOBT (0.187 g), DEC (0.265 g), and 3-amino methyl pyridine (0.16 mL) are added. The reaction mixture is stirred over the weekend, evaporated to dryness, the residue extracted in CH_2Cl_2 (100 mL) and with brine (2 x 100 mL). The organic extract is dried over $MgSO_4$, evaporated to dryness, and chromatographed on a Chiralpak® AD HPLC analytical chiral column (amylose tris(3,5-dimethylphenyl carbamate) coated on a 10 µM silica-gel substrate, trademark of of Chiral Technologies, Exton, Pennsylvania)), using as the eluting solvent,eluting with 80% hexane/isopropanol (containing 0.25 % diethylamine) to give the title compounds:

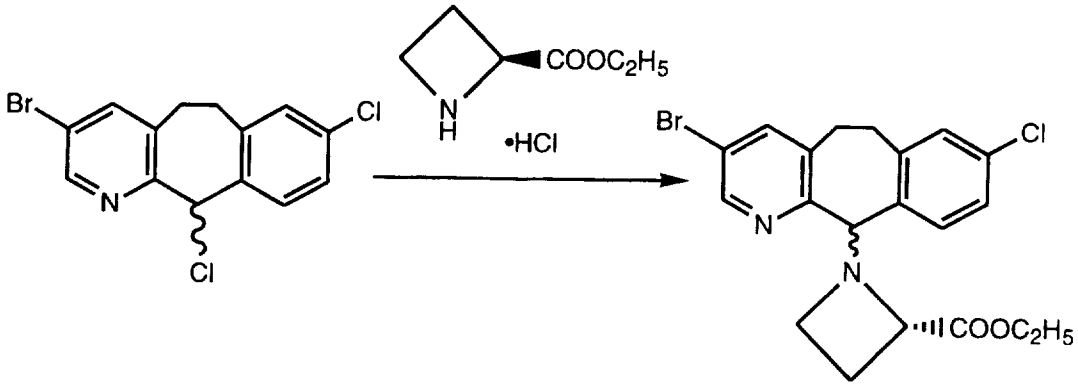
Isomer A (0.124 g) as a foam, Mass Spec. MH^+ 591 (FAB); partial PMR (CDCl3, 400MHz), 8.58 (d, 1H), 8.45 (s, 2H), 8.3 (s, 1H), 7.55 (s, 1H), 7.45(m, 2H),7.28 (m, 2H), 6.82 (s, 1H), 6.81 (t, 1H), 5.72 (s, 1H)
FPT Inhibition: 15% @0.3 µM

Isomer B, 0.165g, Mass spec. MH^+591, partial PMR (CDCl3, 400 MHz), 8.59 (d, 1H), 8.4 (m, 2H), 7.48 (s, 1H), 7.35 (m, 1H), 7.1-7.3 (m, 3H), 6.9 (t, 1H), 5.6 (s, 1H).

FPT IC_{50} = 0.0052 μM

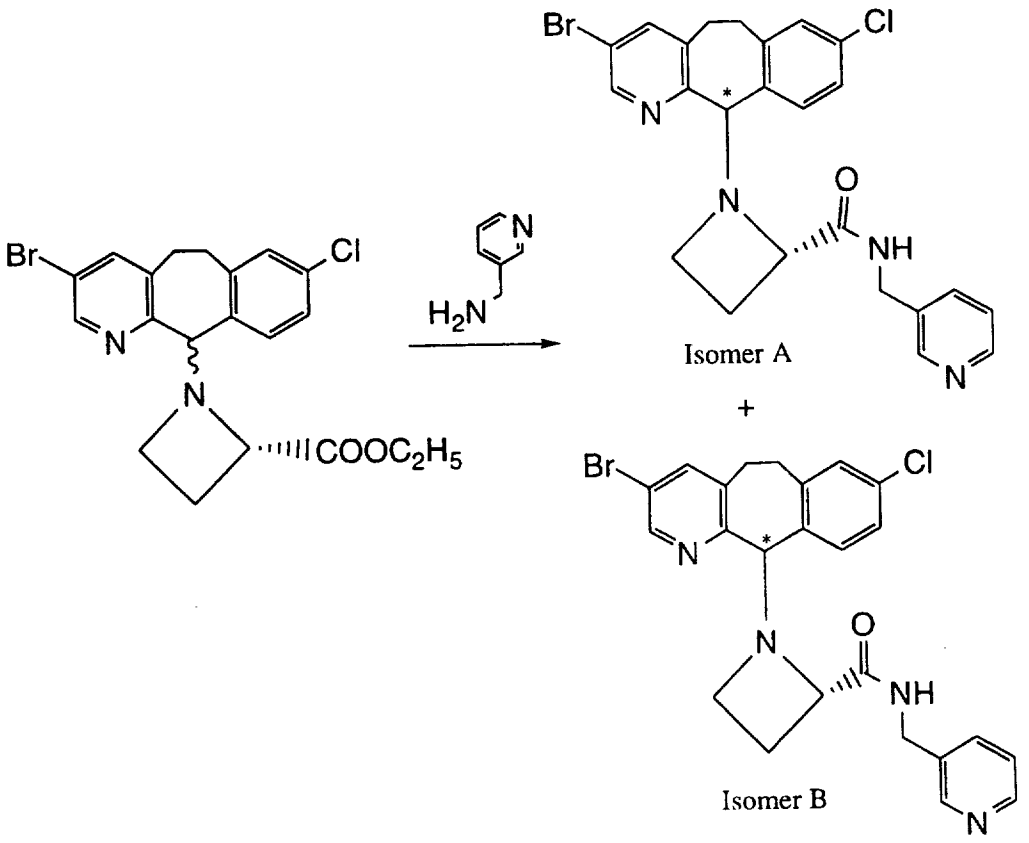
Example 3.

Step A. 1-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-yl)-N-2-azetidine methyl ester



A mixture of 3-bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (1.05 g, 3.06 mmole), azetidine ethyl ester hydrochloride (1.52 g 6.02 mmole) and N-methyl morpholine (1.85 g, 18.32 mmole) in DMF (15 ML) is heated at 85°C overnight. The reaction mixture is evaporated to dryness, extracted with CH_2Cl_2 (100 mL) and washed with water (2 x100 mL). The organic extract is dried over $MgSO_4$ and the solvent is evaporated to give oily residue which is flash chromatographed on a silica gel column eluting with hexane-15% ethyl acetate, to give 0.72 g of the title compound as a foam. Partial PMR ($CDCl_3$, 200 MHz), 8.3 (s, 1H), 7.5 (d, 1H), 7-7.2 (m, 3H), 4.5 (s, 1H), 3.2 (s, 3H).

Step B. 1-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-yl)-N-(3-pyridinylmethyl)2-azetidine carboxamide



The compound of Example 3, Step A (0.7 g) is dissolved in ethanol (10 mL) and heated at 80°C with 1N LiOH (aqueous, 3 mL) overnight. The pH is adjusted to 4 with 1N HCl and the solution evaporated to dryness. The product is dissolved in DMF (10 mL) and NMM (0.32 mL), and HOBT (0.187 g), DEC (0.265 g) and 3-aminomethyl pyridine (0.16 mL) are added. The reaction mixture is stirred over the week end at room temperature, evaporated to dryness, and the residue extracted in CH_2Cl_2 (100 mL). The organic extract is washed with brine (2 x 100 mL), dried over $MgSO_4$, evaporated to dryness and the product is chromatographed on a Chiralpak® AD HPLC analytical chiral column eluting with 80% hexane/Isopropanol (containing 0.25 % diethylamine) to give the title compounds:

Isomer A (0.113 g) as a foam, Mass Spec. MH^+ 499 (FAB); partial PMR (CDCl3, 400MHz), 8.58 (d, 1H), 8.45 (s, 2H), 8.3 (s, 1H), 7.55 (s, 1H), 7.45(m, 2H),7.28 (m, 2H), 6.82 (s, 1H), 6.81 (t, 1H), 5.72 (s, 1H)
FPT IC_{50} = 1.05 μM

Isomer B (0.148g) as a foam, Mass spec. MH^+499, partial PMR (CDCl3, 400 MHz), 8.59 (d, 1H), 8.4 (m, 2H), 7.48 (s, 1H), 7.35 (m, 1H), 7.1-7.3 (m, 3H), 6.9 (t, 1H), 5.6 (s, 1H)

FPT Inhibition: 17% @0.1 μM

PREPARATION OF STARTING MATERIALS

Starting materials useful in preparing the compounds of the present invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. The tricylic compounds (3.0) and substituted piperidinyl compounds (7.0) used as starting materials are known in the art and/or can be prepared using known methods, such as taught in U.S. Patents 5,089,496; 5,151,423; 4,454,143; 4,355,036; PCT /US94/11390 (WO95/10514); PCT/US94/11391 (WO 95/10515); PCT/US94/11392 (WO95/10516); Stanley R. Sandler and Wolf Karo, Organic Functional Group Preparations, 2nd Edition, Academic Press, Inc., San Diego, California, Vol. 1-3, (1983); in J. March, Advanced Organic Chemistry, Reactions & Mechanisms, and Structure, 3rd Edition, John Wiley & Sons, New York, 1346 pp. (1985); A. J. Boulton and A. McKillop (Eds.), Comprehensive Heterocyclic Chemistry, Volume 7, Four Membered Rings With One Nitrogen Atom, Pergamon Press, Elmsford, New York, (1960-1985); A. J. Boulton and A. McKillop (Eds.), Comprehensive Heterocyclic Chemistry, Volume 4, Part 3, Five Membered Rings With One Nitrogen Atom, Pergamon Press, Elmsford, New York, (1960-1985); J. Am. Chem. Soc. 80, pg. 970 (1958); JOC 33, 3637 (1968); Tetra. Letters, pp. 381-382 (1995); Helvetics. Chem. Acta, 59 (6), pp. 1917-24 (1976); and J. Med. Chem., 33, 71-77 (1990). The starting materials may also be prepared as taught in copending U.S. Application Serial No. 08/410,187 filed March 24, 1995, copending U.S. Application Serial No. 08/577,951 filed December 22, 1995, and copending U.S. Application Serial No. 08/615,760 filed March 13, 1996; the disclosures being incorporated herein by reference. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

For example, the pyrrolidine compounds of formula (7.0), wherein T = -CO- can be prepared by initially preparing a pyrole compound substituted with the requisite 2- or 3-$(CH_2)_nCOZ$ moiety, together any optional $-R^5$, $-R^6$, $-R^7$ and/or $-R^8$ moieties, as described in the references cited above and/other known art. The 2- or 3-substituted pyrole compound can subsequently be reduced using conventional reduction

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NOT TO BE CONSIDERED FOR INTERNATIONAL PUBLICATION

Pharmaceutical Dosage Form Examples

EXAMPLE A-Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B-Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	7	7
	Total	253	700

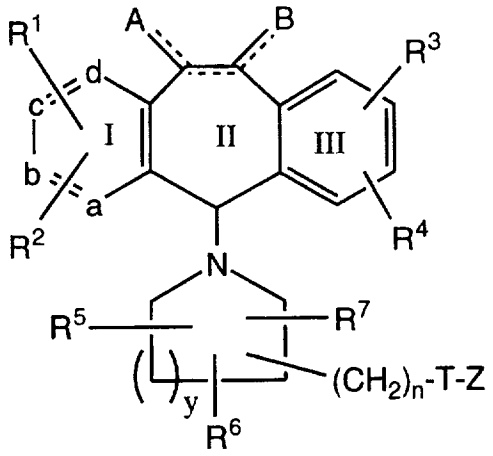
Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound of the formula:



(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or NR^9 wherein R^9 is O^-, $-CH_3$ or $-(CH_2)_nCO_2H$ wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2; each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2), -SCN, $-N(R^{10})_2$, $-NR^{10}R^{11}$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$, $-SR^{11}N(R^{75})_2$ wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$, benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III);

R^5 and R^6 (y=0) or R^5, R^6 and R^7 (y=1) each independently represents H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-NR^{10}COOR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{11}$, $-CO_2R^{10}$, OPO_3R^{10} or one of R^5, R^6 and R^7 can be taken in combination with R^{40} as defined below to represent $-(CH_2)_r-$ wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, $-CF_3$ or aryl, or R^5 is combined with R^6 or R^7 to represent =O or =S;

R^{10} independently represents H, alkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, aryl, aralkyl or $-NR^{40}R^{42}$ wherein R^{40} and R^{42} independently represent H, aryl, alkyl, aralkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl;

R^{11} represents alkyl or aryl;

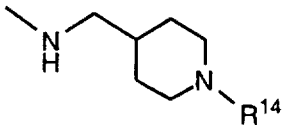
the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-NO_2$, $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{11})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{10}$, H and $-OR^{10}$, oxy, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4; and

y is 0 (zero) or 1;

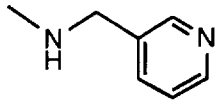
n is 0, 1, 2, 3, 4, 5 or 6;

T is -CO-; -SO-; $-SO_2-$; or $-CR^{30}R^{31}-$ wherein R^{30} and R^{31} independently represent H, alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl; and

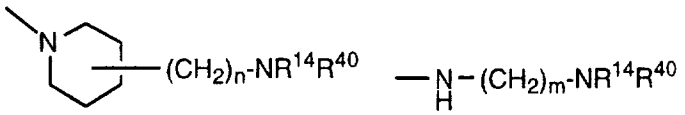
Z represents alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, $-OR^{40}$, $-SR^{40}$, $-CR^{40}R^{42}$,



$-NR^{40}R^{42}$,



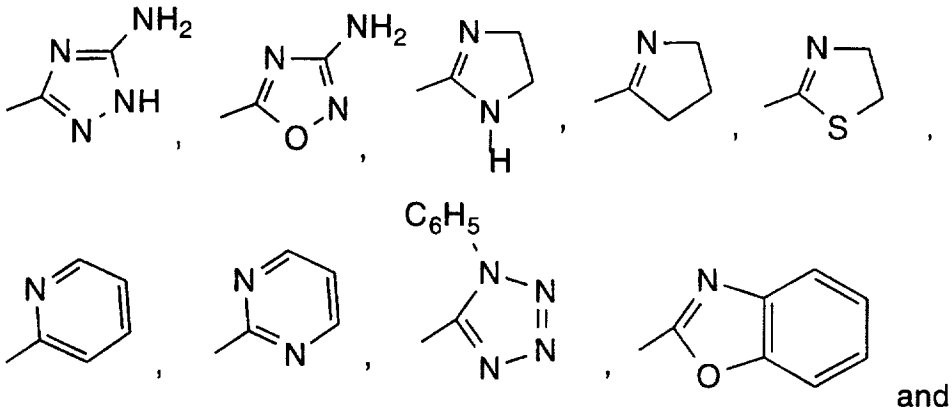
,



wherein n, R^{40} and R^{42} are defined hereinbefore,

m is 2, 3 4, 5, 6, 7 or 8;

and R^{14} represents H, C_{1-6} alkyl, aralkyl, acyl, carboxamido, cyano, alkoxycarbonyl, aralkyloxycarbonyl, D- and L-amino acids covalently bonded through the carboxyl group, imido, imidamido, sulfamoyl, sulfonyl, dialkylphosphinyl, N-glycosyl,



and

$-C(NHCH_3)=CHNO_2$,

with the proviso that when T is -SO-, Z is not $-NR^{40}R^{42}$.

2. The compound of claim 1 wherein a is N; b, c and d are carbon; A and B each represent H_2 and the optional double bond is absent.

3. The compound of claim 2 wherein R^1 and R^4 are H and R^2 and R^3 are halo selected from chloro and bromo; or R^1 is H and R^2, R^3 and R^4 are halo selected from chloro and bromo.

4. The compound of claim 2 wherein R^2 is halo in the 3-position and R^3 is halo in the 8-position.

5. The compound of claim 2 wherein R^2 is Br in the 3-position and R^3 is Cl in the 8-position.

6. The compound of claim 2 wherein R^1 is H and R^2, R^3 and R^4 are halo selected from chloro and bromo.

7. The compound of claim 2 wherein R^2 is halo in the 3-position, R^3 is halo in the 8-position and R^4 is halo in the 10-position.

8. The compound of claim 2 wherein R^2 is bromo in the 3-position, R^3 is chloro in the 8-position and R^4 is bromo in the 10-position.

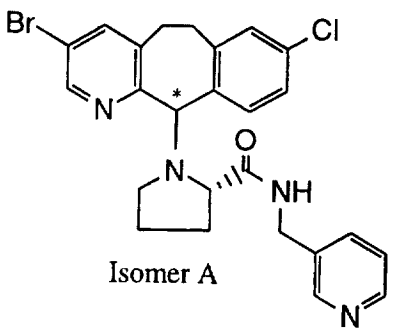
9. The compound of claim 3 wherein the moiety $-(CH_2)_n-T-Z$ is bonded at the 2-position on the pyrrolidine (y=1) or azetidine (y=0) ring.

10. The compound of claim 9 wherein n is zero; T is -CO-and Z is $-NR^{40}R^{42}$.

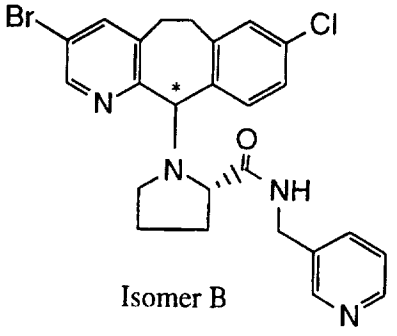
11. The compound of claim 10 wherein R^{40} is H; and R^{42} is 3-pyridylmethyl.

12. The compound of claim 1 selected from any of Examples 1-3.

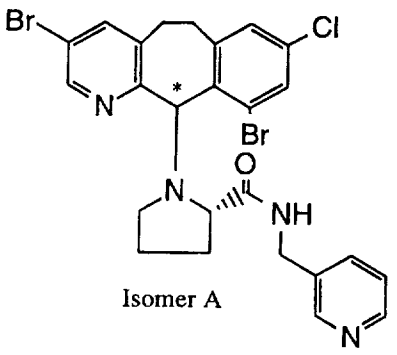
13. The compound of claim 12 which is selected from



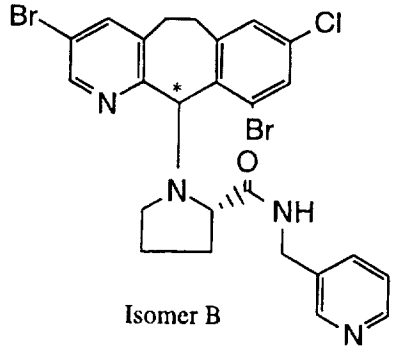
Isomer A



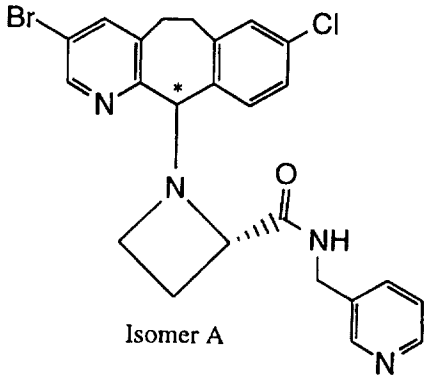
Isomer B



Isomer A

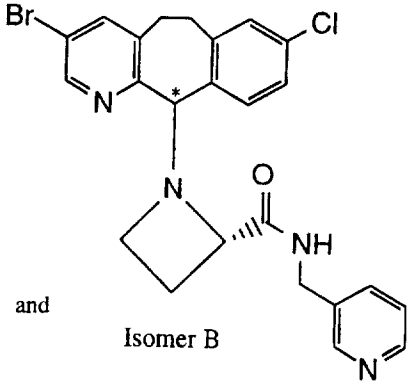


Isomer B



Isomer A

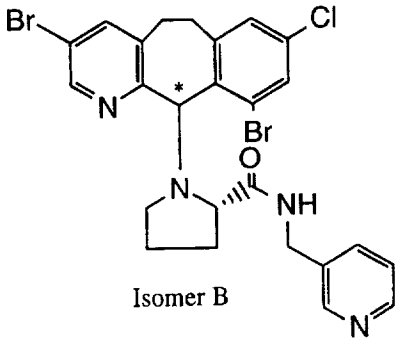
and



Isomer B

or a pharmaceutically acceptable salt thereof.

14. The compound of claim 13 which is



Isomer B

15. A pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound of Claim 1 in combination with a pharmaceutically acceptable carrier.

16. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of claim 1.

17. The method of claim 16 wherein the the cells inhibited are tumor cells expressing an activated ras oncogene.

18. The method of claim 16 wherein the cells inhibited are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells.

19. The method of claim 16 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of ras farnesyl protein transferase.

20. The method of claim 16 wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/US 97/15902

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/14 A61K31/435 C07D401/04

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)
IPC 6 C07D

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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 396 083 A (SCHERING CORP) 7 November 1990 see claims	1,15-20
A	WO 92 00293 A (SCHERING CORP) 9 January 1992 see claims	1,15-20
A	WO 95 10515 A (SCHERING CORP) 20 April 1995 see claims	1,15-20
A	WO 95 10516 A (SCHERING CORP) 20 April 1995 see claims	1,15-20

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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)

"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

"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

"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

"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.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
24 November 1997	02. 12. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

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

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 97/15902

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 1 593 417 A (SQUIBB & SONS INC) 15 July 1981 see page 20, line 15 - page 22, line 5; claims; examples 73-94 -----	1,15-20

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/15902

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 16-20
are directed to a method of treatment of
the human/animal body , the search has been carried out and based on the
alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte .onal Application No
PCT/US 97/15902

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inte ional Application No
PCT/US 97/15902

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