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PYRIDAZINO QUINOLINE COKPOUNDS

This invention relates to pyridazinedione compounds useful in the treatment of neurological disorders generally in mammals such as man. More specifically, the compounds are useful in the treatment of strokes and/or other neurodegenerative disorders such as hypoglycemia, cerebral palsy, transient cerebral ischemic attack, perinatal asphyxia, epilepsy, psychosis, Huntington's chorea, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, Olivo-pontocerebellar atrophy, viral-induced neurodegeneration such as in acquired immunodeficiency syndrome and its associated dementia, anoxia such as from drowning, spinal cord and brain trauma, and chronic pain, for the prevention of drug and alcohol withdrawal symptoms, and for the inhibition of tolerance and dependence to opiate analgesics. The invention particularly relates to novel pyridazinedione compounds useful in reducing neurological degeneration such as can be induced by a stroke and the associated functional impairment which can result. Treatment using a compound of the invention can be remedial or therapeutic as by administering a compound following an ischemic event to mitigate the effects of that event. Treatment can also be prophylactic or prospective by administering a compound in anticipation that an ischemic event may occur, for example in a patient who is prone to stroke.

It is known that ischemic events can trigger a dramatic increase in extracellular concentrations of the excitatory amino acids glutamate and aspartate which can, in turn, cause prolonged neuronal excitation leading to a massive influx of calcium from extracellular to intracellular sites in brain neural cells. A calcium overload can thereby be created which leads to a cascade of events leading to cell catabolism and eventually resulting in cell death. The N-methyl-D-aspartate (NMDA) receptor complex is believed to play a significant role in the cascade of events leading to cell necrosis following an ischemic event.

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The compounds provided by this invention may be useful in a variety of neurodegenerative disorders because they function as excitatory amino acid antagonists. They may do so indirectly, via allosteric modulation of the glutamate binding site, specifically by acting as antagonists of the strychnine-insensitive glycine receptor on the NMDA receptor complex. They may also do so directly, by binding to the glutamate site itself on the NMDA receptor complex.

According to the invention there is provided a compound and pharmaceutical compositions thereof suitable for the treatment of neurological disorders, comprising a compound of formula I or a pharmaceutically acceptable salt thereof (formula set out, together with other formulae referred to by Roman Numerals, on pages following the Examples), and tautomers thereof wherein

Z is selected from O, S or NH (or when the B-ring N tautomerizes or the B-ring is reduced, the Z group may be selected from H, OH, SH or NH_2 to form a compound of I').

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, furyl, pyrrolyl or thienyl either unsubstituted or multi-substituted at a ring carbon atom with R^4 wherein R^4 is independently selected from the group consisting of halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR';a heterocyclic group, NR'COR",COR",$NR'CO_2R"$,CO_2R',CONR'R";

R^1 is selected from H or $-(CH_2)_nL$ wherein L is M or W;

M is

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from -O-(1-4C)alkyl, -O-(2-4C)alkenyl, -O-(2-4C)alkynyl, -O(CO-C6alkyl)phenyl, -OH, -halo, $-NO_2$, -CN, $-CF_3$, -(1-4C)alkylCF_3, -NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluroalkyl, -(1-4Cperfluroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy), -(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', $-(CH)_n$NR'R"COOR' wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', $-NR'(CH_2)_n$COOR', $-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl), $-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S, or aryl or heteroaryl benz derivatives thereof, wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R' or a carbon atom may be disubstituted to form a C5-C7 spiral group or a carbon atom or sulfur atom may be substituted with O to form a carbonyl group or sulfonyl group $(S(O)_m)$ with the proviso that a heterocyclic nitrogen may not be attached to a nitrogen or the tricyclic ring system of formula I;

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole or isothiazole (and oxidized versions thereof selected from $S(O)_m$ wherein m is 0-2), pyridazine, pyrimidine, pyrazine or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or triazine, or those groups containing four heteroatoms such as tetrazole, wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

W is selected from OH, OR', CF_3 OCOR', $S(O)_mR'$, $S(O)_mNR'R"$, halo, NR'R" with the proviso that NR'R" is not equal to NH_2, COR', NR'COR", OCONR', $NR'CO_2R"$, (C3-6)cycloalkyl, NRCONR'R", CO_2R', or CONRR' with the proviso that n is greater than zero and;

n is chosen from 0-6;

R^2 is selected from H or $-(CH_2)_nL$ wherein L is M or W and

M is:

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2 or 3 groups chosen from -O-(1-4C)alkyl, -OH, -halo, $-NO_2$, -CN, $-CF_3$, -NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R",

-NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", $-OCF_3$, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy);

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S, or aryl or heteroaryl benz derivatives thereof, wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R' or a carbon atom may be disubstituted to form a C5-C7 spiral group or a carbon atom or sulfur atom may be substituted with O to form a carbonyl group or sulfonyl group ($S(O)_m$);

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole, or those groups containing four heteroatoms such as tetrazole, wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

W is selected from OH, OR', OCOR', $S(O)_mR'$, halo, $S(O)_mNR'R"$,NR'R" with the proviso that NR'R" is not equal to NH_2, COR', NR'COR", OCONR', $NR'CO_2R"$, (C3-6)cycloalkyl, NRCONR'R", CO_2R', or CONRR'

with the proviso that n is greater than zero and;

n is chosen from 0-4;

R is selected from H or (1-4C)alkyl;

R′ and R″ are independently selected from H, (1-4C)alkyl wherein alkyl includes alkenyl(C2-C4) and alkynyl(C2-C4); (3-6C)cycloalkyl, Phenyl(0-4C)alkyl-, heterocycle(0-4C)alkyl- or heteroaryl(0-4C)alkyl- wherein phenyl or heterocycle or heteroaryl is as defined above and any of the above is optionally substituted at one or more carbon atoms with halo, H, (1-4C)alkyl, (3-6C)cycloalkyl, phenyl, NO_2, CN, CF_3, OH, O-(1-4C)alkyl, NR′R″ $S(O)_mR'$ or $SO_2NR'R''$ wherein NR′R″ may optionally form an N-alkyl(C1-3)oxyalkyl(C2-3) ring with N;

m is chosen from 0-2;

with the proviso that R^1 and R^2 are not both equal to H and, in a pharmaceutical composition, a pharmaceutically acceptable diluent or carrier is added to a compound of formula I or I′.

According to the invention there is provided a compound and pharmaceutical compositions thereof suitable for the treatment of neurological disorders, comprising a compound of formula I or a pharmaceutically acceptable salt thereof (formula set out, together with other formulae referred to by Roman Numerals, on pages following the Examples), and tautomers thereof wherein

Z is selected from O, S or NH (or when the B-ring N tautomerizes or the B-ring is reduced, the Z group may be selected from H, OH, SH or NH_2 to form a compound of I′).

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, furyl, pyrrolyl or thienyl either unsubstituted or multi-substituted at a ring carbon atom with R^4 wherein R^4 is independently selected from the group consisting of halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR′R″, $SO_2NR'R''$, or SO_mR';

R^1 is selected from H or $-(CH_2)_nL$ wherein L is M or W;

M is

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2 or 3 groups chosen from -O-(1-4C)alkyl,-O-(2-4C)alkenyl, -O-(2-4C)alkynyl, -OH, -halo, $-NO_2$, -CN, $-CF_3$, -(1-4C)alkylCF_3, -NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-,hydroxy(C1-C6)alkyloxy-, aryloxy(1-4C)alkyloxy(1-4C)alkyl, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluroalkyl, -(1-4Cperfluroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy);

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R' or a carbon atom may be substituted with O to form a carbonyl group;

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole, wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

W is selected from OH, OR', OCOR', $S(O)_mR'$, NR'R" with the proviso that NR'R" is not equal to NH_2, NR'COR", OCONR', $NR'CO_2R"$, NRCONR'R", CO_2R', or CONRR' with the proviso that n is greater than zero and;

n is chosen from 0-4;

R^2 is selected from H or $-(CH_2)_nL$ wherein L is M or W and

M is:

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2 or 3 groups chosen from -O-(1-4C)alkyl, -OH, -halo, $-NO_2$, -CN, $-CF_3$, -NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6) alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-,-O(C1-C6alkyl) NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", $-OCF_3$, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy);

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R';

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, dithiol, oxathiol, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole, oxadiazole, dioxazole, or oxathiazole wherein the N on the heteroaryl

group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom on the heteroaryl group;

W is selected from OH, OR', OCOR', $S(O)_mR'$, NR'R" with the proviso that NR'R" is not equal to NH_2, NR'COR", OCONR', $NR'CO_2R"$, NRCONR'R", CO_2R', or CONRR' with the proviso that n is greater than zero and;

n is 1-4;

R is selected from H or (1-4C)alkyl;

R' and R" are independently selected from H, (1-4C)alkyl wherein alkyl includes alkenyl and alkynyl; Phenyl(0-4C)alkyl-,heterocycle(0-4C) alkyl- or heteroaryl(0-4C)alkyl- wherein phenyl or heterocycle or heteroaryl is as defined above and is optionally substituted at one or more carbon atoms with halo, H, (1-4C)alkyl, NO_2, CN, CF_3, OH, O-(1-4C)alkyl, NR'R" $S(O)_mR'$ or $SO_2NR'R"$;

m is chosen from 0-2; and, in a pharmaceutical composition, a pharmaceutically acceptable diluent or carrier is added to a compound of formula I or I'.

The present invention also relates to compounds which are useful as key intermediates in the production of glycine receptor antagonists as defined above wherein W is equal to halo species such as Cl, Br, F or I wherein n is greater than zero. In addition, compounds obtained through a novel process for the production of pyridazinoquinolines as herein defined with R^1 selected from aryl or heteroaryl as defined above are key intermediates in the production of said compounds. These key intermediates are 3-carboalkoxy-4-hydroxy quinoline 2-carboxylic acid N-2-aryl (or heteroaryl) hydrazides which

are used to produce the above aryl or heteroaryl species wherein aryl and heteroaryl are as defined above. Other key intermediates include 3-carboxylic acid-4-hydroxy quinoline 2-pyrrolidineamide intermediates which are utilized to react with BOC-protected aryl, heteroaryl or substituted alkyl hydrazines to form after coupling with dicyclohexyldiimide or diisopropyldiimide, in a polar solvent such as THF, methanol, diethylether, dioxane, CH_2Cl_2, CH_3CN or DMF and an acid (e.g. CH_3SO_3H) another key intermediate - a 2-pyrrolidiiocarbamide 3 carboxylic acid-N-1 aryl, heteroaryl, substituted alkyl, aryl alkyl or heteroaryl alkyl hydrazide, which after deprotection or removal of the BOC or other bulk N-protection group, leads selectively to the N-2 substituted PQD. The pyrrolidine may be substituted with an equivalent amine which produces an amide with limited steric hindrance and which acts as an appropriate leaving group.

EPO publication number 0 516 297 A1 describes certain pyridazinediones. In addition, the compounds (1) thieno[2′,3′:5,6]pyrido[2,3-d]pyridazine-5,8,9(4H,6H,7H)-trione and (2) thieno[3′,2′:5,6]pyrido[2,3-d]pyrid-azine-4,5,8(6H,7H,9H)-trione are known, for example from J. Heterocyclic Chem., 28, 205, (1991).

Other pyridazinedione compounds are known from, for example, Beilstein's Handbuch der Organischen Chemie; Godard et. al., Bull. Soc. Chim. Fr., 1588, (1972); and Reid et. al., Chem. Ber., 85, 204, (1952). The compounds of the present invention, on the other hand, relate to novel 2- or 3-substituted pyridazinediones or tautomers thereof as shown above in formula I or I′.

Particular subgroups within the above broadly defined group of compounds include those compounds having the specific formulae II or III, wherein, in the case of formulae II:

Z is chosen from:
O, S, or NH;

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, pyrrolyl or thienyl either unsubstituted or substituted at one or more ring carbon atoms with R^4 wherein R^4 is independently selected from the group consisting of hydrogen, halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR';

R^1 is $-(CH_2)_nL$ wherein

L is chosen from:
-OH, -O(C1-C4alkyl), -O(C1-C4alkyl)aryl, (C1-C4alkyl)COOR', OCOR', $S(O)_mR'$, NR'R" with the proviso that NR'R" is not equal to NH_2, NR'COR", OCONR', $NR'CO_2R"$, NRCONR'R", CO_2R', or CONRR' with the proviso that n is greater than zero;

aryl or benz derivatives thereof either unsubstituted or mono, bi or tri-substituted with aromatic substituents including -halo, -C1-C6alkyl, -(C2-C6)alkenyl or alkynyl, -oxy(C0-6alkyl)phenyl, -OH, C1-C6alkoxy, OCF_3, CF_3, NO_2, CN, NH_2, SO_mR', NH(C1-4alkyl), heteroaryl, or $N(C1-C4alkyl)_2$;

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R' or a carbon atom may be disubstituted to form a C5-C7 spiral group or a carbon atom or sulfur atom may be substituted with O to form a carbonyl group or sulfonyl group ($S(O)_m$); wherein the heterocyclic groups may be selected from, for example, 2-pyrolidinone, piperazine, oxazolidone, 2,5-oxazolidinedione, 2,4-imidazollidinedione, 2,4-thiazolidinedione

or succinimide; aryl or benz or heteroarylbenz derivatives thereof (3,4-pyridinedicarboximide, -1-pthalimido, isatoic anhydride, orthobenzoicsulfimide) either unsubstituted or mono, bi or tri-substituted with alkyl or aromatic substituents including -halo, -C1-C6alkyl, -OH, C1-C6alkoxy, phenyl, OCF_3, CF_3, NO_2, CN, NH_2, SO_mR', NH(C1-4alkyl), or $N(C1-C4alkyl)_2$;

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or those groups containing 4 heteroatoms such as tetrazole wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

n is 0-3;

and pharmaceutically acceptable salts thereof. The present invention also relates to pharmaceutical compositions of a compound of formula II as defined above and a pharmaceutically acceptable excipient. In addition, the present invention relates to important intermediates which are useful in the synthesis of a compound of formula II wherein L in the above formula is chosen from halo (Br, Cl, F or I) and n is greater than zero. This intermediate is useful in the production of certain glycine receptor antagonists of formula II. In the case of a compound of formula III,
Z is chosen from:

O, S, or NH;

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, pyrrolyl or thienyl either unsubstituted or multi-substituted at a ring carbon atom with R4 wherein R^4 is independently selected from the group consisting of hydrogen, halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR';

R^2 is $-(CH_2)_nL$ wherein

L is chosen from:

-OH, -O(C1-C4alkyl), -O(C1-C4alkyl)aryl, (C1-C4alkyl)COOR'; aryl or benz derivatives thereof either unsubstituted or mono, bi or tri-substituted with aromatic substituents including -halo, -C1-C6alkyl, $-S(O)_mR'$, -OH, C1-C6alkoxy; CF_3, OCF_3, NO_2, CN, NH_2, NH(C1-4alkyl), or $N(C1-C4alkyl)_2$ with the proviso that n is greater than zero;

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R';

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole, or those groups containing four heteroatoms such as tetrazole wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic

substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom on the heteroaryl group;

n is 0-3;

and pharmaceutically acceptable salts thereof. The present invention also relates to pharmaceutical compositions of a compound of formula III as defined above and a pharmaceutically acceptable excipient. In addition, the present invention relates to important intermediates which are useful in the synthesis of a compound of formula III wherein L in the above formula is chosen from halo (Br, Cl, F or I). This intermediate is useful in the production of certain glycine receptor antagonists of formula III.

More particular subgroups include those compounds having the specific formulae II and III, wherein Z is selected from oxygen;

Ring A is chosen from phenyl or substituted phenyl wherein the phenyl ring is mono, di or tri-substituted with halo, nitro or simple C1-C4alkyl including methyl, ethyl or propyl;

R^1, in the case of formula II, is chosen from $-(CH_2)_nL$ wherein

L is chosen from:

-OH, -O(C1-C4alkyl), -O(C1-C4alkyl)aryl, (C1-C4alkyl)CO_2R^1, OCOR', $S(O)_mR'$, NR'R" with the proviso that NR'R" is not equal to NH_2, NR'COR", OCONR', NR'CO_2R", NRCONR'R", CO_2R', or CONRR' with the proviso that n is greater than zero;
aryl or benz derivatives thereof either unsubstituted or mono, bi or tri-substituted with aromatic substituents including -halo, -C1-C6alkyl, -OH, C1-C6alkoxy, -oxy(C1-4)alkylphenyl, -C2-4alkenyl, CF_3, OCF_3, NO_2, CN, NH_2, -C(O)NR'R", heteroaryl, SO_mR', NH(C1-4alkyl), or $N(C1-C4alkyl)_2$;

succinimide; oxazolidone; piperazine or substituted versions thereof wherein the substients are selected from (C1-4alkyl), phenyl including substituted phenyl wherein the phenyl substituents are typical aromatic substituents, 2-pyrolidinone and substituted versions thereof (e.g. (C1-6)alkyl, hydroxy); 2,5-oxazolidinedione or substituted versions thereof (e.g. alkyl, dialkyl, phenyl, diphenyl, spiral(C4-6)alkyl), 2,4-thiazolidinedione, 2,4-imidazolidinedione or substituted versions thereof (e.g. alkyl, dialkyl, phenyl, diphenyl),or benz or heteroaryl benz derivatives thereof selected from phthalimido, orthobenzoicsulfimide, isatoic anhydride or 3,4 pyridinedicarboximide;

heteroaryl wherein the groups are selected from thiophene, pyrrole,furan, pyrazole, imidazole, triazole, tetrazole or pyridine;

n is 0-3;

and pharmaceutically acceptable salts including the choline salts thereof. R^2, in the case of formula III and with Z and ring A as defined above, is chosen from $-(CH_2)_nL$ wherein

L is chosen from:

-OH (n>0), (C1-C4alkyl)carboxy, aryl or benz derivatives thereof either unsubstituted or mono, bi or tri-substituted with typical aromatic substituents including halo, C1-C6alkyl, OCF_3, CF_3, hydroxy, C1-C6alkoxy; NO_2, CN, NH_2, NH(C1-4alkyl), $S(O)_mR'$ or $N(C1-C4alkyl)_2$; More particularly, in the case of formula III, R^2 is chosen from $-(CH_2)_n$ wherein n is equal to 0 and L is chosen from 4-$S(O)_mR'$Phenyl wherein m is 0-2, 2-methylphenyl, 2-methyl,4-chlorophenyl, 3-nitrophenyl, 3-chloro-4-methylphenyl, 4-triflouromethylphenyl, 3,4-dimethoxyphenyl, or 2,4-dichlorophenyl.

Preferably, the present invention relates to compounds of formula II or pharmaceutically acceptable salts thereof wherein

Ring A is chosen from an ortho fused phenyl, 7-chlorophenyl, 7,9-dichlorophenyl, 7-chloro-9-methylphenyl, 7-methyl,9-chlorophenyl, 7,9-dimethylphenyl, 7-chloro-8-nitrophenyl, 7,9-dichloro-8-nitrophenyl, 7-chloro-9-ethylphenyl wherein the numeric designations refer to the position on the final pyridazino quinoline ring system;

Z is selected from oxygen;

R^1 is selected from $-(CH_2)_nL$ wherein

L is selected from: -OH, -O(C1-C4alkyl), -O(C1-C4alkyl)aryl, (C1-C4alkyl)CO_2R', OCOR', $S(O)_mR'$, NR'R" with the proviso that NR'R" is not equal to NH_2, NR'COR", OCONR', $NR'CO_2R"$, NRCONR'R", CO_2R', or CONRR' with the proviso that n is greater than zero;

aryl or benz derivatives thereof either unsubstituted or mono, bi or tri-substituted with aromatic substituents including -halo, -C1-C6alkyl, -OH, C1-C6alkoxy, OCF_3, NO_2, CN, CF_3, NH_2, SO_mR', NH(C1-4alkyl), or $N(C1-C4alkyl)_2$;

succinimide, piperazine or substituted versions thereof wherein the substients are selected from (C1-4alkyl), phenyl including substituted phenyl wherein the phenyl substituents are typical aromatic substituents; 2,5-oxazolidinedione and substituted versions thereof selected from C1-C6alkyl, phenyl or substituted phenyl,C3-C6spiralalkyl; pyrrolidone and substituted versions thereof selected from C1-C6alkyl, hydroxy, phenyl; 2,4-imidazolidinedione or substituted versions thereof selected from C1-C6alkyl, phenyl or substituted phenyl; 2,4-thiazolidinedione or substituted versions

thereof selected from C1-C6alkyl or phenyl; or benz or heteroaryl benz heterocyclic derivatives selected from -1-phthalimide, orthobenzoicsulfimide, isatoic anhyrdride or 3,4-dicarboximide;

heteroaryl selected from thiophene, imidazole, triazole, tetrazole furan or pyridine; and n is 0-2. Advantageously, for the compounds of formula II, n is equal to zero and L is selected from: phenyl, 4-methoxyphenyl, 4-hydroxyphenyl, 4-chlorophenyl, 4-methylphenyl, 4-isopropylphenyl, napthyl, 4-flourophenyl, 4-bromophenyl, 2-methoxyphenyl, 2-hydroxyphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 4-triflouromethoxyphenyl, 3-chloro,4-methoxyphenyl, 5-methoxy-3-pyridyl, 4-$S(O)_mR'$phenyl wherein m is 0-2 and R' is methyl; 3-chlorophenyl, 3-chloro-4-hydroxyphenyl, 2-methyl-4-chlorophenyl, 3-methylphenyl, 2-methylphenyl, 3-flourophenyl, 2,4-diflourophenyl, 3,5-triflouromethylphenyl, 3-nitrophenyl, 2-flourophenyl, 2,4-dimethylphenyl, 3-chloro-4-methylphenyl, 4-triflouromethylphenyl, 4-iodophenyl, 3,4-dimethylphenyl, 3,4-dimethoxyphenyl, 2-methyl-4-methoxyphenyl, 2-methoxy,4-bromophenyl, 2-methyl,4-hydroxyphenyl, 4-ethylphenyl, 2,3-dimethylphenyl, 3,4-dihydroxyphenyl, 2,4-dimethoxyphenyl, 2,4-dichlorophenyl, 4-nitrophenyl,2,5-dimethoxyphenyl,2,5-dimethylphenyl, 4-oxybenzylphenyl, 2,5-dihydroxyphenyl, 4-vinylphenyl, 2,5-diflourophenyl, 2-methyl-4-flourophenyl, 3,5-dimethoxyphenyl, 4-carboxyphenyl, 4-formamidophenyl, 4-(N,N-diethylformamido)phenyl, 4-cyanophenyl, or 4-tetrazolephenyl. Advantageously, the present invention also relates to compounds of formula II wherein n is equal to 1 and L is selected from any of the members identified above for n equal to zero and, more particularly to groups selected from 1-flourophenyl, 4-cyanophenyl, 4-triflouromethylphenyl, 4-methylphenyl, pentaflourophenyl or 3,5-ditriflouromethylphenyl or to compounds of formula II wherein n is equal to three and L is selected from any group designated for n equal to zero or one, but more

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particularly to a group selected from phenyl or a phenyl substituted with a typical aromatic substituent. The substituted alkyl(C1-6)aryls disclosed herein which are particularly useful are those containing phenyl substituents which increase lipophilicity to enhance red nucleus activity. For example, the flourinated, alkylflourinated, alkyl(C1-4) or mono-halogenated benzyl compounds have enhanced activity. The (C1-C6) alkyl groups substituted with a terminal CF_3 group are particularly useful because of their unexpected solubility properties and are also useful because of their lipophilicity.

The pyridylbromo salt attached to the N-2 ethyl moiety in the PQD ring and wherein the pyridyl nitrogen is directly attached to the terminal ethyl carbon does not have glycine antagonist properties. The pyridyl rings attached via a carbon atom on the pyridyl ring to the $(CH_2)n$ group of a compound of formula II have significant glycine receptor antagonist activity.

The present invention also preferrably relates to a compound of formula II wherein n is equal to two and a heterocyclic moiety as described herein is bonded to the 2-ethyl carbon and is selected from 1-phthalimido, 4-phenylpiperazine, succinimide,3,3-dimethyl-2,5-oxazolidinedione,1-methylpyrollidine,3-methyl-3-phenyl-2,5-oxazollidinedione, 3-N-methyl,2,5-imidazolidinedione,4,4-dimethyl-2,5-imidazolidinedione, 4,4-diphenyl-2,5-imidazolidinedione, 2,4-thiazolidinedione, 3,4-pyridinedicarboximide, orthobenzoicsulfimide (saccharine),4-cyclochexylspiral,2,5-oxazolidinedione, isatoic anhydride,benzo[e] [1,3]oxazine-2,4-dione, 4-phenyl-2,5-oxazolidinedione or 3-hydroxy, 3-methyl 2-pyrrolidinone. The preferred compounds for which n is equal to one and L is heterocycle include groups selected from tetrahydrofuran, piperidine, N-methylpiperidine, tetrahydropyran, 1,3-dioxane, benzo-1,4-dioxane or orthobenzoicsulfimide. The present invention also preferrably relates to compounds of formula II wherein R^1 is equal to $(CH_2)_nL$ and wherein n is equal to one and L is equal to a heteroaryl selected from thiophene or pyridyl or furan or substituted versions thereof wherein the substituents are selected

from typical aromatic substituents (e.g. hydroxy, halo, C1-C6alkyl, phenyl or heteroaryl) or to those groups selected from imidazole, thiazole, thiadiazole, pyridopyridine, pyrimidine, pyrazine, pyridazine, benzothiophene, furan, benzofuran, indole, or triazole or substituted versions thereof. The preferred groups when n is equal to two and wherein the heteroaryl group is attached to the 2-ethyl carbon include members selected from imidazole, triazole, tetrazole or pyridine.

The present invention also relates advantageously to a compound of formula II wherein n is equal to two and L is equal to W wherein W is selected from the group consisting of: hydroxy, acetoxy, benzoylamido, 2-hydroxy-2-methylpropamido, 4-methoxyaniline, 1-formamidocyclohexanol, 2-hydroxybenzamido, biphenylhydroxyacetamido, -S-CH_3, -$S(O)_2$-CH_3, -S-4-methoxyphenyl, S-cyclopentyl, -$S(O)_2$-ethyl, -S-ethyl, -S-butyl, -$S(O)_2$-butyl, or -S-propyl. In addition, these groups may be selected from -OPh, halo, -CH_2-COOR' or -CH_2CONR'R", -OCH_3, -$OCH_2CH_2OCH_3$, -$OCH_2CH_2OCH_2CH_3$, -O-2-methoxyphenyl, -$S(O)_2$Ph, -$S(O)_2$NR'R", -$CF(CF_3)_2$, -CF_2CF_3, -$CF_2CF_2CF_3$, -$OC_2H_5OC_2H_5$, -CH_2NR'R" or -$CH_2CH_2COCH_3$.

The present invention also relates to pharmaceutical compositions containing a preferred compound of formula II as shown above and a pharmaceutically acceptable carrier.

It will be appreciated that the formulae described herein can be drawn in various tautomeric and positional isomeric forms, as discussed below. The present invention includes such alternate forms unless otherwise indicated, also includes salts thereof, especially the pharmaceutically acceptable addition salts.

Many of the compounds disclosed herein can exist and be drawn in various true tautomeric forms (i.e., for compounds corresponding to a compound of formula I). It is noted that tautomeric forms of these compounds can also exist when Z is hydroxy, thiohydroxy, amino, or alkylamino as shown in formula I'.

It will further be appreciated by those skilled in the art

that certain compounds of formula I contain an asymmetrically substituted carbon atom, and accordingly may exist in, and be isolated in, optically-active and racemic forms. In addition, it will be appreciated that certain compounds of formula I, for example, those containing a double bond, may exist in, and be isolated in, separate stereoisomeric forms ('E' and 'Z') about that group. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the treatment of neurodegenerative disorders, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form or by synthesis from optically-active starting materials) and individual 'E' and 'Z' stereoisomers (for example, by chromatographic separation of a mixture thereof) and how to determine neuroprotective properties by the standard tests described hereinafter.

The invention further provides a method for the treatment of neurological disorders, comprising administering to a mammal in need of such treatment an effective amount of a compound according to the invention as defined above, or a pharmaceutically acceptable salt thereof, or a composition as defined above. The invention also encompasses a method of antagonizing an NMDA receptor in mammals comprising administering a pharmaceutically effective amount of the compound or its salt as claimed herein or a pharmaceutical composition as recited herein to a patient in need of treatment thereof. The preferred therapeutic treatment area is prevention and/or treatment of stroke. A pharmaceutically effective amount of a compound as claimed and disclosed in the present invention may be administered immediately after an ischemic event to prevent cell damage and/or cell death. The present invention is also directed to a method of preventing and/or treating damage induced by the excitatory amino acids such as L-glutamate. The invention also relates to a method of preventing the excessive influx of calcium ions in central neurons. The invention

relates to a method of preventing ischemic neuronal injury following transient global ischemia and a method of reducing infarct volume following focal ischemic insults by treating a patient in need of treatment thereof with a pharmaceutically effective amount of a compound of formula I or I' wherein Z, ring A and R^1 and R^2 are as defined herein. In addition to being useful in the treatment of acute stroke patients, the compounds and compositions of the invention may be extremely beneficial in preventing neurological morbidity during cardiac resuscitation or administered as cerebral prophylatics during high-risk surgery.

In this specification the terms "alkyl" and "alkoxy" include both straight and branched chain radicals, but it is to be understood that references to individual radicals such as "propyl" or "propoxy" embrace only the straight chain ("normal") radical, branched chain isomers such as "isopropyl" or "isopropoxy" being referred to specifically.

The term "halo" is inclusive of fluoro, chloro, bromo, and iodo unless noted otherwise.

The term "heteroaryl" includes those heteroaromatic groups of benz derivatives thereof where are specifically or generally described or disclosed in this specification.

Particular values of (1-4C)alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

Particular values of (2-4C)alkyl containing a double or triple bond include vinyl, 2-propenyl (i.e. allyl), 2-propynyl, (i.e. propargyl), 2-butenyl, and 3-butenyl.

Particular values of (1-4C)alkoxy include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, and t-butoxy.

Particular values of (1-6C)alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl.

Particular values of (2-6C)alkyl containing a double or triple bond include vinyl, 2-propenyl (i.e. allyl), 2-propynyl, (i.e.

propargyl), but-2-enyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-pentynyl, 5-hexenyl, 5-hexynyl.

Particular values of phenyl substituted with from 0-4 substituents may include but are not limited to phenyl; 2-, 3-, and 4-halophenyl; 2-, 3-, and 4-aminophenyl; 2-, 3-, and 4-hydroxyphenyl; 2-, 3-, and 4-cyanophenyl; 2-, 3-, and 4-nitrophenyl; 2-, 3-, and 4-methylphenyl; 2-, 3-, and 4-ethylphenyl; 2-, 3-, and 4-propylphenyl; 2,3 or 4-isopropylphenyl; 2-, 3-, and 4-methoxyphenyl; 2-, 3-, and 4-ethoxyphenyl; 2-, 3-, and 4-propoxyphenyl; and 3,5-dihalophenyl, 3-halo-4-hydroxyphenyl, and 3,5-dihalo-4-hydroxyphenyl and phenyl substituted at 1, 2 or 3 carbon atoms with methoxyethyloxy, methoxyethyloxyethyloxy, N,N-dimethylethyloxy, and N,N-dimethylethylaminyl; 3,4-dimethoxy; 3,4-dihydroxy; 3,5-dimethoxy; 3,5-dihydroxy or 2,3,4-SMe or 2,3,4-SH and further includes groups selected from 4-(SO_2CH_3)phenyl, 2-methyl-4-chlorophenyl, 2,4-dihalophenyl, 4(tetrazole)phenyl, 3,5-trifluoromethylphenyl, 2,4-dimethylphenyl, 3-halo-4-methylphenyl, 4-trifluoromethylphenyl, 3,4-dimethylphenyl, 2-methyl-4-methoxyphenyl, 2-methoxy-4-halophenyl, 2-methyl-4-hydroxyphenyl, 2,3-dimethylphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,5-dimethylphenyl, 4(benyloxy)phenyl, 4-(ethoxy)phenyl, 2,5-dihydroxyphenyl, 4-vinylphenyl,2,5-dihalophenyl, 2-methyl-4-fluorophenyl, or 2,3 or 4 (CONR'R")phenyl.

Particular values of phenyl(1-4C)alkyl substituted with from 0-4 substituents may include benzyl, phenylethyl, phenylpropyl, phenylbutyl; 2-, 3-, 4 and 5-halobenzyl; 2-, 3- and 4- CF_3-benzyl, 2-, 3-, and 4-aminobenzyl; 2-,3-, and 4-cyanobenzyl, 2-, 3-, and 4-nitrobenzyl, 2-, 3-, and 4-methylbenzyl; 2-, 3-, and 4-ethylbenzyl; 2-, 3-, and 4-propylbenzyl; 2-, 3-, and 4-hydroxybenzyl; 2-, 3-, and 4-methoxybenzyl; 2-, 3-, and 4-ethoxybenzyl; 2-, 3-, and 4-propoxybenzyl; and 3,5-dihalobenzyl, 3-halo-4-hydroxybenzyl, 3,5-diCF_3benzyl and 3,5-dihalo-4-hydroxybenzyl or 2,3,4,5,6-pentahalobenzyl; and phenyl(1-4C)alkyl substituted with

methoxyethyloxy, methoxyethyloxyethyloxy, N,N-dimethylethyloxy, and N,N-dimethylethylaminyl; 3,4-dimethoxy; 3,4-dihydroxy; 3,5-dimethoxy; 3,5-dihydroxy or 2,3,4-SMe or 2,3,4-SH.

Particular values of 4- to 7-membered rings containing nitrogen may include piperidino, pyrrolidinyl, and azetidinyl. Particular values of heterocyclic species with 2 heteroatoms include piperazinyl, morpholinyl, oxazolinyl or thiazinyl. Particular values of heterocycles or substituted derivatives thereof include 2-pyrrolidone, succinimide, oxazolidone, 2,5-oxazolidinedione, 2,4-thiazolidinedione, 2,4-imidazolidinedione and various benz derivatives including phthalimido, isatoic anhydride, benzo[e][1,3]oxazine-2,4-dione, 3,4-pyridinedicarboximide, or orthobenzoicsulfimide.

More particular values of halo include chloro and bromo.

More particular values of (1-3C)perfluoroalkyl include trifluoromethyl and pentafluoroethyl.

More particular values of 4- to 7-membered rings containing nitrogen include piperidino, piperazinyl and pyrrolidinyl.

More particular values of (1-3C)alkyl substituted with a trifluoromethyl group include trifluoromethylmethyl and 2-trifluoromethylethyl.

More particular values of heteroaryl include tetrazole,furan thiophene, diazole, imidazole, triazole, pyridine, pyrimidine, pyridazine or pyrazine.

More particular values of m include 0-2.

More particular values of n include 0-2.

More particular values of phenyl substituted with from 0-3 substituents may include phenyl; 2- and 4-halophenyl; 2- and 4-aminophenyl; 2-, 3- and 4-hydroxyphenyl; 2-, 3- and 4-methoxyphenyl; 2,4-dihalophenyl; 3,5-dihalophenyl; 2,6-dihalo-4-hydroxyphenyl, 2-halo-4-methylphenyl; 2-methoxy-4-methylphenyl;2-methyl-4-methoxyphenyl; 3-hydroxy-4-methyl phenyl; 2-hydroxy-4-methyl phenyl, 2-methyl-4-chlorophenyl, 2,4-dimethylphenyl, 3,4-dimethoxyphenyl, 2-methyl-4-methoxyphenyl, 3,4-dihydroxyphenyl or 2,4-dimethylphenyl;

and includes those values specifically exemplified in the examples.

More particular values of phenyl(C1-C4)alkyl substituted with 0-3 substituents may include benzyl; phenylethyl; 2- and 4-halobenzyl; 2- and 4-cyanobenzyl; 2- and 4-nitrobenzyl; 2- and 4-methoxybenzyl; 2,4-dihalobenzyl, 3,5-dihalobenzyl; and 2,6-dihalo-4-hydroxybenzyl. The corresponding phenethyl isomers may also be included.

Preferred values of R^1 include hydroxyethyl, acetoxyethyl, phthalimidoethyl, bromoethyl (as an intermediate in the production of glycine receptor antagonists), phenyl, SO_2Mephenyl, methoxyphenyl, hydroxyphenyl, benzyl, (phenylpiperazino)ethyl, phenethyl, chlorophenyl, methylphenyl, or (C1-C4alkyl)phenyl.

More preferred values of R^1 include 2-hydroxyethyl, 2-acetoxyethyl, 2-phthalimidoethyl, phenyl, 4-methoxyphenyl, 4-hydroxyphenyl, benzyl, 2(4-phenylpiperazino)ethyl, 2-phenethyl, 4-chlorophenyl, 4-methylphenyl or 4-isopropylphenyl. Of course, the preferred values for Z, Ring A, R^1 and R^2 and the other designated values in formulae I, I', II, III etc. include those values or groups which are specifically exemplfied in the examples and/or in the schemes.

Most preferred values of Z include O or OH.

Preferred values of R^4 include hydrogen, fluoro, chloro, bromo, iodo, amino, methyl, ethyl, propyl, allyl, propargyl, trifluoromethyl, pentafluoroethyl, trifluoromethylmethyl, nitro, methoxy, ethoxy, propoxy, and cyano.

More preferred values of R^4 include hydrogen, fluoro, chloro, bromo, iodo, methyl, ethyl, trifluoromethyl, nitro, methoxy, amino, and cyano.

Preferred compounds having formula I (or II) include:

(a)

7-chloro-1-hydroxy-2-(2-hydroxyethyl)-3,4,5,10-tetrahydropyridazino [4,5-b]quinoline-4,10-dione;

(b)
2-(2-Acetoxyethyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione;

(c)
7-chloro-4-hydroxy-2-(2-phthalimidoethyl)-1,2,5,10-tetrohydropyridazino[4.5-b]-quinoline-1,10-dione;

(d)
7-chloro-4-hydroxy-2-phenyl-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione;

(e)
7-Chloro-4-hydroxy-2-(4-methoxyphenyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione;

(f)
7-Chloro-4-hydroxy-2-(4-hydroxyphenyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione;

(g)
4-hydroxy-8-nitro-2-(phenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione;

(h)
2-Benzyl-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

(i)
7-chloro-4-hydroxy-2-[2-(4-phenylpiperazino)ethyl]-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

(j)
7-chloro-4-hydroxy-2-(2-phenethyl)-1,2,5,10-tetrahydropyridazino [4,5,-b]quinoline-1,10-dione;

(k)
7-chloro-4-hydroxy-2-(4-chlorophenyl)-1,2,5,10-tetrahydropyridazino [4,5,-b]quinoline-1,10-dione;

(l)
7-chloro-4-hydroxy-2-(4-methylphenyl)-1,2,5,10-tetrahydropyridazino [4,5,-b]quinoline-1,10-dione;

(m)
7-chloro-4-hydroxy-2-(4-isopropylphenyl)-1,2,5,10-tetrahydropyridazino [4,5,-b]quinoline-1,10-dione;

(n)
7,9-Dichloro-1-hydroxy-2-phenyl-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione;

(o)
7-Chloro-4-hydroxy-2-(1-napthylamino)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione;

(p)
7-Chloro-2-(4-fluorophenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione;

(q)
2-(4-Bromophenyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione;

(r)
7-Chloro-4-hydroxy-2-(2-methoxyphenyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione;

(s)
7-Chloro-4-hydroxy-2-(2-hydroxyphenyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione;

(t)
7-Chloro-4-hydroxy-2-(3-hydroxyphenyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione;

(u)
7-Chloro-4-hydroxy-2-(3-methoxyphenyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione;

(v)
7-Chloro-4-hydroxy-2-(4-trifluoromethoxyphenyl)-1,2,5,10-tetrahydro-pyridazino-[4,5-b]quinoline-1,10-dione;

(w)
7-Chloro-2-(3-chloro-4-methoxyphenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione;

(x)
7-chloro-2-(2-methoxypyrid-5-yl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione and further includes specific and more preferred compounds selected from:

(1)
7-chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione or the N-methylglucamine salt thereof;

(2)
7-chloro-2-(4-chloro-2-methylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazine[4,5-b]quinoline-1,10-dione;

(3)
7-chloro-2-(2,4-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazine[4,5-b]quinoline-1,10-dione;

(4)
7-chloro-2-(3,4-dihydroxyphenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazine[4,5-b]quinoline-1,10-dione;

(5)
7-chloro-2-(3,4-dimethoxyphenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazine[4,5-b]quinoline-1,10-dione;

(6)
7-chloro-4-hydroxy-2-(2-methylthioethyll)-1,2,5,10-tetrahydro-pyridazine[4,5-b]quinoline-1,10-dione or

(7)
7,9-dichloro-2-(2,4-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione and also include the compounds

(8)
7-chloro-4-hydroxy-2-(2-methyl-2-hydroxypropionamidoethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione or

(9)
7-chloro-4-hydroxy-2-(furan-2-ylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione or pharmaceutically acceptable salts thereof. The preferred route of administration is intravaneously.

Pyridazinediones of formula I or I′ (or II or III) can be made by processes which include processes known in the chemical arts for the production of structurally analogous compounds. The preparation of compounds wherein Z is H can be affected by chlorinating the hydroxy group of the dialkyl 4-OH quinoline-2,3-dicarboxylate (starting material) using phosphorous oxychloride. This chlorine is then reduced using tetrakistriphenylphosphine Pd(0) and sodium formate to provide ndimethyl quinoline-2,3-dicarboxylate which is then processed through the remaining chemical steps (e.g. adding the hydrazine etc.) The processes for the manufacture of a pyridazinedione of formula I as defined above are provided as further features of the invention and are illustrated by the following procedures in which the meanings of generic radicals are as given above unless otherwise qualified. Such a process can be effected, generally,

(a) to obtain a compound of formula I, by treating a corresponding diester of formula IV, wherein R^{13} is (C1-C3)alkyl, with an aryl or heteroaryl substituted hydrazine wherein aryl is selected from phenyl or a benz derivative thereof (e.g. napthyl) and is either unsubstituted or substituted with 1, 2 or 3 groups chosen from -O-(1-4C)alkyl, -OH, -halo, $-NO_2$, -CN, $-CF_3$, -NH(CO)R′, -(1-4C)alkyl, -NR′R″, $-CO_2R'$, -CONR′R″, $-SO_mR'$, $-SO_2NR'R''$,(C1-C6)alkyloxy(C1-C6) alkyloxy-, hydroxy(C1-C6)alkyloxy-,(C1-C6)alkyloxy(C1-C6)alkyloxy (C1-C6)alkyloxy-,hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR′R″, -NR′(C1-C6alkyl)NR′R″, -(C1-C6alkyl)NR′R″, $-OCF_3$, -NR′(C1-C6alkyloxy), -NR′(C1-C6alkylhydroxy); and heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole, oxadiazole wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic

substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom on the heteroaryl group; which forms a compound of formula V (a pyrrolo[3,4-b]quinoline) by refluxing the above reactants in (1) ethanol or other suitable solvent for a 12 hour period followed by reflux in acetic acid (AcOH). The compound of formula V is then treated with methanesulfonic acid ($MeSO_3H$) in refluxing methanol or other suitable solvent for an eighteen hour period to form a compound of formula I wherein R^1 or R^2 is aryl as defined above (Scheme 1);

(b) to obtain a compound of formula I, by treating a corresponding diester of formula IV, wherein R^{13} is (C1-C3) alkyl, with a (C1-C6)alkylaryl or (C1-C6)alkylheteroaryl substituted hydrazine wherein aryl and heteroaryl are as defined above in (a) in (1) refluxing ethanol and (2) refluxing acetic acid to form a compound of formula I wherein R^1 or R^2 is selected from (C1-C6)alkylaryl wherein aryl and heteroaryl are defined as above. The positional isomers obtained in this process may readily be separated by fractional acidification of meglumine/choline solutions (Scheme 2);

(c) to obtain a compound of formula I, by treating a compound of formula IV, wherein R^{13} is (C1-C3) alkyl, with a (C1-C6)alkyl substituted hydrazine wherein the alkyl group is further substituted with substituents selected from OH, OR', SR', or NR'R" in refluxing ethanol followed by treatment in refluxing acetic acid to form a compound of formula VI or VI' wherein R^1 or R^2 is a substituted alkyl species as described above. The resulting compounds (when Y is OH, SH or NHR) can then be further derivatized to form compounds wherein W is NR'COR", OCONR', $NR'CO_2R"$, NRCONR'R", CO_2R', or CONRR' or as further defined herein (Scheme 3). The isomeric mixture is treated with aqueous meglumine or aqueous meglumine/choline mixture to form a solution which is further acidfied with acetic acid to pH 6-7. The solid precipitate is then filtered off to separate the 3-positional isomer while the filtrate is then

further treated with acetic acid to a pH of around 5.5 to form a solid which is the 2-positional isomer (VI').

(d) to obtain a compound of formula I as recited in (c) above wherein the substituted alkyl group contains a heterocyclic species, by (1) treating a corresponding compound of formula VI or VI' wherein W is (-OH) with a hydrohalogenic acid (HBr) to form the corresponding halogenated species and (2) treating this compound with a nucleophilic species to form a compound of formula I wherein R^1 or R^2 is $-(CH_2)_n$Heterocycle wherein heterocycle comprises a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2 or 3 heteroatoms chosen from O, N, or S wherein an N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R' or to form a compound of formula I with R^1 as $-(CH_2)_n$Nu wherein Nu is also equal to ArNH-,R'NH-, ArO-, ArS-, or other common nucleophiles which can react with an alkylbromide (Scheme 4). The halogenated intermediate described herein is also used to prepare carboxylic acid and/or ester derivatives thereof by reacting the bromo compound with sodium cyanide and then hydrolyzing and or esterifying the resultant cyano compound.

(e) to obtain a compound of formula I via a novel process as described herein is achieved according to the general procedure described in Scheme 5 and specifically exemplified in Examples within 35-81. A 3-carboalkoxy-4-hydroxyquinoline-2-carboxylic acid (prepared from the corresponding dialkylester(IV')) is reacted with thionyl chloride to form the corresponding 3-carboalkoxy-2-acid chloride which is reacted with either an arylhydrazine wherein aryl is as defined above (under the appropriate conditions as shown in the examples) or an heteroaryl hydrazine wherein heteroaryl is as defined above (under the appropriate conditions as shown in the examples). The solvents used in the formation of the hydrazide include any anhydrous organic solvent selected from, for example THF, toluene CH_2Cl_2, CH_3Cl hexane or any inert organic solvent. The present invention relates to a novel process for producing the 2-substituted pyridazino quinolines of

formula I (or II) wherein R^1 is aryl or heteroaryl comprising the steps of (i) forming the 3-carboalkoxy-2-acid halide intermediate from the corresponding dialkyl ester of formula IV' and (ii) reacting said halide from step (i) with either an arylhydrazine wherein aryl is as defined above under the conditions described in the examples or an heteroarylhydrazine wherein heteroaryl is as defined above under the conditions described in the examples to form a compound of formula II wherein R^1 is aryl or heteroaryl. Variable amounts of the 3-isomer is also produced in this process. The above novel process optionally goes through a novel key intermediate selected from a 3-carboalkoxy-4-hydroxy quinoline-2-carboxylic acid N-2-aryl (or heteroaryl)hydrazide. The cyclization reaction from the acyl hydrazide to the PQD tricyclic ring structure is optimally performed in methanesulfonic acid and methanol. However, lower molecular weight alkyl sulfonic acids (C1-C4) and lower molecular weight alcohols (C2-C6 alkyl) may also be used with optional cosolvents selected from, but not limited to, THF or dioxane or equivalent solvents which solubilize the reactants. In addition, under some circumstances, (e.g. with electron rich substituents on the aromatic ring) alternative acids, e.g. dilute HCl in H_2O, may also be utilized to achieve cyclization. Furthermore, other organic solvents such as ether, dioxane, CH_2Cl_2, CH_3CN, DMF or equivalent solvent, may also be utilized to achieve coupling and cyclization. This intermediate is preferrably used in the production of compounds of formula II wherein R^1 is aryl. The hydrazide may, depending upon the aryl or heteroaryl substituents, proceed directly to the 2-substituted PQD or via the 5-membered pyrrole intermediate which then forms both the 2 and 3 substituted PQD. Electron donating groups on the aryl ring promote selective formation of the 2-substituted PQD. Steric effects may also influence the degree of selectivity.

(f) to obtain a compound of formula I via a novel process as described herein is achieved according to the general procedure described in Scheme 6 and specifically exemplified in non-limiting

examples 42a, 43a and in examples 82-103 and examples 138-142. A 2-pyrrolidinocarbamide quinoline 3 carboxylic acid, prepared from hydrolysis of the corresponding 3-methyl ester which is prepared by reacting the corresponding 3 carbomethoxy quinoline 2 carboxylic acid with dicyclohexylcarbodimide or other appropriate diimide coupling reagent such as diisopropyl carbodiimide and pyrollidine, is reacted with an N-t-butoxycarbonyl-N'-2$(CH_2)_n$M (n=0-4) hydrazine (prepared from the reaction of either (a) t-butylcarbazate and the desired C1-C4 alkylaryl or a substituted alkyl aryl or an alkoxy alkyl compound wherein the terminal alkyl carbon has a suitable leaving group selected from halo (X) or triflate in a solvent such as DMF, CH_2Cl_2 or CH_3CN or equivalent and a base such as NEt_3 or, for n=0 (e.g. direct n-aryl substitution), other groups which may readily react with t-butylcarbazate to form a starting disubstituted hydrazine t-butylO(CO)-N-N-R^1 include any alkylaryl, aryloxyalkyl, alkyloxyalkyl, alkyloxyalkyloxy or alkylheteroaryl recited herein wherein the alkyl group has a suitable leaving group (b) a suitable aryl or substituted aryl hydrazine with di-t-butyl-dicarbonate in an organic solvent (e.g. THF or equivalent) or (c) (for n=1-4) a suitable aryl or substituted aryl aldehyde or substitutes alkylaldehyde with t-butylcarbazate in refluxing hexanes or equivalent organic solvent to form the corresponding imine which is then reduced with a reducing agent (e.g. BH_3 THF or $LiAlH_4$)] to obtain a key intermediate hydrazide which is cyclized in CH_3SO_3H/THF or equivalent solvent to selectively form a 2-substituted aryl or alkyl aryl PQD or substituted alkyl PQD. This process may generally be utilized to selectively form a compound of formula II. t-butylcarbazate is commercially available and the R^1-substituted t-butyl carbonate hydrazines are readily prepared.

(g) N-2 aryl and heteroaryl substituted isomers may readily and selectively be prepared as shown in Scheme 7 by treating an aryl or heteroaryl hydrazine with benzaldehyde followed by a reduction of the hydrazide imine to form an N-aryl-N-benzyl substituted hydrazine. This compound is then reacted with a 3-carboxyester-2-acid halide

quinoline to form a key hydrazide intermediate, e.g. 3-carboalkoxy-4-hydroxy quinoline 2-carboxylic acid N-2-aryl(or heteroaryl)-N-1-benzyl-hydrazide which is treated sequentially with choline hydroxide or heat (80-180°C) and methanesulfonic acid or equivalent acid with or without a suitable solvent to selectively form an N-2-aryl PQD.

It is noted that, in general, when unsymmetrical hydrazines are employed, for example where R^1 and R^2 are different groups or where a monosubstituted hydrazine is employed, a mixture of products (2-substituted versus 3-substituted) will be obtained unless the novel processes recited herein are utilized. Such mixtures are separable by standard (for example chromatographic or recrystallization) techniques known to the art and used for the purpose. A compound of formula I wherein L is a heterocyclic moiety such as a 4-(C1-C6)substituted piperazine or 4-arylsubstituted piperazine or a phthalimido or another commercially available nucleophilic heterocycle may be formed by reacting the heterocyclic nucleophilic species with a 2- or 3-halo(C1-C6alkyl)pyridazino[4,5-b]quinolines of formula I, the latter of which is prepared from the corresponding hydroxy species as described in (d) above. As the following examples will show, compounds within the scope of the present invention are prepared by a variety of chemical synthetic steps or procedures. Key intermediates are shown in the Schemes or described in the text. Examples 1-34 proceed generally from formula IV' and produce, in a non-selective manner, via the intermediate V' (except for those examples which displace or react with an N-2 hydroxy alkyl compound) the desired or preferred N-2 aryl or substituted aryl derivatives (e.g. R^1 = aryl or sub. aryl and n=0). N-2 benzyl or phenethyl compounds and substituted versions thereof are also produced via this process. The isomers produced in this process are readily separable. Other key intermediates in the early examples include the N-2 hydroxy alkyl PQD which is further reacted with lower alkyl (C1-4)-acids to form the corresponding ester. The carbon chain bonded to the N-2 nitrogen may

vary from 1-6 carbon atoms with the hydroxy group on the terminal position. N-2 aryl derivatives are also prepared in examples 35 etc. wherein a key intermediate is the quinoline 2-acid chloride which is reacted with an aryl hydrazine to form, in some cases selectively, the N-2 aryl PQD. Of course N-methyl-glucamine or other salts (e.g. choline, sodium etc.) are readily prepared from the corresponding precursor. The intermediate generated from the acid chloride is the 3-carboalkoxy-4-hydroxyquinoline 2-carboxylic acid N-2 aryl(or sub. aryl) hydrazide which, under favorable conditions, forms the N-2 aryl substituted PQD. Improved conditions using 1 eq of the starting aryl hydrazine are described in the examples. In general methanesulfonic acid in methanol or THF has been utilized to cyclize the intermediate hydrazide. Of course, any methoxyphenyl species may be hydrolyzed with HBr or other acid (e.g. CH_3SO_3H) to form the corresponding hydroxy species.

The N-2 hydroxy alkyl PQD compounds are utilized to form the corresponding N-2 haloalkyl PQD derivatives which are used as intermediates to form, for example, the N-2 alkyl(C1-C4)thio alkyl(C1-C4) glycine receptor antagonists. The appropriate thiolate anion in DMF is reacted with an N-2 haloalkyl PQD. Of course, amines, amilines or other heterocyclic or heteroaryl nucleophiles may react with the N-2-alkyl(C1-C4)halo PQD to form the corresponding nucleophilic substituted PQD. DMF or equivalent organic solvent is utilized in this process.

As exemplified in a non-limiting manner in Example 82, a key process for selectively producing N-2 aryl, heteroaryl, substituted alkyl or other species prepared from any N-2 intermediates involves the initial production of a 2-pyrrolidinoamido substituted quinoline which is formed from the corresponding 2-carboxy 3-carboalkoxy quinoline. This compound or analogous compounds (e.g. with groups equivalent to pyrrolidinoamido) is hydrolyzed to form the corresponding 2-pyrrolidinoamido-3-carboxy quinoline which is then coupled with the selected R^1-N-N-C(O)O-t-butyl hydrazine using a

selected dimide (e.g. DCC or equivalent) to form a key hydrazide intermediate - e.g. 2-pyrrolidinoamido-3-carboxylic acid-NR^1-N(BOC) hydrazide which, under the cyclization conditions, forms the N-2 substituted PQD without any N-3 substituted PQD formed. The hydrazines utilized in this process are readily prepared from commercially available materials as described herein wherein either t-butylcarbazate or di-t-butyldicarbonate are utilized to BOC one N of the hydrazine depending upon whether R^1 is aryl or alkylaryl or substituted alkyl or heteroaryl or alkyl heteroaryl. For example, the benzyl or substituted benzyl compounds described herein are readily and conveniently prepared from the appropriate 2-pyrrolidinoamido 3-carboxylic acid and the N-benzylN^1-t-butyl carboxy hydrazine which was actually prepared from the corresponding aryl alkylhalide and t-butyl carbazate. t-butylcarbazate reacts readily to displace the halide or alcohol such as triflate to form the desired hydrazine.

Another intermediate and glycine receptor antagonist includes N-2-aryl PQDs substituted with a cyano substitutent or substituents. This moeity (CN) can be further manipulated to form carboxylic acids, carbonyl halides, esters, amides, or tetrazoles. As indicated previously, anion displacement (nucleophilic displacement) is utilized to produce various heterocyclic compounds or benz or heteroaryl benz derivatives thereof which are glycine receptor antagonists. An N-2 halo(C1-4) alkyl PQD is reacted with the selected nucleophile (heterocyclic or heteroaryl wherein heteroaryl includes for example, those compounds shown in the examples and described herein) to form the corresponding N-2 Nucleophile-(C1-4) alkyl PQD.

Certain N-2 heterocyclic PQDs can be further hydrolyzed to form amido alcohols within the scope of the present invention. For example, oxizolidine diones are readily hydrolyzed to the corresponding amide alcohols as shown in Example 112 and Table 5. The Formulae pages show some of the key intermediates recited herein. Key intermediates include compounds of formula XIV-XX. The present invention relates to a process for producing a compound of formula II

comprising:

(a) treating a compound of formula V or XIV with an acid selected from a lower alkyl(C1-C4) sulfonic acid in a suitable organic solvent; or

(b) treating a compound of formula IV' with an alkylaryl or alkylheteroaryl hydrazine in a polar solvent and a mild acid; or

(c) treating a compound of formula VI' wherein Y is selected from -OH,-SH or NHR wherein R is (C1-C4)alkyl with a reagent selected from (i) $R^2NC(O)Cl$; or (ii) RC(O)X; or (iii) ROC(O)Cl; or (iv) HBr/NaCN/H_2O or ROH; or (v) RNCO or R'R'NC(O)Cl or other electrophilic group as recited herein to form, in particular, a compound of formula XXI; or

(d) treating a compound of formula XV wherein X is halogen with a nucleophilic reactant selected from heterocycle or benz or heteroarylbenz derivatives thereof; or

(e) treating a compound of formula XXII with a substituted hydrazine to form a compound of formula XVII in an organic solvent under the appropriate conditions; or

(f) treating a compound of formula XVIII with a coupling reagent selected from a diimide with a disubstituted hydrazine of the formula R'-NHNHC(O)Ot-butyl in an organic solvent in the presence of an appropriate acid or

(g) further treating a compound of formula II as claimed in claim 2 wherein the compound contains a phenyl ring substituted with a methoxy group or groups with an acid to form a phenolic substituent or substituents or further treating a compound of formula II wherein the compound is a non-salt form with a pharmaceutically acceptable base to form a pharmaceutically acceptable salt or further treating a compound of formula II wherein the compound contains a phenyl ring substituted with a cyano group or groups with (i) a base to form a carboxlic acid substituent or substituents or (ii) an acid to form an amide substituent or (iii) an azide to form a tetrazole substituent wherein the carboxlic acid moiety may be further treated with a halogenating agent and a substituted amine of formula HNR'R" to form a substituted

amide substituent or the carboxylic acid moiety may be further treated with an alcohol (C1-C6) in the presence of an acid to form an ester substituent (C1-C6) or

(h) further treating a compound of formula II wherein the compound contains an oxozolidine dione with a base in aqueous solution to form an amido alcohol substituent as W off the $(CH_2)_n$ carbon chain with n equal to 1-4; or

(i) further treating a compound of formula II wherein the compound contains a sulfide moiety with an oxidizing agent under the appropriate conditions to form an $S(O)_1$ or $S(O)_2$ moiety.

If not commercially available, the necessary starting materials for the procedures such as that described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the above described procedure or the procedures described in the examples.

Certain diesters of formula IV for use in reacting with substituted hydrazine to make a compound of formula I, can be made by treating a compound of formula VII with a suitable base, such as an alkali metal alkoxide (e.g., potassium t-butoxide) in a suitable solvent such as t-butanol to effect ring closure and thereby yield the desired diester. In said compound of formula VII, the value of Y corresponds to the following to yield a corresponding value for Z as noted:

a. CHO if a value for Z of hydrogen is desired;

b. $COOR^{15}$ wherein R^{15} is (C1-C3)alkyl if a value for Z of hydroxy (or the tautomerically equivalent oxo) is desired; (It is noted that higher alkyl esters can be employed, but they do not provide any synthetic advantage.)

c. $CSOR^{15}$ or $CSSR^{15}$ if a value for Z of thiohydroxy (SH) is desired; and

d. CN if a value for Z of amino is desired.

The compound of formula VII need not be isolated to make the corresponding compound of formula IV'. Rather the diester of formula IV' can be made in a one-pot process without separating the compound of formula VII from the reaction mixture.

A diester of formula IV' wherein Z is hydroxy (or oxo) can also be made by treating an isatoic anhydride of formula X directly with a sodium or potassium salt of a (C1-C3)dialkyl (e.g. diethyl) ester of 2-oxosuccinic acid in a suitable solvent such as dimethylformamide.

A diester of formula IV' wherein Z is thiohydroxy can be made by treating a corresponding diester of formula IV wherein R^3 is hydroxy with Lawesson's reagent, 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, in a suitable solvent such as toluene or dimethoxyethane and at a temperature in the range of 50-110 °C.

A substituted imide of formula V' wherein the B-ring N loses its H and Z is, for example, NH_2 can be made by treating a diester of formula IV', wherein the value corresponding to Z is a halo group such as chloro or bromo, with ammonia which forms the corresponding phthalimide which is then further reacted with arylhydrazine to form V' which is then reacted in typical fashion (Scheme 1) to form the final pyridazinoquinoline.

A compound of formula VII, wherein Y is CN, CHO, $COOR^{15}$, $CSOR^{15}$, or $CSSR^{15}$ wherein R^{15} is a C1-C10 alkyl, alkenyl or alkynyl group can be made by treating a corresponding ortho amine of formula VIII with a dialkyl acetylenedicarboxylate, such as dimethyl acetylenedicarboxylate, in a suitable solvent such as a (C1-C4)alcohol. As solvent, t-butanol is preferred.

An ortho amine of formula VIII'can be made by esterifying a corresponding acid of formula VIII' by conventional methods. An acid of formula VIII' can in turn be made by deprotecting a corresponding compound of formula VIII" wherein the amino group has been protected with a conventional protecting group Pr (such as tert-butoxycarbonyl,

t-BOC). A compound of formula VIII" can in turn be made by sequentially reacting an amine of formula IX first with two equivalents of an organolithium compound (for example t-butyllithium) to form a dilithiated species which can be carboxylated by reacting with carbon dioxide. An amine of formula IX can be prepared by protecting a corresponding (unprotected) amine by conventional methods.

An ortho amine of formula VIII, wherein Y is $COOR^{15}$, can also be made by a process which differs from that described immediately above in that the esterification step is effected by using a base (for example, sodium hydride) followed by an alkylating agent $R^{15}X$ on the protected acid of formula VIII" rather than on the acid of formula VIII'.

An ortho amine of formula VIII', wherein Y is $COOR^{15}$, can also be made by treating a corresponding isatoic anhydride of formula X with base (such as an alkali metal hydroxide) in alcoholic solvent of formula $R^{15}OH$.

An isatoic anhydride of formula X can be made by treating an isatin of formula XI with chromium trioxide in the presence of acetic anhydride, or with a peroxycarboxylic acid such as the magnesium salt of monoperoxyphthalic acid, and in a suitable solvent such as acetic acid.

An isatin of formula XI can be made by cyclizing a hydroxyimino acetamide of formula XII in concentrated sulfuric acid at a temperature of 60-80 °C.

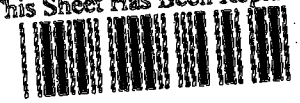
A hydroxyimino acetamide of formula XII can be made by treating an amine of formula XIII with chloral hydrate in the presence of sodium sulfate and hydroxylamine hydrochloride and in a suitable solvent such as water. The N-t-butoxy carbonyl hydrazines utilized in the present invention may be prepared according to the procedure set forth in Example 82C. For example, N-t-butoxy carbonyl-N'-pentafluorobenzylhydrazine; N-t-butoxy carbonyl-N'-2-cyanobenzyl-hydrazine; N-t-butoxy carbonyl-N'-3-chlorobenzyl hydrazine; N-t-butoxy

carbonyl-N'-3,5-ditrifluoromethyl benzyl hydrazine; N-t-butoxy carbonyl-N'-3-phenylpropylhydrazine; N-t-butoxycarbonyl-N'-4-methylbenzyl hydrazine; N-t-butoxy carbonyl-N'-4-trifluoromethylbenzyl hydrazine; N-t-butoxy carbonyl-N'-4-cyanobenzyl hydrazine; and N-t-butoxy carbonyl-N'-2 4-dimethylphenyl hydrazine. The present invention, therefore, also relates to these novel hydrazine moieties and to processes for their production and use as intermediates to couple with the key intermediate 2-pyrolidinocarbamide quinoline 3-carboxylic acid to form a compound of formula II via a novel and inventive process as described herein which selectively forms the N-2-substituted PQD. The intermediate hydrazines utilized to prepare N-2-aryl or N-2-substituted aryl PQDs may also be prepared according to the non-limiting example 42a. N'-t-butoxy carbonyl-N'-aryl or substituted aryl compounds are produced via this novel process to enable selective formation of the N-2-substituted PQDs. This process may be the preferred route to aryl substituted compounds claimed and recited herein.

It is noted that many of the starting materials for synthetic methods as described above are commercially available and/or widely reported in the scientific literature.

Examples of suitable pharmaceutically acceptable salts are salts formed with bases which form a physiologically acceptable cation, such as alkali metal (especially lithium, sodium and potassium), alkaline earth metal (especially calcium and magnesium), aluminum and ammonium salts, as well as salts made with appropriate organic bases such as choline hydroxide, triethylamine, morpholine, piperidine, ethylenediamine, lysine, ethanolamine, diethanolamine, triethanolamine, N-methyl-D-glucamine (meglumine), arginine, and tris(hydroxymethyl)aminomethane. Choline and meglumine sodium and potassium salts are preferred. Choline sodium and potassium salts are especially preferred.

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When used to intervene therapeutically following a stroke, a pyridazinedione of formula I generally is administered as an appropriate pharmaceutical composition which comprises a compound according to the invention as defined hereinbefore together with a pharmaceutically acceptable diluent or carrier, the composition being adapted for the particular route of administration chosen. Such compositions are provided as a further feature of the invention. They may be obtained employing conventional procedures and excipients and binders and may be in a variety of dosage forms. For example, they may be in the form of tablets, capsules, solutions or suspensions for oral administration; in the form of suppositories for rectal administration; in the form of sterile solutions or suspensions for administration by intravenous or intramuscular injection or infusion; and in the form of powders together with pharmaceutically acceptable inert solid diluents such as lactose for administration by insufflation.

The dose of a compound according to the invention which is administered will necessarily be varied according to principles well known in the art taking account of the route of administration, the severity of the postischemic disorder, and the size and age of the patient. In general, a compound of according to the invention will be administered to a warm blooded animal (such as man) so that an effective dose is received, generally a dose in the range of about 0.01 to about 100 mg/kg body weight. For example, if the compound is administered intravenously, it is administered in the range of about 0.01 to about 10 mg/kg body weight. If it is administered orally, it is administered in the range of about 0.5 to about 100 mg/kg body weight.

It will be apparent to those skilled in the art that a compound according to the invention can be co-administered with other therapeutic or prophylactic agents and/or medicaments that are not medically incompatible therewith.

The actions of compounds according to the invention as

antagonists at the glycine receptor of the NMDA receptor complex can be shown by one or more standard tests such as the [^{3}H]-glycine binding assay (Test A) and by tests in vivo such as ischemia induced by carotid occlusion in the gerbil model (Test B). In addition to these tests, compounds of the invention are assayed in the red nucleus test (Test C) and in the Rat Middle Cerebral Artery test (Test D). These tests confirm that compounds of the invention are NMDA receptor antagonists in vitro and in vivo. Certain compounds of the invention are highly potent NMDA receptor antagonists. Some of the recited compounds (i.e. 3-(2-Acetoxyethyl), 3-(p-methoxyphenyl), or 3-(p-hydroxyphenyl)7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-diones) have IC_{50}'s in the [^{3}H]Gly test of greater than 100 micromolar and are thus less active than their more potent counterparts. In particular, the compounds of the present invention with R^1 as an alkyl, aryl or heterocycle as defined herein and R^2 as H are highly potent NMDA receptor (Glycine) antagonists.

Test A

In the [^{3}H]-glycine binding assay, neuronal synaptic membranes are prepared from adult (about 250 g) male Sprague-Dawley rats. Freshly dissected cortices and hippocampi are homogenized in 0.32 M sucrose (110 mg/mL). Synaptosomes are isolated by centrifugation (1000 xg, 10 min), the supernatant is pelleted (20,000 xg, 20 min) and resuspended in double-distilled water. The suspension was centrifuged for 20 minutes at 8,000 xg. The resulting supernatant and buffy coat are washed twice (48,000 xg, 10 mins, resuspension in double-deionized water). The final pellet is quickly frozen (dry ice/ethanol bath) under double-deionized water and stored at -70 °C.

On the day of the experiment, thawed synaptic membranes are homogenized with a Brinkmann Polytron (tm, Brinkmann Instruments, Westbury, N.Y.) tissue homogenizer in 50 millimolar tris(hydroxymethyl)aminomethane citrate, pH 7.1. The membranes are incubated with 0.04% Sufact-AMPS X100 (tm, Pierce, Rockford, IL) in

buffer for 20 minutes at 37 °C and washed six times by centrifugation (48,000 xg, 10 min) and resuspended in buffer. The final pellet is homogenized at 200 mg wet weight/mL of the buffer for the binding assay.

For [^{3}H]-glycine binding at the N-methyl-D-aspartate receptor, 20 nanomolar [^{3}H]-glycine (40-60 Ci/mmol, New England Nuclear, Boston, MA) is incubated with the membranes suspended in 50 millimolar tris (hydroxymethyl)aminomethane citrate, pH 7.1 for 30 minutes at 4 °C. Glycine, 1 millimolar, is used to define the nonspecific binding. Bound [^{3}H]-glycine is isolated from free using a Brandel (Biomedical Research and Development Laboratories, Gaithersburg, MD) cell harvester for vacuum filtration over glass fiber filters (Whatman GF/B from Brandel, Gaithersburg, MD) presoaked in 0.025% polyethylenimine. The samples retained on the glass fiber filters are rinsed 3 times with a total of 2.5 mL ice cold buffer. Radioactivity is estimated by liquid scintillation counting. IC_{50} values are obtained from a least-squares regression of a logit-log transformation of the data. Typical IC_{50} values for compounds of the invention are usually less than 50 μM (micromolar) and are illustrated by the compound of Example 1 (IC_{50}= 40 μM), Example 2 (IC_{50}=0.50 μM), and Example 10 (IC_{50}= .12 μM). The other examples disclosed herein are glycine antagonists.

Test B

When testing in vivo using the gerbil ischemic model, adult female Mongolian gerbils (50-70 g) are anesthetized with 2 to 3 % halothane. The bilateral common carotid arteries at the neck are exposed and occluded with microaneurysm clips. After 10 min (unless specified), the clips are removed and the blood flow through the carotid arteries is restored and the skin is sutured. Test compounds are administered intraperitoneally both pre- and post-occlusion, for example 45 minutes before and 5 minutes after occlusion of the carotid arteries. Sham-operated animals are treated in the same manner except

that the arteries are not clamped. Gross behavioral observations along with motor activity are recorded for 2 hr on the first (24 hr) day following the occlusion. After 4 days, subjects are sacrificed (decapitation), brains are removed, fixed, sectioned and stained with hematoxylin/eosin and cresyl violet.

The brain sections are rated for neuronal damage in the hippocampus using the following rating scale:

0 = undamaged, normal

1 = slight damage (up to 25%) - restricted to CA1/subiculum border

2 = moderate damage (up to 50%) - obvious damage, restricted to less than half of CA1 field

3 = marked damage (up to 75%) - involving greater than half of CA1 field

4 = damage extending beyond CA1 field

Sections (7 micron) are evaluated from each brain. Occasionally, asymmetrical damage may be noted and the rating assigned is the average score of the two sides. The average brain damage rating score for each group is recorded, and the damage scores of the drug treated group are compared to the vehicle-treated group using Wilcoxon-Rank Sum test.

Typical values in this test for compounds according to the invention are illustrated by the following results: 35% neuroprotection (relative to sham-operated control) for the compound of Example 4, and over 80% neuroprotection for the compound of Example 10, when each compound was administered intraperitoneally (ip) at a level of 10 mg/Kg body weight according to the above regimen.

Test C

Red Nucleus Test

The purpose of this test is to determine the effects of intravenously administered glycine antagonists on the NMDA-induced excitatory response of red nucleus cells. HA-966 (racemic) and CGP 37849 are reference agents that have been shown active in this test (ID50s of 7.9 and 1.7 mg/kg iv, respectively).

The procedure for the red nucleus test is as follows. Rats are anesthetized with chloral hydrate (400 mg/kg ip) and the femoral vein is catheterized for iv drug administration. Five-barrel micropipettes are stereotaxically positioned in the red nucleus. Typically, three to four of the five barrels are filled as follows: the recording barrel with 2M potassium citrate, the current balancing barrel with 4M NaCl, the drug barrel with 25mM NMDA, and another drug barrel with 2.5mM quisqualic acid (QA is only used in selectivity studies). NMDA is iontophoretically applied with an ejection current that is adjusted depending on the sensitivity of each individual red nucleus cell. The NMDA is cycled on and off (usually 30 - 60 sec. on and 60 - 120 sec. off) and the firing rate of the cell during each period is recorded. Once the baseline firing rate of the cell has been established, the test drug is administered iv. The effect of the drug on the NMDA-induced excitatory response of the red nucleus cell can be both qualitatively and quantitatively evaluated from the recordings and the raw data accumulated. Compounds of the invention exhibited a significant antagonist response.

Test D

Rat Middle Cerebral Artery Test

Male SHR rats weighing 280-320 g are used for these studies. The method used for permanent middle cerebral artery (MCA) occlusion is as described by Brint et al (1988). Briefly, focal ischemia is produced by occluding first the left common carotid artery and then the left middle cerebral artery just superior to the rhinal fissure. Following occlusions, drugs are administered intravenously via jugular

catheter. Twenty-four hours after MCA/common carotid artery occlusion, the animals are sacrificed and their brains quickly removed. Coronal sections of 1 mm thickness are cut using a vibratome and stained with 2,3,5, triphenyl, 2H-tetrazolium chloride (TTC) dye. Following staining, necrotic tissue is readily distinguished from the intact brain and the area of infarcted cortex can be traced on an image analyzer. The infarct volume for each section is quantified with an image analyzer, and the total infarct volume is calculated with a program that summed all interval volume. See S. Brint et al. J. Cerebral Blood Flow 8:474-485 (1988). The statistical analysis of the difference between the volume of ischemic damage in the vehicle control and drug-treated animals is analyzed by student's-t-test. All data are presented as the mean $\pm$ S.E. of the mean for n animals. Compounds of the invention reduced ischemic damage.

The invention will now be illustrated by the following non-limiting examples. In the Examples, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C;

(ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60 °C;

(iii) flash chromatography was carried out on Merck Kieselgel (Art 9385) and column chromatography on Merck Kieselgel 60 (Art 7734); [these materials were obtained from E. Merck, Darmstadt, W. Germany]; thin layer chromatography (TLC) was carried out on Analtech 0.25 mm silica gel GHLF plates (Art 21521), obtainable from Analtech, Newark, DE, USA;

(iv) in general, the course of reactions was followed by TLC or HPLC and reaction times are given for illustration only;

(v) melting points are uncorrected and (d) indicates decomposition; the melting points given are those obtained for the

materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(vi) all final products were essentially pure by TLC or HPLC and had satisfactory nuclear magnetic resonance (NMR) spectra (300 MHz ^{1}H NMR in D-DMSO unless otherwise specified) and microanalytical data;

(vii) yields are given for illustration only;

(viii) reduced pressures are given as absolute pressures in Pascals (Pa); other pressures are given as gauge pressures in bars;

(ix) chemical symbols have their usual meanings; the following abbreviations have also been used: v (volume), w (weight); mp (melting point), L [liter(s)], mL (milliliters), mM (millimoles), g [gram(s)], mg [milligram(s)], min (minutes), h (hour); and

(x) solvent ratios are given in volume: volume (v/v) terms.

With respect to N-2 aryl compounds within the scope of this invention, ortho-substituents on the phenyl ring had a profound effect on the solubility (aqueous) of glycine receptor antagonists. In particular, ortho methyl substituents increased solubility and in vivo activity. In addition, the route presented in Scheme 7 (infra) provided an efficient process for producing the N-2 heteroaryls within the scope of the present invention. Applicants' invention further relates to a process for cleaving N-benzyl groups with methanesulfonic acid.

Example 1. 7-Chloro-1-hydroxy-3-(2-hydroxyethyl)-3,4,5,10-tetrahydropyridazino[4,5-b]quinoline-4,10-dione.

To a stirred mixture of dimethyl 7-chloro-4-hydroxy-quinoline-2,3-dicarboxylate (50.0 g, 0.169 M, in ethanol (750 mL) was added 2-hydroxyethylhydrazine (286 g, 3.38 M of 90% pure material). The resulting dark brown mixture was stirred at reflux for 18 hr and then allowed to cool to room temperature without stirring. The mixture was filtered, and the collected solids were washed once with ethanol and then refluxed for 3 hr in glacial acetic acid (1.0 L). The resulting mixture was allowed to cool to room temperature and then was filtered to separate a yellow solid. This material was dried overnight in vacuo to provide (41.83 g) a mixture of the isomeric 2- and 3-(2-hydroxyethyl) compounds as a yellow solid. This mixture was split into two fractions of 20.23 g and 21.6 g. The smaller fraction (20.23 g) was dissolved with vigorous stirring in water (2700 mL) containing N-methylglucamine (54.0 g). This solution was carefully acidified with glacial acetic acid until the pH just reached 7.0, and the precipitate which formed during the acidification was separated by filtration. The collected solids were washed once with water, dried, and saved. The filtrate and wash were also combined and saved. The larger (21.6 g) of the two original fractions was likewise dissolved in water (2880 mL) containing N-methylglucamine (57.6 g) and similarly acidified with glacial acetic acid to pH 7.0 to provide a second crop of solids. The filtrate and wash from this acidification were also combined and saved. The two crops of collected solids were combined to provide the title 3-(2-hydroxyethyl) compound as a bright yellow solid (19.27 g, 37.0%). Recrystallizaton of a portion of this material from acetic acid provided an analytical sample of the title compound as bright yellow crystals, mp 377-378°C; MS(CI): 308 (M+H). Analysis for $C_{13}H_{10}ClN_3O_4$: Calculated: C, 50.75; H, 3.28; N, 13.66; Found: C, 50.65; H, 3.39; N, 13.78; NMR: 13.19 (s, 1H,

exchangeable), 12.32 (s, 1H, exchangeable), 8.22 (d, J = 9.0 Hz, 1H), 8.15 (d, J = 1.8 Hz, 1H), 7.56 (dd, J = 9.0, 1.8 Hz, 1H), 4.83 (br s, 1H, exchangeable), 4.10 (t, J = 5.7 Hz, 2H), 3.75 (t, J = 5.7 Hz, 2H).

The starting dimethyl 7-chloro-4-hydroxyquinoline-2,3-dicarboxylate was prepared as follows:

a. dimethyl 7-chloro-4-hydroxyquinoline-2,3-dicarboxylate.

A stirred mixture of methyl 2-amino-4-chlorobenzoate (2.50 g, 13.5 mM) and dimethyl acetylenedicarboxylate (2.05 g, 14.4 mM) in t-butanol (22 ml) was refluxed for 7 hours under a nitrogen atmosphere. After adding additional dimethyl acetylenedicarboxylate (1.16 g, 8.13 mM) and refluxing another 2.5 hours, the reaction mixture was allowed to cool to room temperature and potassium t-butoxide (1.56 g, 13.9 mM) was added in one portion. A precipitate formed and the resulting mixture was refluxed for 1.5 hours. The mixture was cooled to room temperature and filtered to separate the solids, which were washed with t-butanol and ether. The solids were dissolved in water and acidified with 1N sulfuric acid to form a precipitate. The resulting mixture was extracted with methylene chloride and the combined extracts were washed with brine and water, dried ($MgSO_4$), filtered and concentrated to give a green solid. Recrystallization of this material from methanol provided dimethyl 7-chloro-4-hydroxyquinoline-2,3-dicarboxylate (1.15 g, 28.94) as an off-white solid, mp 232-233 °C; MS (Cl):296 (M+H). Analysis for $C_{13}H_{10}ClNO_5$: Calculated: C, 52.81; H, 3.41; N, 4.74; Found: C, 52.75; H, 3.47; N, 4.69.

Example 2. 7-Chloro-4-hydroxy-2-(2-hydroxyethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

All of the filtrates and washes saved from Example 1 were combined and further acidified with glacial acetic acid to pH 5.0.

The precipitate which formed was collected, washed with water, and dried to provide the title compound as a pale yellow solid (12.27 g, 23.5%). Recrystallization of a portion of this material from acetic acid provided an analytical sample of the title compound as an off-white crystalline solid, mp 335-336°C; MS(CI): 308 (M+H). Analysis for $C_{13}H_{10}ClN_3O_4$: Calculated: C, 50.75; H, 3.28; N, 13.66; Found: C, 50.54; H, 3.39; N, 13.65; NMR: 12.53 (br s, 1H, exchangeable), 11.87 (br s, 1H, exchangeable), 8.17 (d, J = 8.7 Hz, 1H), 8.04 (s, 1H), 7.45 (d, J = 8.7, 1H), 4.82 (br s, 1H, exchangeable), 3.99 (t, J = 6.1 Hz, 2H), 3.70 (t, J = 6.1 Hz, 2H).

Example 3. 2-(2-Acetoxyethyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

An orange suspension of 7-chloro-4-hydroxy-2-(2-hydroxyethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione (0.250 g, 0.81 mM) in a 30% solution of hydrobromic acid in glacial acetic acid (5 mL) was gently refluxed for 16 hours under nitrogen. The mixture was cooled to room temperature and diluted with water (20 mL) to form a precipitate. The collected solids were washed with water and methanol and then dried to give the title compound (0.242 g, 86%) as a tan solid, mp = 307-309°C; MS(CI): 350 (M+H). Analysis for $C_{15}H_{12}ClN_3O_5 \cdot 0.2\ CH_3CO_2H$: Calculated: C, 51.10; H, 3.57; N, 11.60; Found: C, 50.81; H, 3.45; N, 11.86; NMR: 12.64 (br s, 1H, exchangeable), 11.91 (br s, 1H, exchangeable), 8.14 (d, J = 8.64 Hz, 1H), 8.02 (d, J = 1.74 Hz, 1H), 7.43 (dd, J = 1.74, 8.64 Hz), 4.32 (t, J = 5.54 Hz, 2H), 4.13 (t, J = 5.54 Hz), 1.98 (s, 3H).

Example 4. 7-Chloro-4-hydroxy-2-(2-phthalimidoethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione.

2-(2-Bromoethyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione (5.00 g, 13.50 mM) and

potassium phthalimide (10.50 g, 56.70 mM) were stirred and refluxed in DMF (100 mL) for 22 hours. The cooled yellow suspension was poured into dilute hydrochloric acid (1N, 1.0 L) with good stirring. A white precipitate formed and was collected. This solid was resuspended in aqueous methanol (50%, 1.0 L) and stirred/sonicated to give a fine white suspension. Filtration and resuspension in methanol (0.25 L) gave a free-flowing white suspension after sonication and brief warming. The solids were finally collected and washed with methanol to give the title compound (4.65 g, 79%) as a white powder, mp 349-352°C; MS(CI): 437 (M+H). Analysis for $C_{21}H_{13}ClN_4O_5 \cdot 0.35\ H_2O \cdot 0.10\ CH_3OH$: Calculated: C, 56.78; H, 3.18; N, 12.55; Found: C, 56.40; H, 2.76; N, 12.59; NMR: 12.54 (br s, 1H, exchangeable), 11.88 (br s, 1H, exchangeable), 8.11 (d, J = 8.67 Hz, 1H), 8.00 (br s, 1H), 7.83 (s, 4H), 7.42 (d, J = 8.67 Hz, 1H), 4.13 (br m, 2H), 3.93 (br m, 2H).

The starting 2(2-Bromoethyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione was prepared as follows:
a. 2(2-Bromoethyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione.

7-Chloro-4-hydroxy-2-(2-hydroxyethyl)-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione (8.00 g, 26.00 mM) was stirred in a mixture of aqueous hydrobromic acid (50%, 80 mL), 30% hydrobromic acid in glacial acetic acid (160 mL) and methanesulfonic acid (8 mL) to give a red solution. This solution was refluxed for 20 hours during which time a precipitate formed. The yellow suspension was cooled to room temperature and stirred for 2 hours. The solids were collected and washed with acetonitrile/ether and ether and air dried to give the title bromoethyl compound (8.40 g, 88%) as an off-white powder, MS(CI): 370 (M+H). NMR: 13.00 (br s, 1H, exchangeable), 8.23-8.18 (m, 2H), 7.60 (dd, J = 2.04, 5.73 Hz), 5.20 (t, J = 9.37 Hz, 2H), 4.66 (t, J = 9.37 Hz, 2H).

Example 5. 7-Chloro-1-hydroxy-3-phenyl-3,4,5,10-tetrahydropyridazino[4,5-b]-quinoline-4,10-dione, choline salt.

6-Chloro-2-anilino-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]-quinoline-1,3,9-trione (1.70 g, 5.00 mM) was stirred in methanol (0.85 L), and methanesulfonic acid (85 mL) was added. The yellow suspension was heated to reflux for 16 hours and cooled to room temperature. The resulting mixture was filtered (the filtrate was saved for use in Example 6), and the collected solids were washed with methanol and dried to give 7-chloro-4-hydroxy-3-phenyl-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione (0.48 g, 28%) as a yellow powder. This powder was stirred in methanol, and choline hydroxide (45 weight% in methanol, 0.5 mL) was added to give an amber solution. This solution was concentrated and the residue diluted with toluene and concentrated. The residue was diluted with toluene and concentrated two additional times, and the resulting solid residue was triturated with ethanol/toluene (20%, 25 mL) to provide a crystalline solid. The solid was collected to give the title compound (0.49 g, 78%) as a yellow powder, mp 253-257°C; MS(CI): 340 (M+H). Analysis for $C_{17}H_{10}ClN_3O_3 \cdot C_5H_{14}NO \cdot 0.30\ H_2O$: Calculated: C, 58.90; H, 5.31; N, 12.50; Found: C, 58.88; H, 5.18; N, 12.41; NMR: 15.00 (s, 1H, exchangeable), 8.22 (d, J = 8.79 Hz, 1H), 7.85 (d, J = 2.01 Hz, 1H), 7.61 (d, J = 7.53 Hz, 2H), 7.45 (t, J = 7.53 Hz, 2H), 7.38-7.28 (m, 2H), 5.31 (s, 1H, exchangeable), 3.83 (br m, 2H), 3.39 (br m, 2H), 3.10 (s, 9H).

The starting 6-Chloro-2-anilino-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione was prepared in the following manner:

a. 6-Chloro-2-anilino-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]-quinoline-1,3,9-trione.

To a stirred suspension of dimethyl 7-chloro-4-hydroxyquinoline-2,3-dicarboxylate (2.50 g, 8.45 mM) in ethanol (35 mL) was added phenyl hydrazine (5.82 mL, 59.20 mM) to give a brown solution. This solution was heated to reflux for 16 hours during which time a precipitate formed. The suspension was filtered hot, and the collected solids were washed with ethanol to give the phenyl hydrazine salt of the title compound as a white powder (2.10 g). This material was stirred and refluxed in glacial acetic acid (50 mL) for 2 hours. The resulting yellow suspension was cooled to room temperature and filtered to give the title compound (1.70 g, 59%) as a yellow solid, mp 397°C; MS(CI): 340 (M+H). Analysis for $C_{17}H_{10}ClN_3O_3$: Calculated: C, 60.10; H, 2.97; N, 12.40; Found: C, 59.96; H, 2.79; N, 12.45; NMR: 13.80 (br s, 1H, exchangeable), 8.54 (s, 1H, exchangeable), 8.23 (d, J = 8.70 Hz, 1H), 7.89 (d, J = 1.89 Hz, 1H), 7.58 (dd, J = 1.89, 8.70 Hz, 1H), 7.18 (t, J = 8.01 Hz, 2H), 6.82 (m, 3H).

Example 6. 7-Chloro-4-hydroxy-2-phenyl-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

The saved filtrate from Example 5 was diluted with water (0.80 L), and the resulting tan suspension was stirred for 1 hour. The solids were collected and washed with aqueous methanol (50%) to give the title compound (1.20 g, 71%) as an off-white powder, mp 347-349°C; MS(CI): 340 (M+H). Analysis for $C_{17}H_{10}ClN_3O_3 \cdot 0.10\ H_2O$: Calculated: C, 59.80; H, 3.01; N, 12.30; Found: C, 59.64; H, 2.76; N, 12.27; NMR: 12.8 (br s, 1H, exchangeable), 12.1 (br s, 1H, exchangeable), 8.16 (d, J = 8.67 Hz, 1H), 8.06 (d, J = 1.80 Hz, 1H), 7.56-7.33 (m, 6H).

Example 7. 7-Chloro-1-hydroxy-3-(4-methoxyphenyl)-3,4,5,10-tetrahydropyridazino[4,5-b]quinoline-4,10-dione.

6-Chloro-2-(4-methoxyanilino)-2,3,4,9-tetrahydro-1H-

pyrrolo[3,4-b]-quinoline-1,3,9-trione (2.72 g, 7.40 mM) was stirred in methanol (200 mL), and methanesulfonic acid (50 mL) was added. The tan suspension was heated to reflux for 16 hours during which it turned yellow. This yellow suspension was cooled to room temperature and filtered (the filtrate was saved for use in Example 8). The collected solids were washed with methanol to give the title compound as a yellow powder (1.19 g, 44%), mp 371-373°C; MS(CI): 370 (M+H). Analysis for $C_{18}H_{12}ClN_3O_4$: Calculated: C, 58.50; H, 3.27; N, 11.36; Found: C, 58.30; H, 3.41; N, 10.92; NMR: 13.33 (br s, 1H, exchangeable), 12.47 (s, 1H, exchangeable), 8.30 (d, J = 8.73 Hz, 1H), 8.23 (br s, 1H), 7.61 (m, 3H), 7.08 (d, J = 8.90 Hz, 2H), 3.83 (s, 3H).

The starting 6-Chloro-2-(4-methoxyanilino)-2,3,4,9-tetrahydro-1H-pyrrolo-[3,4-b]-quinoline-1,3,9-trione was prepared in the following manner:

a. 6-Chloro-2-(4-methoxyanilino)-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]-quinoline-1,3,9-trione.

To a stirred suspension of dimethyl 7-chloro-4-hydroxyquinoline-2,3-dicarboxylate (0.500 g, 1.69 mM) in ethanol (17 mL) was added 4-methoxyphenyl hydrazine hydrochloride (2.07 g, 11.83 mM). Triethylamine (1.88 mL, 13.52 mM) was added, and the mixture was heated to reflux for 40 hours. The resulting suspension was filtered hot, and the collected solids were washed with ethanol to give the 4-methoxyphenyl hydrazine salt of the title compound (0.700 g) as a light tan solid. This material was heated to reflux in glacial acetic acid (20 mL) for 2 hours to give a brown suspension. The suspension was cooled to room temperature. The solids were collected and washed with glacial acetic acid, methanol and ether to give the title compound (0.331 g, 53%) as a tan powder, mp 365°C (decomp.); MS(CI): 370 (M+H). Analysis for $C_{18}H_{12}ClN_3O_4$: Calculated: C, 58.50; H, 3.27; N, 11.36; Found: C, 58.29; H, 3.41; N, 11.14; NMR: 13.79

(br s, 1H, exchangeable), 8.22 (br d, J = 8.70 Hz, 2H, 1H exchangeable), 7.88 (d, J = 1.79 Hz, 1H), 7.57 (dd, J = 1.79, 8.70 Hz, 1H), 6.78 (s, 4H), 3.67 (s, 3H).

Example 8. 7-Chloro-4-hydroxy-2-(4-methoxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

The saved filtrate from Example 7 was diluted with water (250 mL) to give a yellow suspension. The solids were collected and washed with aqueous methanol (50%) to give the title compound (1.22 g, 45%) as a dull yellow powder, mp 351-353°C; MS(CI): 370 (M+H). Analysis for $C_{18}H_{12}ClN_3O_4$: Calculated: C, 58.50; H, 3.27; N, 11.36; Found: C, 58.51; H, 3.44; N, 11.03; NMR: 12.74 (s, 1H, exchangeable), 12.01 (s, 1H, exchangeable), 8.15 (d, J = 8.70 Hz, 1H), 8.05 (br s, 1H), 7.44 (multiplet, 3H), 7.02 (br d, J = 6.96 Hz, 2H), 3.80 (s, 3H).

Example 9. 7-Chloro-1-hydroxy-3-(4-hydroxyphenyl)-3,4,5,10-tetrahydropyridazino[4,5-b]quinoline-4,10-dione.

7-Chloro-1-hydroxy-3-(4-methoxyphenyl)-3,4,5,10-tetrahydropyridazino[4,5-b]-quinoline-4,10-dione (0.800 g, 2.16 mM) was stirred in methanesulfonic acid (16 mL) to give an amber solution. This solution was heated to 160°C for 6 hours and cooled to room temperature. Addition of ethyl ether (250 mL) gave a tan precipitate which was stirred for 1 hour. The solid was collected and washed with methanol/ether to give the title compound (0.661 g, 77%) as a tan powder, mp 393-395°C; MS(CI): 356 (M+H). Analysis for $C_{17}H_{10}ClN_3O_4 \cdot 0.2CH_3SO_3H \cdot 1.3\ H_2O$: Calculated: C, 51.86; H, 3.39; N, 10.55; Found: C, 51.76; H, 3.02; N, 10.37; NMR: 13.30 (s, 1H, exchangeable), 12.5 (v br s, 1H, exchangeable), 10.8 (br s, 1H, exchangeable), 8.29 (d, J = 8.76 Hz, 1H), 8.23 (br s, 1H), 7.61 (br d, J = 8.76 Hz, 1H), 7.45 (d, J = 8.81 Hz, 2H), 6.88 (d, J = 8.81 Hz, 2H), 2.32 (s, 0.5H).

Example 10. 7-Chloro-4-hydroxy-2-(4-hydroxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

7-Chloro-4-hydroxy-2-(4-methoxyphenyl)-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione (0.800 g, 2.16 mM) was stirred in methanesulfonic acid (16 mL) to give an amber solution. This solution was heated to 150°C for 6 hours and cooled to room temperature. Addition of ethyl ether (250 mL) and methanol (50 mL) gave a tan precipitate. The solid was collected and washed with methanol/ether to give the title compound (0.530 g, 51%) as a tan powder, mp 316-318°C; MS(CI): 356 (M+H). Analysis for $C_{17}H_{10}ClN_3O_4 \cdot CH_3SO_3H \cdot 1.3\ H_2O$: Calculated: C, 45.49; H, 3.52; N, 8.84; Found: C, 45.45; H, 3.24; N, 8.64; NMR: 12.80 (v br s, 1H, exchangeable), 8.15 (d, J = 8.68 Hz, 1H), 8.04 (d, J = 1.84 Hz, 1H), 7.44 (dd, J = 1.84, 8.68 Hz, 1H), 7.28 (d, J = 8.74 Hz, 2H), 6.81 (d, J = 8.74 Hz, 2H), 2.35 (s, 3H).

Example 11. 4-hydroxy-8-nitro-2-phenyl-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

2-Anilino-7-nitro-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione (0.830 g, 2.37 mM) was dissolved with stirring in methanesulfonic acid (42 mL) to give a deep orange solution. Methanol (420 mL) was added and the resulting yellow solution heated to reflux for 2 hours to give a yellow suspension. Heat was removed and the suspension was stirred at room temperature for 3 hours. The solids were removed by filtration, and the filtrate was allowed to stand for 20 hours. More solids formed in the filtrate during this time, and the suspension was refiltered. This filtrate was then concentrated to about 250 mL and diluted with water (400 mL) to give a yellow precipitate. These solids were collected and washed with aqueous methanol (50%) and then ether to give the title compound (0.590 g, 71%) as a yellow powder, mp 382-385°C; MS(CI): 351 (M+H). Analysis

for $C_{17}H_{10}N_4O_5 \cdot 0.1C_4H_{10}O \cdot 1.1\ H_2O$: Calculated: C, 55.40; H, 3.52; N, 14.80; Found: C, 55.42; H, 3.46; N, 14.60; NMR: 12.91 (br s, 1H, exchangeable), 12.44 (br s, 1H, exchangeable), 8.86 (s, 1H), 8.53 (d, J = 9.18 Hz, 1H), 8.15 (d, J = 9.18 Hz, 1H), 7.57-7.35 (m, 5H).

The starting 2-anilino-7-nitro-2,3,4,9-tetrahydro-1H-pyrrolo-[3,4-b]quinoline-1,3,9-trione was prepared in the following manner:

a. 2-Anilino-7-nitro-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]-quinoline-1,3,9-trione.

To a stirred suspension of diethyl 6-nitro-4-hydroxy-quinoline-2,3-dicarboxylate (1.670 g, 5.00 mM) in ethanol (30 mL) was added phenyl hydrazine (3.44 mL, 35.00 mM) to give a deep red solution. The solution was heated to reflux for 1 hour and concentrated to about 15 mL. Continued heating gave a thick suspension which was diluted with ethanol (5 mL) and refluxed for 16 additional hours. The mixture was cooled to room temperature and filtered to give the phenyl hydrazine salt of the title compound as a tan solid. This material was refluxed in glacial acetic acid (25 mL) for 2 hours and cooled to room temperature. Filtration gave the title compound (1.01 g, 58%) as a tan powder, mp 368°C (decomp.); MS(CI): 351 (M+H). Analysis for $C_{17}H_{10}N_4O_5$: Calculated: C, 58.30; H, 2.88; N, 16.00; Found: C, 58.21; H, 3.07; N, 16.15; NMR: 8.91 (d, J = 2.76 Hz, 1H), 8.60 (dd, J = 2.76, 9.18 Hz, 1H), 8.06 (d, J = 9.18 Hz, 1H), 7.18 (t, J = 7.23 Hz, 2H), 6.82 (m, 3H).

Example 12. 2-Benzyl-7-chloro-4-hydroxy-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione.

To a stirred suspension of dimethyl 7-chloro-4-hydroxyquinoline-2,3-dicarboxylate (5.00 g, 16.90 mM) and benzyl hydrazine dihydrochloride (46.15 g, 236.50 mM) in ethanol (100 mL) was added triethylamine (75.8 mL, 541.0 mM). The mixture was heated to give a

brown solution which was refluxed for 40 hours during which time a precipitate formed. The suspension was cooled to room temperature and filtered to give the benzyl hydrazine salt of the title compound as an impure yellow solid. Multiple crystallizations from ethanolic hydrogen chloride and methanol gave the title compound (0.370 g, 6%) as a white powder, mp = 347-350°C; MS(CI): 354 (M+H). Analysis for $C_{18}H_{12}ClN_3O_3$: Calculated: C, 61.10; H, 3.42; N, 11.90; Found: C, 60.68; H, 3.61; N, 11.80; NMR: 12.65 (br s, 1H, exchangeable), 11.93 (br s, 1H, exchangeable), 8.15 (d, J = 8.67 Hz, 1H), 8.02 (d, J = 1.83, 1H), 7.43 (d, J = 8.55 Hz, 1H), 7.36-7.23 (m, 5H), 5.11 (s, 2H).

Example 13. 7-Chloro-4-hydroxy-2-[2-(4-phenylpiperazino)ethyl]-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

2(2-Bromoethyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydro-pyridazino[4,5-b]-quinoline-1,10-dione (0.500 g, 1.35 mM) was stirred in dimethylformamide (10 mL), and N-phenylpiperazine (10 mL, 10.6 g, 65.5 mM) was added. The resulting yellow suspension was heated to ~110°C to form a clear yellow solution. The solution was heated for 6 hours during which time a precipitate formed. The suspension was cooled to room temperature and stirred for five days. The resulting yellow suspension was dissolved into aqueous methanol (500 mL, 50%). The pH of this solution was carefully adjusted to pH=6 with 1N hydrochloric acid (~20 mL) which gave a yellow precipitate. This suspension was stirred for 1 hour and filtered to give the title compound contaminated with N-phenylpiperazine (0.753 g). This material was recrystallized from hot ethanol (200 mL) to give the title compound (0.428 g, 70%) as a yellow powder, mp 361-364°C; MS(CI): 452 (M+H). Analysis for $C_{23}H_{22}ClN_5O_3$: Calculated: C, 61.10; H, 4.91; N, 15.50; Found: C, 60.72; H, 5.06; N, 15.30; NMR: 7.95 (d, J = 8.67 Hz, 1H), 7.64 (br s, 1H), 7.26-7.18 (m, 3H), 6.95 (d, J = 8.07 Hz, 2H), 6.78 (t, J = 7.32 Hz, 1H), 4.15 (br s, 2H), 3.55-2.85 (br m, 10H).

Example 14. 7-Chloro-1-hydroxy-3-(2-phenethyl)-3,4,5,10-tetrahydropyridazino[4,5-b]quinoline-4,10-dione, choline salt.

To a stirred solution of sodium hydroxide (9.46 g, 236.6 mM) in ethanol (100 mL) at 45°C was added 2-phenethylhydrazine sulfate salt (27.6 g, 118.3 mM) along with additional ethanol (50 mL). The resulting thick white suspension was stirred for 2 hours. The solids were removed by filtration and washed with ethanol (50 mL). The clear combined filtrates were concentrated to ~75 mL, and dimethyl 7-chloro-4-hydroxyquinoline-2,3-dicarboxylate (2.50 g, 8.45 mM) was added to give a brown solution. The solution was refluxed for 16 hours during which time a yellow precipitate formed. The suspension was filtered hot and washed with ethanol (50 mL) to give the 2-phenethylhydrazine salt of 7-chloro-1-hydroxy-3-(2-phenethyl)-3,4,5,10-tetrahydropyridazino[4,5-b]quinoline-4,10-dione as a yellow powder (2.90 g). This material was refluxed in glacial acetic acid (50 mL) for 2 hours and, after cooling to room temperature, the resulting suspension was filtered to give a mixture of 7-chloro-1-hydroxy-3-(2-phenethyl)-3,4,5,10-tetrahydropyridazino[4,5-b]quinoline-4,10-dione and the corresponding 2-substituted phenethyl isomer as a yellow solid (2.20 g, 68%). This mixture was stirred in methanol (250 mL) and methyl-D-glucamine solution (15.0 g methyl-D-glucamine in 250 mL water). Choline hydroxide solution (9.0 mL, 50 weight % in water) was then added to give a deep amber solution. This solution was carefully acidified to pH 9 with glacial acetic acid whereupon a yellow precipitate formed. After stirring this yellow suspension for 1 hour, the solids were collected and washed successively with aqueous methanol (50%), methanol/ether and ether to give the title compound (free acid, 1.13 g, 54%) as a yellow powder. The filtrate and washes from this collection were saved for use in Example 15.

The 7-Chloro-1-hydroxy-3-(2-phenethyl)-3,4,5,10-tetrahydropyridazino[4,5-b]-quinoline-4,10-dione (1.00 g, 2.72 mM) isolated

above was stirred in methanol (50 mL), and choline hydroxide solution (1.0 mL, 45 weight % in methanol) was added. The resulting suspension was stirred and sonicated for 1 hour to give an amber solution. This solution was azeotroped 3 times from methanol/toluene (10%, 50 mL) to give an orange solid. Trituration from toluene (50 mL) containing ethanol (3 mL) gave a free-flowing suspension which was stirred for 16 hours. The solids were collected and washed with toluene and ether to give a tan powder (1.19 g). This powder was dried under high vacuum (50 mT) at 100°C for 72 hours to give the title compound (1.00 g, 78%) as a gold powder, mp 227-229°C; MS(CI): 368 (M+H). Analysis for $C_{19}H_{13}ClN_3O_3 \cdot C_5H_{14}NO \cdot 0.2\ H_2O$: Calculated: C, 60.70; H, 5.82; N, 11.81; Found: C, 60.41; H, 5.74; N, 11.68; NMR: 14.86 (s, 1H, exchangeable), 8.17 (d, J = 8.82 Hz, 1H), 7.80 (s, 1H), 7.33-7.19 (m, 6H), 5.37 (br s, 1H, exchangeable), 4.13 (t, J = 7.29 Hz, 2H), 3.84 (br s, 2H), 3.37 (m, 2H), 3.10 (s, 9H), 3.00 (t, J = 7.29 Hz, 2H).

Example 15. 7-Chloro-4-hydroxy-2-(2-phenethyl)-1,2,5,10-tetrahydropyridazino[4,5,-b]quinoline-1,10-dione.

The filtrate and washes saved from Example 14 were acidified with glacial acetic acid to give a precipitate. The solids were collected and washed successively with methanol, water, methanol, and ether to give the title compound (0.81 g, 39%) as a light yellow powder, mp 327-330°C; MS(CI): 368 (M+H). Analysis for $C_{19}H_{14}ClN_3O_3 \cdot 0.1\ H_2O$: Calculated: C, 61.70; H, 3.87; N, 11.36; Found: C, 61.60; H, 3.99; N, 10.98; NMR: 12.60 (v br s, 1H, exchangeable), 11.95 (v br s, 1H, exchangeable), 8.15 (d, J = 8.63 Hz, 1H), 8.01 (d, J = 1.35 Hz, 1H), 7.43 (d, J = 8.63 Hz, 1H), 7.33-7.22 (m, 5H), 4.11 (t, J = 7.46 Hz, 2H), 2.99 (t, J = 7.46 Hz, 2H).

Example 16. 7-Chloro-1-hydroxy-3-(4-chlorophenyl)-3,4,5,10-tetrahydropyridazino[4,5-b]quinoline-4,10-dione.

A stirred suspension of 6-chloro-2-(4-chloroanilino)-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione (0.670 g, 1.79 mM) in methanol (60 mL) and methanesulfonic acid (15 mL) was refluxed for 3 hours and cooled to room temperature. The mixture was filtered (the filtrate was saved for use in Example 17), and the collected yellow solids were washed with methanol and ether to give the title compound (0.156 g, 23%) as a yellow powder, mp > 400°C; MS(CI): 374 (M+H). Analysis for $C_{17}H_9Cl_2N_3O_3$: Calculated: C, 54.60; H, 2.42; N, 11.23; Found: C, 54.29; H, 2.19; N, 11.20; NMR: 13.40 (s, 1H, exchangeable), 12.54 (s, 1H, exchangeable), 8.30 (d, J = 8.79 Hz, 1H), 8.23 (d, J = 1.89 Hz, 1H), 7.75 (d, J = 6.90 Hz, 2H), 7.63 (m, 3H).

The starting 6-chloro-2-(4-chloroanilino)-2,3,4,9-tetrahydro-1H-pyrrolo-[3,4-b]quinoline-1,3,9-trione was prepared as follows:

a. 6-chloro-2-(4-chloroanilino)-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione.

To a stirred suspension of dimethyl 7-chloro-4-hydroxyquinoline-2,3-dicarboxylate (2.50 g, 8.45 mM) and 4-chlorophenyl hydrazine (10.60 g, 59.20 mM) in ethanol (50 mL) was added triethylamine (9.43 mL) to give a brown solution. This solution was refluxed for 24 hours and then cooled to room temperature. Dilution with water (25 mL) gave a brown precipitate. This suspension was stirred for 16 hours and filtered to remove the solids which were discarded. The filtrate formed another precipitate after standing for seven days. This solid was collected and washed with aqueous methanol (50%) and ether to give the 4-chlorophenyl hydrazine salt of the title compound as a brown powder (1.20 g). This material was refluxed in glacial acetic acid (25 mL) for 3 hours and cooled to room temperature. The resulting orange suspension was filtered, and the solids were washed with glacial acetic acid and ether to give the title compound (0.810 g, 25%) as a light orange powder, mp 399-401°C; MS(CI): 374 (M+H).

Analysis for $C_{17}H_9Cl_2N_3O_3$: Calculated: C, 54.60; H, 2.42; N, 11.23; Found: C, 54.29; H, 2.61; N, 11.12; NMR: 13.80 (v br s, 1H, exchangeable), 8.67 (s, 1H, exchangeable), 8.22 (d, J = 8.67 Hz, 1H), 7.88 (d, J = 1.73 Hz, 1H), 7.57 (dd, J = 1.73, 8.67 Hz, 1H), 7.21 (d, J = 8.79 Hz, 2H), 6.87 (d, J= 8.79 Hz, 2H).

Example 17. 7-Chloro-4-hydroxy-2(4-chlorophenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

The filtrate saved from Example 16 was diluted with water (75 mL) to give a white suspension which was stirred for 16 hours. This suspension was filtered, and the collected solids were washed successively with water, aqueous methanol, methanol/ether and ether to give the title compound (0.420 g, 63%) as a white powder, mp 359-36°C; MS(CI): 374 (M+H). Analysis for $C_{17}H_9Cl_2N_3O_3 \cdot 0.5H_2O \cdot 0.2CH_3SO_3H$: Calculated: C, 51.30; H, 2.71; N, 10.40; Found: C, 51.44; H, 2.64; N, 0.60; NMR: 12.91 (br s, 1H, exchangeable), 12.07 (br s, 1H, exchangeable), 8.16 (d, J = 8.64 Hz, 1H), 8.06 (d, J = 1.62 Hz, 1H), 7.63-7.46 (m, 5H).

Example 18. 7-Chloro-1-hydroxy-3-(4-methylphenyl)-3,4,5,10-tetrahydropyridazino[4,5-b]quinoline-4,10-dione.

A stirred suspension of 6-chloro-2-(4-methylanilino)-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione (1.60 g, 4.53 mM) in a solution of methanol (128 mL) and methanesulfonic acid (32 mL) was refluxed for 4 hours and cooled to room temperature. The resulting yellow suspension was stirred at room temperature for five days and then filtered (the filtrate was saved for use in Example 19). The collected solids were washed with methanol and then ether to give the title compound (0.594 g, 37%) as a yellow powder, mp > 400°C; MS(CI): 354 (M+H). Analysis for $C_{18}H_{12}ClN_3O_3 \cdot 0.4$ H2O: Calculated: C, 59.89; H, 3.57; N, 11.64; Found: C, 59.47; H, 3.14; N, 11.57; NMR: 13.34 (s, 1H, exchangeable), 12.48 (s, 1H, exchangeable), 8.30 (d, J =

8.75 Hz, 1H), 8.22 (br s, 1H), 7.62 (d, J = 8.75 Hz, 1H), 7.55 (d, J = 8.01 Hz, 2H), 7.33 (d, J = 8.01 Hz, 2H), 2.38 (s, 3H).

The starting 6-chloro-2-(4-methylanilino)-2,3,4,9-tetrahydro-1H-pyrrolo-[3,4-b]quinoline-1,3,9-trione was prepared in the following manner:

a. 6-chloro-2-(4-methylanilino)-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione.

To a stirred suspension of dimethyl 7-chloro-4-hydroxyquinoline-2,3-dicarboxylate (3.90 g, 13.3 mM) and 4-methylphenyl hydrazine hydrochloride (14.8 g, 93.2 mM) in ethanol (140 mL) was added triethylamine (14.8 mL, 106.4 mM). The resulting brown solution was refluxed for 16 hours during which time a precipitate formed. The resulting suspension was cooled to room temperature and filtered to give the 4-methylphenyl hydrazine salt of the title compound as a grey powder (2.30 g). This material was refluxed in glacial acetic acid (45 mL) for 2 hours and cooled to room temperature. The resulting brown suspension was filtered to give the title compound (1.60 g, 34%) as a tan powder, mp 380-382°C; MS(CI): 354 (M+H). Analysis for $C_{18}H_{12}ClN_3O_3 \cdot 0.2\ H_2O$: Calculated: C, 60.49; H, 3.50; N, 11.76; Found: C, 60.66; H, 3.26; N, 11.76; NMR: 13.81 (v br s, 1H, exchangeable), 8.39 (s, 1H, exchangeable), 8.22 (d, J = 8.58 Hz, 1H), 7.89 (d, J = 1.97 Hz, 1H), 7.58 (dd, J = 1.97, 8.58 Hz, 1H), 6.98 (d, J = 8.28 Hz, 2H), 6.73 (d, J = 8.28 Hz, 2H), 2.19 (s, 3H).

Example 19. 7-Chloro-4-hydroxy-2-(4-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

The filtrate saved from Example 18 was diluted with water (160 mL) to give a tan suspension which was stirred for 3 hours. The suspension was filtered, and the collected solids were washed successively with water, methanol/ether, and ether to give the title

compound (0.855 g, 53%) as a tan powder, mp 368-370°C; MS(CI): 354 (M+H). Analysis for $C_{18}H_{12}ClN_3O_3 \cdot 0.2\ H_2O$: Calculated: C, 60.50; H, 3.50; N, 11.76; Found: C, 60.52; H, 3.23; N, 11.79; NMR: 12.75 (br s, 1H, exchangeable), 12.00 (br s, 1H, exchangeable), 8.15 (d, J = 8.61 Hz, 1H), 8.04 (d, J = 1.50 Hz, 1H), 7.43 (m, 3H), 7.26 (d, J = 8.25 Hz, 2H), 2.36 (s, 3H).

Example 20. 7-Chloro-1-hydroxy-3-(4-isopropylphenyl)-3,4,5,10-tetrahydropyridazino[4,5-b]-quinoline-4,10-dione.

A stirred suspension of 6-chloro-2-(4-isopropylanilino)-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione (1.13 g, 2.98 mM) in a solution of methanol (90 mL) and methanesulfonic acid (23 mL) was refluxed for 7 hours and cooled to room temperature. The mixture was filtered (the filtrate was saved for use in Example 21), and the collected yellow solids were washed with methanol and ether to give the title compound (0.401 g, 35%) as a yellow powder, mp 93-394°C; MS(CI): 382 (M+H). Analysis for $C_{20}H_{16}ClN_3O_3 \cdot 0.2\ H_2O$: Calculated: C, 62.33; H, 4.29; N, 10.90; Found: C, 62.16; H, 3.98; N, 10.82; NMR: 13.33 (s, 1H, exchangeable), 12.48 (s, 1H, exchangeable), 8.28 (d, J = 8.76 Hz, 1H), 8.22 (d, J = 1.77 Hz, 1H), 7.63-7.58 (m, 3H), 7.40 (d, J = 8.49 Hz, 2H), 2.98 (septet, J = 6.96 Hz, 1H), 1.25 (d, J = 6.96 Hz, 6H).

The starting 6-chloro-2-(4-isopropylanilino)-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione was prepared in the following manner:

a. 6-chloro-2-(4-isopropylanilino)-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]-quinoline-1,3,9-trione.

To a stirred suspension of dimethyl 7-chloro-4-hydroxyquinoline-2,3-dicarboxylate (2.01 g, 6.80 mM) and 4-isopropylphenyl hydrazine

hydrochloride (8.90 g, 47.6 mM) in ethanol (72 mL) was added triethylamine (7.6 mL, 54.5 mM) to give a brown solution. This solution was refluxed for 16 hours, cooled to room temperature, and then added slowly to a mixture of hydrochloric acid (12N, 100 mL) and ice (100 mL) with vigorous stirring whereupon a pink suspension formed. The suspension was filtered, and the collected solids were washed with a cold solution made by mixing methanol (100 mL), hydrochloric acid (100 mL, 12N) and ice (100 g) to give the 4-isopropylphenyl hydrazine salt of the title compound as a purple powder (1.80 g). This material was refluxed in glacial acetic acid (15 mL) for 3 hours to give a tan suspension. The suspension was cooled to room temperature and filtered. The collected solids were washed with glacial acetic acid (10 mL) and ether to give the title compound (1.125 g, 43%) as a tan powder, mp 367-369°C; MS(CI): 382 (M+H). Analysis for $C_{20}H_{16}ClN_3O_3 \cdot 0.1\ H_2O$: Calculated: C, 62.60; H, 4.26; N, 10.95; Found: C, 62.60; H, 4.35; N, 10.73; NMR: 13.82 (v br s, 1H, exchangeable), 8.41 (s, 1H, exchangeable), 8.23 (d, J = 8.64 Hz, 1H), 7.89 (d, J = 1.98 Hz, 1H), 7.61 (dd, J = 1.98, 8.64 Hz, 1H), 7.04 (d, J = 8.42 Hz, 2H), 6.74 (d, J = 8.42 Hz, 2H), 2.78 (septet, J = 6.87 Hz, 1H), 1.15 (d, J = 6.87 Hz, 6H).

Example 21. 7-Chloro-4-hydroxy-2-(4-isopropylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione.

The filtrate saved from Example 20 was diluted with water (115 mL) to give a light yellow suspension which was stirred for 5 hours at room temperature. The suspension was filtered, and the collected solids were washed successively with water, aqueous methanol (50%), methanol/ether and ether to give the title compound (0.418 g, 37%) as a tan powder, mp 323-326°C; MS(CI): 382 (M+H). Analysis for $C_{20}H_{16}ClN_3O_3 \cdot 0.5\ H_2O \cdot 0.1\ CH_3SO_3H$: Calculated: C, 60.29; H, 4.38; N, 10.49; Found: C, 60.13; H, 4.10; N, 10.40; NMR: 12.73 (br s, 1H, exchangeable), 12.00 (br s, 1H, exchangeable), 8.15 (d, J = 8.70 Hz,

1H), 8.05 (d, J = 1.74 Hz, 1H), 7.45 (m, 3H), 7.33 (d, J = 8.40 Hz, 2H), 2.95 (septet, J = 6.90 Hz, 1H), 1.24 (d, J = 6.90 Hz, 6H).

Example 22. 7,9-Dichloro-1-hydroxy-2-phenyl-1,2,5,10-tetrahydro-pyridazino [4,5-b]-quinoline-1,10-dione.

6,8-Dichloro-2-anilino-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione (0.60 g, 1.60 mM) was stirred in methanol (200 mL) and methanesulfonic acid (20 mL) was added with cooling, maintaining the temperature below 20 °C. The resulting orange solution was stirred overnight at room temperature. A precipitate formed overnight and the orange suspension was heated to reflux for 1 hour. The suspension was cooled to room temperature and allowed to stand overnight without stirring. The suspension was filtered and the filtrates were slowly diluted with water (200 mL) to give a yellow suspension. This suspension was stirred for two hours and the solids were collected and washed with water, aqueous methanol, 50% methanol/ether, and ether to give the title compound (0.368 g, 61%) as a light tan powder, mp 361-363 °C; MS(CI): 374 (M+H).
Analysis for C17H9Cl2N3O3 . 0.3OH2O: Calculated: C, 53.80; H, 2.55; N, 11.07
Found: C, 53.71; H, 2.64; N, 10.97
1H NMR 12.84 (s, 1H, exchangeable), 11.96 (s, 1H, exchangable), 8.04 (d, J=2.02 Hz, 1H), 7.55-7.45 (m, 5H), 7.36 (t, J=6.84 Hz, 1H).

The starting 6,8-dichloro-2-anilino-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]-quinoline-1,3,9-trione was prepared in the following manner:

a. 6,8-Dichloro-2-anilino-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]-quinoline-1,3,9-trione.

To a stirred suspension of dimethyl5,7-dichloro-4-hydroxy-quinoline-2,3-dicarboxylate (3.00 g, 9.09 mM) in ethanol (42 mL) was added phenyl hydrazine (6.26 mL, 63.6 mM). The resulting green

solution was heated to reflux for 16 hours during which time a small amount of red precipitate formed. This suspension was cooled to room temperature with stirring and additional precipitation occurred to give a thick tan suspension. The solids were collected and washed with ethanol (the ethanol washes were saved). The collected solids were recrystallized from ethanol (1.20 L) to give the phenyl hydrazine salt of the title compound (1.17 g) as a tan powder. This material was stirred and refluxed in glacial acetic acid (15 mL) for 2.5 hours and then cooled to room temperature with stirring. The resulting orange suspension was filtered to give the title compound (0.629 g, 19%) as an orange powder which was slightly impure. An analytical sample of the title compound was obtained from the above saved ethanol washes by filtration of a precipitate which formed after these washes stood for several hours. Recrystallization of this collected tan powder (0.126 g) from glacial acetic acid (2 mL) gave the pure title compound (0.083 g) as an orange powder, mp 364-367 °C; MS(CI): 374 (M+H).

Analysis for C17H9Cl2N3O3 . 0.3OH2O . 0.1OCH3CO2H: Calculated: C, 53.60; H, 2.61; N, 10.90 Found: C, 53.49; H, 2.77, N, 10.82
1H NMR 8.53 (s, 1H, exchangeable), 7.85 (d, J=1.94 Hz, 1H), 7.65 (d, J=1.94 Hz, 1H), 7.18 (t, J=7.84 Hz, 2H), 6.82 (d, J=7.84 Hz, 3H).

Example 23. 7-Chloro-1-hydroxy-3-(1-naphthyl)-3,4,5,10-tetrahydro-pyridazino[4,5-b]quinoline-4,10-dione.

6-Chloro-2-(1-naphthylamino)-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b] quinoline-1,3,9-trione (1.30 g, 3.34 mM) was stirred in methanol (0.65 L) and methanesulfonic acid (65 mL) was added. The brown suspension was heated to reflux for 16 hours during which the solids dissolved to give a brown solution. This solution was cooled to room temperature. Addition of ice (10 mL) gave a tan suspension which was stirred for 1.5 hours. The suspension was filtered (the filtrate was saved for

use in Example 24) and the collected solids were washed with methanol and ether to give the title compound (0.560 g, 43%) as a dull yellow powder, mp 374-376 °C; MS(CI): 390 (M+H).
Analysis for C21H12ClN3O3 . 0.2OH2O: Calculated: C, 64.10; H, 3.18; N, 10.68 Found: C, 63.91; H, 3.42; N, 10.61
1H NMR 13.40 (s, 1H, exchangeable), 12.58 (s, 1H, exchangeable), 8.35 (d, J=8.70 Hz, 1H), 8.25 (d, J=1.76 Hz, 1H), 8.12-8.07 (m, 2H), 7.74-7.53 (m, 6H).

The starting 6-chloro-2-(1-naphthylamino)-2,3,4,9-tetrahydro-1H-pyrrolo-[3,4-b]quinoline-1,3,9-trione was prepared as follows:

a. 6-chloro-2-(1-naphthylamino)-2,3,4,9-tetrahydro-1H-pyrrolo [3,4-b]quino-line-1,3,9-trione.

To a stirred suspension of dimethyl7-chloro-4-hydroxyquinoline-2,3-dicarboxylate (2.00 g, 6.80 mM) and 1-naphthyl hydrazine hydrochloride (9.26 g, 47.6 mM) in ethanol (72 mL) was added triethylamine (7.60 mL) to give a brown solution. After refluxing for 4 days, the solution was cooled to room temperature and diluted with ethyl acetate (0.35 L) to give a tan suspension. This suspension was filtered to remove the solids which were discarded. The filtrate was then poured into ethyl acetate (500 mL) which was washed with hydrochloric acid (3 x 500 mL, 1N). The washed solution was diluted with ether (250 mL) to give a tan suspension. The solids were collected to give the 1-naphthyl hydrazine salt of the title compound as a tan powder (2.09 g). This material was refluxed in glacial acetic acid (50 mL) for 2 hours, cooled to room temperature and filtered. The collected solids were washed with glacial acetic acid and ether to give the title compound (1.44 g, 54%) as a tan powder, mp 368 °C (decomp.); MS(CI): 390 (M+H).
Analysis for C21H12ClN3O3 . 0.3OCH3CO2H: Calculated: C, 63.60; H, 3.26; N, 10.30 Found: C, 63.90; H, 3.43; N, 9.97
1H NMR 9.06 (s, 1H, exchangeable), 8.27-8.22 (m, 2H), 7.92-7.88 (m,

2H), 7.63-7.52 (m, 3H), 7.41 (d, J=8.17 Hz, 1H), 7.27 (t, J=7.86 Hz, 1H), 6.80 (d, J=7.86 Hz, 1H).

Example 24. 7-Chloro-4-hydroxy-2-(1-naphthyl)-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione.

The filtrate saved from Example 23 was diluted with water (0.75 L) and then partially concentrated on a rotary evaporator to give a brown suspension. The solids from the suspension were collected and washed with water, methanol/ether and ether to give a brown powder (0.535 g). This material was heated to reflux in methanol (23 mL) and filtered hot to remove undissolved solids which were discarded. The filtrate was concentrated to dryness and triturated with ethyl acetate (20 mL). The resulting suspension was filtered and the collected solids washed with ethyl acetate and ether to give the title compound (0.240 g, 18%) as a grey powder, mp 335-337 °C; MS(CI): 390 (M+H).

Analysis for C21H12ClN3O3 . 0.60H2O . 0.40CH3SO3H . 0.20C4H10O . 0.15C4H8O2:
Calculated: C, 58.60; H, 3.88; N, 9.00
Found: C, 58.37; H, 3.53; N, 9.14 1H NMR 12.80 (br s, 1H, exchangeable), 12.1 (br s, 1H, exchangable), 8.15-8.03 (br m, 4H), 7.67-7.50 (br m, 6H).

Example 25. 7-Chloro-3-(4-fluorophenyl)-1-hydroxy-3,4,5,10-tetra-hydropyridazino[4,5-b]quin-oline-4,10-dione.

A stirred suspension of 6-chloro-2-(4-fluoroanilino)-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione (1.40 g, 3.90 mM) in a solution of methanol (0.73 L) and methanesulfonic acid (73 mL) was refluxed for 16 hours and cooled to room temperature. The resulting orange suspension was filtered (the filtrate was saved for use in Example 26) and the collected solids were washed successively

with methanol and ether to give the title compound (0.374 g, 27%) as a light orange powder, mp > 400 °C; MS(CI): 358 (M+H).
Analysis for C17H9ClFN3O3 . H2O: Calculated: C, 54.30; H, 2.95; N, 11.20 Found: C, 54.08; H, 2.62; N, 10.98
1H NMR 13.38 (s, 1H, exchangeable), 12.51 (s, 1H, exchangeable), 8.30 (d, J=8.75 Hz, 1H), 8.22 (d, J=1.78 Hz, 1H), 7.76-7.71 (m, 2H), 7.63 (dd, J=1.78, 8.75 Hz, 1H), 7.40-7.35 (m, 2H).

The starting 6-chloro-2-(4-fluoroanilino)-2,3,4,9-tetrahydro-1H-pyrrolo-[3,4-b]quinoline-1,3,9-trione was prepared in the following manner:

a. 6-chloro-2-(4-fluoroanilino)-2,3,4,9-tetrahydro-1H-pyrrolo [3,4-b]quinoline-1,3,9-trione.

To a stirred suspension of dimethyl7-chloro-4-hydroxyquinoline -2,3-dicarboxylate (2.59 g, 8.79 mM) and 4-fluorophenyl hydrazine hydrochloride (10.0 g, 61.5 mM) in ethanol (48 mL) was added triethylamine (9.8 mL, 70.3 mM). The resulting brown solution was refluxed for 48 hours, cooled to room temperature and diluted with ethyl acetate (150 mL) to give a white crystalline precipitate which was removed by filtration and discarded. The filtrate was washed with hydrochloric acid (3 x 500 mL, 1N) which caused precipitation in the ethyl acetate layer. The precipitate was collected and washed successively with ethyl acetate/ether and ether to give the 4-fluorophenyl hydrazine salt of the title compound (2.14 g). This material was refluxed in glacial acetic acid (20 mL) for 2 hours. After cooling the acetic acid solution to room temperature, a precipitate formed and the solids were collected to give the title compound (1.48 g, 47%) as a yellow powder, mp 390-392 °C; MS(CI): 358 (M+H).

Analysis for C17H9ClFN3O3 . 0.40H2O:
Calculated: C, 55.95; H, 2.71; N, 11.51
Found: C, 56.01; H, 2.67; N, 11.54 1H NMR 13.78 (br s, 1H, exchangeable), 8.52 (s, 1H, exchangeable), 8.22 (d, J=8.71 Hz, 1H), 7.89 (d, J= 2.01 Hz, 1H), 7.58 (dd, J=2.01, 8.71 Hz, 1H), 7.05-6.98 (m, 2H), 6.89-6.85 (m, 2H).

Example 26. 7-Chloro-2-(4-fluorophenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quin-oline-1,10-dione.

The filtrate saved from Example 25 was diluted with water (800 mL) to give a light green suspension which was stirred for 3 hours. The suspension was filtered and the collected solids were washed successively with water, methanol/ether and ether to give the title compound (0.910 g, 65%) as a grey powder, mp= 353-356 °C; MS(CI): 358 (M+H).
Analysis for C17H9ClFN3O3 . 2.00H2O . 0.06CH3SO3H: Calculated: C, 51.30; H, 3.34; N, 10.52 Found: C, 51.58; H, 3.00; N, 10.47
1H NMR 11.95 (br s, 1H, exchangeable), 12.50 (br s, 1H, exchangeable), 8.15 (br d, J=8.26 Hz, 1H), 8.07 (br s, 1H), 7.58 (br s, 2H), 7.43 (br d, J=8.26 Hz, 1H), 7.29-7.24 (br m, 2H).

Example 27. 3-(4-Bromophenyl)-7-chloro-1-hydroxy-3,4,5,10-tetrahydropyridazino[4,5-b]quino-line-4,10-dione.

A stirred suspension of 2-(4-bromoanilino)-6-chloro-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione (1.00 g, 2.39mM) in a solution of methanol (500 mL) and methanesulfonic acid (50 mL) was refluxed for 16 hours and cooled to room temperature. The resulting yellow suspension was filtered (the filtrate was saved for use in Example 28). The collected solids were washed with methanol and then ether to give the title compound (0.222 g, 22%) as a yellow powder, mp > 400 °C; MS(CI): 420 (M+H).

Analysis for C17H9BrClN3O3 . 0.30H2O:
Calculated: C, 48.15; H, 2.28; N, 9.91
Found: C, 48.15; H, 2.36; N, 9.88 1H NMR 13.36 (s, 1H, exchangeable), 12.51 (s, 1H, exchangeable), 8.25 (d, J= 8.73 Hz, 1H), 8.19 (d, J= 1.55 Hz, 1H), 7.75-7.67 (m, 4H), 7.60 (dd, J=1.55, 8.73 Hz, 1H).

The starting 2-(4-bromoanilino)-6-chloro-2,3,4,9-tetrahydro-1H-pyrrolo-[3,4-b]quinoline-1,3,9-trione was prepared in the following manner:

a. 2-(4-Bromoanilino)-6-chloro-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione.

To a stirred suspension of dimethyl7-chloro-4-hydroxyquinoline-2,3-dicarboxylate (1.90 g, 6.40 mM) and 4-bromophenyl hydrazine hydrochloride (10.0 g, 44.7 mM) in ethanol (35 mL) was added triethylamine (7.1 mL, 51.1 mM). The resulting brown solution was refluxed for 22 hours during which time a tan precipitate formed. This mixture was cooled to room temperature and filtered to give the 4-bromophenyl hydrazine salt of the title compound as a white powder (1.69 g). This material was refluxed in glacial acetic acid (20 mL) for 3 hours and cooled to room temperature. The resulting tan suspension was filtered and the solids washed with glacial acetic acid and then ether to give the title compound (1.15 g, 43%) as a tan powder, mp 393-394 °C; MS(CI): 420 (M+H).
Analysis for C17H9BrClN3O3: Calculated: C, 48.77; H, 2.17; N, 10.04
Found: C, 48.52; H, 2.26; N, 10.00
1H NMR 13.84 (br s, 1H, exchangeable), 8.71 (s, 1H, exchangeable), 8.23 (d, J=8.63 Hz, 1H), 7.89 (d, J=1.98 Hz, 1H), 7.58 (dd, J=1.98, 8.63 Hz, 1H), 7.32 (d, J=8.70 Hz, 2H), 6.84 (d, J=8.70 Hz, 2H).

Example 28. 2-(4-Bromophenyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quino-line-1,10-dione.

The filtrate saved from Example 27 was diluted with water (550 mL) to give a tan suspension which was stirred for 2 hours. The suspension was filtered and washed successively with water, methanol/ether and ether to give the title compound (0.716 g, 72%) as a tan powder, mp 359-361 °C; MS(CI): 420 (M+H).
Analysis for C17H9BrClN3O3 . 1.30H2O: Calculated: C, 46.20; H, 2.64; N, 9.51 Found: C, 46.26; H, 2.66; N, 9.37
1H NMR 12.60 (br s, 1H, exchangeable), 11.95 (br s, 1H, exchangeable), 8.16 (d, J=8.61 Hz, 1H), 8.06 (d, J=1.67 Hz, 1H), 7.64 (d, J=8.78 Hz, 2H), 7.55 (d, J= 8.78 Hz, 2H), 7.43 (d, J= 8.61 Hz, 1H).

Example 29. 7-Chloro-1-hydroxy-3-(2-methoxyphenyl)-3,4,5,10-tetrahydropyridazino[4,5-b]quin-oline-4,10-dione.

A stirred suspension of 6-chloro-2-(2-methoxyanilino)-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione (1.78 g, 4.81 mM) in a solution of methanol (285 mL) and methanesulfonic acid (89 mL) was refluxed for 8 hours during which time a tan precipitate formed. The resulting suspension was cooled to room temperature and stirred for 16 hours. The suspension was filtered (the filtrate was saved for use in Example 30) and the collected solids were washed with methanol and then ether to give the title compound (0.889 g, 50%) as a yellow powder, mp 356-359 °C; MS(CI): 370 (M+H).
Analysis for C18H12ClN3O4 . 1.20CH3OH: Calculated: C, 56.50; H, 4.15; N, 10.30 Found: C, 56.50; H, 4.15; N, 10.55
1H NMR 13.34 (s, 1H, exchangeable), 12.45 (s, 1H, exchangeable), 8.30 (d, J= 8.61 Hz, 1H), 8.21 (s, 1H), 7.63 (d, J= 8.61 Hz, 1H), 7.48 (t, J=8.10 Hz, 1H), 7.40 (d, J= 7.46 Hz, 1H), 7.23 (d, J=8.10 Hz, 1H), 7.10 (t, J=7.46 Hz, 1H), 3.77 (s, 3H).

The starting 6-chloro-2-(2-methoxyanilino)-2,3,4,9-tetrahydro-1H-pyrrolo-[3,4-b]quinoline-1,3,9-trione was prepared in the following manner:

a. 6-Chloro-2-(2-methoxyanilino)-2,3,4,9-tetrahydro-1H-pyrrolo-[3,4-b]quinoline-1,3,9-trione.

To a stirred suspension of dimethyl-7-chloro-4-hydroxyquinoline -2,3-dicarboxylate (0.218 g, 0.74 mM) and 2-methoxyphenyl hydrazine hydrochloride (0.900 g, 5.20 mM) in ethanol (4 mL) was added triethylamine (0.83 mL, 5.9 mM). The resulting brown solution was refluxed for 22 hours. The solution was cooled to room temperature and precipitation occurred to give a tan suspension which was stirred for 16 hours. The suspension was filtered and the collected solids were discarded. The filtrate was diluted with ethyl acetate (50 mL) and washed with hydrochloric acid (3 x 50 mL, 1N) and brine (50 mL). Concentration of the washed solution under a nitrogen gas stream gave a tan powder (0.527 g). This material was refluxed in glacial acetic acid (5 mL) for 2 hours to give a thick tan suspension. This suspension was cooled to room temperature and stirred for 16 hours. The suspension was filtered and the collected solids washed with glacial acetic acid and then ether to give a tan powder (0.378 g). This material was stirred in a solution of water (5 mL) and methanol (1 mL) to give a tan suspension which was stirred for 16 hours. The suspension was filtered and the collected solids were washed successively with water, methanol and then ether to give the title compound (0.126 g, 46%) as a tan powder, mp 390 °C (decomp.); MS(CI): 370 (M+H).
Analysis for C18H12ClN3O4 . 0.20H2O:
Calculated: C, 57.90; H, 3.35; N, 11.25
Found: C, 57.92; H, 3.48; N, 10.93 1H NMR 13.80 (br s, 1H, exchangeable), 8.23 (d, J= 8.67 Hz, 1H), 7.89 (d, J=1.98 Hz, 1H), 7.79 (s, 1H, exchangeable), 7.58 (dd, J=1.98, 8.67 Hz, 1H), 6.97 (d, J=7.62 Hz, 1H), 6.80-6.73 (m, 3H), 3.86 (s, 3H).

Example 30. 7-Chloro-4-hydroxy-2-(2-methoxyphenyl)-1,2,5,10-tetra-hydropyridazino[4,5-b]quin-oline-1,10-dione.

The filtrate saved from Example 30 was diluted with water (600 mL) to give a tan suspension which was stirred at 0 °C for 1 hour and filtered to remove the solids. The filtrate was partially concentrated under a nitrogen gas stream to give a white suspension. This suspension was filtered and the collected solids were washed with water to give the title compound (0.347 g, 19%) as a white powder, mp 347-349 °C; MS(CI): 370 (M+H).
Analysis for C18H12ClN3O4 . 1.30H2O . 0.10CH3SO3H: Calculated: C, 54.00; H, 3.75; N, 10.43 Found: C, 54.07; H, 3.33; N, 10.41
1H NMR 12.68 (br s, 1H, exchangeable), 12.00 (br s, 1H, exchangeable), 8.16 (d, J= 8.61 Hz, 1H), 8.07 (s, 1H), 7.48-7.40 (m, 2H), 7.32 (d, J= 7.59 Hz, 1H), 7.16 (d, J=8.31 Hz, 1H), 7.05 (t, J= 7.59 Hz, 1H), 3.75 (s, 3H).

Example 31. 7-Chloro-4-hydroxy-2-(2-hydroxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quin-oline-1,10-dione.

A solution of 7-chloro-4-hydroxy-2-(2-methoxyphenyl)-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione (0.288 g, 0.78 mM) in methanesulfonic acid (5 mL) was heated to 140 °C for 7 hours and cooled to room temperature. The brown solution was diluted with water (5 mL) which caused an exotherm to 80 °C and a precipitate formed to give a brown suspension. This suspension was further diluted with water (10 mL) and filtered. The collected solids were washed with water (25 mL) and ether to give a brown solid (0.23 g). This material was suspended in water (13 mL) and choline hydroxide solution (45 wt% in methanol, 0.5 mL) was added to give a brown solution. This solution was warmed to 50 °C for 2 hours and cooled to room temperature. Hydrochloric acid (5 mL, 1N) was added to give a grey suspension. This suspension was filtered and the collected solids were washed with water and then ether to give the title compound (0.225 g, 81%) as a grey powder, mp > 400 °C; MS(CI): 356 (M+H).

Analysis for C17H10ClN3O4 . 0.80H2O . 0.10C4H10O:
Calculated: C, 55.35; H, 3.36; N, 11.13
Found: C, 55.53; H, 3.00; N, 10.89 1H NMR 12.68 (s, 1H, exchangeable), 12.01 (s, 1H, exchangeable), 9.53 (s, 1H, exchangeable), 8.16 (d, J=8.18 Hz, 1H), 8.06 (s, 1H), 7.46 (d, J= 8.18 Hz, 1H), 7.23 (m, 2H), 6.95 (d, J=7.80 Hz, 1H), 6.87 (t, J=7.17 Hz, 1H).

Example 32. 7-Chloro-4-hydroxy-3-(3-methoxyphenyl)-3,4,5,10-tetrahydropyridazino[4,5-b]quin-oline-4,10-dione.

A stirred suspension of 6-chloro-2-(3-methoxyanilino)-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione (1.85 g, 5.00 mM) in a solution of methanol (0.93 L) and methanesulfonic acid (93 mL) was refluxed for 16 hours to give a tan suspension. This suspension was cooled to room temperature and stirred for 24 hours. The suspension was filtered (the filtrate saved for use in Example 33) and the collected solids were washed with methanol and then ether to give the title compound (0.385 g, 21%) as a tan powder, mp 393-395 °C; MS(CI): 370 (M+H).

Analysis for C18H12ClN3O4 . 0.50H2O . 0.05CH3OH:
Calculated: C, 57.00; H, 3.50; N, 11.05
Found: C, 56.73; H, 3.11; N, 10.98 1H NMR 13.35 (s, 1H, exchangeable), 12.47 (s, 1H, exchangeable), 8.28 (d, J=8.75 Hz, 1H), 8.20 (d, J=1.83 Hz, 1H), 7.60 (dd, J=1.83, 8.75 Hz, 1H), 7.47-7.42 (t, J=8.06 Hz, 1H), 7.28-7.26 (m, 2H), 7.01 (dd, J=1.38, 8.06 Hz, 1H), 3.81 (s, 3H).

The starting 6-chloro-2-(3-methoxyanilino)-2,3,4,9-tetrahydro-1H-pyrrolo-[3,4-b]quinoline-1,3,9-trione was prepared in the following manner:

a. 6-chloro-2-(3-methoxyanilino)-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,9-trione.

To a stirred suspension of dimethyl 7-chloro-4-hydroxyquinoline -2,3-dicarboxylate (4.61 g, 15.6 mM) and 3-methoxyphenyl hydrazine hydrochloride (19.10 g, 109 mM) in ethanol (84 mL) was added triethylamine (17.4 mL, 125 mM). The resulting brown solution was refluxed for 40 hours and cooled to room temperature. Ethyl acetate (430 mL) was added to give a tan suspension. This suspension was filtered to remove the solids which were discarded. The filtrate was washed with hydrochloric acid (3 x 750 mL, 1N) which caused precipitation from the ethyl acetate layer. This ethyl acetate suspension was filtered to give a tan solid (0.940 g). The filtrate was saved. The combined hydrochloric washes were reextracted with ethyl acetate and these extracts were combined with the saved ethyl acetate filtrate from above. This solution was concentrated to provide a solid which was triturated with ether/ethyl acetate to give a tan suspension. This suspension was filtered to give a second crop of tan solid (1.60 g). The filtrate was concentrated to a solid and triturated with ether/ethyl acetate to give a suspension. This suspension was filtered to give a third crop of tan solid (0.70 g). The solids saved from the above filtrations were combined (3.24 g) and refluxed in glacial acetic acid (32 mL) for 3 hours. The resulting suspension was cooled to room temperature and stirred for 16 hours. This suspension was filtered and the collected solids were washed with glacial acetic acid, and then ether to give the title compound (1.93 g, 33 %) as a tan powder, mp 369 °C (decomp.); MS(CI): 370 (M+H).

Analysis for C18H12ClN3O4 . 0.5OH2O:
Calculated: C, 57.10; H, 3.46; N, 11.10
Found: C, 57.21; H, 3.53; N, 10.86 1H NMR 13.75 (br s, 1H, exchangeable), 8.51 (s, 1H, exchangeable), 8.23 (d, J=8.69 Hz, 1H), 7.89 (d, J=1.87 Hz, 1H), 5.58 (dd, J= 1.87, 8.69 Hz, 1H), 7.08 (t, J=7.96 Hz, 1H), 6.42-6.39 (m, 3H), 3.69 (s, 3H).

Example 33. 7-Chloro-4-hydroxy-2-(3-methoxyphenyl)-1,2,5,10-tetra-hydropyridazino[4,5-b]quin-oline-1,10-dione.

The filtrate set aside and saved from Example 32 was diluted with water/ice (1.0 L) to give a brown suspension which was stirred for 16 hours. The suspension was filtered and the collected solids were washed with water and then ether to give the title compound (1.04 g, 56%) as a tan powder, mp 312-315 °C; MS(CI): 370 (M+H).
Analysis for C18H12ClN3O4 . 0.20H2O . 0.10CH3SO3H: Calculated: C, 56.80; H, 3.37; N, 10.97 Found: C, 56.90; H, 3.55; N, 10.93
1H NMR 8.17 (d, J=8.64 Hz, 1H), 8.06 (d, J=1.71 Hz, 1H), 7.43 (dd, J=1.71, 8.64 Hz, 1H), 7.36 (t, J=8.49, 1H), 7.15-7.12 (m, 2H), 6.93 (d, J=8.49 Hz, 1H), 3.79 (s, 3H).

Example 34. 7-Chloro-4-hydroxy-2-(3-hydroxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quin-oline-1,10-dione.

A solution of 7-chloro-4-hydroxy-2-(3-methoxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione (0.600 g, 1.62 mM) in methanesulfonic acid (12 mL) was heated to 130-140 °C for 3.5 hours and cooled to room temperature. The brown solution was diluted with water (36 mL) which caused an exotherm and a precipitate formed to give a brown suspension. This suspension was filtered and the collected solids were washed with water (50 mL) and ether to give a brown solid (0.447 g). This material was suspended in water (26 mL) and choline hydroxide solution (45 wt% in methanol, 1.5 mL) was added to give a brown solution. This solution was warmed to 50 °C for 3 hours and cooled to room temperature. Hydrochloric acid (10 mL, 1N) was added to give a brown suspension which was filtered. The collected solids were washed with water and then ether to give a brown powder (0.302 g). This brown powder was suspended in methanol and the resulting suspension concentrated to leave a brown solid. The solid was suspended in methanol and concentrated two additional times to give the title compound (0.260 g, 45%) as a brown powder; mp 333 °C (dec.); MS (CI) : 356 (M+H).

Analysis for C17H10ClN3O4. 1.0H2O. 1.4OHCl:
Calculated: C, 48.1; H, 3.18; N, 9.89
Found: C, 48.5; H, 3.16; N, 9.45 1H NMR 9.6 (br s, 1H, exchangeable), 8.15 (br s, 1 H), 8.06 (br s, 1H), 7.46 (br s, 1H), 7.23 (br s, 1H), 6.95 (br s, 1H), 6.75 (br s, 1H).

Example 35. 7-Chloro-4-hydroxy-2-(4-trifluoromethoxyphenyl)-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione.

To a stirred suspension of 3-carbomethoxy-7-chloro-4-hydroxy-quinoline-2-carboxylic acid N-2-(4-trifluoromethoxyphenyl) hydrazide (600 mg, 1.3 mM) in methanol (85 mL) at ambient temperature was added methanesulfonic acid (3 mL). The reaction mixture was heated to reflux for 68 hours during which time a slight precipitate formed. The solid was removed by filtration. Water (150 mL) was added to the filtrate to produce a light suspension which was isolated via vacuum filtration and dried over phosphorous pentoxide to provide the title compound (467 mg, 84%) as a peach colored solid, mp 320-322 °C; MS (CI): 424 (M+H).

Analysis for $C_{18}H_9N_3O_4F_3Cl$. 0.8 H_2O:
Calculated: C, 49.34; H, 2.44; N, 9.59
Found: C, 49.01; H, 2.10; N, 9.55 ^{1}H NMR 12.90 (s,1H, exchangeable), 12.07 (br s, 1H, exchangeable), 8.16 (d, J = 8.64 Hz, 1H), 8.06 (s, 1H), 7.71 (d, 2H, J = 8.82), 7.45 - 7.50 (m, 3H).

The starting 3-carbomethoxy-7-chloro-4-hydroxy quinoline-2-carboxylic acid N-2-(4-trifluoromethoxyphenyl) hydrazide was prepared in the following manner:

a. 3-Carbomethoxy-7-chloro-4-hydroxyquinoline-2-carboxylic acid.

To a stirred suspension of dimethyl 7-chloro-4-hydroxy quinoline-2,3-dicarboxylate (1.0 g, 3.38 mM) in water (20 mL) was added an aqueous solution of sodium hydroxide (0.27 g, 6.75 mM). Upon addition, the suspension dissolved. The reaction mixture was warmed to 60 °C for 1 hour. After this time the reaction was cooled to room temperature and acidified with concentrated hydrochloric acid. The product was then extracted into diethyl ether and ethyl acetate. The organic extracts were dried over magnesium sulfate, filtered and concentrated in vacuo to provide the title compound as a crude solid (900 mg). This material was purified by recrystalization employing an ethyl acetate/hexane co-solvent system to provide the title compound (571 mg, 60%) as a white solid mp 296 °C (dec); MS (CI) = 238 (M+H).

Analysis for $C_{12}H_8NO_5Cl$. 0.45 $CH_3CO_2CH_2CH_3$. 0.10 H_2O:
Calculated: C, 51.30; H, 3.68; N 4.34
Found: C, 51.28; H, 3.62; N 3.97 ^{1}H NMR 8.22 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 1.8 Hz, 1H), 7.28 (dd, J = 8.7, 1.8 Hz, 1H), 3.90 (s, 3H).

b. 3-carbomethoxy-7-chloro-4-hydroxy quinoline-2-carboxylic acid N-2-(4-trifluoromethoxyphenyl)hydrazide.

The free base of 4-(trifluoromethoxy)phenyl hydrazine was prepared from the hydrochloride salt by treatment of the suspended salt (400 mg, 1.75 mM) in ethyl acetate (50 mL) with 2N sodium hydroxide(50 mL). The organic layer was separated, dried over magnesium sulfate and concentrated in vacuo to provide the free base of 4-(trifluoromethoxy)phenyl hydrazine (325 mg, 1.69 mM). This material was placed into anhydrous tetrahydrofuran (5 mL) and cooled to 0 °C under a nitrogen atmosphere. Concurrently, 3-carbomethoxy-7-chloro-4-hydroxyquinoline-2-carbonyl chloride was prepared from 3-carbomethoxy-7-chloro-4-hydroxyquinoline-2-carboxylic acid (121 mg, 0.43 mM) by heating to 60 °C in thionyl chloride (4 mL). After 3 hours the crude acid chloride was isolated by distilling away the

excess thionyl chloride. The crude3-carbomethoxy-7-chloro-4-hydroxyquinoline-2-carbonyl chloride (130 mg, 0.43 mM) was then placed in anhydrous tetrahydrofuran (3 mL) at ambient temperature and added via cannula to the 4-(trifluoromethoxy)phenyl hydrazine solution. After 30 minutes the reaction mixture was poured into 1.0N hydrochloric acid producing a precipitate. The solid was isolated to yield the title compound (185 mg, 95%) as an off-white solid, mp 346-350 °C; MS 456 (M+H). ^{1}H NMR 12.67 (s, 1H, exchangeable), 10.79 (s, 1H, exchangeable), 8.37 (br s, 1H, exchangeable), 8.13 (d, J = 8.61 Hz, 1H), 7.83 (d, J = 1.76 Hz, 1H), 7.48 (dd, J = 8.61, 1.76 Hz, 1H), 7.21 (d, J = 8.50 Hz, 2H), 6.94 (d, J = 8.50 Hz, 2H), 3.70 (s, 3H).

Example 36. 7-Chloro-3-(3-chloro-4-methoxyphenyl)-1-hydroxy-3,4,5,10-tetrahydropyridazino-[4,5-b]quinoline-4,10-dione.

A stirred solution of 3-carbomethoxy-7-chloro-4-hydroxy-quinoline-2-carboxylic acid N-2-(3-chloro-4-methoxyphenyl)hydrazide (2.25 g, 5.16 mM) in methanol (1.13 L) and methanesulfonic acid (113 mL) was refluxed for 1 hour during which time a brown precipitate formed. This suspension was cooled to room temperature, stirred for 16 hours and filtered (the filtrate was saved for use in Example 37). The collected solids were washed with methanol and then ether to give the title compound (0.153 g, 7%) as a yellow powder, mp 395-396 °C; MS(CI): 404 (M+H).

Analysis for C18H11Cl2N3O4 . 1.20H2O:
Calculated: C, 50.77; H, 3.17; N, 9.87
Found: C, 50.33; H, 2.87; N, 9.61 1H NMR 13.36 (s, 1H, exchangeable), 12.50 (s, 1H, exchangeable), 8.28 (d, J=8.78 Hz, 1H), 8.22 (d, J=1.74 Hz, 1H), 7.77 (d, J=2.42 Hz, 1H), 7.67 (dd, J=2.42, 8.91 Hz, 1H), 7.62 (dd, J=1.74, 8.78 Hz, 1H), 7.30 (d, J=8.91 Hz, 1H), 3.94 (s, 3H).

The starting 3-carbomethoxy-7-chloro-4-hydroxyquinoline-2-carboxylic acid N-2-(3-chloro-4-methoxyphenyl)hydrazide was prepared in the following manner:

a. 3-Chloro-4-methoxyphenylhydrazine

A solution of 3-chloro-p-anisidine hydrochloride (10 g, 52 mM) in hydrochloric acid (48 mL, 12N) was cooled to -10 °C. A solution of sodium nitrite (3.56 g, 52 mM) in water (19.5 mL) was slowly added to the reaction such that the temperature did not exceed -5 °C. The reaction mixture was then stirred for 1 hour at 0 °C. The resulting diazonium salt solution was then added to a cold (0 °C, ice bath) solution of tin chloride dihydrate (44 g, 193mM) in hydrochloric acid (29 mL, 12N) at a rate such that the temperature did not exceed 5 °C. A purple foamy suspension was formed and, after adding water (20 mL), the mixture was stirred for 3 hours at 0 °C. The purple solids were filtered, washed with ethyl acetate and then added to aqueous sodium bicarbonate solution. The resulting mixture was partitioned with ethyl acetate and the entire mixture filtered to separate insoluble tin salts. The collected tin salts were washed with water and ethyl acetate. The ethyl acetate layer from the initial filtration and the ethyl acetate from the washes of the tin salts were combined, dried over magnesium sulfate and concentrated to provide the title compound (4.49 g, 51%) as a brown solid; MS(CI) : 172 (M-1) 1H NMR 6.94-6.90 (m, 2H), 6.71 (dd, J = 2.70, 9.00 Hz, 1H), 3.73 (s, 3H).

b. 3-carbomethoxy-7-chloro-4-hydroxyquinoline-2-carboxylic acid N-2-(3-chloro-4-methoxyphenyl)hydrazide.

To a solution of 3-chloro-4-methoxyphenyl hydrazine (4.26 g, 24.7 mM) in 35b.) in tetrahydrfuran (200 mL) was added a solution of 3-carbomethoxy-7-chloro-4-hydroxyquinoline-2-carbonyl chloride (3.54 g, 11.8 mM, as prepared in Example 35b.) in tetrahydrofuran (100 mL) at 0 °C. The resulting yellow suspension was stirred at 0 °C for 30 minutes and diluted with water (200 mL) to give a yellow solution.

This solution was further diluted with hydrochloric acid (600 mL, 1N) to give a tan suspension which was stirred for 1 hour. The suspension was filtered (the filtrate was saved) and the collected solids were washed with water and then ether to give the title compound (2.30 g, 45%) as a tan powder, MS(CI): 436 (M+H), which was used above in the synthesis described for 7-chloro-3-(3-chloro-4-methoxyphenyl)-1-hydroxy-3,4,5,10-tetrahydropyrida-zino[4,5-b]quinoline-4,10-dione. 1H NMR 12.69 (s, 1H, exchangeable), 10.72 (s, 1H, exchangeable), 8.14 (d, J=8.50 Hz, 1H), 8.00 (br s, 1H, exchangeable), 7.76 (s, 1H), 7.48 (d, J=8.50 Hz, 1H), 7.05 (d, J=8.80 Hz, 1H), 6.98 (d, J=2.28 Hz, 1H), 6.85 (dd, J=2.28, 8.80 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H).

After sitting for five days, further precipitation occurred in the above saved acidic filtrate. The solids were collected to provide material (1.80 g) consisting of a mixture of the title compound (60%), 7-chloro-2-(3-chloro-4-methoxyphenyl)-1-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione (35%) and 7-chloro-3-(3-chloro-4-methoxyphenyl)-1-hydroxy-3,4,5,10-tetra-hydropyridazino[4,5-b]quinoline-4,10-dione (5%).

Example 37. 7-Chloro-2-(3-chloro-4-methoxyphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione.

The filtrate saved from Example 36 was concentrated to approximately 500 mL and diluted with water/ice (1.1 L) to give a light green suspension which was stirred for 3 hours. The suspension was filtered and the collected solids were resuspended in water (500 mL) and stirred for 16 hours. This suspension was filtered and the collected solids were washed successively with water, acetonitrile/ether and then ether to give the title compound (1.42 g, 68%) as a green powder, mp 348-351 °C; MS(CI): 404 (M+H).

Analysis for C18H11Cl2N3O4 . 1.20H2O . 0.50CH3SO3H:
Calculated: C, 46.89; H, 3.27; N, 8.87
Found: C, 46.54; H, 2.96; N, 8.91 1H NMR 12.82 (br s, 1H, exchangeable), 12.05 (br s, 1H, exchangeable), 8.16 (d, J=9.01 Hz, 1H), 8.06 (d, J=1.56 Hz, 1H), 7.64 (d, J=2.37 Hz, 1H), 7.52 (dd, J=2.37, 8.89 Hz, 1H), 7.45 (dd, J=1.56, 9.01 Hz, 1H), 7.23 (d, J=8.89 Hz, 1H), 3.91 (s, 3H).

Example 38. 7-Chloro-2-(2-methoxypyrid-5-yl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione.

To a cold (ice bath) stirred solution of 5-hydrazino-2-methoxypyridine (0.839 g, 6.03 mM) in anhydrous THF (40 mL) was added dropwise a solution of 3-carbomethoxy-7-chloro-4-hydroxy quinoline-2-carbonyl chloride (1.67 g, 5.59 mM) in THF (40 mL). After stirring at 0 °C for 3 hr, the reaction mixture was allowed to warm to room temperature and stirred an additional 17 hr. The reaction mixture was diluted with water/ethyl acetate (30 mL/40 mL) and the pH of the resulting mixture adjusted to 4 by adding 2N sodium hydroxide. The resulting mixture was filtered and the collected orange solid was then triturated in warm methanol (10 mL) and filtered to separate the title compound (0.17 g, 5.7%) as a brown solid, mp 235-237 °C (dec); MS(CI): 371 (M+H).

Analysis for C17H11ClN4O4 . 1.45H2O
Calculated: C, 51.45; H, 3.53; N, 14.12
Found: C, 51.26; H, 2.95; N, 14.18 1H NMR 12.88 (br s, 1H, exchangeable), 12.09 (br s, 1H, exchangeable), 8.34 (d, J=2.24 Hz, 1H), 8.16 (d, J=7.6 Hz, 1H), 8.05 (s, 1H), 7.85 (dd, J=8.7, 2.24 Hz, 1H), 7.46 (d, J=7.6 Hz, 1H), 6.93 (d, J=8.7 Hz, 1H), 3.88 (s, 3H).

The starting 3-carbomethoxy-7-chloro-4-hydroxyquinoline-2-carbonyl chloride and 5-hydrazino-2-methoxypyridine were prepared in

the following manner:

a. 3-Carbomethoxy-7-chloro-4-hydroxyquinoline-2-carbonyl chloride.

After refluxing a mixture of 3-carbomethoxy-7-chloro-4-hydroxyquinoline-2-carboxylic acid (1.56 g, 5.6 mM) and thionyl chloride (5 mL, 68.5 mM) in methylene chloride (12 mL) for 2 hr, the resulting cloudy solution was concentrated to leave a solid. This residue was diluted with THF and reconcentrated to leave a solid which was again treated with THF and concentrated to leave the crude title compound (1.67 g, 100%) as a cream colored solid.

b. 5-Hydrazino-2-methoxypyridine.

To a stirred cold (-10 °C) solution of 5-amino-2-methoxypyridine (5.01 g, 40.4 mM) in concentrated hydrochloric acid (50 mL) was added dropwise a solution of sodium nitrite (2.9 g, 42 mM) in water (10 mL). After stirring at -10 °C for 10 min, the reaction mixture was added in portions to a cold (-20 °C) stirred solution of stannous chloride dihydrate (22.9 g, 101 mM) in concentrated hydrochloric acid (15 mL). The resulting thick mixture was diluted with water (10 mL) and concentrated hydrochloric acid (15 mL) and stirring at -10 °C was continued for an additional 1 hr. The mixture was then filtered and the collected solids washed with ether (three 40 mL portions) and dried in vacuo to afford the crude hydrochloride salt (7.03 g, 125%) of the title compound as a pink solid. A portion (3.97 g, ca. 22 mM) of this material was suspended in ethyl acetate/ether (75 mL/25 mL) and 2N sodium hydroxide was added to the resulting stirred suspension until the pH reached 6.5. After stirring for 15 min, the the organic phase was separated and the aqueous phase was extracted twice with 50 mL portions of ethyl acetate/ether (1:1). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated to leave the title compound (0.839 g, 27%) as a crude solid which was used without further purification.

Example 39

7-Chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

To a stirred suspension of 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid N-2-(4-methoxy-2-methylphenyl) hydrazide (3.0 g, 7.2 mM) and the solids (0.6 g,1.6 mM, of a mixture consisting of 7-chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl) -1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione and 6-chloro-2-(4-methoxy-2-methylanilino)-2,3,4,9-tetrahydro-1H-pyrrolo-[3,4-b]quinoline-1,3,9-trione) collected from the concentrated filtrate described in Example 1a) below in methanol (500 mL) was added methanesulfonic acid (50 mL) and the resulting amber suspension was refluxed for 7 hr. The resulting solution was stirred at room temperature overnight and then diluted with ~ 600 mL of ice/water to give a tan suspension. After stirring for 2 hr, the suspension was filtered to give a solid (2.8 g, 100%). Recrystallization of this material from boiling methanol (500 mL) gave the title compound as a white powder (1.7 g, 61%), mp 354-356 C.
Analysis for C19H14ClN3O4 . 1.5 H2O . 0.2 CH3OH . 0.2 (C2H5)2O:
Calculated: C, 55.60; H, 4.62; N, 9.73
Found: C, 55.25; H, 4.35; N, 9.60

1H NMR (DMSO-d6): 12.74 (br s, 1H, exchangeable), 12.00 (br s, 1H, exchangeable), 8.16 (d, J = 8.8 Hz, 1H), 8.06 (s, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.91 (s, 1H), 6.85 (d, J = 8.6 Hz, 1H), 3.79 (s, 3H), 2.08 (s, 3H).

The starting 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(4-methoxy-2-methylphenyl)hydrazide was prepared in the following manner:

a) 7-Chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(4-methoxy-2-methylphenyl)hydrazide.

4-Methoxy-2-methylphenylhydrazine hydrochloride (4.7 g, 25 mM) was partitioned between diethyl ether (300 mL) and 2N sodium hydroxide (50 mL). The ether layer was separated and the aqueous layer was extracted with an additional portion of ether (300 mL). The combined ether extracts were dried (Na_2SO_4), filtered and concentrated to leave the free hydrazine as a yellow powder. This hydrazine was dissolved in anhydrous tetrahydrofuran (180 mL). After cooling the resulting amber solution to 0 C, a solution of 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carbonyl chloride (3.0 g, 10.0 mM) in THF (90 mL) was added dropwise over 15 minutes. When the addition was completed, the resulting yellow suspension was stirred at 0 C for 30 minutes and then at room temperature for 2 hr. The reaction mixture was quenched by adding ~200 g of water/ice followed by 500 mL of cold 1N hydrochloric acid. The resulting yellow suspension was stirred for 1 hr and the yellow solids were collected via filtration, washed with water and then ether and air dried to provide the title compound as a white powder (3.3 g, 79%). The filtrate was partially concentrated to remove most of the THF and the resulting suspension was filtered to provide an additional ~ 0.6 g of solids consisting (HPLC analysis) of 35% of 7-chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione and 65% of 6-chloro-2-(4-methoxy-2-methylanilino)-2,3,4,9-tetrahydro-1H-pyrrolo-[3,4-b]quinoline-1,3,9-trione.

The 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carbonyl chloride used in Example 39a was prepared in the following manner:

b) 7-Chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carbonyl chloride.

To a stirred suspension of 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquino-line-2-carboxylic acid (prepared from the diester) (35.0 g, 0.124 M) in alcohol free chloroform (850 mL) under nitrogen

was added thionyl chloride (60.3 g, 37 mL, 0.507 M) in one portion. The resulting mixture was refluxed until solution occurred (1.5 hr). After cooling to room temperature, the solution was concentrated using a rotary evaporator (bath temperature = 25 C) to give a tan solid. This material was dried in vacuo at room temperature for two days to provide the title acid chloride (34.7 g, 93.2%) as a tan solid.

The 2-methyl-4-methoxyphenylhydrazine hydrochloride used in Example 39a was prepared in the following manner:

c) 2-Methyl-4-methoxyphenylhydrazine hydrochloride.

A solution of sodium nitrate (5.60 g, 81.2 mM) in water (56 mL) was added in the course of 20 minutes to a mechanically stirred suspension of 2-methyl-4-methoxyaniline (10.42 mL, 81.0 mM) in a mixture of 12N HCl (60 mL) and water (64 mL) maintained at -5 C. The dark solution was cooled to -15 C over 15 minutes and a solution of SnCl2.2H2O (53.3 g, 236.2 mM) in 12N HCl (36 mL) was added over 30 minutes, the temperature being maintained between -15 and -10 C. The pink suspension was stirred at -15 C for 30 minutes and ethanol (25 mL) was added dropwise. The suspension was stirred at -15 C for 3 hours and filtered under N2(g). The filtration was done at -10 C (jacketed funnel) and took 2 hours. The cake was sucked dry and washed with 50% ethanol/ether (200 mL) and ether (500 mL). The solid was dried under a N2(g) stream for 20 hours to give the hydrochloride salt of the title compound (8.60 g, 56%) as a grey powder, mp = 107 (decomp.); MS(CI) : 152 (M+H).

Analysis for C8H12N2O . HCl . H2O:
Calculated: C, 46.49; H, 7.32; N, 13.55
Found: C, 46.46; H, 6.92; N, 13.00

300 MHz 1H NMR (DMSO-d6): 10.01 (s, 3H, exchangeable), 7.48 (br s, 1H, exchangeable), 6.94 (d, J=8.8 Hz, 1H), 6.77-6.74 (m, 2H), 3.70 (s, 3H), 2.19 (s, 3H).

Example 39(2)

An alternate synthesis of 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acidN-2-(4-methoxy-2-methylphenyl) hydrazide is provided below. 4-Methoxy-2-methylphenylhydrazine hydrochloride (11.38g, 60.32mM) was suspended in dry tetrahydrofuran (264 mL) under argon and treated with 2,6-lutidine (14.06 mL, 120.6mM). This reaction mixture was cooled in an ice bath and a solution of 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carbonyl chloride (18.14g, 60.32mM) in THF (328 mL) was added at a rate to maintain the reaction temperature at 2-5^{0}C. After the addition was completed, the reaction mixture was stirred 25 minutes at 0-2^{0}C and then added with stirring to ice cold 1.0 N HCl (1300mL). Stirring was continued for several hours until the mixture became a free flowing suspension. The solids were filtered off, washed with water and air dried to give the title compound (17.57g, 70%) as a tan solid which was cyclized to title compound (39) using standard conditions.

Note: 2,6-di-tert-butylpyridine may be used in place of 2,6-lutidine(2,6-dimethylpyridine) in the above procedure.

Example 40.

7-Chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione N-methylglucamine salt.

7-Chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione (0.45 g, 1.17 mM) was stirred in methanol (20 mL) and N-Methyl-D-Glucamine (0.23 g, 1.17 mM) was added to give a clear yellow solution. This solution was concentrated

and the residue was dissolved in water (20 mL) to give a yellow solution. This solution was filtered through a Gellman 0.45 um Acrodisc and concentrated to give a yellow residue. The residue was triturated with 2-propanol (20 mL) to give a yellow suspension. The solids were collected and washed with 2-propanol to give the title compound (0.20 g, 29%) as a yellow powder, mp = 177 C (decomp.).

Analysis for C19H14ClN3O4 . C7H18NO5 . 1.5H2O:
Calculated: C, 51.53; H, 5.65; N, 9.24
Found: C, 51.17; H, 5.28; N, 8.88

300 MHz 1H NMR (DMSO-d6): 8.14 (s, 1H), 8.10 (d, J=8.6 Hz, 1H), 7.33 (d, J=8.6 Hz, 1H), 7.06 (d, J=8.0 Hz, 1H), 6.76 (br m, 2H), 3.84 (m, 1H), 3.76 (s, 3H), 3.65-3.56 (m, 2H), 3.48-3.38 (m, 3H), 2.95-2.87 (m, 2H), 2.51-2.46 (m, 3H), 2.02 (s, 3H).

Example 41

7-Chloro-3-(4-chloro-2-methylphenyl)-4-hydroxy-3,4,5,10-tetrahydro-pyridazino[4,5-b]quinoline-4,10-dione.

7-Chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(4-chloro-2-methylphenyl)hydrazide (2.00 g, 4.76 mM) was suspended in methanol (1.0 L) and methanesulfonic acid (100 mL) was added at a fast dropwise rate with good stirring. The resulting yellow suspension was refluxed for four days to give an orange solution. Methanol (500 mL) was distilled off and the concentrated solution was cooled to room temperature to give a yellow suspension. This suspension was filtered (the filtrate was saved for use in Example 42). The collected solids were washed with methanol and ether to give the title compound (0.72 g, 39%) as a yellow powder, mp 336-339 C; MS(CI) : 388 (M+H).
Analysis for C18H11Cl2N3O3 . 1.15H2O :
Calculated: C, 52.87; H, 3.27; N, 10.28

Found: C, 52.51; H, 2.87; N, 10.12
300 MHz 1H NMR (DMSO-d6): 13.40 (s, 1H, exchangeable), 12.55 (s, 1H, exchangeable), 8.30 (d, J=8.8 Hz, 1H), 8.20 (s, 1H), 7.62 (d, J=8.8 Hz, 1H), 7.53 (s, 1H), 7.43 (s, 2H), 2.16 (s, 3H).

Example 42

7-Chloro-2-(4-chloro-2-methylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

The saved filtrate from Example 41. was diluted with water (1.0 L) and the resulting suspension was stirred for 2 hours. The solids were collected and washed with water and then ether to give the title compound (0.54 g, 29%) as an off-white powder, mp 355-357 C; MS(CI) : 388 (M+H).

Analysis for C18H11Cl2N3O3 . 0.20H2O :
Calculated: C, 55.18; H, 2.93; N, 10.72
Found: C, 55.00; H, 2.62; N, 10.66

300 MHz 1H NMR (DMSO-d6): 12.84 (br s, 1H, exchangeable), 12.07 (br s, 1H, exchangeable), 8.16 (d, J=8.6 Hz, 1H), 8.07 (s, 1H), 7.47-7.33 (m, 4H), 2.12 (s, 3H).

Example 42a

Alternatively, the title compound was prepared by the following procedure described generally in Scheme 6 and similar conditions to that described in Example 82 wherein to a stirred suspension of 2-pyrrolidinocarbamide-7-chloro-4-hydroxy quinoline 3-carboxylic acid in THF was added DCC. A THF solution of N-t-butoxy carbonyl-N'-4-chloro-2-methylphenyl hydrazine was immediately added to the above suspension. The reaction mixture was stirred at room temperature for 4 hours. Upon completion of the coupling (after monitoring by an appropriate chromalographic method - e.g. TLC or HPLC) the byproduct

urea was removed via vacuum filtration. Partial purification by flash chromatography employing 5% methanol/CH_2Cl_2 yielded the desired hydrazide. To the hydrazide suspended in THF was added methanesulfonic acid. The reaction was stirred at room temperature for 24 hours and then poured into ice water. The resulting precipitate was isolated, dried and triturated/sonicated with methanol and isolated to yield the title compound.
The starting 2-pyrrolidinocarbamide-7-chloro-4-hydroxyquinoline-3-carboxylic acid and related starting materials were prepared according to the procedures described for example 82a and b (infra).

The starting N-t-butoxycarbonyl-N^1-4-chloro-2-methylphenyl hydrazine was prepared in the following manner:

To a suspension of 4-chloro-2-methyl-phenylhydrazine (992 mg, 6.33 MM) and potassium carbonate (1.44g, 10..4 MM) in saturated aqueous sodium bicarbonate solution (12 ML) was added a solution of di-t-butyl dicarbonate (1.52g, 6.96 MM) in THF (24 ML). After 2.5 hours, the mixture was partitioned between diethyl ether and the aqueous layer. The organic extracts were combined and washed with water and brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by flash column chromatography with 25% diethyl ether-hexanes as eluant yielding the title compound (1.56g, 96%) as a tan solid, MS(CI): 256,(M). 300MH^2 H NMR (DMSO-d6); 8.81(br S, 1H), 7.17(br S, 1H), 7.00-7.08(m, 2H), 6.55-6.62(m, 1H), 2.09(s, 3H), 1.41(s,9H).

Example 43

7-Chloro-2-(2,4-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione.

7-Chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(2,4-dimethylphenyl)hydrazide (3.80 g, 9.50 mM) was suspended in methanol (330 mL) and methanesulfonic acid (83 mL) was added at a

fast dropwise rate with good stirring. The resulting orange suspension was refluxed for 20 hours to give an amber solution. This solution was cooled to room temperature and water (75 mL) was added dropwise to give a yellow suspension which was stirred for 2 hours. The solids were filtered off and the filtrate was diluted with water (300 mL) to give a yellow suspension which was stirred for 20 hours. The solids were collected and washed with water, methanol/ether, then ether to give the crude title compound (1.80 g). Recrystallization from methanol gave the title compound (0.58 g, 17%) as a tan powder, mp = 349-351 C; MS(CI): 368 (M+H).

Analysis for C19H14ClN3O3 . H2O . 0.5CH3OH:
Calculated: C, 56.25; H, 4.34; N, 10.06
Found: C, 56.01; H, 4.36; N, 9.90

300 MHz 1H NMR (DMSO-d6): 12.72 (br s, 1H, exchangeable), 12.02 (br s, 1H, exchangeable), 8.16 (d, J=8.7 Hz, 1H), 8.06 (s, 1H), 7.46 (d, J=8.7 Hz, 1H), 7.18 (m, 3H), 2.33 (s, 3H), 2.07 (s, 3H).
The starting hydrazide was prepared from the corresponding acid chloride which was prepared from the corresponding diester.

Example 43a

Alternatively, the title compound was prepared according to the general procedure described in 42a except using the appropriate N-t-butoxy carbonyl-N'-2,4-dimethyl phenylhydrazine which was prepared as described in 42a except 2, 4-dimethyl phenylhydrazine was reacted with di-t-butyldicarbonate.

Example 44

7-Chloro-2-(3,4-dihydroxyphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

7-Chloro-4-hydroxy-2-(3,4-dimethoxyphenyl)-1,2,5,10-tetrahydropyrida-

zino-[4,5-b]quinoline-1,10-dione (1.00 g, 2.50 mM) was refluxed in 48% HBr (40 mL) for 6 hours to give an orange suspension. Heat was removed and the suspension was filtered while still warm. The collected solids were washed with water and then ether to give the crude product (0.94 g) as a yellow powder. This material was recrystallized from refluxing methanol (600 mL) to give the title compound (0.63 g, 68%) as a yellow powder, mp = 269-272 C; MS(CI): 372 (M+H).

Analysis for C17H10ClN3O5 . 0.5H2O . 0.75CH3OH:
Calculated: C, 52.67; H, 3.49; N, 10.38
Found: C, 52.66; H, 3.64; N, 10.14

300 MHz 1H NMR (DMSO-d6): 12.67 (br s, 1H, exchangeable), 11.97 (br s, 1H, exchangeable), 9.19 (br s, 1H, exchangeable), 9.10 (br s, 1H, exchangeable), 8.15 (d, J=8.3 Hz, 1H), 8.04 (s, 1H), 7.44 (d, J=8.3 Hz, 1H), 6.89-6.73 (m, 3H).

The starting 7-chloro-4-hydroxy-2-(3,4-dimethoxyphenyl)-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione was prepared as described in Example 45.

Example 45.
7-Chloro-4-hydroxy-2-(3,4-dimethoxyphenyl)-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione.

7-Chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carbonyl chloride (7.00 g, 23.3 mM) was dissolved in tetrahydrofuran (210 mL) and added dropwise over 20 minutes to a cold (0 C) solution of 3,4-dimethoxyphenylhydrazine (9.80 g, 58.3 mM) in tetrahydrofuran (420 mL) with stirring. The resulting brown suspension was stirred at 0 C for 30 minutes and at room temperature for 2 hours. Ice/water slurry (450 mL) was added to the reaction mixture followed by 1N HCl (1.2 L)

and the brown suspension was stirred for 1 hour. The solids were separated by filtration and washed with water and then ether to provide7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(2,4-dimethoxyphenyl)hydrazide (15 g, wet). The combined filtrate and washes were partially concentrated to remove the THF whereupon a precipitate formed. This precipitate was collected and washed with water and then ether to give the crude title compound (2.00 g). Recrystallization of this crude from refluxing methanol (500 mL) gave the title compound (0.98 g, 10%) as a tan powder, mp = 334-336 C; MS(CI): 400 (M+H).

Analysis for C19H14ClN3O5 . CH3OH:
Calculated: C, 55.63; H, 4.20; N, 9.73
Found: C, 55.27; H, 4.31; N, 9.56

300 MHz 1H NMR (DMSO-d6): 12.75 (s, 1H, exchangeable), 12.01 (s, 1H, exchangeable), 8.16 (d, J=8.6 Hz, 1H), 8.05 (s, 1H), 7.45 (d, J=8.6 Hz, 1H), 7.13 (S, 1H), 7.03 (S, 2H), 3.80 (S, 3H), 3.76 (S, 3H).

Example 46

7-Chloro-4-hydroxy-2-(2-methylthioethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

To a suspension of sodium thiomethoxide (230mg, 3.2mM) in dimethylformamide (20mL), was added in one portion 2-(2-bromoethyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione (0.4 g, 1.08 mM, prepared in Example 4a. of docket No. 37811) as a dry powder. This mixture was warmed to gentle reflux for about three hours. At this point the heat was removed and the reaction mixture was poured into ice cold 1.2N HCl (100mL) and stirred about one hour. The resulting precipitate was vacuum filtered and washed with water and ether, then vacuum dried at 50oC to yield 330mg (91%) of the title

compound as an off white powder. mp = 275-277oC; MS: 338(M+1).

Analysis for C14H12ClN3O3S
Calculated: C, 49.78; H, 3.58; N, 12.44
Found: C, 49.73; H, 3.73; N, 12.30
NMR : 2.11(s, 3H), 2.79 (t, 2H, J=7.13 Hz), 4.09 (t, 2H, J=7.08 Hz), 7.42(dd, 1H, J=8.59, 1.6Hz), 8.57(d, 1H, J=1.77Hz), 8.13(d, 1H, J=8.64 Hz), 11.8 (brs, 1H), 12.64(brs, 1H).

Example 47

7,9-dichloro-2-(2,4-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione.
To a stirred suspension of 5,7-dichloro-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid N-2-(2,4-dimethylphenyl) hydrazide (3.60 g, 8.31 mM) in methanol (151 mL) was slowly added methanesulfonic acid (7.2 mL) and the resulting mixture was heated to reflux. After 2 hr at reflux, the reaction mixture was allowed to cool to room temperature and then filtered to separate the precipitated solids. The filtrate was diluted with water (150 mL) whereupon a white precipitate formed. This mixture was stirred overnight at room temperature and the solids were collected by filtration, then washed with water and ether and air dried to give the title compound as a white powder (2.78 g, 84%), mp 335-336 C; MS(CI): 402 (M+H).

Analysis for C19H13Cl2N3O3 . 0.2 H2O
Calculated: C, 56.25; H, 3.37; N, 10.09
Found: C, 56.23; H, 3.33; N, 10.35 NMR: 12.73 (br s, 1H, exchangeable), 11.92 (br s, 1H, exchangeable), 8.03 (s, 1H), 7.51 (s, 1H), 7.17-7.08 (m, 3H), 2.32 (s, 1H), 2.06 (s, 1H).

The starting 5,7-dichloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(2,4-dimethylphenyl)hydrazide was prepared in

the following manner:

a) 3-Carbomethoxy-5,7-dichloro-4-hydroxyquinoline-2-carboxylic acid.

To a stirred suspension of dimethyl 5,7-dichloro-4-hydroxyquinoline-2,3-dicarboxylate (4.0 g, 12.2 mM) in water (72 mL) was added an aqueous solution of sodium hydroxide (0.97 g, 24.2 mM in 22 mL water). The solids immediately dissolved and the resulting solution was heated at 55 oC for 30 min. The reaction mixture was then slowly cooled to 20 oC and acidified by adding 6N hydrochloric acid (4 mL) while maintaining the temperature below 20 oC. A precipitate formed and, after stirring the suspension for 2 hr, the mixture was filtered and the collected solids washed successively with water, ether/methanol, and ether. Air drying provided the title compound (2.82 g, 74%) as a tan solid. An analytical sample of the title compound was obtained by recrystalliazton of a small portion of the isolated solid from ethyl acetate to provide a tan solid, mp 339-340 oC; MS(CI): 315 (M+H).

Analysis for C12H7Cl2N3O5N
Calculated: C, 45.6; H, 2.23; N, 4.43
Found: C, 45.78; H, 2.43; N, 4.52 1H NMR (MeOD): 7.82 (d, J=2.0 Hz, 1H), 7.44 (d, J=2.0 Hz, 1H), 3.86 (s, 3H).

b) 3-Carbomethoxy-5,7-dichloro-4-hydroxyquinoline-2-carbonyl chloride.

Thionyl chloride (1.50 g, 12.6 mM) was added to a stirred suspension of 3-carbomethoxy-5,7-dichloro-4-hydroxyquinoline-2-carboxylic acid (1.0 g, 3.17 mM) in ethanol free chloroform (25 mL). The resulting suspension was refluxed for 5 hr whereupon solution occurred. The reaction mixture was allowed to cool to room temperature and then concentrated to leave the title acid chloride (0.88 g, 83%) as a tan solid. This material was used as is for the formation of acid hydrazides.

c)

5,7-Dichloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(2,4-dimethylphenyl)hydrazide.

3-Carbomethoxy-5,7-dichloro-4-hydroxyquinoline-2-carbonyl chloride (3.65 g, 11.0 mM) was dissolved in tetrahydrofuran (274 mL) and added dropwise to a cooled (0 oC) solution of 2,4-dimethylphenylhydrazine (3.13 g, 23.0 mM) in tetrahydrofuran (172 mL) with stirring. A brown/red suspension slowly formed and the resulting mixture was stirred at 0 oC for 30 min. The reaction was quenched by adding cold water (223 mL) followed by 1N HCl (669 mL). The resulting mixture was stirred for 1 hr and then filtered to separate the precipitated solids. The collected solids were washed with water and then ether to provide, after air drying, the title compound (3.60 g, 76%) as a white powder; MS(CI): 434 (M+H).

1H NMR (DMSO-d6): 12.55 (br s, 1H, exchangeable), 10.67 (br s, 1H, exchangeable), 7.76 (d, J=1.6 Hz, 1H), 7.54 (d, J=1.6 Hz, 1H), 7.19 (br s, exchangeable, 1H), 6.91-6.76 (m, 3 H), 3.69 (s, 3 H), 2.19 (s, 6H).

Example 48.

7-Chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione sodium salt.

To a stirred suspension of 7-chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione (2.00 g, 5.22 mM) in 0.1N sodium hydroxide (52.2 mL, 5.22 mM) was added water (100 mL) and methanol (3 mL). After brief sonication, the solids dissolved and the resulting solution was filtered through a Gelman Glass Acrodisc frit (0.45 um) and concentrated to dryness. The residue was triturated with isopropanol (100 mL) and filtered to separate the solids. The solids were washed several times with isopropanol and then dried under vacuum at 100 oC overnight to provide the title compound (1.64 g, 78%) as a yellow powder, mp 356 (dec).

Analysis for C19H13ClN3O4 . 1.0 Na . 0.02 (CH3)2CHOH . 1.8 H2O
Calculated: C, 52.10; H, 3.84; N, 9.56
Found: C, 52.10; H, 3.71; N, 9.40 1H NMR (DMSO-d6): 8.15-8.17 (m, 2H), 7.31 (dd, J=8.7, 2.0 Hz, 1H), 7.11 (d, J=8.4 Hz, 1H), 6.83-6.76 (m, 2H), 3.76 (s, 3H), 2.07 (s, 3H).

Example 49.
7-Chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione choline salt.

To a stirred suspension of 7-chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione (400 mg, 1.03 mM) in methanol (4 mL) was added choline hydroxide (45% by weight in methanol, 295.6 uL, 1.03 mM). After brief sonication, all solids dissolved and the resulting solution was filtered through a Gelman Glass Acrodisc filter (0.45 um) along with an additional quantity of methanol (8 mL). The filtrate was concentrated to dryness and the residual oil was stirred with isopropanol (15 mL) and ethanol (8 mL) whereupon crystallization occurred. The solids were collected and dried under vacuum at 100 oC overnight to give the title compound (411 mg, 81%) as a yellow solid, mp 229-230 oC.

Analysis for C19H13ClN3O4 . C5H14NO . 1.1 H2O
Calculated: C, 56.88; H, 5.81; N, 11.06
Found: C, 56.91; H, 5.47; N, 10.98 1H NMR (DMSO-d6): 8.09-8.12 (m, 2H), 7.31 (dd, J-8.6, 2.1 HZ, 1H), 7.07 (d, j=8.5 Hz, 1H), 6.75-6.82 (m, 2H), 3.80-3.85 (m, 2H), 3.77 (s, 3H), 3.37-3.40 (m, 2H), 3.09 (s, 9H), 2.04 (2, 3H).

Example 50. 2-(4-Benzyloxyphenyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione choline salt.

To a stirred suspension of 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(4-benzyloxyphenyl)hydrazide (1.19 g, 2.50 mM) in methanol (50 mL) was added methanesulfonic acid (2.4 mL) and the resulting mixture was refluxed for 1 hr. After cooling to room temperature, the reaction mixture was filtered and the collected solids washed with ether and air dried to give 900 mg of material which was saved for further purification. The filtrate was diluted with an equal volume of water and, after stirring for 30 min, the resulting suspension was filtered; the collected solids were washed with water and ether and air dried to provide the title compound (151.8 mg) in the free acid form. The solids (900 mg) which were initially collected and saved were recrystallized by dissolving in a hot mixture of methanol (3.8 L) and methanesulfonic acid (63 mL) and then allowing to cool to room temperature. The resulting suspension was filtered to remove a precipitate and the filtrate was diluted with an equal volume of water and stirred overnight. The resulting precipitate which formed was collected, washed with water and ether and then air dried to give the title compound (422.2 mg) in the free acid form (total combined yield of the free acid title compound: 574 mg, 52%); MS(CI): 446 (M+H).
300 MHz 1H NMR (DMSO-d6): 12.71 (br s, 1H, exchangeable), 11.98 (br s, 1H, exchangeable), 8.14 (d, J=8.6 Hz, 1H), 8.03 (s, 1H), 7.47-7.32 (m, 9H), 7.07 (d, J=8.9 Hz, 1H), 5.14 (s, 2H).

To a stirred suspension of 2-(4-benzyloxyphenyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione (515 mg, 1.16 mM) in methanol (77 mL) was added choline hydroxide (45 weight % in methanol, 0.36 mL, 1.28 mM). The resulting mixture was filtered to separate a small quantity of fine solids and the filtrate was concentrated to leave an oily residue. This residue was diluted with toluene (70 mL) and concentrated. The residue was diluted with toluene/ethanol (70 mL/20 mL) and concentrated. The residue was diluted with a final portion of toluene (70 mL) and concentrated to provide the choline salt title compound (640 mg, 99%) as a yellow-green solid, mp 304-306 oC; MS(FAB): 446 (M+1), 444 (M-1).

Analysis for $C_{24}H_{16}ClN_3O_4$. 0.5 H_2O. 1.0 $C_5H_{14}NO$
Calculated: C, 61.95; H, 5.43; N, 9.89
Found: C, 62.31; H, 5.59; N, 10.02

300 MHz- 1H NMR (DMSO-d6): 8.11-8.09 (m, 2H), 7.48-7.28 (m, 8H), 7.00 (d, J = 8.88 Hz, 2H), 5.13 (s, 2H), 3.83 (br s, 2H), 3.39 (br s, 2H), 3.09 (s, 9H)

a) 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(4-benzyloxyphenyl)hydrazide.

The 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(4-benzyloxyphenyl)hydrazide used in Example 50 was prepared according to the procedure used in Example 41) except that 4-benzyloxyphenylhydrazine was used instead of 4-chloro-2-methylphenyl-hydrazine.

Example 51.
7-Chloro-2-(2,4-dichlorophenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione.

To a stirred suspension of 7-chloro-3-methoxycarbonyl-4-oxo-1, 4-dihydroquino-line-2-carboxylic acid N-2-(2,4-dichlorophenyl) hydrazide (3.00 g, 6.81 mM) in methanol (1500 mL) was added methanesulfonic acid (150 mL). The resulting suspension was refluxed for 9 days and the resulting solution was then cooled to ambient temperature and concentrated to one-half its original volume using a rotary evaporator. The suspension which was obtained was stirred at room temperature for 30 min and filtered to separate the solids. The filtrate was diluted with an equal volume of water whereupon a precipitate formed. This mixture was stirred at ambient temperature overnight and then filtered. The collected solids were washed with ether and then suspended in methanol (500 mL) and sonicated for 5 min. The resulting mixture was

filtered to separate the solids and the filtrate was concentrated. The residue was suspended in ether and filtered. The collected solids were washed with water and ether and then air-dried to provide the title compound (198.5 mg, 7%) as a yellow solid, mp 360-361 oC; MS(CI): 408 (M+H).

Analysis for C17H8Cl3N3O3. 0.2 H2O. 0.10 CH3SO3H
Calculated: C, 49.02; H, 2.35; N, 9.75
Found: C, 48.69; H, 2.10; N, 9.96

300-MHz 1H NMR (DMSO-d6): 12.99 (br s, 1H, exchangeable), 12.12 (br s, 1H, exchangeable), 8.15 (d, J = 8.67 Hz, 1H), 8.07 (d, J = 1.23 Hz, 1H), 7.85 (d, J = 1.02 Hz, 1H), 7.60 (s, 2H), 7.47 (dd, J = 1.61, 8.63 Hz, 1H)

a) 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(2,4-dichlorophenyl)hydrazide.

The 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(2,4-dichlorophenyl)hydrazide used in Example 51 was prepared according to the procedure used in Example 41a) except that 2,4-dichlorophenylhydrazine was used instead of 4-chloro-2-methylphenylhydrazine.

Example 52.
7-Chloro-3-(2,4-dichlorophenyl)-1-hydroxy-3,4,5,10-tetrahydropyridazino[4,5-b]quinoline-4,10-dione.

To a stirred suspension of 7-chloro-3-methoxycarbonyl-4-oxo-1, 4-dihydroquino-line-2-carboxylic acid N-2-(2,4-dichlorophenyl) hydrazide (1.28 g, 2.92 mM) in methanol (645 mL) was added methanesulfonic acid (65 mL). The resulting suspension was refluxed for 10 days and the resulting solution was then cooled to ambient temperature whereupon a precipitate formed. The mixture was filtered to separated the solids and

the filtrate was diluted with water (300 mL) to form another precipitate. This precipitate was collected and dried to provide the title compound (266.5 mg, 22%) yellow solid, mp 342-343 oC; MS(CI): 408 (M+H).

Analysis for C17H8Cl3N3O3. 0.1 CH3SO3H. 0.2 H2O
Calculated: C, 48.73; H, 2.16; N, 9.95
Found: C, 48.69; H, 2.10; N, 9.96

300-MHz 1H NMR (DMSO-d6): 13.50 (br s, 1H, exchangeable), 8.29 (d, J = 8.76 Hz, 1H), 8.19 (d, J = 1.26 Hz, 1H), 7.92 (d, J = 1.71 Hz, 1H), 7.70-7.61 (m, 3H)

a) 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(2,4-dichlorophenyl)hydrazide.

The 7-chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-2-(2,4-dichlorophenyl)hydrazide used in Example 52 was prepared according to the procedure used in Example 51).

Example 53.

7-Chloro-4-hydroxy-2-[2-(4-methoxyanilino)ethyl]-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

2-(2-Bromoethyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b] quin-oline-1,10-dione (1.00 g, 2.7 mM, prepared in Example 4a. and p-anisidine (1.33 g, 10.8 mM) were stirred and heated to reflux in DMF (20 mL) for 1.5 hours to give a brown solution. The solution was cooled to room temperature and ether (80 mL) was added to give a dark suspension. The suspension was stirred for two hours and filtered. The collected solids were washed with ether (150 mL) to give the title compound as a tan powder (1.17 g, 60%), mp 239-241 oC; MS(CI):413.

Analysis for C20H17ClN4O4.HBr. 3.0 C3H7NO. 0.5H2O:
Calculated: C, 48.24; H, 5.58; N, 13.58
Found: C, 47.80; H, 5.20; N, 13.93

300 MHz 1H NMR (DMSO-d6): 8.14 (d, J=8.7 Hz, 1H), 8.09 (d, J=1.9 Hz, 1H), 7.35 (d, J=8.7 Hz, 1H), 6.75 (d, J=8.9 Hz, 2H), 6.58 (d, J=8.9 Hz, 2H), 3.96 (t, J=6.8 Hz, 2H), 3.62 (s, 3H), 3.27 (t, J=6.8 Hz, 2H).

Example 54.

7-Chloro-2-(3-chloro-4-hydroxyphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

7-Chloro-2-(3-chloro-4-methoxyphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione (previously prepared in Example 37 1.00 g, 2.47 mM) was stirred in methanesulfonic acid (20 mL) to give a black solution. This solution was heated to 145 oC for 6 hours and cooled to room temperature. Water (60 mL) was added to give a tan suspension which was stirred for 3 hours and filtered. The collected solids were washed with water and ether to give the title compound as a gold powder (0.98 g, 76 %), mp 350-353 oC; MS(CI): 390.

Analysis forC17H9Cl2N3O4.H2O.1.2CH3SO3H:
Calculated: C, 41.76; H, 3.04; N, 8.02
Found: C, 41.74; H, 2.76; N, 7.68

300 MHz 1H NMR (d6-DMSO): 8.15 (d, J=8.5 Hz, 1H), 8.05 (d, J=1.9 HZ, 1H), 7.53 (d, J=2.2 HZ, 1H), 7.45 (d, J=8.5 Hz, 1H), 7.33 (dd, J=2.2,8.7 Hz, 1H), 7.03 (d, J=8.7 Hz, 1H).

Example 55.

7-Chloro-4-hydroxy-2-(4-hydroxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

7-Chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione (1.00 g, 2.61 mM) was stirred in methanesulfonic acid (10 mL) to give a brown solution. This solution was heated to 150 oC for 3 hours and cooled to room temperature. The cooled

solution was added dropwise to water (50 mL) with stirring to give a grey suspension which was stirred for 20 hours and filtered. The collected solids were washed with water and then suspended in water (50 mL). To this suspension was added choline hydroxide solution (2 mL, 45 wt % in methanol) which dissolved the solids to give a brown solution. This solution was heated to reflux for 1 hour, additional choline hydroxide solution (2 mL) was added and the solution was heated to reflux for 3 hours. The solution was cooled to room temperature and acidified to pH = 1 with 1N HCl to give a brown suspension. The suspension was filtered and the collected solids were washed with water to give a brown solid. Several recrystallizations from hot methanol gave the title compound as an off-white powder (0.35 g, 36%), mp 287 (decomp.); MS(CI): 370.

Analysis for C18H12ClN3O4.H2O.0.7CH3OH:
Calculated: C, 54.75; H, 4.13; N, 10.24
Found: C, 54.75; H, 3.87; N, 10.18

300 MHz 1H NMR (d6-DMSO): 12.60 (br s, 1H, exchang.), 12.00 (br s, 1H, exchang.), 9.55 (br s, 1H, exchang.), 8.16 (d, J=8.6 Hz, 1H), 8.06 (s, 1H), 7.45 (d, J=8.6Hz, 1H), 7.07 (d, J=8.4 Hz, 1H), 6.70 (s, 1H), 6.66 (d, J=8.4 Hz, 1H), 2.00 (s, 3H).

Example 56.

7-Chloro-2-(4-chloro-2-methylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione. This is an alternate synthesis of this compound previously described in Example 42.

3-Benzyl-7-chloro-2-(4-chloro-2-methylphenyl)-1,2,3,4,5,10-hexahydropyridazino-[4,5-b]quinoline-1,4,10-trione, 0.61 g, 1.28 mM) was stirred in methanesulfonic acid (12 mL) to give a viscous amber solution. This solution was warmed to 45 oC for 6.5 hours to give a pea green suspension which was cooled to room temperature. Ice (50 mL) was added with stirring to give a light green suspension which was filtered. The collected solids

were washed with water and ether to give a grey powder (0.49 g). A portion of this powder (0.36 g) was stirred in methanol and choline hydroxide solution (2 mL, 1M) was added. Most of the solids dissolved and the mixture was filtered to remove the insoluble material. The filtered solution was acidified to pH = 1 with 1N HCl to give a tan suspension. Methanol (2 mL) was removed under a N2 (g) stream and the suspension filtered. The collected solids were washed with water and ether to give the title compound as an off-white powder (0.30 g, 82%), identical to the material previously prepared in Example 42.

The starting 3-benzyl-7-chloro-2-(4-chloro-2-methylphenyl)-1,2,3,4,5,10-hexa-hydropyridazino[4,5-b]quinoline-1,4,10-trione was prepared according to the following procedures:

a) 2-Benzylidene-1-(4-chloro-2-methylphenyl)hydrazine.
To a stirred suspension of 4-chloro-2-methylphenylhydrazine hydrochloride (1.00 g, 5.18 mM) in ethanol (15 mL) was added benzaldehyde (0.66 g, 6.22 mM) and sodium acetate (0.51 g, 6.2 mM). After stirring the resulting mixture for 3 hr at room temperature, an additional quantity of benzaldehyde (0.11 g, 1.3 mM) was added and stirring continued for 30 min. The reaction mixture was poured into water and the resulting mixture extracted with ether. The combined ether extracts were dried (MgSO4), filtered and concentrated to leave a yellow oil (1.71 g) which contained the title compound contaminated with the diethyl acetal of benzaldehyde. The acetal was distilled off by warming (70 oC) the mixture under high vacuum. The residue consisted of the pure title compound (1.23 g, 97%) as an orange solid which was used as is in the next step.

300 MHz 1H NMR (CDCl3): 7.79 (s, 1H), 7.68 (s, 1H), 7.65 (s, 1H), 7.49 (d, J=6.3, 1H), 7.42-7.26 (m, 4H), 7.16 (dd, J= 2.5, 6.0 Hz, 1H), 7.06 (d, J=2.5 Hz, 1H), 2.21 (s, 3H).

b) 1-Benzyl-2-(4-chloro-2-methylphenyl)hydrazine.

To a stirred solution of 2-benzylidene-1-(4-chloro-2-methylphenyl) hydrazine (2.40 g, 9.81 mM) in anhydrous tetrahydrofuran (43 mL) was added dropwise a solution of borane in tetrahydrofuran (4.6 mL of a 1M solution, 4.6 mM). A gas evolution occurred during and after the addition. After the addition was completed, the reaction mixture was stirred for 20 min at room temperature and then saturated carefully with hydrogen chloride gas at room temperature. A white precipitate gradually formed as the HCl gas was added to the reaction mixture. The reaction mixture was stirred for 20 min after the addition of the HCl and then quenched by the careful dropwise successive addition of water (150 mL) and 10% hydrochloric acid (5 mL). The resulting solution was concentrated to remove most of the tetrahydrofuran. The residual mixture was made basic by adding solid potassium carbonate and then extracted with ether. The combined extracts were dried ($MgSO_4$), filtered and concentrated to leave a pale yellow oil (2.38 g). This material was flash chromatographed over silica gel using hexane/ether (3:1) as the eluant. The fractions containing the desired material were combined and concentrated to leave the title compound as a yellow oil (1.30 g, 53.7%); MS(CI): 247 (M+H).

300 MHz 1H NMR ($CDCl_3$): 7.22-7.41 (m, 6H), 7.14 (d, J=2.4 Hz, 1H), 7.01 (d, J=2.4 Hz), 4.90 (br s, 1H, exchangeable), 3.95 (s, 2H), 3.77 (br s, 1H, exchangeable), 1.98 (s, 3H).

c) 7-Chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-1-benzyl-N-2-(4-chloro-2-methylphenyl)hydrazide.

7-Chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carbonyl chloride (0.58 g, 1.93 mM) was dissloved in tetrahydrofuran (50 mL) and added dropwise over 15 minutes to a solution of 1-benzyl-2-(4-chloro-2-methylphenyl)hydrazine (1.00 g, 4.05 mM) in tetrahydrofuran (100 mL) at 0 oC. The resulting amber solution was stirred for 45 minutes at 0 oC and diluted with water (75 mL) maintaining 0 oC with cooling. The resulting

solution was further diluted at 0 oC with 1N HCl (180 mL) to give a white suspension. The suspension was stirred at 0 oC for 1 hour and filtered. The collected solids were washed with 1N HCl, water, and ether to give, after air drying, the title compound as a white powder (0.83 g, 84%), mp 172-175 oC.

Analysis for C26H21Cl2N3O4.0.6H2O.0.4C4H10O:
Calculated: C, 60.18; H, 4.79; N, 7.63
Found: C, 60.21; H, 4.44; N, 7.70

300 MHz 1H NMR (d6-DMSO): 12.44 (s, 1H, exchang.), 8.04 (d, J=8.6 Hz, 1H), 7.52 (d, J=1.4 Hz, 1H), 7.43-7.31 (m, 6H), 7.11-6.85 (m, 3H), 4.85 (br s, 2H), 3.69 (s, 3H), 1.76 (s, 3H).

d) 3-Benzyl-7-chloro-2-(4-chloro-2-methylphenyl)-1,2,3,4,5,10-hexahydropyridazino[4,5-b]quinoline-1,4,10-trione.

7-Chloro-3-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-2-carboxylic acid N-1-benzyl-N-2-(4-chloro-2-methylphenyl)hydrazide (0.92 g, 1.80 mM) was stirred in methanol (37 mL) and choline hydroxide solution (1.03 mL, 45 weight % in methanol) was added to give a slightly brown solution. This solution was heated to reflux for 12 hours and cooled to room temperature. The methanol was removed under a N2 (g) stream to give an amber residue. Choline hydroxide solution (1 mL, 45 weight % in methanol) was added and the resulting thick solution was stirred for 1 hour. Methanol (40 mL) was added and the solution was cooled to -15 oC. 1N HCl (10 mL) was added dropwise at -15 oC with stirring to give a white suspension. Methanol (15 mL) was removed under a N2 (g) stream and the suspension was filtered. The collected solids were washed with water and ether to give the title compound as an off-white powder (0.76 g, 89%), mp 279-281 oC; MS(CI):478.

Analysis forC25H17Cl2N3O3.H2O.0.3CH3OH:
Calculated: C, 60.06; H, 4.02; N, 8.31
Found: C, 60.14; H, 3.90; N, 8.34

300 MHz 1H NMR (d6-DMSO): 12.68 (s, 1H, exchang.), 8.19 (d, J=1.9 Hz, 1H), 8.16 (d, J=8.6 Hz, 1H), 7.50 (dd, J=1.9, 8.6 Hz, 1H), 7.35-7.24 (m, 6H), 6.94-6.91 (m, 2H), 5.28 (d, J=16.3 Hz, 1H), 4.60 (d, J=16.3 Hz, 1H), 1.69 (s, 3H).

Example 57.

7,9-Dichloro-2-(2,4-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione sodium salt. This is the sodium salt of the compound prepared in Example 47.

7,9-Dichloro-2-(2,4-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione (prepared as described in Example 47, 375.6 mg, 0.925 mM) was dissolved in water (20 mL) containing 0.1N sodium hydroxide (9.25 mL, 0.925 mM) and methanol (4 mL) by swirling and sonication. The resulting solution was filtered through a Gelman Glass Acrodisc filter (0.45 microns) and the filtrate concentrated to dryness. The residue was triturated with isopropanol (10 mL) and the resulting mixture was filtered. The collected solids were washed with isopropanol (5 mL) and then dried under high vacuum at 100 oC overnight to provide the title compound as a yellow solid (310.4 mg, 79%), mp 369-370 oC.

Analysis for C19H12Cl2N3O3 . 1.0 Na . 1.70 H2O . 0.02 (CH3)2CHOH
Calculated: C, 50.32; H, 3.12; N, 9.08
Found: C, 50.20; H, 3.44; N, 9.21

1H NMR (DMSO-d6): 8.01 (d, J=2.2 Hz, 1H), 7.28 (d, J=2.0 Hz, 1H), 7.01-7.08 (m, 3H), 2.30 (s, 3H), 2.04 (s, 3H).

Examples 58 - 81 are presented in Table 1 adjacent to the formula and scheme pages before the claims.

Example 82

7-chloro-4-hydroxy-2-(2-fluorobenzyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

To a stirred suspension of 2-pyrrolidinocarbamide-7-chloro-4-hydroxy quinoline-3-carboxylic acid (1.068 g, 3.3 mM) in tetrahydrofuran (60 mL) at ambient temperature was added dicyclohexylcarbodiimide(0.795 g, 3.85 mM). A tetrahydrofuran solution (20 mL) of N-t-butoxycarbonyl-N'-2-fluorobenzylhydrazine (1.10 g,4.59 mM, prepared as described in 82c) was immediately added to the above suspension. The reaction mixture was stirred at room temperature for four hours. Upon completion of the coupling, the byproduct urea was removed via vacuum filtration. Partial purification by flash column chromatography employing 5% methanol in methylene chloride yielded the desired hydrazide (1.67 g, 3.0 mM, 92%). To the hydrazide suspended in tetrahydrofuran (80 mL) was added methanesulfonic acid (9.0 mL, 139 mM). The reaction was stirred at room temperature for 24 hours then poured into ice water (600 mL). The resulting precipitate was isolated, dried, and triturated/sonicated with methanol (20 mL) and isolated to yield after drying under vacuum at 50 °C 0.733 g (65.9%) of the title compound as an off-white solid, mp >300 °C; MS (CI): 372 (M+H).

Analysis for $C_{18}H_{11}N_3O_3FCl$:
Calculated: C, 58.16; H, 2.98; N, 11.30
Found: C, 57.81; H, 3.20; N, 11.08

300 MHz ^1H NMR (DMSO-d_6): 12.68 (s,1H, exchangeable), 11.96 (s, 1H, exchangeable), 8.15 (d, J = 8.7 Hz, 1H), 8.03 (s, 1H), 7.43 (d, 1H, J = 8.6 H_2), 7.15 - 7.32 (m, 4H), 5.17 (s, 2H).

a) The starting 2-pyrrolidinocarbamide-7-chloro-4-hydroxyquinoline-3-carboxylic acid was prepared in the following manner:

To a suspension of 3-carbomethoxy-2-pyrrolidinocarbamide-7-chloro-4-hydroxy quinoline (2.52g, 7.5 mM) in de-ionized water (40 mL) was

added dropwise a solution (20 mL) of an aqueous potassium hydroxide (882 mg, 15.75 mM). Upon complete addition, the reaction was warmed to 60 °C. After 3 hours, the reaction was filtered to remove a small amount of insoluble material. The filtrate was then acidified to pH=1 which yield a wite precipitate. The solid was isolated by vacuum filtration, washed with water, and dried at 30 oC under vacuum for 16 hours. This provided the desired title compound (1.5 g, 64%) as a white solid, mp = 225-8 °C; MS (CI): 321 (M+H).

300 MHz ^{1}H NMR (DMSO-d_6): 8.28 (d, J = 8.8 Hz, 1H), 7.77 (s, 1H), 7.64 (d, 1H, J = 8.7), 3.52-3.57 (m, 2H), 3.17-3.19 (m, 2H), 1.83-1.98 (m, 4H).

b) The starting 3-carbomethoxy-2-pyrrolidinocarbamide-7-chloro-4-hydroxyquinoline was prepared in the following manner:

To a suspension of 3-carbomethoxy-7-chloro-4-hydroxy quinoline-2-carboxylic acid (2.25 g, 8.0 mM) in tetrahydrofuran (20 mL) at ambient temperature under a N_2 atmosphere was added dicyclohexylcarbodiimide (1.65 g, 8.0 mM) and pyrrolidine (0.596 g, 8.4 mM). The reaction was stirred room temperature for 15 hours after which time the byproduct urea was removed via filtration. The desired product was purified via flash column chromatography employing 5% methanol in chloroform to provide the title compound (2.52 g, 94.3%) as a tan solid, mp = 215 °C; MS (CI): 335 (M+H).

300 MHz ^{1}H NMR (DMSO-d_6): 8.12 (d, J = 8.7 Hz, 1H), 7.60 (d, 1H, J = 1.8 Hz), 7.47 (dd, 1H, J = 8.8, 2.0 Hz), 3.69 (s, 3H), 3.40-3.49 (m, 2H), 3.27-3.33 (m, 2H), 1.80-1.96 (m, 4H).

The starting N-t-butoxycarbonyl-N'-2-fluorobenzylhydrazine was prepared in the following manner:

c) To a mixture of t-butylcarbazate (17.84 g, 135 mM) and 2-fluorobenzylbromide (3.2 mL, 26.5 mM) in dimethyl formamide (30 mL) warmed to 50 °C was added triethylamine (7.4 mL, 53.1 mM). After stirring at 50 °C for 30 minutes, the reaction mixture was diluted with water and extracted with methylene chloride. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography employing 1:1 diethyl ether:hexanes as eluant. This provided the title compound (5.13 g, 80%) as a white solid; MS (CI): 241 (M+H).

300 MHz ^{1}H NMR (DMSO-d_6): 8.27 (br s, 1H), 7.40-7.50 (m, 1H), 7.25-7.36 (m, 1H), 7.09-7.20(m, 2H), 4.48 (br s, 1H), 3.87-3.94 (m, 2H), 1.37 (s, 9H).

Example 83.

7-chloro-1-hydroxy-3-(3-nitrophenyl)-3,4,5,10-tetrahydropyridazino [4,5-b]quinoline-4,10-dione.

The title compound was made generally as set forth in Example 14 using appropriate corresponding precursors to make the title compound using butanol in the place of ethanol. Also, the product was isolated prior to treatment in methanol with methanesulfonic acid.

Analysis for $C_{17}H_9N_4O_5Cl$

Calculated: 53.07; H, 2.36; N, 11.02

Found: 53.55; H, 2.54; N, 10.94 NMR (DMSO -d_6): 7.63 (d, J=8.9 Hz, 1H), 7.80-7.91 (m, 1H), 8.18-8.36 (m, 4H), 8.64 (s, 1H), 12.71 (br s, 1H), 13.36 (br s, 1H)

MS(CI): 385 (M+H)

m.p. (°C): >250

Example 84

7-chloro-2-(3-flourophenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione.

The title compound was made general as set forth in Example 15, using appropriate corresponding precursors to make the compounds listed.

Analysis for $C_{17}H_9N_3O_3ClF$
Calculated: C, 53.57; H, 3.07; N, 14.56
Found: C, 53.55; H, 2.94; N, 14.44 NMR (DMSO - d_6)
7.18-7.32 (m, 1H), 7.46-7.60 (m, 4H), 8.06 (s, 1H), 8.17 (d, J=8.7 Hz, 1H), 12.09 (br s, 1H), 12.92 (br s, 1H) MS(Cl): 358 (M+H)
m.p. (^{0}C): >250

Examples 85-94 were made generally as set forth in Example 35 using the appropriate corresponding precursors. The physical data and yields from the precursor acyl hydrazide are presented in Table 2 in the pages prior to the claims.

Examples 95-103 were made as generally set forth in Example 80 using the appropriate corresponding precursors with physical data and yeilds from the 2-pyrrolidino quinoline precursors presented in Table 3 before the claims.

Example 104

7-chloro-4-hydroxy-2-(2,6-dihydroxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

A suspension of 7-chloro-4-hydroxy-2-(2,6-dimethoxyphenyl)-1,2,5,10-tetrahydropyr idazino[4,5-b]quinoline-1,10-dione (0.5618 g, 1.4 mM) was allowed to reflux in 50 mL of 48% hydrobromic acid. After approximately 45 minutes the suspension became an orange solution. After 2 hours at reflux HPLC analysis indicated that the reaction was

complete. Upon cooling, the solution afforded a precipitate that was removed via filtration and washed with water until the aqueous washing were no longer acidic. The solid was then dissolved in 4 mL of 45% choline hydroxide in methanol and filtered through a fine fritted buchner funnel to remove any particulate matter. Acidification with concentrated HCl afforded a tan precipitate that was removed via filtration. The wet solid was dissolved in methanol and the solvent was evaporated to afford the desired product (0.230 g, 44.3%) as a tan solid.

Analysis for $C_{17}H_{11}N_3O_5Cl$. 0.7 HBr
Calculated: C, 47.55 H, 2.75 N, 9.78
Found: C, 47.85 H, 3.85 N, 9.70

Chemical Ionization: m+1: 372
300 MHz Proton NMR (DMSO-d6/TFA-d): 12.65 (br s, 1H, exchangeable), 8.2 (d,1H, J = 9.0 Hz), 8.12 (s, 1H), 7.47 (d, 1H J = 9.0 Hz), 6.80 (d, 1H, J = 6.0 Hz) 6.74 (d, 1H), 6.70 (s, 1H).

Example 105

7-chloro-4-hydroxy-2-(4-carboxyphenyl)-1,2,5,10-tetrahydropyridaz ino[4,5-b]quinoline-1,10-dione.

A suspension of 7-chloro-4-hydroxy-2-(4-cyanophenyl)-1,2,5,10-tetrahydropyridazin o[4,5-b]quinoline-1,10-dione (0.400 g, 1.04 mM) in 50 mL of 1N KOH was allowed to reflux over a 5 hour period as the reaction was monitored via HPLC. The initial suspension slowly became a yellow solution. Total conversion to a new material was accomplished after 5 hours of reflux as judged via HPLC. The solution was cooled to 0 ^{0}C and acidified with concentrated HCl. Upon acidification a precipitate formed immediately and was removed via suction filtration. The yellow filter cake was washed with water and then suspended in a 1:1 solution of ethanol:methanol and the solvent

was removed under vacuum at 50 ^{0}C. This was repeated until the yellow powder was a free flowing solid affording (0.400 g, 100%) of the desired product.

Analysis for $C_{18}H_{10}N_3O_5Cl$. 2.7 HCl
Calculated: C, 44.38 H, 2.87 N, 9.15
Found: C, 44.83 H, 2.65 N, 8.71

Chemical Ionization: m+1: 384
300 MHz Proton NMR (DMSO-d6/TFA-d): 13.04 (br s, 1H, exchangeable), 12.20 (br s, 1H exchangeable), 8.1 (d,1H, J = 9.0 Hz), 8.08 (s, 1H), 8.03 (d, 2H J = 9.0 Hz), 7.70 (d, 2H, J = 9.0 Hz) 7.465 (d, 1H).

Example 106

7-chloro-4-hydroxy-2-(4-hydroxyphenyl)-1,2,5,10-tetrahydropyridaz ino[4,5-b]quinoline-1,10-dione.

To a 50 mL solution of 5:1 48% HBr:methanesulfonic acid was added 7-chloro-4-hydroxy-2-(4-methoxyphenyl)-1,2,5,10-tetrahydropy ridazino[4,5-b]quinoline-1,10-dione (1.0328 g, 27.9 mM). The resulting suspension was heated to 110 ^{0}C over 3.5 hours. HPLC analysis afforded a total conversion to a new material. The suspension was cooled to room temperature and filtered through a buchner funnel. The yellow solid was washed 2x with 100 mL portions of distilled water followed by 200 mL of a 1:1 solution of THF:ether. The material was then washed with hexanes until the yellow solid was free flowing. This solid was allowed to air dry for 72 hours prior to submission for analysis. No percent yield was recorded for this reaction.

Analysis for $C_{17}H_9N_3O_4Cl_2$. 2.3 HBr
Calculated: C, 35.43 H, 1.97 N, 7.29
Found: C, 35.40 H, 1.95 N, 6.85

Chemical Ionization: m+1: 390
300 MHz Proton NMR (DMSO-d6/TFA-d): 8.08 (s,1H), 7.49 (s, 1H), 7.30 (d, 2H J = 8.73 Hz), 6.8 (d, 2H, J = 8.73).

Example 107

7-chloro-4-hydroxy-2-(4-carboxamidephenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

Into a 50 mL round bottom flask was placed 7-chloro-4-hydroxy-2-(4-cyanophenyl)-1,2,5,10-tetrahydropyridazin o[4,5-b]quinoline-1,10-dione (0.2040 g, 0.558 mM). This was dissolved in 6 mL of H_2SO_4 and warmed to 50 ^{0}C. The warm solution was then poured onto 10.0 g of crushed ice affording a yellow solid. The solid was removed from the aqueous solution via suction filtration and washed with 60 mL of distilled water followed by 30 mL of .1N $NaHCO_3$. The resulting yellow paste was suspended in 1:1 ethanol:methanol and the solvent was removed under vacuum until the solid was free flowing. Additional washing with 60 mL of methanol followed by 200 mL of THF afforded a yellow solid that was free flowing. After additional air drying (0.187 g, 87.7%) of desired product was recovered as a yellow solid.

Analysis for $C_{18}H_{11}N_4O_4Cl$. 1.3 H_2SO_4
Calculated: C, 42.37 H, 2.68 N, 10.98
Found: C, 42.75 H, 3.10 N, 10.61
FAB: m+1: 277.2, 257.1, 299.1, 383.1
300 MHz Proton NMR (DMSO-d6/TFA-d): 8.23 (s, 1H), 8.10 (s, 1H), 8.05 (d, 2H J = 8.49 Hz), 7.70 (d, 2H, J = 8.49), 7.465 (d, J = 8.49 Hz).

Example 108

7-chloro-4-hydroxy-2-(4-tetrazolephenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

To 10 mL of NMP was added 7-chloro-4-hydroxy-2-(4-cyanophenyl)-1,2,5,10-tetrahydropyridazin o[4,5-b]quinoline-1,10-dione (0.5 g, 1.37 mM) followed by triethylamine (.206 g, 1.57 mM) and sodium azide (.534 g, 8.22 mM). This suspension was vigorously stirred and heated to 170 ^{0}C over a period of 6 hours . At this time HPLC analysis indicated that the reaction was completed. The solution was allowed to cool and a precipitate began to form. To the cooled suspension was added diethyl ether until no further precipitation was observed. The solid was removed via suction filtration and washed with ether until the solid was a free flowing tan powder. This was then suspended in 100 mL of 1N HCl to remove any excess sodium azide and triethylamine hydrochloride. The solid was removed via filtration and washed with a 1:1 methanol:ether solution until the tan solid was a free flowing powder. After additional air drying (0.552 g, 99.1%) of the desired product was recovered.

Analysis for $C_{18}H_{11}N_4O_4Cl$. 2.4 H_2O
Calculated: C, 47.93 H, 3.30 N, 21.73
Found: C, 47.36 H, 3.32 N, 10.57
FAB: m+1: 277.2, 257.1
300 MHz Proton NMR (DMSO-d6): 12.10 (br s, 1H exchangeable) 8.19-8.12 (m, 4H), 8.065 (s, 1H), 7.85 (d, 3H J = 9.00 Hz).

Example 109

7-chloro-4-hydroxy-2-(4-N,N-diethylcarboxamidophenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

To 20 mL of anhydrous THF was suspended 7-chloro-4-hydroxy-2-(4-carboxyphenyl)-1,2,5,10-tetrahydropyridaz ino[4,5-b]quinoline-1,10-dione (0.3436 g, .897 mM) under an atmosphere of nitrogen. To this suspension was added $SOCl_2$ (0.13 mL, 1.79 mM). This was then heated to reflux over a 60 minute period at which point 1 mL of DMF was then added. Upon the addition of the DMF the suspension instantaneously

became a light yellow solution which eventually reverted back to a yellow suspension after 5 minutes. The THF was removed under reduced pressure and 10 mL of DMF was added at room temperature. The resulting dark orange solution was cooled to -10°C. To this was added diethylamine, (0.27 mL, 2.69 mM). Immediately upon addition of the diethylamine a dark red precipitate formed. This suspension was kept cold while 50 mL of 1N HCl was slowly added along with 50 mL of saturated NaCl affording a yellow precipitate. The precipitate was removed via filtration and washed with 200 mL of water followed by 1000 mL of ether. Additional washing with 4:1 ether:methanol afforded a free flowing solid. After additional air drying the desired product (0.1485 g, 38.1%) was obtained as a yellow solid.

Analysis for $C_{22}H_{19}N_4O_4Cl$. 1.7 HCl
Calculated: C, 52.75 H, 4.16 N, 11.18
Found: C, 52.63 H, 4.45 N, 10.85
Chemical Ionization: m+1: 439
300 MHz Proton NMR (DMSO-d6/TFA-d): 12.90 (br s, 1H exchangeable), 12.08 (br s, 1H exchangeable), 8.21 (s,1H J = 9.00), 8.11 (s, 1H), 87.67 (d, 2H J = 9.00 Hz), 7.48-7.46 (m, 3H, J = 6.15), 3.47-3.25 (br m, 4H), 1.15 (br s, 6H).

Example 110

7-chloro-4-hydroxy-2-(4-carboxymethylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

To 50 mL of absolute methanol was added 7-chloro-4-hydroxy-2-(4-carboxyphenyl)-1,2,5,10-tetrahydropyridaz ino[4,5-b]quinoline-1,10-dione (0.30g, 0.785 mM). To this white suspension was added two drops of concentarted H_2SO_4 and the suspension was allowed to reflux as the reaction was monitored via HPLC over a 26 hour period. The suspension was allowed to cool to room temperature upon which the suspension was diluted 100 mL of ether affording additional precipitate. The

precipitate was removed via suction filtration and washed with 50 mL of 7:1 ether:methanol. After air drying the desired product (0.327 g, 100%) was obtained as a white solid.

Analysis for $C_{19}H_{12}N_3O_5Cl$. 1.5 HCl
Calculated: C, 50.43 H, 3.01 N, 9.21
Found: C, 50.91 H, 3.60 N, 9.36
Chemical Ionization: m+1: 398
300 MHz Proton NMR (DMSO-d6/TFA-d): 8.15 (d,1H J = 9.00), 8.05 (d, 3H), 7.75 (d, 2H J = 9.00 Hz), 7.47 (d, 1H, J =9.00), 3.87 (s, 3H).

Example 111

7-Chloro-4-hydroxy-2-(4,4-dimethyl-2,5-dioxooxaxolidin-1ylethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione.

Sodium hydride, 60% in mineral oil (150mg, 3.75mM) was washed with dry hexane and suspended in dimethylformamide (20mL). 4,4-dimethyl-oxazoline-2,5-dione (580mg, 4.5mM) was added portionwise over 15 minutes at room temperature. The resulting mixture was stirred 15-20 minutes at room temperature. At this point the starting 7-Chloro-4-hydroxy-2-(2-bromoethyl)-1,2,5,10-tetrahydropyrid azino[4,5-b]quinoline-1,10-dione was added and the reaction mixture was warmed quickly to 150°C. After about three hours at this temperature, the heat was removed and the reaction mixture was poured into ice-cold 1N HCl (100mL). This mixture was stirred about 5-10 minutes and suction filtered. The filter cake was washed with water and ether, then vacuum dried to yield the desired product as a white solid (280mg = 67%).

Example 112

7-Chloro-4-hydroxy-2-(2-methyl-2-hydroxypropionamidoethyl)-1 ,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione (9740-178-1).

The starting 7-Chloro-4-hydroxy-2-(4,4-dimethyl-2,5-dioxooxaxolidin-1ylet hyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dion e (400mg, 0.95mM) was suspended in water (30mL) at room temperature. To this was added 1N NaOH (2.0mL). A clear solution resulted, which was warmed to 50°C for 2 hours. At this time 1.2N HCl (5mL) was added. The mixture was stirred another 30 minutes at 50°C, then cooled to room temperature. A white precipitate was recovered by filtration and dried to yield the desired compound as a white solid (330mg = 89%).

Example 113

7-Chloro-4-hydroxy-2-(2-methylthioethyl)-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione.

To a suspension of $NaSCH_3$ (230mg, 3.2mM) in dimethylformamide (20mL), was added in one portion 7-Chloro-4-hydroxy-2-(2-bromoethyl)-1,2,5,10-tetrahydropyrid azino[4,5-b]quinoline-1,10-dione as a dry powder. This mixture was warmed to gentle reflux for about three hours. At this point the heat was removed and the reaction mixture was poured into ice cold 1.2N HCl (100mL) and stirred about one hour. The resulting precipitate was vacuum filtered and washed with water and ether, then vacuum dried at 50°C to yield 330mg (91%) of an off white powder. mp = 275-277°C; MS: 338(M+1). NMR: 2.11(s, 3H), 2.79(t, 2H, j=7.13), 4.09(t, 2H, j=7.08), 7.42(dd, 1H, J1=8.59, J2=1.6), 8.57(d, 1H, J=1.77), 8.13(d, 1H, J=8.64), 11.8 (brs, 1H), 12.64(brs, 1H).

Example 114

7-Chloro-4-hydroxy-2-(2-methylsulfonylethyl)-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione.

To a solution of 7-Chloro-4-hydroxy-2-(2-methylthioethyl)-1,2,5,10-tetrahydro pyridazino[4,5-b]quinoline-1,10-dione (.11g, 0.33mM) in methanol (5mL) stirred at room temperature, was added OXONE, a monopersulfate compound (250mg, 1.0mM) dissolved in water (1mL). The resulting mixture

was stirred at room temperature for 17 hours. Water (10 mL) was added and the reaction mixture was filtered. The crude product was again stirred with warm water to completely remove the oxidant. Filtration and vacuum drying yielded the product analytically pure as a white solid. Isolated 95mg, 75%.

Example 115

7-Chloro-4-hydroxy-2-(thiophen-2-ylmethyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione.

To a solution of 2-(thiophen-2-ylmethyl)-t-butylcarbazate (1.0g, 4.4mM) and 2-pyrrolamido-3-carboxy-7-chloroquinoline-4-one (1.2g, 3.6mM) in tetrahydrofuran (75mL) stirred at room temperature, was added diisopropylcarbodiimide (0.84mL, 5.4mM). This mixture was stirred at room temperature for 2.5 hours, then suction filtered into a second reaction flask. To the filtrate (stirred at room temperature) was added methanesulfonic acid (12mL, 185mM). The resulting solution was stirred 17 hours at room temperature. TLC analyses at this time indicated complete reaction. The reaction mixture was poured into ice water (200mL). This suspension was stirred about 15 minutes and filtered. The filter cake was washed with water and ether, then vacuum dried to yield the desired compound analytically pure (1.1g, 84%).

The physical data for examples 111-144 are presented in Tables 4-8 before the claims.

Alkyl(C1-C6)amino compounds are readily reacted with benzoylchlorides to form the alkylbenzamide PQDs. For example, R^1 as the 2-ethylbenzamide derivative was prepared and active as a glycine receptor antagonist.

Example 145

The following illustrate representative pharmaceutical dosage forms containing a compound of formula I, or a pharmaceutically acceptable sal thereof, for example as illustrated in any of the previous Examples, (hereafter referred to as "compound X"), for therapeutic or prophylactic use in humans:

(a) Tablet

	mg/tablet
Compound X.....	50.0
Mannitol, USP.....	223.75
Croscarmellose sodium.....	6.0
Maize starch.....	15.0
Hydroxypropylmethylcellulose (HPMC), USP.....	2.25
Magnesium stearate.....	3.0

(b) Capsule

Compound X.....	10.0
Mannitol, USP.....	488.5
Croscarmellose sodium.....	15.0
Magnesium stearate.....	1.5

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

Example 146

This is an example of a formulation suitable for parenteral use made with the compound of Example 2:

Parenteral Formulation:	mg/mL
Compound.....	10.0
Meglumine.....	19.5
Dextrose, anhydrous.....	39.5
Sterile Water for Injection.....	qs ad 1 mL

The solution was prepared by conventional measures well known in the pharmaceutical field. General formulations for this class of compounds

and their salts, other than for acylated compounds, may be prepared by solubilizing the active compound in an aqueous meglumine (N-methyl-glucamine) solution containing an equimolar, or if solubilization is difficult, a molar excess of meglumine relative to Compound. Choline salts are preferred for use in making formulations. Excipients such has dextrose may be added to adjust the osmolality of the formulation. Water for Injection is added to bring the solution to final volume. Alternately, other amine bases such as tromethamine or l-arginine may be used to solubilize the active compound.

Example 147

A formulation is made as in Example 49, except that the choline salt of Compound X is used in place of the compound of Example 2.

Example 148

A formulation is made comprising a 5% aqueous solution of dextrose made to 10 mg/mL in the choline salt of Compound X.

The previous examples are considered to be non-limiting and thus, the compounds of formula I or I' (or II or III) and pharmaceutical compositions containing same may be used to treat and/or prevent stroke and the other diseases as related herein. The following schemes and formulae are presented to clarify how to make the compounds of the invention. The compounds depicted in examples 5,7,9,16,18 and 20 were inactive in the in-vitro glycine receptor assay and are specifically excluded from the compounds of formula I or III.

This Sheet Has Been Replaced

Table 1. The following Examples were prepared according to previously described Examples (designated under Synthetic Procedures ures) using the corresponding acyl hydrazides as starting materials. The acyl hydrazides were prepared according to the procedures described in Example 41a) and Example 47c) for the 7-chloro- and 5,7-dichloro-substituted isomers, respectively. For the acyl hydrazide syntheses, the appropriate aryl hydrazines were employed in place of the 4-chloro-2-methylphenylhydrazine and 2,4-dimethylphenylhydrazine used in Examples 41a) and 47c, respectively.

#	Name	Synthetic Procedures	Yield	m.p.	MS(CI)	NMR (DMSO-d_6)	Analysis (found/calculated)
58	7-Chloro-1-hydroxy-3-(2-methylphenyl)-3,4,5,10-tetrahydropyridazino[4,5-b]quinoline-4,10-dione	Example 41	36	315-317	354 (M+1)	13.38 (s, 1H, exchang.), 12.52 (s, 1H, exchang.), 8.31 (d, j=8.8 Hz, 1H), 8.22 (d, j=1.9 HZ, 1H), 7.63 (dd, j=1.9,8.8 Hz, 1H) 7.40 (m, 4H), 2.16 (s, 3H)	C = 60.95/61.10 H = 3.20/3.42 N = 11.65/11.90 C18H12ClN3O3
59	7-Chloro-4-hydroxy-2-(2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	Example42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41.	33	338-340	354 (M+1)	12.76 (s, 1H, exchang.), 12.04 (s, 1H, exchang.), 8.16 (d, j=8.6 Hz, 1H), 8.07 (s, 1H), 7.45 (d, j=8.6 Hz, 1H), 7.33 (m, 4H), 2.12 (s, 3H)	C = 60.86/61.10 H = 3.20/3.42 N = 11.55/11.90 C18H12ClN3O3
60	7-Chloro-3-(3,4-dimethoxyphenyl)-1-hydroxy-3,4,5,10-tetrahydropyridazino[4,5-b]quinoline-4,10-dione	Example 41	16	367-369	400 (M+1)	13.34 (s, 1H, exchang.), 12.46 (br s, 1H, exchang.) 8.29 (d, j=8.8 Hz, 1H), 8.21 (d, j=1.8 Hz, 1H), 7.61 (dd, j=1.8,8.8 Hz, 1H), 7.27 (d, j=2.3 Hz, 1H), 7.23 (dd, j=2.3,8.6 Hz, 1H), 7.08 (d, j=8.6 Hz, 1H) 3.83 (s, 3H), 3.78 (s, 3H)	C = 55.84/55.82 H = 3.43/3.70 N = 9.96/10.28 C19H14ClN3O5·0.5H2O

TABLE 1 (cont'd)

61	7-Chloro-2-(3,4-dimethyl-phenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione	Example 42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41.	75	344-347	368 (M+1)	12.73 (s, 1H, exchang.), 12.00 (s, 1H, exchang.), 8.16 (d, j=8.7 Hz, 1H), 8.05 (d, j=1.5 Hz, 1H), 7.45 (dd, j=1.5,8.7 Hz, 1H), 7.30-7.20 (m, 3H) 2.26 (s, 6H)	C = 61.53/61.45 H = 3.99/3.91 N = 11.20/11.31 C19H14ClN3O3• 0.2H2O
62	7-Chloro-2-(2,4-dimethoxy-phenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione	Example 42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example41.	56	307-309	400(M+1)	12.63 (br s, 1H, exchang.), 11.98 (br s, 1H, exchang.), 8.15 (d, j=8.7 Hz, 1H), 8.06 (s, 1H), 7.45 (d, j=8.7 Hz, 1H), 7.21 (d, 8.6 Hz, 1H), 6.69 (d, j=2.4 Hz, 1H), 6.59 (dd, j=2.4,8.6 Hz, 1H), 3.82 (s, 3H), 3.73 (s, 3H)	C = 52.39/52.36 H = 3.78/4.16 N = 9.53/9.64 C19H14ClN3O5• 2.0H2O
63	7-Chloro-2-(2,5-dimethoxy-phenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione	Example 42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example41.	53	237-239	400(M+1)	12.60 (br s, 1H, exchang.) 12.00 (br s, 1H, exchang.) 8.16 (d, j=8.7 Hz, 1H), 8.06 (d, j=2.0 Hz, 1H), 7.46 (dd, j=2.0,8.7 Hz, 1H), 7.09 (d, j=9.0 Hz, 1H), 6.99 (dd, j= 3.0,9.0 Hz, 1H) 6.96 (d, j=3.0 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H)	C = 51.38/51.08 H = 3.76/4.00 N = 9.07/9.26 C19H14ClN3O5• 1.4H2O• 0.3CH4SO3

TABLE 1 (CONT'd)

64	7-Chloro-2-(2,5-dimethyl-phenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione	Example 42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41.	47	330-332	368 (M+1)	12.71 (s, 1H, exchang.), 12.02 (s, 1H, exchang.), 8.15 (d, j=8.6 Hz, 1H), 8.06 (s, 1H), 7.45 (d, j=8.6 Hz, 1H), 7.21 (d, j=7.7 Hz, 1H), 7.13 (d, j=7.7 Hz, 1H), 7.11 (s, 1H), 2.30 (s, 3H), 2.06 (s, 3H)	C = 61.89/62.05 H = 3.95/3.84 N = 11.35/11.43 C19H14ClN3O3
65	7-Chloro-2-(4-ethoxyphenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione	Example 42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 5.	42	317-321	384 (M+1)	12.74 (s, 1H, exchang.), 12.00 (s, 1H, exchang.), 8.16 (d, j=8.6 Hz, 1H), 8.05 (s, 1H), 7.45 (d, j=8.6 Hz, 1H), 7.41 (d, j=8.9 Hz, 2H), 6.98 (d, j=8.9 Hz, 2H), 4.06 (q, j=6.8 Hz, 2H), 1.35 (t, j=6.8 Hz, 3H)	C = 55.38/55.55 H = 4.00/4.17 N = 10.00/10.23 C19H14ClN3O4• 1.5H2O
66	7-Chloro-2-(3-chlorophenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione	Example 42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41	78	333	374 (M+1)	12.91 (br s, 1H, exch.), 8.14 (br m,1H), 8.05 (brs, 1H), 7.68-7.43 (m, 5H)	C= 48.40 / 48.53, H= 2.88 / 2.95, N= 9.79 /9.76 $C_{17}H_9Cl_2O_3N_3$. 1.0 H_2O. 0.4 CH_3SO_3H

TABLE 1 (cont'd)

67	7-Chloro-4-hydroxy-2-(3-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	Example 42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41.	77	343-346	354 (M+1)	12.77 (br s, 1H, exch.), 8.16 (d, J= 8.61, 1H), 7.46 (dd, J= 1.95, 8.66,1H), 7.35-7.33 (m, 3H), 7.17 (m, 1H), 2.36 (s, 3H)	C= 50.94 / 50.65, H= 3.62 / 3.98, N= 9.76 /9.42 $C_{18}H_{12}ClN_3O_3$. 1.2 H_2O. 0.1 CH_3OH. 0.7 CH_3SO_3H
68	7-Chloro-4-hydroxy-2-(4-thiomethoxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	Example 42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41.	89	340-342	386 (M+1)	12.86 (br s, 1H, exch.) 12.09 (br s, 1H, exch.) 8.15 (d, J= 8.55, 1H) 8.05 (s, 1H) 7.50-7.45 (m, 3H) 7.31 (d, J = 8.34, 2H)	C= 50.84 / 50.79 H= 3.24 / 3.32 N= 9.70 / 9.61 $C_{18}H_{12}ClN_3O_3S$. 0.2 H_2O. 0.5 CH_3SO_3H
69	7-Chloro-1-hydroxy-3-(4-thiomethoxyphenyl)-3,4,5,10-tetrahydropyridazino[4,5-b]quinoline-4,10-dione	Example 41	5	386	386 (M+1)	13.35 (br s, 1H, exch.) 12.49 (br s, 1H, exch.) 8.28 (d, J = 8.76, 1H) 8.21 (s, 1H) 7.65-7.59 (m, 3H) 7.39 (d, J = 8.46, 2H) 2.53 (s, 3H)	C= 55.09 / 55.01 H= 3.27 / 3.28 N= 10.46 / 10.69 $C_{18}H_{12}ClN_3O_3S$. 0.4 H_2O

70	7-Chloro-2-(3-chloro-4-methylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione	Example 42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41.	83	360-364	388 (M+1)	12.89 (br s, 1H, exch.) 12.09 (br s, 1H, exch.) 8.16 (d, J = 8.88, 1H) 8.06 (s, 1H) 7.66 (s, 1H) 7.47 - 7.43 (m, 3H) 2.37 (s, 3H)	C= 50.91 / 50.73 H= 3.25 / 3.13 N= 9.62 / 9.65 $C_{18}H_{11}Cl_2N_3O_3$. 0.5 H_2O. 0.4 CH_3SO_3H
71	7-Chloro-3-(3-chloro-4-methylphenyl)-1-hydroxy-3,4,5,10-tetrahydropyridazino-[4,5-b]quinoline-4,10-dione	Example 41	6	decomp. 398	388 (M+1)	12.48 (br s, 1H, exch.) 8.32 (d, J = 8.61, 1H) 8.25 (d, J = 1.77, 1H) 7.80 (d, J = 2.04, 1H) 7.65 - 7.59 (m, 2H) 7.49 (d, J = 8.34, 1H) 2.41 (s, 3 H)	C= 54.92 / 54.68 H= 3.04 / 3.01 N= 10.52 / 10.63 $C_{18}H_{11}Cl_2N_3O_3$. 0.4 H_2O
72	7-Chloro-2-(2,3-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	Example 42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41.	37 [1]	335-336	368 (M+1)	8.15 (d, J= 8.67,1H) 8.09 (d, J=1.93, 1H) 7.44 (dd, J= 2.0,8.66, 1H) 7.17-7.07 (m, 3H) 2.27 (s, 3H) 1.95 (s, 3H)	C= 57.99 / 58.33 H= 3.87 / 4.27 N= 10.5 / 10.74 $C_{19}H_{14}ClN_3O_3$. 1.3 H_2O

[1] This compound was purified using flash chromatography over silica gel using 15% methanol in methylene chloride as the eluant.

73	7-Chloro-2-(4-ethylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	Example 42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41.	65	319-320	369 (M+1)	12.76 (br s, 1H, exch.) 12.02 (br s, 1H, exch.) 8.16 (d, J= 8.67, 1H) 8.05 (s, 1H) 7.46-7.42 (m, 3H) 7.30 (d, J=8.34, 2H) 2.69-2.62 (m, 2H) 1.24-1.19 (m, 3H)	C= 58.79 / 58.60 H= 3.94 / 4.24 N= 10.81 / 10.79 $C_{19}H_{14}ClN_3O_3$. 1.2 H_2O
74	7-Chloro-2-(4-fluoro-2-methylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	Example 42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41.	45[2]	361-363	372 (M+1)	12.80 (br s, 1H, exch.) 12.05 (br s, 1H, exch.) 8.16 (d, J = 8.67, 1H) 8.06 (s, 1H) 7.46 (d, J = 8.58, 1H) 7.38-7.34 (m, 1H) 7.23 (dd, J = 2.42,9.58, 1H) 7.17-7.11 (m, 1H) 2.12 (s, 3H)	C= 57.78 / 58.16 H= 2.82 / 2.98 N= 11.32 / 11.30 $C_{18}H_{11}ClN_3O_3F$

TABLE 1 (cont'd)

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[2] a) The cyclization of the appropriate acyl hydrazide was carried out as in Example 41 except at twice the stated concentration of acyl hydrazide.

b) This compound was purified using preperative HPLC according to the following prodecure: Approximately 1 g of the crude N-2 and N-3 aryl isomeric mixture obtained from the cyclization of the appropriate acyl hydrazide according to the procedure outlined in Example 41 was dissolved in 1M aqueous choline hydroxide (4 mL) and the resulting solution diluted with methanol (4 mL). This solution was injected (10 mL injection loop) onto a Dynamax C# 60A column (41.4 mm x 25 cm) with a guard column (41.4 mm x 5 cm). The flow rate was 50 mL/min and the initial mobile phase was 40% methanol/buffer (buffer is 0.1% trifluoroacetic acid adjusted to pH 3 with triethylamine). Gradients of 40 to 60% methanol/buffer over 25 min and 60 to 100% over the next 10 min followed by a methanol (100%) flush (15 min) were used. The flow rate was increased to 70 mL/min during the methanol flush. Detection was done at 230 nm and the desired product eluted at 5 to 10 min in one large peak. The fraction contain-

TABLE 1 (cont'd)

75	7-Chloro-2-(3,5-dimethoxy-phenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione	Example42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41.	11[3]	299-300	400 (M+1)	12.77 (br s, 1H, exch.) 8.16 (d, J = 8.67, 1H) 8.05 (d, J = 1.86, 1H) 7.46 (dd, J = 1.97,8.66,1H) 6.73 (d, J = 2.19, 2H) 6.51 (m, 1H) 3.76 (s, 6H)	C= 53.79 / 53.92 H= 3.86 / 3.95 N= 9.97 / 9.93 $C_{19}H_{14}ClN_3O_5$. 1.3 H_2O
76	7-Chloro-4-hydroxy-2-(2-iso-propylphenyl)-1,2,5,10-tetra-hydropyridazino[4,5-b]quino-line-1,10-dione	Example 42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41.	34[4]	345-346	382 (M+1)	12.74 (br s, 1H, exch.) 12.03 (br s,1H, exch.) 8.16 (d, J = 8.67, 1H) 8.07 (d, J=1.59, 1H) 7.47-7.39 (m, 3H) 7.33-7.23 (m, 2H) 2.86-2.82 (m, 1H) 1.53-1.09 (m, 6H)	C= 62.57 / 62.62 H= 4.33 / 4.26 N= 11.05 / 10.95 $C_{20}H_{16}ClN_3O_3$. 0.10 H_2O

ing the desired product was diluted with hydrochloric acid (1N) to pH 1 to give a suspension. This suspension was concentrated on a rotary evaporator to remove the

methanol and the resulting suspension was filtered and the collected solids washed with water and air-dried to provide the desired 2-aryl isomer.

[3] This compound was purified using preperative HPLC according to the procedure in footnote 2 b).

[4] a) The cyclization of the appropriate acyl hydrazide was carried out as in Example 41 except at twice the stated concentration of acyl hydrazide.

b) This compound was purified using preperative HPLC according to the procedure in footnote 2 b).

TABLE 1 (cont'd)

80	7-chloro-4-hydroxy-2-(4-iodophenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	Example42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41.	40	>250	466 (M+1)	7.38 (dd,J=8.6, 1.9 Hz, 1H), 7.45 (d,J=8.6 Hz, 2H), 7.70 (d, J=8.5 Hz, 2H), 8.14 (d, J=8.8 Hz, 2H)	C17H9ClIN3O3. 1.0 HCl C 40.58/40.67 H 2.01/2.01 N 8.09/8.37
81	7-chloro-2-(4-bromo-2-methoxyphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione	Example42, using the filtrate obtained by filtration of the 3-aryl isomer via the procedure of Example 41.	74	>260	450 (M+1)	3.77 (s,3H), 7.23 (m,2H), 7.38 (d, J=1.6 Hz, 1H), 7.44 (dd, J=8.7, 1.6 Hz, 1H), 8.05 (s, 1H), 8.13 (d, J=8.7 Hz, 1H), 12.03 (bs, 1H), 12.77 (bs, 1H)	C18H11ClBrN3O4. 0.6 CH3SO3H C 44.04/44.12 H 2.48/2.67 N 8.47/8.30

Table 2. The following Examples were made generally as set forth in Example 35 using appropriate corresponding precursors to make the compounds listed. (Yield is from the acyl hydrazide)

Ex. #	Name	Yield	m.p.(°C)	MS(CI)	NMR (DMSO -d_6)*	Analysis (cal'd/found)
85	7-chloro-2-(2-flourophenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	13	>250	358 (M+H)	7.26-7.64(m, 5H), 8.07 (s, 1H), 8.16 (d, *J*=8.6 Hz, 1H), 12.09 (br s, 1H), 12.93 (br s, 1H)	for $C_{17}H_9N_3O_3FCl \circ 0.45\ H_2O$ C=55.81/55.84, H=2.73/2.38, N=11.49/11.23
86	7-chloro-2-(3,5-ditriflouromethylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione	12	>250	476 (M+H)	7.48 (dd, *J*=8.7, 2.0 Hz, 1H), 8.02-8.13 (m, 2H), 8.18 (d, *J*=8.6 Hz, 1H) 8.40 (s, 2H), 12.20 (br s, 1H), 13.13 (br s, 1H)	for $C_{19}H_8N_3O_3F_6Cl$ C=47.25/47.35, H=1.84/1.83, N=8.70/8.70
87	7-chloro-2-(2,4-difluorophenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	32	>250	376 (M+H)	7.20-7.30 (m,1H), 7.45-7.56 (m, 2H), 7.58-7.70 (m, 1H), 8.07 (s, 1H), 8.16 (d, *J*=8.7 Hz, 1H),	for $C_{17}H_8N_3O_3F_2Cl \circ 0.50\ H_2O$ C=53.07/53.08, H=2.36/2.37, N=10.92/10.72
88	7-chloro-2-(2,5-difluorophenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	13	>250	376 (M+H)	7.31-7.56 (m, 4H), 8.06 (s, 1H), 8.16 (d, *J*=8.7 Hz, 1H), 12.12 (br s, 1H), 13.00 (br s, 1H)	for $C_{17}H_8N_3O_3F_2Cl$ C=54.35/54.14, H=2.15/2.34, N=11.18/11.19
89	7-chloro-4-hydroxy-2-(4-nitrophenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	25	>250	385 (M+H)	7.48 (dd, *J*=8.7, 1.7 Hz, 1H), 7.95-8.00 (m, 2H), 8.06 (d, *J*=1.8 Hz, 1H), 8.17 (d, *J*=8.7 Hz, 1H), 8.32-8.41 (m, 2H), 12.16 (br s, 1H), 13.15 (br s, 1H)	for $C_{17}H_9N_3O_3F_2Cl \circ 0.085$ CH_3SO_3H C=51.06/51.18, H=2.59/2.58, N=13.94/13.90
90	7-chloro-1-hydroxy-3-(4-triflouromethylphenyl)-3,4,5,10-tetrahydropyridazino-[4,5-b]quinoline-4,10-dione	12	>250	408 (M+H)	7.64 (dd, *J*=8.8, 2.0 Hz, 1H), 7.91-8.04 (m, 4H), 8.24 (d, *J*=1.9 Hz, 1H), 8.32 (d, *J*=8.8 Hz, 1H), 12.61 (br s, 1H), 13.45 (br s, 1H)	for $C_{18}H_9N_3O_3F_3Cl \circ 0.30\ H_2O$ C=52.33/52.39, H=2.34/2.36, N=10.17/9.91
91	7-chloro-4-hydroxy-2-(4-triflouromethylphenyl)-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione	49	>250	408 (M+H)	7.48 (dd, *J*=8.6, 2.0 Hz, 1H), 7.86 (s, 4H), 8.07 (d, *J*=2.0 Hz, 1H), 8.17 (d, *J*=2.0 Hz, 1H), 12.09 (br s, 1H), 13.04 (br s, 1H)	for $C_{18}H_9N_3O_3F_3Cl \circ 0.35\ H_2O$ C=52.22/52.19, H=2.36/2.01, N=10.15/9.82

TABLE 2 (cont'd)

92	7-chloro-4-hydroxy-2-(3-nitrophenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	15	>250	385 (M+H)	7.46 (dd, *J*=8.6, 1.8 Hz, 1H), 7.70-7.79 (m, 1H), 8.05 (d, *J*=1.6 Hz, 1H), 8.07-8.25 (m, 3H), 8.49 (s, 1H), 12.15 (br s, 1H), 13.07 (br s, 1H)	for $C_{18}H_9N_3O_3F_3Cl \circ 0.40\ H_2O \circ 0.30\ CH_3SO_3H$ C=49.38/49.54, H=2.63/2.35, N=13.31/12.98
93	7-chloro-1-hydroxy-3-(4-sulfonylmethylphenyl)-3,4,5,10-tetrahydropyridazino-[4,5-b]quinoline-4,10-dione	12	>250	418 (M+H)	3.31 (s, 3H), 7.64 (dd, *J*=8.8, 1.9 Hz, 1H), 8.01-8.11 (m, 4H), 8.24 (d, *J*=1.7 Hz, 1H), 8.31 (d, *J*=8.8 Hz, 1H), 12.61 (br s, 1H), 13.47 (br s, 1H)	for $C_{18}H_{12}N_3O_5ClS \circ 0.25\ H_2O$ C=51.19/51.20, H=2.98/2.75, N=9.95/10.01
94	7-chloro-4-hydroxy-2-(4-sulfonylmethylphenyl)-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione	48	>250	418 (M+H)	3.28 (s, 3H), 7.47 (dd, *J*=8.6, 2.0 Hz, 1H), 7.90-7.93 (m, 2H), 8.01-8.06 (m, 3H), , 8.17 (d, *J*=8.7 Hz, 1H), 13.07 (br s, 1H)	

Table 3. The following Examples were made generally as set forth in Example 82, using appropriate corresponding precursors to make the compounds listed. (Yields are overall from the 3-carbomethoxy-2-pyrrolidinocarbamide-7-chloro-4-hydroxy quinoline)

Ex. #	Name	Yield	m.p.(°C)	MS(CI)	NMR (DMSO -d_6)	Analysis (cal'd/found)
95	7-chloro-4-hydroxy-2-(pentafluorobenzyl)-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione	54%	>300	444(M+H)	5.21(s, 2H), 7.43(dd, *J*=8.6, 1.6 Hz, 1H), 8.01 (d, *J*=1.6 Hz, 1H), 8.13 (d, *J*=8.6 Hz, 1H)	for $C_{18}H_7N_3O_3F_5Cl$ C=48.72/48.40, H=1.59/1.82, N=9.47/9.28
96	7-chloro-2-(2-cyanobenzyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazino[4,5-bquinoline-1,10-dione	61	>250	379(M+H)	5.27 (s, 2H), 7.36-7.52 (m, 3H), 7.62-7.70 (m, 1H), 7.87 (dd, *J*=7.7, 1.0 Hz, 1H), 8.04 (d, *J*=1.8 Hz, 1H), 8.15 (d, *J*=8.7 Hz, 1H), 12.00 (br s, 1H), 12.75 (br s, 1H)	for $C_{19}H_{11}N_4O_3Cl \cdot 0.30\ H_2O$ C=59.40/59.44, H=3.04/3.10, N=14.58/14.36
97	7-chloro-2-(3-cholorobenzyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione	77	>250	388(M+H)	5.11 (s, 2H), 7.24-7.46 (m, 5H), 8.03 (s, 1H), 8.15 (d, *J*=8.7 Hz, 1H), 11.95 (br s, 1H), 12.68 (br s, 1H)	for $C_{18}H_{11}N_3O_3Cl$ C=55.69/55.68, H=2.86/3.03, N=10.82/10.59
98	7-chloro-2-(3,5-ditrifluoro-methylbenzyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino-[4,5-b] quinoline-1,10-dione	52	>250	490(M+H)	5.29 (s, 2H), 7.43 (dd, *J*=8.7, 1.9 Hz, 1H), 8.00-8.08 (m, 4H), 8.15 (d, *J*=8.7 Hz, 1H), 11.94 (br s, 1H), 12.67 (br s, 1H)	for $C_{20}H_{10}N_3O_3F_6Cl$ C=59.05/58.71 H=4.66/4.74 N=12.15/11.85
99	7-chloro-4-hydroxy-2-(3-phenylpropyl)-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione	57	>250	382(M+H)	1.92-2.06 (m, 2H), 2.58-2.68 (m, 2H), 3.88-3.98 (m, 2H), 7.12-7.32 (m, 5H), 7.41 (d, *J*=8.2 Hz, 1H), 8.01 (s,1H), 8.13 (d, *J*=8.5 Hz, 1H), 11.87 (br s, 1H), 12.53 (br s, 1H)	for $C_{20}H_{16}N_3O_3Cl$ C=62.91/62.75, H=4.22/4.38, N=11.00/10.92
100	7-chloro-4-hydroxy-2-(4-methylbenzyl)-1,2,5,10-tetrahydropyridazino[4,5-b]-quinoline-1,10-dione	72	>250	368(M+H)	2.27 (s, 3H), 5.05 (s, 2H), 7.08-7.22 (m, 4H), 7.43 (d, *J*=8.7 Hz, 1H), 8.02 (s, 1H), 8.14 (d, *J*=8.7 Hz, 1H), 11.92 (br s, 1H), 12.62 (br s, 1H)	for $C_{19}H_{14}N_3O_3Cl$ C=62.05/61.86, H=3.84/4.00, N=11.42/11.34

TABLE 3 (con't)

101	7-chloro-4-hydroxy-2-(4-trifluoromethylbenzyl)-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione	60	>250	422(M+H)	5.19 (s, 2H), 7.40-7.56 (m, 3H), 7.70 (d, *J*=8.1 Hz, 2H), 8.03 (s, 1H), 8.14 (d, *J*=8.6 Hz, 1H), 11.96 (br s, 1H), 12.71 (br s, 1H)	for $C_{19}H_{11}N_3O_3F_3Cl$ C=54.11/54.01 H=2.63/2.82, N=9.969.62
102	7-chloro-2-(4-cyanobenzyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione	43	>250	379(M+H)	5.18 (s, 2H), 7.40-7.50 (m, 3H), 7.80 (d, *J*=8.2 Hz, 2H), 8.03 (s, 1H), 8.14 (d, *J*=8.7 Hz, 1H), 11.96 (br s, 1H), 12.72 (br s, 1H)	for $C_{19}H_{11}N_4O_3Cl \cdot 0.23\ H_2O$ C=59.60/59.57, H=3.02/3.10, N=14.63/14.85
103	7-chloro-2-(2-fluorobenzyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione	59	>250	372(M+H)	5.16 (s, 2H), 7.12-7.40 (m, 4H), 7.43 (dd, *J*=8.6, 1.3 Hz, 1H), 8.03 (s, 1H), 8.15 (d, *J*=8.6 Hz, 1H), 11.94 (br s, 1H), 12.66 (br s, 1H)	for $C_{18}H_{11}N_3O_3FCl \cdot 0.50\ H_2$ C=56.78/56.84 H=3.18/3.13, N=11.03/10.98

Table 4. The following Examples were made generally as set forth in Example 111, using appropriate corresponding precursors to make the compounds listed.

Ex. #	Name	Yield	m.p.	MS(CI)	NMR (DMSO -d_6)	Analysis (calculated/found)
116	7-Chloro-4-hydroxy-2-(succinimid-1-yl-ethyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	77%	359-363d	389(M+1)	2.57(s, 4H), 3.30(m, 2H), 4.02(m, 2H), 7.43(d, 1H, J=8.6Hz), 8.02(s, 1H), 8.13(d, 1H, J=8.7Hz), 11.91 (brs, 1H), 12.61(brs, 1H)	C=51.80/51.91, H=3.48/3.56, N=14.21/14.08 $C_{17}H_{13}N_4O_5Cl$ - 0.3H_2O
111	7-Chloro-4-hydroxy-2-(4,4-dimethyl-2,5-dioxooxaxolidin-1-ylethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	67%	350-351d	419(M+1)	1.42(s, 6H), 3.76(m, 2H), 4.13(m, 2H), 7.43(m, 2H, J=8.7Hz), 8.02(s, 1H), 8.13(d, 1H, J=8.8Hz), 11.9 (brs, 1H), 12.7(brs, 1H)	C=51.18/51.23, H=3.67/3.80, N=13.26/13.04 $C_{18}H_{15}N_4O_6Cl$ - 0.2H_2O
117	7-Chloro-4-hydroxy-2-(5-methyl-5-phenyl-2,4-dioxoimidazo-3-ylethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	54%	165-170	480(M+1)	1.61(s, 3H), 3.71(m, 2H), 4.13(m, 2H), 7.37(m, 5H), 7.44(dd, 1H, J1=8.7Hz, J2=1.95Hz), 8.02(d, 1H, J=2.0Hz), 8.15(d, 1H, J=8.7Hz), 8.84(s, 1H), 11.9(brs, 1H), 12.64(brs, 1H)	C=55.09/55.00, H=4.10/3.98 N=13.96/13.81 $C_{23}H_{18}N_5O_5Cl$ - 1.2H_2O
118	7-Chloro-4-hydroxy-2-(1-methyl-2,4-dioxoimidazo-3-ylethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	97%	>250C	404(M+1)	2.78(s, 3H), 3.69(t, 2H, J=5.6Hz), 3.89(s, 2H), 4.03(t, 2H, J=5.6Hz), 7.44(dd, 1H, J1=8.7Hz, J2=2.0Hz), 8.02(d, 1H, J=2.0Hz), 8.13(d, 1H, J=8.7Hz), 11.9(brs, 1H), 12.61(brs, 1H)	C=48.62/48.94, H=3.79/3.63, N=16.67/16.33 $C_{17}H_{14}N_5O_5Cl$ - 0.9H_2O
119	7-Chloro-4-hydroxy-2-(5,5-dimethyl-2,4-dioxoimidazo-3-ylethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	91%	>250C	418(M+1)	1.41(s, 6H), 3.76(m, 2H), 4.11(m, 2H), 7.43(d, 1H, J=8.6Hz), 8.02(s, 1H), 8.13(d, 1H, J=8.6Hz), 11.94 (brs, 1H), 12.71(brs, 1H)	C=50.87/50.97, H=3.98/4.05, N=16.48/16.14 $C_{18}H_{16}N_5O_5Cl$ - 0.4H_2O
120	7-Chloro-4-hydroxy-2-(imidazo-3-ylethyl)-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	59%	>250C	358(M+1)	4.3(m, 2H), 4.60(m, 2H), 7.41(d, 1H, J=7.1Hz), 7.52(s, 1H), 7.75(s, 1H), 7.93(s, 1H), 8.06(d, 1H, J=8.7Hz), 9.18(s, 1H), 3.35(brs)	C=44.72/44.95, H=3.52/3.41, N=16.29/16.24 $C_{16}H_{12}N_5O_3Cl$ - 1.0 HCl - 1.0 H_2O - 0.5 NaCl

TABLE 4 (cont'd)

121	7-Chloro-4-hydroxy-2-(5,5-diphenyl-2,4-dioxoimidazo-3-ylethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	64%	272-276	542(M+1)	3.82(m, 2H), 4.16(m, 2H), 7.23(m, 10H), 7.44(d, 1H, J=8.7Hz), 8.03(s 1H), 8.17(d, 1H, J=8.7Hz), 9.54(s, 1H), 11.89(s, 1H), 12.63(s, 1H)	C=59.87/59.90, H=3.98/3.81, 12.47/11.75 $C_{16}H_{11}ClN_4O_5S$ - $1.0H_2O$
122	7-Chloro-4-hydroxy-2-(2,5-dioxothiazolidin-1-ylethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	77%	323-326d	407(M+1)	3.82(m, 2H), 4.06(m, 2H), 4.12(s, 2H), 7.44(dd, 1H, J1=8.6Hz, J2=1.9Hz), 8.02(d, 1H, J=1.9Hz), 8.14(d, 1H, J=8.7Hz), 11.9(brs, 1H), 12.7(brs,1H)	C=45.24/45.23, H=3.08/3.01, N=13.16/12.21 $C_{28}H_{20}N_5O_5Cl$ - $1.1H_2O$
123	7-Chloro-4-hydroxy-2-(1,3-dioxopyridino[2,3-c]pyrrolidin-2-ylethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	61%	311-314	438(M+1)	3.94(t, 2H, J=5.4Hz), 4.14(t, 2H, J=5.4Hz), 7.42(dd, 1H, J1=8.7Hz, J2=1.7Hz), 7.87(dd, 1H, J1=4.8Hz, J2=1.1Hz), 7.99(d, 1H, J=1.9Hz), 8.11(d, 2H, J=8.7Hz), 9.10(m, 2H), 11.89(brs, 1H), 12.53(brs,1H)	C=52.70/52.75, H=3.10/2.82, N=15.36/15.43 $C_{20}H_{12}ClN_5O_5$ - $1.0H_2O$
124	7-Chloro-4-hydroxy-2-(o-benzoicsulfimid-2-ylethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	59%	>250C	473(M+1)	4.04(t, 2H, J=5.46Hz), 4.27(t, 2H, J=5.43Hz), 7.18(dd, 1H, J1=8.7Hz, J2=1.56Hz), 8.03(m, 2H), 8.12(dd, 2H, J1=6.7Hz, J2=1.2Hz), 8.24(dd, 1H, J1= 6.7Hz, J2=1.53Hz), 11.90 (brs, 1H), 12.59(brs, 1H)	C=48-94/49.27, H=3.08/3.48, N=11.41/11.09 $C_{20}H_{13}N_4O_6S_1Cl_1$ - $1.0H_2O$
125	7-Chloro-4-hydroxy-2-(5,5-hexamethylene-2,5-dioxooxazolidin-1-ylethyl)-1.2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	80%	>250C	459(M+1)	1.45(m, 10H), 3.76(m, 2H), 4.12(m 2H), 7.44(d, 1H, J=8.6Hz), 8.02(s, 1H), 8.15(d, 1H, J=8.6Hz), 11.95(brs, 1H), 12.70(brs, 1H)	C=52.89/52.81, H=4.44/4.20, N=11.75/11.51 $C_{21}H_{19}N_4O_6Cl$ - $1.0H_2O$
126	7-Chloro-4-hydroxy-2-(benzo[e][1,3]oxazinyl-2,4-dioneethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	92%	>250C	453(M+1)	4.23(m, 4H), 7.41(m, 3H), 7.78(m, 1H), 7.85(m, 1H), 7.99(m, 1H), 8.10(d, 1H, J=8.7Hz), 11.90(brs, 1H), 12.6(brs, 1H)	C=55.24/55.26, H=3.16/2.96, N=12.22/12.28 $C_{21}H_{13}ClN_4O_6$ - $0.2H_2O$
127	7-Chloro-4-hydroxy-2-(1,2,4-triazol-2-ylethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	70%	>250C	359(M+1)	4.23(t, 2H, J=5.65Hz), 4.54(t, 2H, J=5.66Hz), 7.40(dd, 1H, J1=8.7Hz, J2=1.9Hz), 7.93(s, 1H), 7.98(d, 1H J=1.9Hz), 8.09(d, 1H, J=8.7Hz), 8.48(s, 1H), 11.9(brs, 1H), 12.6(brs, 1H)	C=49.31/49.58, H=3.12/3.35, N=22.40/22.38 $C_{15}H_{11}ClN_6O_3$ - $0.2NaCl$

TABLE 4 (con't)

128	7-Chloro-4-hydroxy-2-(1,2,3-triazol-2-ylethyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	75%	>250C	359(M+1)	4.32(m, 2H), 4.77(m, 2H), 7.45(m, 1H), 7.75(s, 1H), 8.01(m, 1H), 8.13(m, 2H), 11.9(brs, 1H), 12.6(brs, 1H)	C=48.80/48.82, H=3.57/3.33, N=20.69/20.42 $C_{15}H_{11}ClN_6O_3 \cdot 0.7H_2O$
129	7-Chloro-4-hydroxy-2-(1,2,3,4-tetrazol-1-ylethyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione 7-Chloro-4-hydroxy-2-(1,2,3,4-tetrazol-2-ylethyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	83% 1:1 mix of 2 isomers	>250C	360(M+1)	4.32(t, 1.5H, J=5.57Hz), 4.39(t, 1.5H, J=5.55Hz), 4.87(t, 1.5H, J=5.31Hz), 5.08(t, 1.5H, J=5.60Hz), 7.45(m, 1H), 8.01(m, 1H), 8.94(s, 0.5H), 9.47(s, 0.5H), 11.92(brs, 1H), 12.59(brs, 0.5H), 12.63(brs, 0.5H)	C=46.74/46.70, H=2.86/3.16, N=27.26/26.09 $C_{14}H_{10}ClN_7O_3 \cdot 0.5H_2O$
130	7-Chloro-4-hydroxy-2-(5-phenyl-2,5-dioxooxazolidin-1-ylethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	74%	>250C	467(M+1)	3.80(m, 1.5H), 3.92(m, 1.5H), 4.00(m, 1.5H), 4.38(m, 1.5H), 7.40(m, 6H), 8.00(s, 1H), 8.18(d, 1H, J=8.6Hz), 11.95(brs, 1H), 12.75(brs, 1H)	C=55.12/54.91, H=3.50/3.48, N=11.65/11.64 $C_{22}H_{15}ClN_4O_6 \cdot 0.2H_2O$

Table 5. The following Examples were made generally as set forth in Example 112, using appropriate corresponding precursors to make the compounds listed.

Ex. #	Name	Yield	m.p.	MS(CI)	NMR (dmso-d6)	Analysis (calc./found)
112	7-Chloro-4-hydroxy-2-(2-methyl-2-hydroxypropionamidoethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	84%	300-303	392(M+1)	1.18(s, 3H), 1.38(s, 3H), 3.4(m, 2H) 3.95(m, 2H), 7.26(m, 0.5H), 7.42(d, 1H, J=8.7Hz), 7.83(m, 0.5H), 8.01 (s, 1H), 8.13(d, 1H, J=8.6Hz), 11.9 (brs, 1H), 12.6(brs, 1H)	C=50.48/50.58, H=4.24/4.25, N=13.85/13.84 $C_{17}H_{17}N_4O_5Cl$ - 0.2NaCl
131	7-Chloro-4-hydroxy-2-(1-hydroxycyclo hexylcarboxamidoethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	81%	>250C	433(M+1)	1.50(m, 10H), 3.43(m, 2H), 3.98(m, 2H), 7.43(d, 1H, J=8.3Hz), 7.88(bt, 1H, J=5.8Hz), 8.01(s, 1H), 8.13(d, 1H, J=8.7Hz),11.9(brs, 1H), 12.6(brs, 1H)	C=53.28/53.17, H=5.14/5.00, N=12.43/12.08 $C_{20}H_{21}ClN_4O_4$ - 1.0H_2O
132	7-Chloro-4-hydroxy-2-(2-hydroxybenz amidoethyl)-1,2,5,10-tetrahydro pyridazino[4,5-b]quinoline-1,10-dione	84%	>250C	427(M+1)	3.71(m, 2H), 4.11(m, 2H), 6.88(m, 2H), 7.39(m, 2H), 7.86(d, 1H, J=8.0Hz), 7.94(d, 1H, J=1.5Hz), 8.04(d, 1H, J=8.7Hz), 8.09(bt, 1H, J=5.6Hz)	C=54.44/54.37, H=3.79/3.73, N=12.70/12.63 $C_{20}H_{15}ClN_4O_5$ - 0.8H_2O
133	7-Chloro-4-hydroxy-2-(2-hydroxy-2,2-diphenylacetamidoethyl)-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione	66%	>250C	517(M+1)	3.50(m, 2H), 4.05(t, 2H, J=6.0Hz), 7.22(m, 6H), 7.36(m, 4H), 7.43(m, 1H), 8.05(d, 1H, J=1.42Hz), 8.15(d, 1H, J=8.6Hz), 8.26(bt, 1H), 11.90(brs, 1H), 12.68(brs, 1H)	C=62.73/59.69, H=4.09/3.95, N=10.84/11.11 $C_{27}H_{21}ClN_4O_5$
134	7-Chloro-4-hydroxy-2-(2-methyl-2-hydroxybutyramidoethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione	76%	>250C	407(M+1)	0.70(t, 3H, J=7.35Hz), 1.17(s, 3H), 1.38(m, 1H), 1.56(m, 1H), 3.46(m, 2H), 3.98(m, 2H), 7.42(d, 1H, J=7.95Hz), 7.82(bt, 1H, J=5.6Hz), 8.00(d, 1H, J=8.6Hz), 11.87(brs, 1H), 12.57(brs, 1H)	C=51.66/51.89, H=4.57/4.62, N=13.39/13.31 $C_{18}H_{19}ClN_4O_5$ - 0.2NaCl

TABLE 5

Table 6. The following Examples were made generally as set forth in Example 113, using appropriate corresponding precursors to make the compounds listed.

Ex. #	Name	Yield	m.p.	MS(CI)	NMR (DMSO -d_6)	Analysis (calculated/found)
113	7-Chloro-4-hydroxy-2-(2-methylthio ethyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	85%	282-284	338(M+1)	2.11(s, 3H), 2.79(t, 2H, J=7.1Hz), 4.08(t, 2H, J=7.1Hz), 7.42(d, 1H, J=7.8Hz), 8.01(s, 1H), 8.13(d, 1H, J=8.6Hz), 11.91(brs, 1H), 12.64(brs, 1H)	C=49.78/49.73, H=3.58/3.73, N=12.44/12.30 $C_{14}H_{12}ClN_3O_3S_1$
135	7-Chloro-4-hydroxy-2-(2-ethylthio ethyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	53%	264-266	352(M+1)	1.20(t, 3H, J=7.35Hz), 2.56(q, 2H, J=7.38Hz), 2.82(t, 2H, J=7.26Hz), 4.06(t, 2H, J=7.31Hz), 7.43(dd, 1H, J1=8.64Hz, J2=1.95Hz), 8.02(d, 1H, J=1.98Hz), 8.13(d, 1H, J=8.61Hz), 11.9(brs, 1H), 12.6(brs, 1H)	C=51.07/51.21, H=4.04/4.01, N=11.99/11.94 $C_{15}H_{14}ClN_3O_3S$
136	7-Chloro-4-hydroxy-2-(2-n-butylthio ethyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	75%	248-250	380(M+1)	0.88(m, 3H), 1.36(m, 2H), 2.52(m, 2H), 2.80(t, 2H, J=7.2Hz), 4.06(t, 2H, J=7.2Hz), 7.42(m, 1H), 8.02(s, 1H), 8.13(d, 1H, J=8.6Hz), 11.92(brs, 1H), 12.63(brs, 1H)	C=53.45/53.43, H=4.78/4.95, N=11.06/11.21 $C_{17}H_{18}ClN_3O_3S$
137	7-Chloro-4-hydroxy-2-(2-n-propylthio ethyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	78%	265-268	366(M+1)	0.94(t, 3H, J=7.3Hz), 1.55(sx, 2H, J=7.3Hz), 2.53(m, 2H), 2.80(t, 2H, J=7.3Hz), 4.05(t, 2H, J=7.3Hz), 7.42(dd, 1H, J1=8.6Hz, J2=1.8Hz), 8.02(d, 1H, J=1.9Hz), 8.13(d, 1H, J=8.7Hz), 11.9(brs, 1H)	C=52.21/52.53, H=4.53/4.41, N=11.80/11.49 $C_{16}H_{10}ClN_3O_4 \cdot 0.2H_2O$

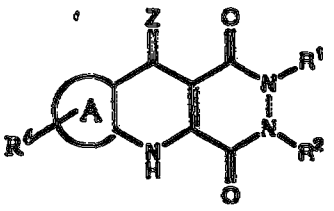
Table 7. The following Examples were made generally as set forth in Example 114, using appropriate corresponding precursors to make the compounds listed.

Ex. #	Name	Yield	m.p.	MS(CI)	NMR (DMSO -d_6)	Analysis (calculated/found)
114	7-Chloro-4-hydroxy-2-(2-methylsulfonyl ethyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	75%	>250C	370(M+1)	2.51(s, 3H), 3.53(t, 2H, J=6.9Hz), 4.31(m, 2H), 7.43(dd, 1H, J1=8.6Hz, J2=1.2Hz), 8.02(d, 1H, J=1.5Hz), 8.14(d, 1H, J=8.6Hz), 12.5(brs, 2H)	C=43.36/43.33, H=3.64/3.64, N=10.84/10.57 $C_{14}H_{12}ClN_3O_5S_1 \cdot 1.0H_2O$
138	7-Chloro-4-hydroxy-2-(2-ethylsulfonyl ethyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	89%	270-274	384(M+1)	1.22(m, 3H), 3.18(m, 2H), 3.49(t, 2H, J=7.13Hz), 4.30(t, 2H, J=7.16Hz), 7.44(dd, 1H, J1=8.7Hz, J2=1.9Hz), 8.02(d, 1H, J=1.9Hz), 8.13(d, 1H, J=8.7Hz), 11.9(brs, 1H), 12.7(brs, 1H)	C=44.84/44.71, H=4.01/4.02, N=10.46/10.44 $C_{15}H_{14}ClN_3O_5S_1 \cdot 1.0H_2O$
139	7-Chloro-4-hydroxy-2-(2-n-butylsulfonyl ethyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	100%	288-290	412(M+1)	0.89(t, 3H, J=7.26Hz), 1.39(m, 2H), 1.63(m, 2H), 3.17(m, 2H), 3.50(t, 2H, J=6.96Hz), 4.30(t, 2H, J=6.99Hz), 7.44(d, 1H, J=8.8Hz), 8.02(s, 1H), 8.13(d, 1H, J=8.6Hz), 11.97(brs, 1H), 12.79(brs, 1H)	C=47.50/47.14, H=4.69/4.68, N=9.77/9.71 $C_{17}H_{18}ClN_3O_5S \cdot 1.0H_2O$

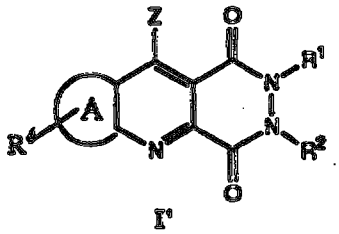
Table 8. The following Examples were made generally as set forth in Example 115, using appropriate corresponding precursors to make the compounds listed:

Ex. #	Name	Yield	m.p.	MS(CI)	NMR (DMSO -d6)	Analysis (calc./found)
115	7-Chloro-4-hydroxy-2-(thiophen-2-yl methyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	84%	>250C	360(M+1)	5.23(s, 2H), 6.98(m, 1H), 7.10(m, 1H), 7.43(m, 2H), 8.02(d, 1H, J=1.95Hz), 8.14(d, 1H, J=8.7Hz), 11.92(brs, 1H), 12.7(brs, 1H)	C=52.11/52.10, H=3.01/3.32, N=11.39/11.10 $C_{16}H_{10}ClN_3O_3S \cdot 0.5H_2O$
140	7-Chloro-4-hydroxy-2-(furan-2-yl methyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	51%	>250C	344(M+1)	5.09(s, 2H), 6.36(d, 1H, J=3.1Hz), 6.42(m, 1H), 7.42(m, 1H), 7.59(d, 1H, J=1.0Hz), 8.02(d, 1H, J=1.9Hz), 8.14(d, 1H, J=8.7Hz), 11.9 (brs, 1H), 12.7(brs, 1H)	C=55.46/55.33, H=3.12/3.02, N=11.39/11.10 $C_{16}H_{10}ClN_3O_4 \cdot 0.2H_2O$
141	7-Chloro-4-hydroxy-2-(thiophene-3-yl methyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	65%	>250C	360(M+1)	5.08(s, 1H), 7.08(d, 1H, J=4.86Hz), 7.37(s, 1H), 7.43(d, 1H, J=8.6Hz), 7.50(m, 1H), 8.02(s, 1H), 8.14(d, 1H, J=8.6Hz), 11.92(brs, 1H), 12.65(brs, 1H)	C=52.88/52.91, H=2.88/3.12, N=11.56/11.35 $C_{16}H_{10}ClN_3O_3S \cdot 0.2H_2O$
142	7-Chloro-4-hydroxy-2-(furan-3-yl methyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	59%	>250C	344(M+1)	4.92(s, 1H), 6.46(s, 1H), 7.43(d, 1H, J=8.46Hz), 7.63(m, 1H), 8.02(d, 1H, J=1.6), 8.14(d, 1H, J=8.61Hz), 11.92(brs, 1H), 12.67(brs, 1H)	C=55.91/55.58, H=4.01/4.03, N=12.22/11.89 $C_{16}H_{14}ClN_3O_4$
143	7-Chloro-4-hydroxy-2-(3-methylthio propyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	64%	263-265C (decomp)	352(M+1)	1.93(p, 2H, J=5.37Hz), 3.33(m, 1H, [superimposed on water peak]), 7.41(d, 1H, J=8.64Hz), 8.01(s, 1H), 8.12(d, 1H, J=8.73Hz), 11.88(brs, 1H), 12.58(brs, 1H)	C=51.21/50.98, H=4.01/4.13, N=11.94/11.89 $C_{15}H_{14}ClN_3O_3S$
144	7-Chloro-4-hydroxy-2-(2-cyanoethyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione	55%	>250C	317(M+1)	2.96(t, 2H, J=6.4Hz), 4.14(t, 2H, 6.42Hz), 7.43(dd, 1H, J1=8.69Hz, J2=1.18Hz), 8.03(d, 1H, J=1.68Hz), 8.13(d, 1H, J=8.64Hz), 11.98(brs, 1H), 12.81(brs, 1H)	C=51.91/52.16, H=3.05/3.03, N=17.30/17.18 $C_{14}H_9ClN_4O_3 \cdot 0.4H_2O$

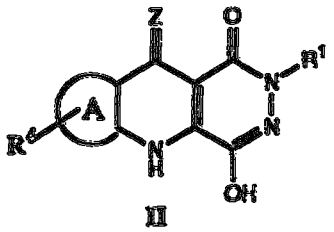
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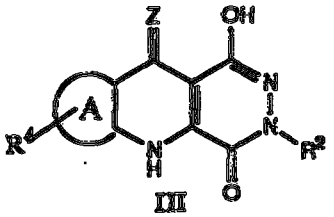
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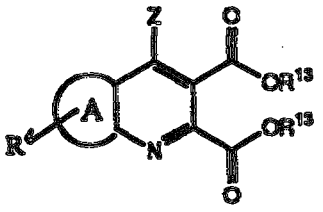
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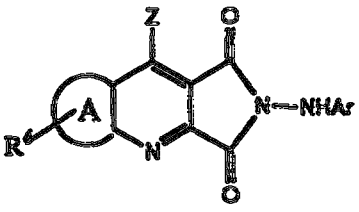
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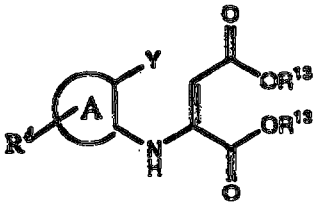
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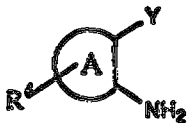
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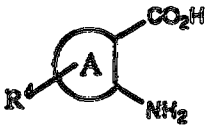
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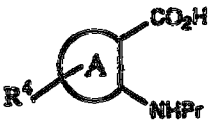
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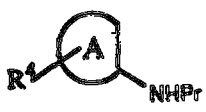


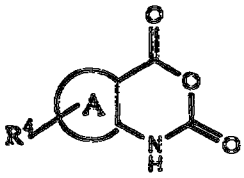
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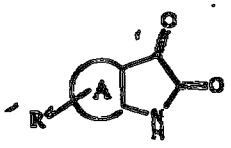
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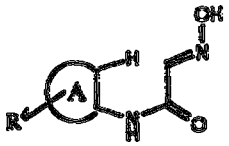




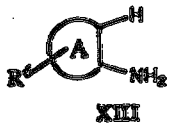
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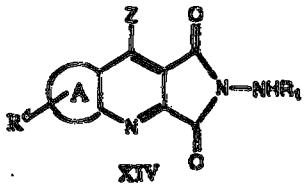
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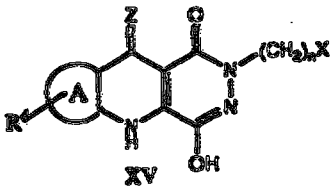
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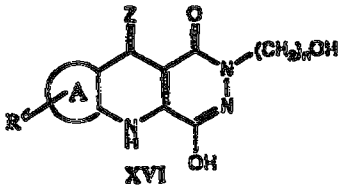
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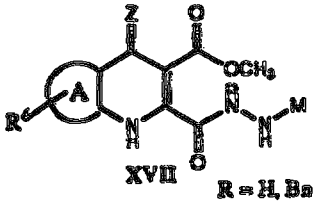
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XV

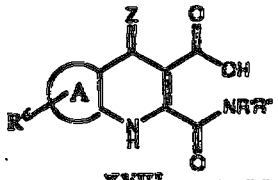


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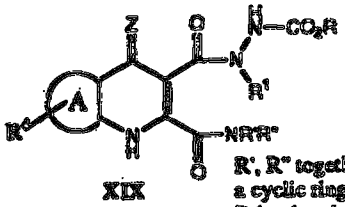
XVII

R = H, Ba



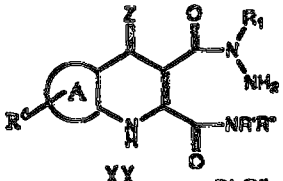
XVIII

R', R" together form a cyclic ring with N.



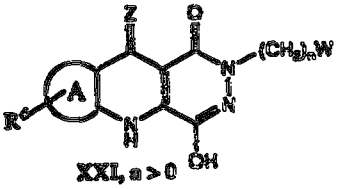
XIX

R', R" together form a cyclic ring with N. R is t-butyl or a bulky alkyl substituent.



XX

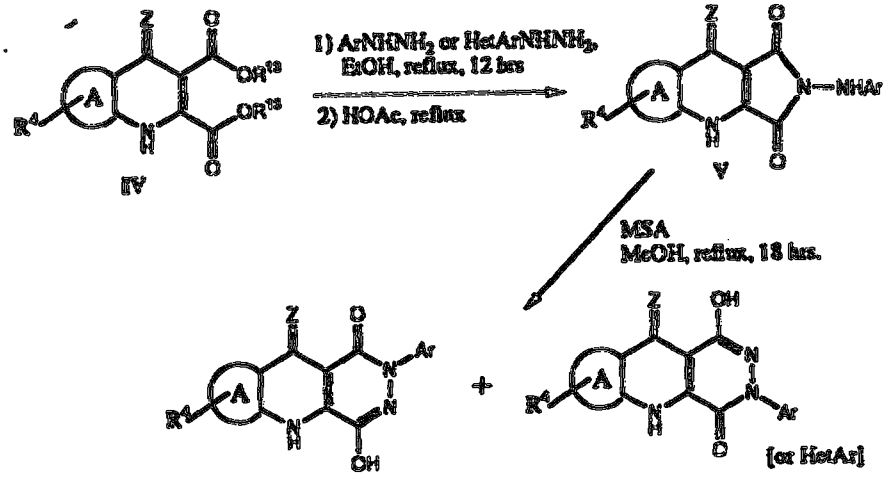
R', R" together form a cyclic ring with N.



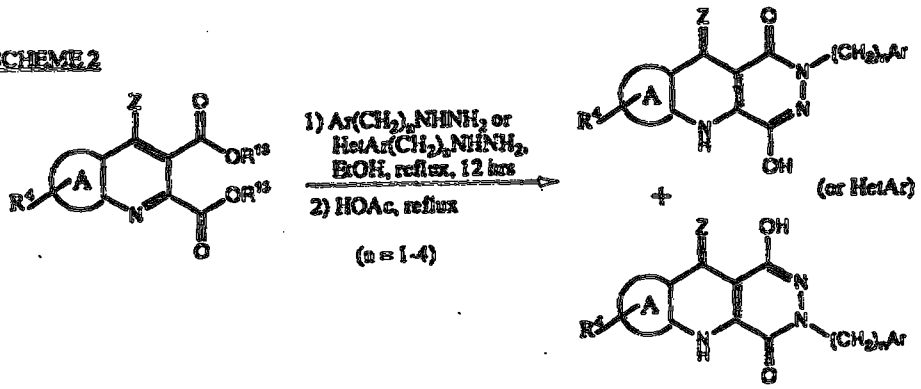
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SCHEME 1 & 2

SCHEME 1



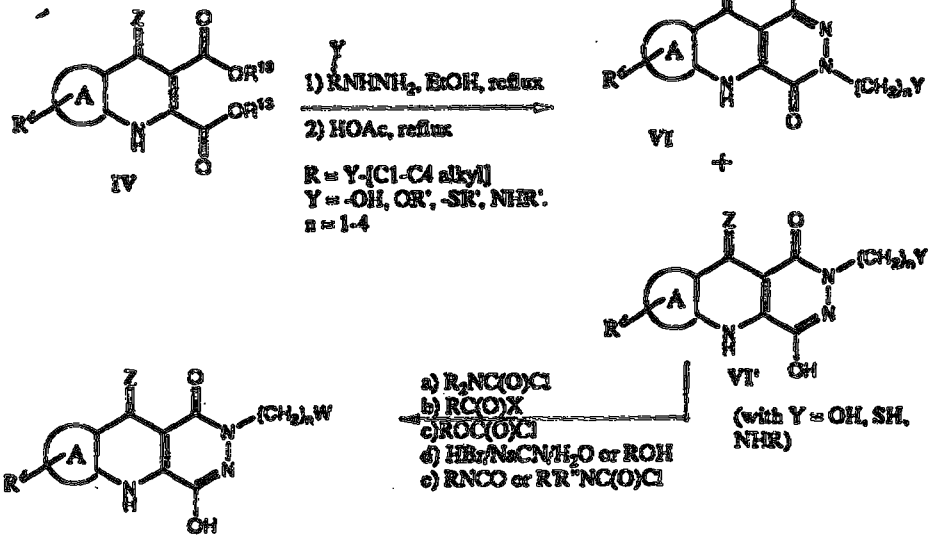
SCHEME 2



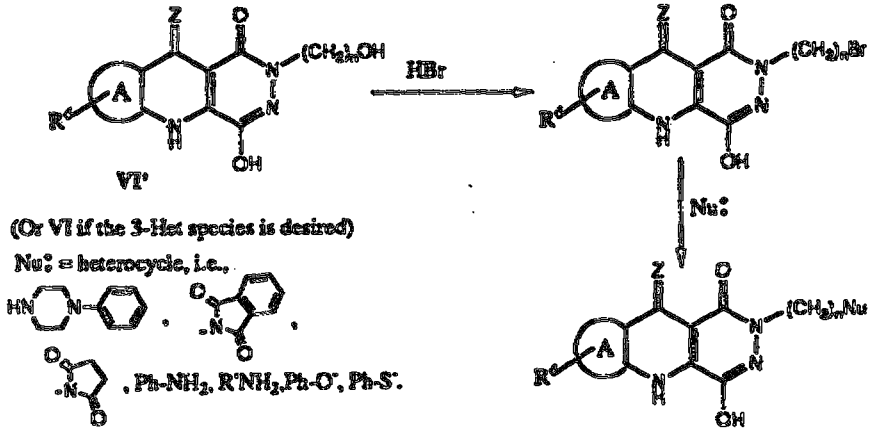
The isomers may be separated by fractional acidification of meglumine/choline solutions.

SCHEME 3 & 4

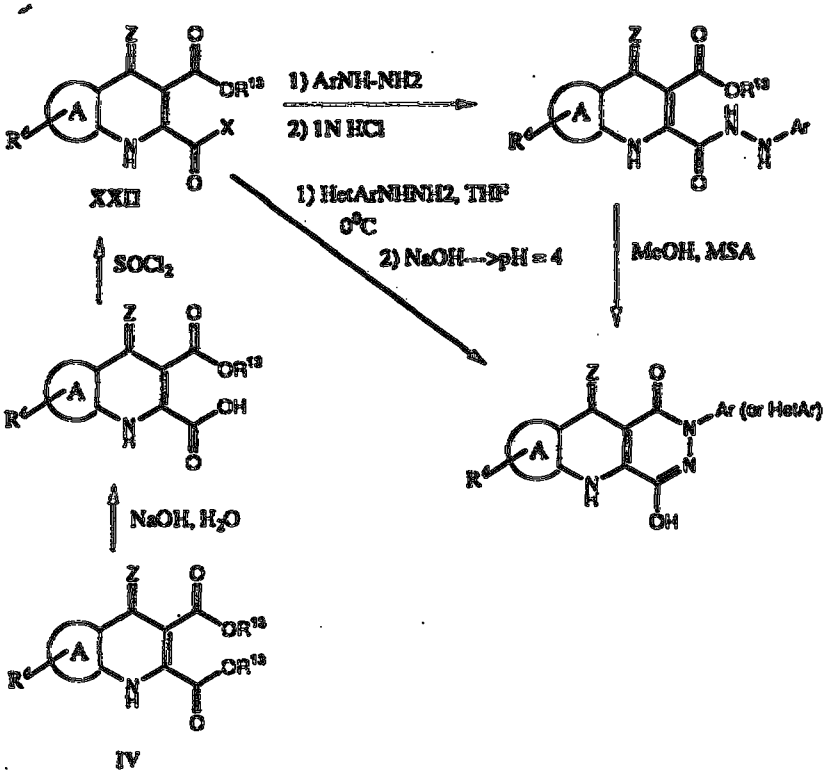
SCHEME 3



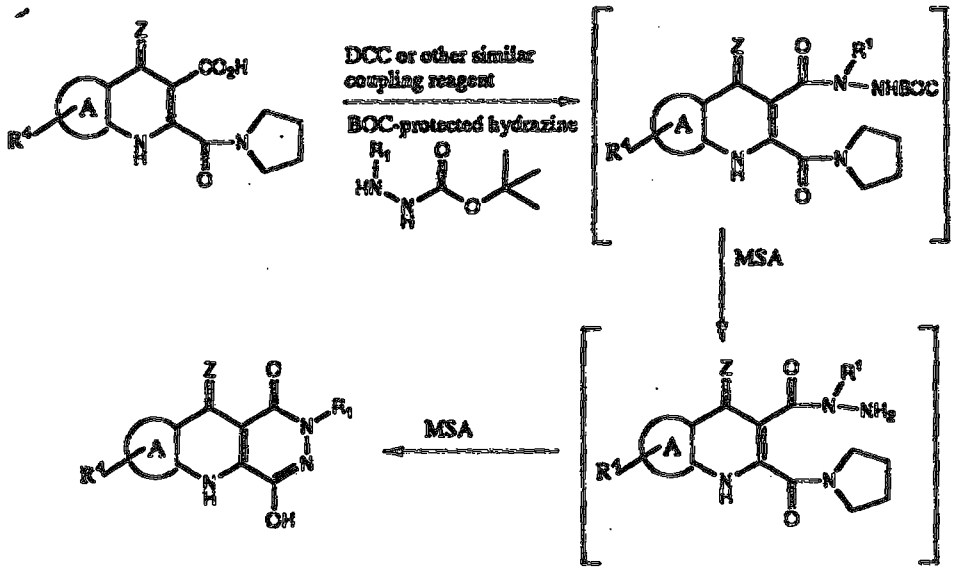
SCHEME 4



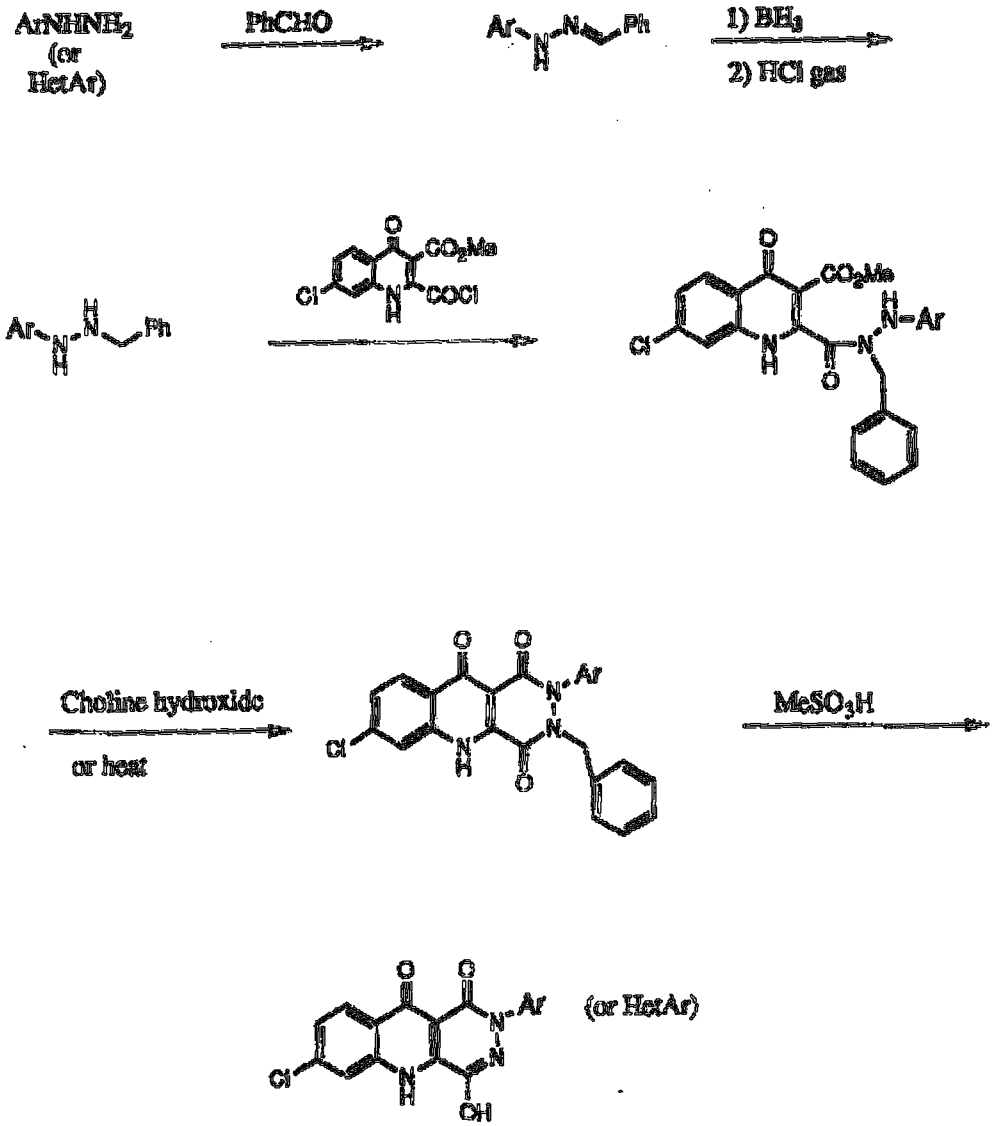
SCHEME 5


1) ArNH-NH2
2) 1N HCl
XXII
1) HetArNHNH2, THF
0°C
2) NaOH--->pH = 4
MeOH, MSA
SOCl2
NaOH, H2O
Ar (or HetAr)
IV

SCHEME 6

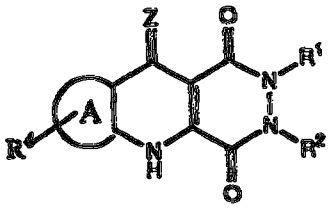

DCC or other similar coupling reagent
BOC-protected hydrazine
MSA
MSA

SCHEME 7


ArNHNH2
(or
HetAr)
PhCHO
Ar
N
Ph
1) BH3
2) HCl gas
Ar
N
H
Ph
Cl
CO2Me
COCl
CO2Me
N–Ar
Choline hydroxide
or heat
MeSO3H
Cl
N–Ar
(or HetAr)
OH

WHAT IS CLAIMED IS:

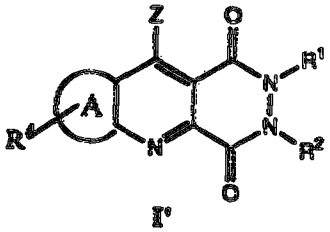
1. A compound of formula 1 or a pharmaceutically acceptable salt thereof and tautomers thereof



I

wherein:

Z is selected from O, S or NH, or when the B-ring N tautomerizes or the B-ring is reduced, the Z group may be selected from H, OH, SH or NH_2 to form a compound of I'



I'

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and wherein:

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, furyl, pyrrolyl or thienyl either unsubstituted or multi-substituted at a ring carbon atom with R^4 wherein R^4 is independently selected from the group consisting of halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR';a heterocyclic group, NR'COR",COR",NR'CO_2R",CO_2R',CONR'R";

R^1 is selected from H or -$(CH_2)_n$L wherein L is M or W;

M is

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from -O-(1-4C)alkyl,-O-(2-4C)alkenyl, -O-(2-4C)alkynyl, -O(CO-C6alkyl)phenyl, -OH, -halo, -NO_2, -CN, -CF_3, -(1-4C)alkylCF_3, -NH(CO)R', -(1-4C)alkyl, -NR'R", -CO_2R', -CONR'R", -SO_mR', -$SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluroalkyl, -(1-4Cperfluroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy), -(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', -$(CH)_n$NR'R"COOR' wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', -NR'$(CH_2)_n$COOR', -$S(O)_m$(C1-4alkyl)oxy(C1-4alkyl), -$S(O)_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

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heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S, or aryl or heteroaryl benz derivatives thereof, wherein the N on the heterocycle is optionally substituted with R′ and a carbon or nitrogen atom on the heterocycle may be substituted with R or R′ or a carbon atom may be disubstituted to form a C5-C7 spiral group or a carbon atom or sulfur atom may be substituted with O to form a carbonyl group or sulfonyl group ($S(O)_m$) with the proviso that a heterocyclic nitrogen may not be attached to a nitrogen on the tricyclic ring system of formula I;

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole or isothiazole (and oxidized versions thereof selected from $S(O)_m$ wherein m is 0-2), pyridazine, pyrimidine, pyrazine or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or triazine, or those groups containing four heteroatoms such as tetrazole, wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

W is selected from OH, OR′, OCOR′, $S(O)_mR'$, $S(O)_mNR'R''$, halo, CF_3 NR′R″ with the proviso that NR′R″ is not equal to NH_2; or W is COR′, NR′COR″, OCONR′, $NR'CO_2R''$, (C3-6)cycloalkyl, NRCONR′R″, CO_2R', or CONRR′ with the proviso that n is greater than zero and;

n, for groups other than W, is chosen from 0-6;

R^2 is selected from H or $-(CH_2)_nL$ wherein L is M or W and

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M is:

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2 or 3 groups chosen from -O-(1-4C)alkyl, -OH, -halo, $-NO_2$, -CN, $-CF_3$, -NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", $-OCF_3$, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy);

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S, or aryl or heteroaryl benz derivatives thereof, wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R' or a carbon atom may be disubstituted to form a C5-C7 spiral group or a carbon atom or sulfur atom may be substituted with O to form a carbonyl group or sulfonyl group $(S(O)_m)$;

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole, or those groups containing four heteroatoms such as tetrazole, wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

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W is selected from OH, OR', OCOR', $S(O)_mR'$, halo, $S(O)_mNR'R''$,$NR'R''$ with the proviso that NR'R'' is not equal to NH_2; or W is COR', NR'COR'', OCONR', $NR'CO_2R''$, (C3-6)cycloalkyl, NRCONR'R'', CO_2R', or CONRR' with the proviso that n is greater than zero and;

n, for groups other than W, is chosen from 0-6;

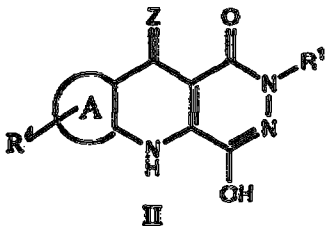
R is selected from H or (1-4C)alkyl;

R' and R'' are independently selected from H, (1-4C)alkyl wherein alkyl includes alkenyl(C2-C4) and alkynyl(C2-C4); (3-6C)cycloalkyl, Phenyl(0-4C)alkyl-, heterocycle(0-4C)alkyl- or heteroaryl(0-4C)alkyl- wherein phenyl or heterocycle or heteroaryl is as defined above and any of the above is optionally substituted at one or more carbon atoms with halo, H, (1-4C)alkyl, (3-6C)cycloalkyl, phenyl, NO_2, CN, CF_3, OH, O-(1-4C)alkyl, NR'R'' $S(O)_mR'$ or $SO_2NR'R''$ wherein NR'R'' may optionally form an N-alkyl(C1-3)oxyalkyl(C2-3) ring with N;

m is chosen from 0-2;

with the proviso that R^1 and R^2 are not both equal to H.

2. A compound according to claim 1 of formula II or pharmaceutically acceptable salts thereof:



II

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wherein:

Z is selected from O, S or NH, or when the B-ring N tautomerizes or the B-ring is reduced, the Z group may be selected from H, OH, SH or NH_2,

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, furyl, pyrrolyl or thienyl either unsubstituted or multi-substituted at a ring carbon atom with R^4 wherein R^4 is independently selected from the group consisting of halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR', a heterocyclic group, NR'COR",COR",NR'CO_2R",CO_2R',CONR'R";

R^1 is selected from H or -$(CH_2)_n$L wherein L is M or W;

M is

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from -O-(1-4C)alkyl,-O-(2-4C)alkenyl, -O-(2-4C)alkynyl, -O(CO-C6alkyl)phenyl, -OH, -halo, -NO_2, -CN, -CF_3, -(1-4C)alkylCF_3, -NH(CO)R', -(1-4C)alkyl, -NR'R", -CO_2R', -CONR'R", -SO_mR', -$SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluroalkyl, -(1-4Cperfluroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy), -(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', -$(CH)_n$NR'R"COOR' wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', -NR'$(CH_2)_n$COOR', -$S(O)_m$(C1-4alkyl)oxy(C1-4alkyl),

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$-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl),
-NR'(C1-4alkyl)oxy(C1-4alkyl),
-NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S, or aryl or heteroaryl benz derivatives thereof, wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R' or a carbon atom may be disubstituted to form a C5-C7 spiral group or a carbon atom or sulfur atom may be substituted with O to form a carbonyl group or sulfonyl group ($S(O)_m$) with the proviso that a heterocyclic nitrogen may not be attached to a nitrogen or the tricyclic ring system of formula I;

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole or isothiazole (and oxidized versions thereof selected from $S(O)_m$ wherein m is 0-2), pyridazine, pyrimidine, pyrazine or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or triazine, or those groups containing four heteroatoms such as tetrazole, wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

W is selected from OH, OR', OCOR', $S(O)_mR'$, $S(O)_mNR'R"$, halo, CF_3 NR'R" with the proviso that NR'R" is not equal to NH_2; or W is COR', NR'COR", OCONR', $NR'CO_2R"$, (C3-6)cycloalkyl, NRCONR'R", CO_2R', or CONRR' with the proviso that n is greater than zero and;

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n, for groups other than W, is chosen from 0-6;

R is selected from H or (1-4C)alkyl;

R′ and R" are independently selected from H, (1-4C)alkyl wherein alkyl includes alkenyl(C2-C4) and alkynyl(C2-C4); (3-6C)cycloalkyl, Phenyl(0-4C)alkyl-, heterocycle(0-4C)alkyl- or heteroaryl(0-4C)alkyl- wherein phenyl or heterocycle or heteroaryl is as defined above and any of the above is optionally substituted at one or more carbon atoms with halo, H, (1-4C)alkyl, (3-6C)cycloalkyl, phenyl, NO_2, CN, CF_3, OH, O-(1-4C)alkyl, NR′R" $S(O)_m$R′ or SO_2NR′R" wherein NR′R" may optionally form an N-alkyl(C1-3)oxyalkyl(C2-3) ring with N;

m is chosen from 0-2.

3. A compound according to claim 2 and pharmaceutically acceptable salts thereof wherein:

Z is chosen from:
O, S, or NH;

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, pyrrolyl or thienyl either unsubstituted or substituted at one or more ring carbon atoms with R^4 wherein R^4 is independently selected from the group consisting of hydrogen, halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR′R", SO_2NR′R", or SO_mR′;

R^1 is $-(CH_2)_nL$ wherein

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L is chosen from:
-OH, -O(C1-C4alkyl), -O(C1-C4alkyl)aryl, (C1-C4alkyl)COOR', OCOR', $S(O)_m$R', NR'R" with the proviso that NR'R" is not equal to NH_2, NR'COR", OCONR', NR'CO_2R", NRCONR'R", CO_2R', or CONRR' with the proviso that n is greater than zero;

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from -O-(1-4C)alkyl, -O-(2-4C)alkenyl, -O-(2-4C)alkynyl, -O(CO-C6alkyl)phenyl, -OH, -halo, -NO_2, -CN, -CF_3, -(1-4C)alkylCF_3, -NH(CO)R', -(1-4C)alkyl, -NR'R", -CO_2R', -CONR'R", -SO_mR', -SO_2NR'R", (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluroalkyl, -(1-4Cperfluroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy), -(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', -$(CH)_n$NR'R"COOR' wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', -NR'$(CH_2)_n$COOR', -$S(O)_m$(C1-4alkyl)oxy(C1-4alkyl), -$S(O)_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R' or a carbon atom may be disubstituted to form a C5-C7 spiral group or a carbon atom or sulfur atom may be substituted with O to form a carbonyl group or sulfonyl group ($S(O)_m$); wherein the heterocyclic groups may be selected from,

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for example, 2-pyrolidinone, piperazine, oxazolidone, 2,5-oxazolidinedione, 2,4-imidazollidinedione, 2,4-thiazolidinedione or succinimide; aryl or benz or heteroarylbenz derivatives thereof (3,4-pyridinedicarboximide, -1-pthalimido, isatoic anhydride, orthobenzoicsulfimide) either unsubstituted or mono, bi or tri-substituted with alkyl or aromatic substituents including -halo, -C1-C6alkyl, -OH, C1-C6alkoxy, phenyl, OCF_3, CF_3, NO_2, CN, NH_2, SO_mR', NH(C1-4alkyl), or N(C1-C4alkyl)$_2$;

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or those groups containing 4 heteroatoms such as tetrazole wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to -$(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

n is 0-3; R, R', R" and m are as defined in claim 2.

4. A compound according to claim 2 and pharmaceutically acceptable salts thereof wherein:

Z is chosen from:
O, S, or NH;

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, pyrrolyl or thienyl either unsubstituted or substituted at one or more ring

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carbon atoms with R^4 wherein R^4 is independently selected from the group consisting of hydrogen, halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR';

R^1 is $-(CH_2)_nL$ wherein

L is chosen from:

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from -O-(1-4C)alkyl,-O-(2-4C)alkenyl, -O-(2-4C)alkynyl, -O(CO-C6alkyl)phenyl, -OH, -halo, $-NO_2$, -CN, $-CF_3$, -(1-4C)alkylCF_3, -NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluroalkyl, -(1-4Cperfluroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy), -(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', $-(CH)_nNR'R"COOR'$ wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', $-NR'(CH_2)_nCOOR'$, $-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl), $-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three

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heteroatoms chosen from N, O or S such as triazole or oxadiazole or those groups containing 4 heteroatoms such as tetrazole wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

n is 0; R, R', R" and m are as defined in claim 2.

5. A compound according to claim 2 or a pharmaceutically acceptable salt thereof wherein:

Z is chosen from:
O, S, or NH;

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, pyrrolyl or thienyl either unsubstituted or substituted at one or more ring carbon atoms with R^4 wherein R^4 is independently selected from the group consisting of hydrogen, halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR';

R^1 is $-(CH_2)_nL$ wherein

L is chosen from:
-OH, -O(C1-C4alkyl), CF_3-O(C1-C4alkyl)aryl, (C1-C4alkyl)COOR', OCOR', $S(O)_mR'$, NR'R" with the proviso that NR'R" is not equal to NH_2, NR'COR", OCONR', $NR'CO_2R"$, NRCONR'R", CO_2R', or CONRR';

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from

-O-(1-4C)alkyl,-O-(2-4C)alkenyl, -O-(2-4C)alkynyl,
-O(CO-C6alkyl)phenyl, -OH, -halo, $-NO_2$, -CN, $-CF_3$, -(1-4C)alkylCF_3,
-NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$,
(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-,
oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl,
(C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-,
hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R",
-NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluroalkyl,
-(1-4Cperfluroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy),
-(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', $-(CH)_nNR'R"COOR'$
wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', $-NR'(CH_2)_nCOOR'$,
$-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl),
$-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl),
-NR'(C1-4alkyl)oxy(C1-4alkyl),
-NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);
heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R' or a carbon atom may be disubstituted to form a C5-C7 spiral group or a carbon atom or sulfur atom may be substituted with O to form a carbonyl group or sulfonyl group ($S(O)_m$); wherein the heterocyclic groups may be selected from, for example, 2-pyrolidinone, piperazine, oxazolidone, 2,5-oxazolidinedione, 2,4-imidazollidinedione, 2,4-thiazolidinedione or succinimide; aryl or benz or heteroarylbenz derivatives thereof (3,4-pyridinedicarboximide, -1-pthalimido, isatoic anhydride, orthobenzoicsulfimide) either unsubstituted or mono, bi or tri-substituted with alkyl or aromatic substituents including -halo, -C1-C6alkyl, -OH, C1-C6alkoxy, phenyl, OCF_3, CF_3, NO_2, CN, NH_2, SO_mR', NH(C1-4alkyl), or $N(C1-C4alkyl)_2$;

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or those groups containing 4 heteroatoms such as tetrazole wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

n is 1; R, R′, R″ and m are as defined in claim 2.

6. A compound according to claim 2 or pharmaceutically acceptable salts thereof wherein:

Z is chosen from:
O, S, or NH;

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, pyrrolyl or thienyl either unsubstituted or substituted at one or more ring carbon atoms with R^4 wherein R^4 is independently selected from the group consisting of hydrogen, halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR′R″, $SO_2NR'R''$, or SO_mR';

R^1 is $-(CH_2)_nL$ wherein

L is chosen from:
-OH, -O(C1-C4alkyl),CF_3-O(C1-C4alkyl)aryl, (C1-C4alkyl)CO_2R', OCOR′,

$S(O)_mR'$, NR'R" with the proviso that NR'R" is not equal to NH_2, NR'COR", OCONR', $NR'CO_2R"$, NRCONR'R", CO_2R', or CONRR';

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from -O-(1-4C)alkyl, -O-(2-4C)alkenyl, -O-(2-4C)alkynyl, -O(C0-C6alkyl)phenyl, -OH, -halo, $-NO_2$, -CN, $-CF_3$, -(1-4C)alkylCF_3, -NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluroalkyl, -(1-4Cperfluroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy), -(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', $-(CH)_nNR'R"COOR'$ wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', $-NR'(CH_2)_nCOOR'$, $-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl), $-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R' or a carbon atom may be disubstituted to form a C5-C7 spiral group or a carbon atom or sulfur atom may be substituted with 0 to form a carbonyl group or sulfonyl group ($S(O)_m$); wherein the heterocyclic groups may be selected from, for example, 2-pyrolidinone, piperazine, oxazolidone, 2,5-oxazolidinedione, 2,4-imidazollidinedione, 2,4-thiazolidinedione or succinimide; aryl or benz or heteroarylbenz derivatives thereof (

3,4-pyridinedicarboximide, -1-pthalimido, isatoic anhydride, orthobenzoicsulfimide) either unsubstituted or mono, bi or tri-substituted with alkyl or aromatic substituents including -halo, -C1-C6alkyl, -OH, C1-C6alkoxy, phenyl, OCF_3, CF_3, NO_2, CN, NH_2, SO_mR', NH(C1-4alkyl), or $N(C1-C4alkyl)_2$;

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or those groups containing 4 heteroatoms such as tetrazole wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, -alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

n is 2; R, R', R" and m are as defined in claim 2.

7. A compound according to claim 2 or pharmaceutically acceptable salts thereof wherein:

Z is chosen from:
O, S, or NH;

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, pyrrolyl or thienyl either unsubstituted or substituted at one or more ring carbon atoms with R^4 wherein R^4 is independently selected from the group consisting of hydrogen, halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR';

R^1 is $-(CH_2)_nL$ wherein

L is chosen from:
-OH, -O(C1-C4alkyl), -O(C1-C4alkyl)aryl, (C1-C4alkyl)CO_2R', OCOR', $S(O)_mR'$, NR'R" with the proviso that NR'R" is not equal to NH_2, NR'COR", OCONR', $NR'CO_2R"$, NRCONR'R", CO_2R', or CONRR';

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from
-O-(1-4C)alkyl,-O-(2-4C)alkenyl, -O-(2-4C)alkynyl,
-O(CO-C6alkyl)phenyl, -OH, -halo, $-NO_2$, -CN, $-CF_3$, -(1-4C)alkylCF_3,
-NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$,
(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-,
oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl,
(C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-,
hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R",
-NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluroalkyl,
-(1-4Cperfluroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy),
-(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', $-(CH)_nNR'R"COOR'$
wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', $-NR'(CH_2)_nCOOR'$,
$-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl),
$-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl),
-NR'(C1-4alkyl)oxy(C1-4alkyl),
-NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R' or a carbon atom may be disubstituted to form a C5-C7 spiral group or a carbon atom or sulfur atom may be substituted with O to form a carbonyl group or sulfonyl

group ($S(O)_m$); wherein the heterocyclic groups may be selected from, for example, 2-pyrolidinone, piperazine, oxazolidone, 2,5-oxazolidinedione, 2,4-imidazollidinedione, 2,4-thiazolidinedione or succinimide; aryl or benz or heteroarylbenz derivatives thereof (3,4-pyridinedicarboximide, -1-pthalimido, isatoic anhydride, orthobenzoicsulfimide) either unsubstituted or mono, bi or tri-substituted with alkyl or aromatic substituents including -halo, -C1-C6alkyl, -OH, C1-C6alkoxy, phenyl, OCF_3, CF_3, NO_2, CN, NH_2, SO_mR', NH(C1-4alkyl), or $N(C1-C4alkyl)_2$;

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or those groups containing 4 heteroatoms such as tetrazole wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

n is 3; R, R', R" and m are as defined in claim 2.

8. A compound according to claim 2 or pharmaceutically acceptable salts thereof wherein:

Z is chosen from:
O, S, or NH;

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, pyrrolyl or thienyl either unsubstituted or substituted at one or more ring carbon atoms with R^4 wherein R^4 is independently selected from the group consisting of hydrogen, halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR';

R^1 is $-(CH_2)_nL$ wherein

L is chosen from:
-OH, -O(C1-C4alkyl), -O(C1-C4alkyl)aryl, (C1-C4alkyl)'CO_2R', OCOR', $S(O)_mR'$, NR'R" with the proviso that NR'R" is not equal to NH_2, NR'COR", OCONR', $NR'CO_2R"$, NRCONR'R", CO_2R', or CONRR';

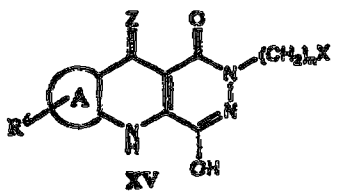
phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from
-O-(1-4C)alkyl,-O-(2-4C)alkenyl, -O-(2-4C)alkynyl, -O(CO-C6alkyl)phenyl, -OH, -halo, $-NO_2$, -CN, $-CF_3$, -(1-4C)alkylCF_3, -NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluroalkyl, -(1-4Cperfluroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy), -(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', $-(CH)_nNR'R"COOR'$ wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', $-NR'(CH_2)_nCOOR'$, $-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl), $-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S wherein the N on the heterocycle is optionally substituted with R′ and a carbon or nitrogen atom on the heterocycle may be substituted with R or R′ or a carbon atom may be disubstituted to form a C5-C7 spiral group or a carbon atom or sulfur atom may be substituted with O to form a carbonyl group or sulfonyl group ($S(O)_m$); wherein the heterocyclic groups may be selected from, for example, 2-pyrolidinone, piperazine, oxazolidone, 2,5-oxazolidinedione, 2,4-imidazollidinedione, 2,4-thiazolidinedione or succinimide; aryl or benz or heteroarylbenz derivatives thereof (3,4-pyridinedicarboximide, -1-pthalimido, isatoic anhydride, orthobenzoicsulfimide) either unsubstituted or mono, bi or tri-substituted with alkyl or aromatic substituents including -halo, -C1-C6alkyl, -OH, C1-C6alkoxy, phenyl, OCF_3, CF_3, NO_2, CN, NH_2, SO_mR', NH(C1-4alkyl), or $N(C1-C4alkyl)_2$;

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or those groups containing 4 heteroatoms such as tetrazole wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

n is 4; R, R′, R″ and m are as defined in claim 2.

9. A compound of formula XV



XV

wherein:

Z is chosen from:
O, S, or NH;

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, pyrrolyl or thienyl either unsubstituted or substituted at one or more ring carbon atoms with R^4 wherein R^4 is independently selected from the group consisting of hydrogen, halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR', a heterocyclic group, NR'COR", COR", NR'CO_2R", CO_2R', CONR'R";

X is halogen; and

n is 1-4; R, R', R" and m are as defined in claim 2.

10. A compound of formula XVII or XVII' wherein XVII' is defined as XVII except R^1 is bonded to N instead of M

wherein:

Z is chosen from:
O, S, or NH;

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, pyrrolyl or thienyl either unsubstituted or substituted at one or more ring carbon atoms with R^4 wherein R^4 is independently selected from the group consisting of hydrogen, halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR', a heterocyclic group, NR'COR",COR",NR'CO_2R",CO_2R',CONR'R";

M, for compound XVII and n equal to 0, is chosen from phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from -O-(1-4C)alkyl,-O-(2-4C)alkenyl, -O-(2-4C)alkynyl, -O(CO-C6alkyl)phenyl, -OH, -halo, -NO_2, -CN, -CF_3, -(1-4C)alkylCF_3, -NH(CO)R', -(1-4C)alkyl, -NR'R", -CO_2R', -CONR'R", -SO_mR', -SO_2NR'R", (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluroalkyl, -(1-4Cperfluroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy), -(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', -$(CH)_n$NR'R"COOR' wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', -NR'$(CH_2)_n$COOR', -$S(O)_m$(C1-4alkyl)oxy(C1-4alkyl), -$S(O)_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl) and R is equal to Bz;

or heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or those groups containing 4 heteroatoms such as tetrazole wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

or, for a compound of formula XVII',

R^1 is selected from H or $-(CH_2)_nL$ wherein L is M or W;

M is

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from -O-(1-4C)alkyl,-O-(2-4C)alkenyl, -O-(2-4C)alkynyl, -O(CO-C6alkyl)phenyl, -OH, -halo, $-NO_2$, -CN, $-CF_3$, -(1-4C)alkylCF_3, -NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluroalkyl, -(1-4Cperfluroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy), -(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', $-(CH)_nNR'R"COOR'$ wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', $-NR'(CH_2)_nCOOR'$,

-S(O)$_m$(C1-4alkyl)oxy(C1-4alkyl),
-S(O)$_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl),
-NR'(C1-4alkyl)oxy(C1-4alkyl),
-NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S, or aryl or heteroaryl benz derivatives thereof, wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R' or a carbon atom may be disubstituted to form a C5-C7 spiral group or a carbon atom or sulfur atom may be substituted with O to form a carbonyl group or sulfonyl group (S(O)$_m$);

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole or isothiazole (and oxidized versions thereof selected from S(O)$_m$ wherein m is 0-2), pyridazine, pyrimidine, pyrazine or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or triazine, or those groups containing four heteroatoms such as tetrazole, wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to -(CH$_2$)$_n$ via a carbon atom or a heteroatom on the heteroaryl group;

W is selected from OH, OR'; OCOR', S(O)$_m$R', S(O)$_m$NR'R", halo, NR'R", COR', NR'COR", OCONR', NR'CO$_2$R", (C3-6)cycloalkyl, NRCONR'R", CO$_2$R', or CONRR' and;

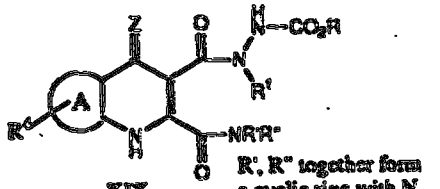
n is chosen from 1-4;

R is selected from H or (1-4C)alkyl or Bz;

R' and R" are independently selected from H, (1-4C)alkyl wherein alkyl includes alkenyl(C2-C4) and alkynyl(C2-C4); (3-6C)cycloalkyl, Phenyl(0-4C)alkyl-, heterocycle(0-4C)alkyl- or heteroaryl(0-4C)alkyl- wherein phenyl or heterocycle or heteroaryl is as defined above and any of the above is optionally substituted at one or more carbon atoms with halo, H, (1-4C)alkyl, (3-6C)cycloalkyl, phenyl, NO_2, CN, CF_3, OH, O-(1-4C)alkyl, NR'R" S(O)mR' or $SO_2NR'R"$ wherein NR'R" may optionally form an N-alkyl(C1-3)oxyalkyl(C2-3) ring with N;

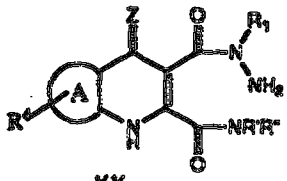
m is chosen from 0-2.

11. A compound of formula XIX or XX



XIX

R', R" together form a cyclic ring with N, R is t-butyl or a bulky alkyl substituent.



XX

R', R" together form a cyclic ring with N.

wherein:

Z is selected from O, S or NH, or when the B-ring N tautomerizes or the B-ring is reduced, the Z group may be selected from H, OH, SH or NH_2,

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, furyl, pyrrolyl or thienyl either unsubstituted or multi-substituted at a ring carbon atom with R^4 wherein R^4 is independently selected from the group

consisting of halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR', a heterocyclic group, NR'COR", COR", NR'CO_2R", CO_2R', CONR'R";

R^1 is selected from H or $-(CH_2)_nL$ wherein L is M or W;

M is

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from -O-(1-4C)alkyl, -O-(2-4C)alkenyl, -O-(2-4C)alkynyl, -O(CO-C6alkyl)phenyl, -OH, -halo, $-NO_2$, -CN, $-CF_3$, -(1-4C)alkylCF_3, -NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluroalkyl, -(1-4Cperfluroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy), -(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', $-(CH)_nNR'R"COOR'$ wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', $-NR'(CH_2)_nCOOR'$, $-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl), $-S(O)_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

heterocycle wherein heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1,2,or 3 heteroatoms chosen from O, N, or S, or aryl or heteroaryl benz derivatives thereof, wherein the N on the heterocycle is optionally substituted with R' and a carbon or nitrogen atom on the heterocycle may be substituted with R or R' or a carbon atom may be disubstituted

to form a C5-C7 spiral group or a carbon atom or sulfur atom may be substituted with O to form a carbonyl group or sulfonyl group ($S(O)_m$);

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole or isothiazole (and oxidized versions thereof selected from $S(O)_m$ wherein m is 0-2), pyridazine, pyrimidine, pyrazine or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or triazine, or those groups containing four heteroatoms such as tetrazole, wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to $-(CH_2)_n$ via a carbon atom or a heteroatom on the heteroaryl group;

W is selected from OH, OR', OCOR', $S(O)_mR'$, $S(O)_mNR'R"$, halo, NR'R" with the proviso that NR'R" is not equal to NH_2; or W is COR', NR'COR", OCONR', $NR'CO_2R"$, (C3-6)cycloalkyl, NRCONR'R", CO_2R', or CONRR' with the proviso that n is greater than zero and;

n, for groups other than W, is chosen from 0-4;

R is selected from H or (1-4C)alkyl;

R' and R" are independently selected from H, (1-4C)alkyl wherein alkyl includes alkenyl(C2-C4) and alkynyl(C2-C4); (3-6C)cycloalkyl, Phenyl(0-4C)alkyl-, heterocycle(0-4C)alkyl- or heteroaryl(0-4C)alkyl- wherein phenyl or heterocycle or heteroaryl is as defined above and any of the above is optionally substituted at one or more carbon atoms

with halo, H, (1-4C)alkyl, (3-6C)cycloalkyl, phenyl, NO_2, CN, CF_3, OH, O-(1-4C)alkyl, NR'R" $S(O)_mR'$ or $SO_2NR'R"$ wherein NR'R" may optionally form an N-alkyl(C1-3)oxyalkyl(C2-3) ring with N;

m is chosen from 0-2.

12. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable excipient or diluent.

13. A pharmaceutical composition comprising a compound according to claim 2 and a pharmaceutically acceptable excipient or diluent.

14. A pharmaceutical composition comprising a compound according to any of claims 3-8 and a pharmaceutically acceptable excipient or diluent.

15. A method of treating or preventing ischemic damage in a patient in need of such treatment comprising administering a pharmaceutically effective amount of a compound according to claim 2 to said patient.

16. A method of treating or preventing neurological damage associated with excitatory amino acids in a patient in need of such treatment comprising administering a pharmaceutically effective amount of a compound according to claim 2 to said patient.

17. A method of treating stroke or epileptic convulsions or diseases or disorders associated with excessive calcium influx in the brain caused by excitatory amino acids comprising administering to a patient in need of treatment thereof a pharmaceutically effective amount of a compound according to claim 2.

18. A process for producing a compound according to claim 2, comprising:

(a) treating a compound of formula V or XIV with an acid selected from a lower alkyl(C1-C4) sulfonic acid in a suitable organic solvent; or

(b) treating a compound of formula IV' with an alkylaryl or alkylheteroaryl hydrazine in a polar solvent and a mild acid; or

(c) treating a compound of formula VI' wherein Y is selected from -OH,-SH or NHR wherein R is (C1-C4)alkyl with a reagent selected from (i) $R^2NC(O)Cl$; or (ii) RC(O)X; or (iii) ROC(O)Cl; or (iv) HBr/NaCN/H_2O or ROH; or (v) RNCO or R'R'NC(O)Cl or other electrophilic group as recited herein to form, in particular, a compound of formula XXI; or

(d) treating a compound of formula XV wherein X is halogen with a nucleophilic reactant selected from heterocycle or benz or heteroarylbenz derivatives thereof; or

(e) treating a compound of formula XXII with a substituted hydrazine to form a compound of formula XVII in an organic solvent under the appropriate conditions; or

(f) treating a compound of formula XVIII with a coupling reagent selected from a diimide with a disubstituted hydrazine of the formula R^1-NHNHC(O)Ot-butyl in an organic solvent in the presence of an appropriate acid or

(g) further treating a compound of formula II as claimed in claim 2 wherein the compound contains a phenyl ring substituted with a methoxy group or groups with an acid to form a phenolic substituent or substituents or further treating a compound of formula II wherein the compound is a non-salt form with a pharmaceutically acceptable base to form a pharmaceutically acceptable salt or further treating a compound of formula II wherein the compound contains a phenyl ring substituted with a cyano group or groups with (i) a base to form a carboxlic acid substituent or substituents or (ii) an acid to form an amide substituent or (iii) an azide to form a tetrazole substituent wherein

the carboxlic acid moiety may be further treated with a halogenating agent and a substituted amine of formula HNR'R" to form a substituted amide substituent or the carboxylic acid moiety may be further treated with an alcohol (C1-C6) in the presence of an acid to form an ester substituent (C1-C6) or

(h) further treating a compound of formula II wherein the compound contains an oxozolidine dione with a base in aqueous solution to form an amido alcohol substituent as W off the $(CH_2)_n$ carbon chain with n equal to 1-4; or

(i) further treating a compound of formula II wherein the compound contains a sulfide moiety with an oxidizing agent under the appropriate conditions to form an $S(O)_1$ or $S(O)_2$ moiety.

19. A process for producing a compound of formula II according to claim 18 wherein the compounds are selected from:

7-chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione or the N-methylglucamine salt thereof;

7-chloro-2-(4-chloro-2-methylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazine[4,5-b]quinoline-1,10-dione;

7-chloro-2-(2,4-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazine[4,5-b]quinoline-1,10-dione;

7-chloro-2-(3,4-dihydroxyphenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazine[4,5-b]quinoline-1,10-dione;

7-chloro-2-(3,4-dimethoxyphenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazine[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(2-methylthioethyll)-1,2,5,10-tetrahydro-pyridazine[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(2-methyl-2-hydroxypropionamidoethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

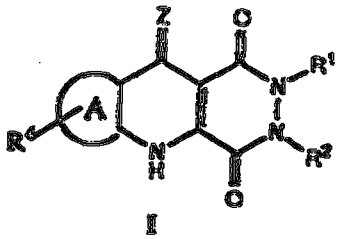
7-chloro-4-hydroxy-2-(furan-2-ylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7,9-dichloro-2-(2,4-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydro-pyridazine[4,5-b]quinoline-1,10-dione or their pharmaceutically acceptable salts.

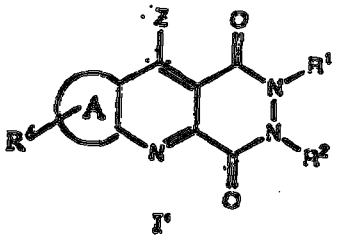
20. A compound according to claim 2 for use in medicine.

21. The use of a compound according to claim 2 for preparation of a medicament for the treatment of stroke or epipeptic convulsions or disorders or conditions associated with excessive influx of calcium ions in the brain.

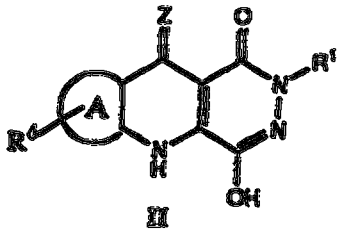
FORMULAE FOR CLAIMS



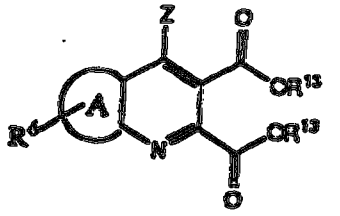
I



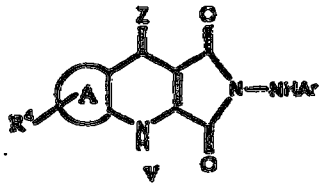
I'



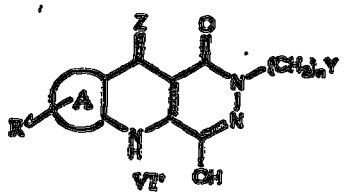
II



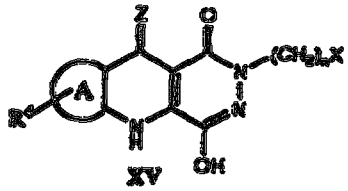
IV'



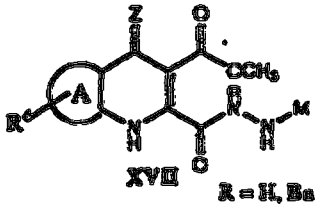
V



VI'

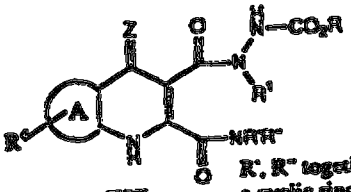


XV



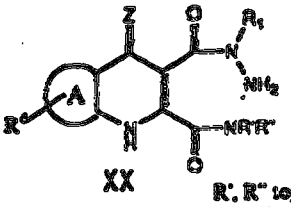
XVII

R = H, Bn



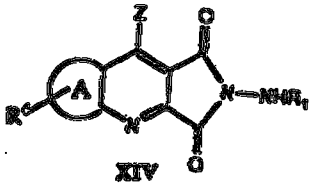
XIX

R', R" together form a cyclic ring with N. R is t-butyl or a bulky alkyl substituent.

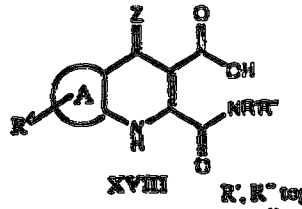


XX

R', R" together form a cyclic ring with N.

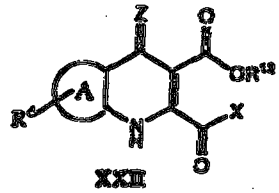


XIV

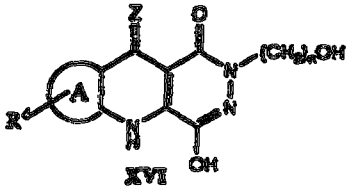


XVIII

R', R" together form a cyclic ring with N.



XXII

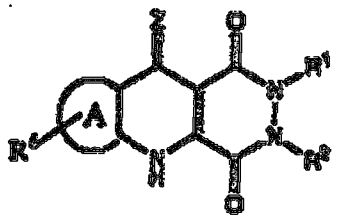


XVI

ABSTRACT

PYRIDAZINO QUINOLINE COMPOUNDS

The present invention relates to compounds, pharmaceutical compositions and methods of using compounds of formula I in the treatment and/or prevention of certain diseases or conditions wherein formula I is



I

and A is chosen from ortho substituted aryl or heteroaryl species, X is chosen from -OH, -sh, NHR and R^1 or R^2 is chosen from $-(CH_2)_nL$ wherein L may be selected from a variety of substitiuents including aryl, heteroaryl and heterocyclic groups. The compounds are useful in treating and/or preventing neurological disorders associated with excitatory amino acids.

carbonyl-N'-3,5-ditrifluoromethyl benzyl hydrazine; N-t-butoxy carbonyl-N'-3-phenylpropylhydrazine; N-t-butoxycarbonyl-N'-4-methylbenzyl hydrazine; N-t-butoxy carbonyl-N'-4-trifluoromethylbenzyl hydrazine; N-t-butoxy carbonyl-N'-4-cyanobenzyl hydrazine; and N-t-butoxy carbonyl-N'-2 4-dimethylphenyl hydrazine. The present invention, therefore, also relates to these novel hydrazine moieties and to processes for their production and use as intermediates to couple with the key intermediate 2-pyrolidinocarbamide quinoline 3-carboxylic acid to form a compound of formula II via a novel and inventive process as described herein which selectively forms the N-2-substituted PQD. The intermediate hydrazines utilized to prepare N-2-aryl or N-2-substituted aryl PQDs may also be prepared according to the non-limiting example 42a. N'-t-butoxy carbonyl-N'-aryl or substituted aryl compounds are produced via this novel process to enable selective formation of the N-2-substituted PQDs. This process may be the preferred route to aryl substituted compounds claimed and recited herein.

It is noted that many of the starting materials for synthetic methods as described above are commercially available and/or widely reported in the scientific literature.

Examples of suitable pharmaceutically acceptable salts are salts formed with bases which form a physiologically acceptable cation, such as alkali metal (especially lithium, sodium and potassium), alkaline earth metal (especially calcium and magnesium), aluminum and ammonium salts, as well as salts made with appropriate organic bases such as choline hydroxide, triethylamine, morpholine, piperidine, ethylenediamine, lysine, ethanolamine, diethanolamine, triethanolamine, N-methyl-D-glucamine (meglumine), arginine, and tris(hydroxymethyl)aminomethane. Choline, meglumine, sodium and potassium salts are preferred. Choline, sodium and potassium salts are especially preferred.

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☑ Description : paged 40/1, 2, 3 to paged .....
☑ Claim(s) : paged 159 to paged 160
☐ Drawing(s) : paged ..... to paged .....
☐ Abstract : paged ..... to paged .....
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and their salts, other than for acylated compounds, may be prepared by solubilizing the active compound in an aqueous meglumine (N-methyl-glucamine) solution containing an equimolar, or if solubilization is difficult, a molar excess of meglumine relative to Compound. Choline salts are preferred for use in making formulations. Excipients such has dextrose may be added to adjust the osmolality of the formulation. Water for Injection is added to bring the solution to final volume. Alternately, other amine bases such as tromethamine or l-arginine may be used to solubilize the active compound.

Example 147

A formulation is made as in Example 146, except that the choline salt of Compound X is used in place of the compound of Example 2.

Example 148

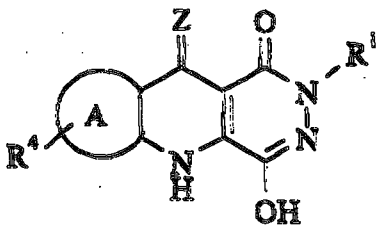
A formulation is made comprising a 5% aqueous solution of dextrose made to 10 mg/mL in the choline salt of Compound X.

The previous examples are considered to be non-limiting and thus, the compounds of formula I or I' (or II or III) and pharmaceutical compositions containing same may be used to treat and/or prevent stroke and the other diseases as related herein. The following schemes and formulae are presented to clarify how to make the compounds of the invention. The compounds depicted in examples 5,7,9,16,18 and 20 were inactive in the in-vitro glycine receptor assay and are specifically excluded from the compounds of formula I or III.

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1. A compound of formula II or a pharmaceutically acceptable salts or tautomer thereof



II

wherein:

Z is chosen from:
O, S, or NH;

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, pyrrolyl or thienyl either unsubstituted or substituted at one or more ring carbon atoms with R^4 wherein R^4 is independently selected from the group consisting of hydrogen, halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR';

R^1 is:

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from -O-(1-4C)alkyl, -O-(2-4C)alkenyl, -O-(2-4C)alkynyl, -O(C0-C6alkyl)phenyl, -OH, halo, $-NO_2$, -CN, $-CF_3$, -(1-4C)alkylCF_3, -NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluoroalkyl, -(1-4C)perfluoroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy), -(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', $-(CH)_nNR'R"COOR'$ wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', $-NR'(CH_2)_nCOOR'$,

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-S(O)$_m$(C1-4alkyl)oxy(C1-4alkyl), -S(O)$_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or those groups containing 4 heteroatoms such as tetrazole wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to the pyridazine ring of formula (I) via a carbon atom or a heteroatom on the heteroaryl group;

R is selected from H or (1-4C)alkyl;

R' and R" are independently selected from H, (1-4C)alkyl wherein alkyl includes alkenyl(C2-C4) and alkynyl(C2-C4); (3-6C)cycloalkyl, Phenyl(0-4C)alkyl-, heterocycle(0-4C)alkyl- or heteroaryl(0-4C)alkyl- wherein phenyl or heteroaryl is as defined above and or heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1, 2 or 3 heteroatoms chosen from O, N or S or aryl or heteroaryl benz derivatives thereof, and any of the above is optionally substituted at one or more carbon atoms with halo, H, (1-4C)alkyl, (3-6C)cycloalkyl, phenyl, NO_2, CN, CF_3, OH, O-(1-4C)alkyl, NR'R" S(O)$_m$R' or SO_2NR'R" wherein NR'R" may optionally form an N-alkyl(C1-3)oxyalkyl(C2-3) ring with N;

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m is chosen from 0-2.

2. A compound according to claim 1 wherein R^1 is selected from: phenyl, 4-methoxyphenyl, 4-hydroxyphenyl, 4-chlorophenyl, 4-methylphenyl, 4-isopropyl-phenyl, naphthyl, 4-fluorophenyl, 4-bromophenyl, 2-methoxyphenyl, 2-hydroxyphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 4-trifluoromethoxyphenyl, 3-chloro-4-methoxyphenyl, 5-methoxy-3-pyridyl, 4-S(O)$_m$R'phenyl wherein m is 0-2 and R' is methyl; 3-chlorophenyl, 3-chloro-4-hydroxyphenyl, 2-methyl-4-chlorophenyl, 3-methylphenyl, 2-methylphenyl, 3-

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fluorophenyl, 2,4-difluorophenyl, 3,5-trifluoromethylphenyl, 3-nitrophenyl, 2-fluorophenyl, 2,4-dimethylphenyl, 3-chloro-4-methylphenyl, 4-trifluoromethylphenyl, 4-iodophenyl, 3,4-dimethylphenyl, 3,4-dimethoxyphenyl, 2-methyl-4-methoxyphenyl, 2-methoxy-4-bromophenyl, 2-methyl-4-hydroxyphenyl, 4-ethylphenyl, 2,3-dimethylphenyl, 3,4-dihydroxyphenyl, 2,4-dimethoxyphenyl, 2,4-dichlorophenyl, 4-nitrophenyl, 2,5-dimethoxyphenyl, 2,5-dimethylphenyl, 4-oxybenzylphenyl, 2,5-dihydroxyphenyl, 4-vinylphenyl, 2,5-difluorophenyl, 2-methyl-4-fluorophenyl, 3,5-dimethoxyphenyl, 4-carboxyphenyl, 4-carboxamido-phenyl, 4-(N,N-diethylcarboxamido)phenyl, 4-cyanophenyl, or 4-tetrazolephenyl.

3. A compound according to claim 1 selected from the group consisting of:

7-chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione;

7-chloro-2-(4-chloro-2-methylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(2,4-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(3,4-dihydroxyphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(3,4-dimethoxyphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione; and

7,9-dichloro-2-(2,4-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione; or pharmaceutically acceptable salts thereof.

4. 7-Chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione; or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 4 selected from the group consisting of:

7-chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione N-methylglucamine salt;

7-chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione sodium salt; and

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7-chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione choline salt.

6. 7-Chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino [4,5-b]quinoline-1,10-dione sodium salt.

7. A compound according to claim 1 selected from the group consisting of:

7-chloro-4-hydroxy-2-phenyl-1,2,5,10-tetrahydropyridazino-[4,5-b]-quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-methoxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-hydroxyphenyl)-1,2,5,10-tetrahydropyridazino-[4,5-b] quinoline-1,10-dione;

4-hydroxy-8-nitro-2-phenyl-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-chlorophenyl)-1,2,5,10-tetrahydropyridazino-[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-isopropylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7,9-dichloro-4-hydroxy-2-phenyl-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(1-naphthyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(4-fluorophenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

2-(4-bromophenyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(2-methoxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(2-hydroxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione;

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7-chloro-4-hydroxy-2-(3-methoxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(3-hydroxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-trifluoromethoxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(3-chloro-4-methoxyphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione; and

7-chloro-4-hydroxy-2-(2-methoxypyrid-5-yl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

or pharmaceutically acceptable salts thereof.

8. A compound according to claim 1 selected from the group consisting of:

2-(4-benzyloxyphenyl)-7-chloro-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(2,4-dichlorophenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(3-chloro-4-hydroxyphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-hydroxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(4-chloro-2-methylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7,9-dichloro-2-(2,4-dimethylphenyl)-4-hydroxy-1,2,5-10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(3,4-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(2,4-dimethoxyphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(2,5-dimethoxyphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

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7-chloro-2-(2,5-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione;

7-chloro-2-(3-chlorophenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(3-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-thiomethoxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione;

7-chloro-2-(3-chloro-4-methylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione;

7-chloro-2-(2,3-dimethylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione;

7-chloro-2-(4-ethylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(4-fluoro-2-methylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione;

7-chloro-2-(3,5-dimethoxyphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-iodophenyl)-1,2,5,10-tetrahydro-pyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(4-bromo-2-methoxyphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione;

7-chloro-2-(3-fluorophenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(2-fluorophenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-2-(3,5-ditrifluoromethylphenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione;

7-chloro-2-(2,4-difluorophenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione;

7-chloro-2-(2,5-difluorophenyl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b] quinoline-1,10-dione;

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7-chloro-4-hydroxy-2-(4-nitrophenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-trifluoromethylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(3-nitrophenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-sulfonylmethylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(2,5-dihydroxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-carboxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-hydroxyphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-carboxamidophenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(4-tetrazolephenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione; and

7-chloro-4-hydroxy-2-(4-N,N-diethylcarboxamidophenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

or pharmaceutically acceptable salts thereof.

9. A compound according to claim 1 selected from the group consisting of:

7-chloro-2-(4-ethoxyphenyl)-4-hydoxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

7-chloro-4-hydroxy-2-(2-isopropylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione; and

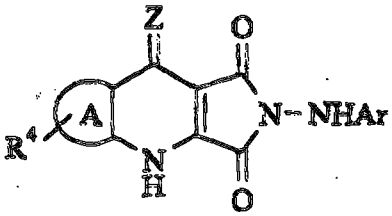
7-chloro-4-hydroxy-2-(4-carboxymethylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione;

or pharmaceutically acceptable salts thereof.

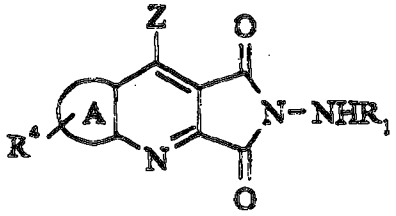
10. A process for producing a compound as claimed in any one of claims 1 to 9, comprising:

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(a) treating a compound of formula V or XIV



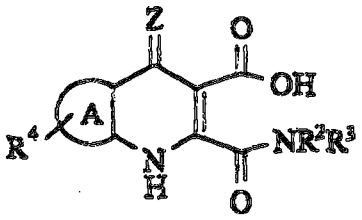
V



XIV

with an acid selected from a lower alkyl(C1-C4) sulfonic acid in a suitable organic solvent; or

(b) treating a compound of formula XVIII



XVIII

R^2, R^3 together form a cyclic ring with N.

with a coupling reagent selected from a diimide with a disubstituted hydrazine of the formula R^1-NHNHC(O)Ot-butyl in an organic solvent in the presence of an appropriate acid or

(c) further treating a compound of formula II as claimed in claim 2 wherein the compound contains a phenyl ring substituted with a methoxy group or groups with an acid to form a phenolic substituent or substituents or further treating a compound of formula II wherein the compound is a non-salt form with a pharmaceutically acceptable base to form a pharmaceutically acceptable salt or further treating a compound of formula II wherein the compound contains a phenyl ring substituted with a cyano group or groups with (i) a base to form a carboxylic acid substituent or substituents or (ii) an acid to form an amide substituent or (iii) an azide to form a tetrazole substituent wherein the carboxylic acid moiety may be further treated with a halogenating agent and a substituted amine of formula HNR'R" to form a substituted amide substituent or the carboxylic acid moiety may be further treated with an alcohol (C1-C6) in the presence of an acid to form an ester substituent (C1-C6) or

(d) further treating a compound of formula II wherein the compound contains a sulfide moiety with an oxidizing agent under the appropriate conditions to form an $S(O)_1$ or $S(O)_2$ moiety.

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11. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 9 and a pharmaceutically acceptable excipient or diluent.

12. A pharmaceutical composition comprising 7-Chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or diluent.

13. A compound as claimed in any one of claims 1 to 9 for use in medicine.

14. The use of a compound as claimed in any one of claims 1 to 9 for the preparation of a medicament for treating or preventing ischemic damage in a patient in need of such treatment.

15. The use of a compound as claimed in any one of claims 1 to 9 for the preparation of a medicament for treating or preventing neurological damage associated with excitatory amino acids in a patient in need of such treatment.

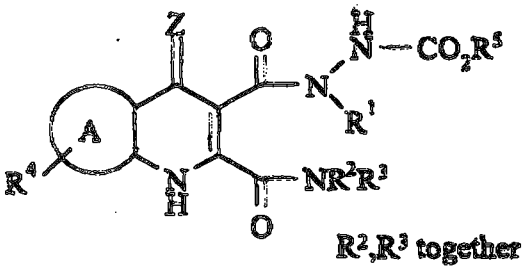
16. The use of a compound as claimed in any one of claim 1 to 9 for the preparation of a medicament for treating stroke or epileptic convulsions or diseases or disorders associated with excessive calcium influx in the brain.

17. The use of a compound as claimed in any one of claims 1 to 9 for the preparation of a medicament for the treatment of neurological disorders.

18. The use of a compound according to anyone of claims 13-17 for the preparation of a medicament for the treatment of neurological disorders.

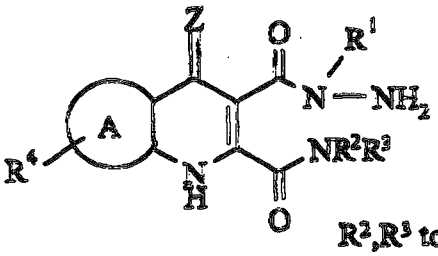
19. A compound of formula XIX or XX

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XIX

R^2,R^3 together form a cyclic ring with N, R^5 is t-butyl or bulky alkyl substituent.



XX

R^2,R^3 together form a cyclic ring with N

wherein:

Z is selected from O, S or NH, or when the B-ring N tautomerizes or the B-ring is reduced, the Z group may be selected from H, OH, SH or NH_2,

Ring A is chosen from an ortho fused aromatic or heteroaromatic five- or six-membered ring selected from phenyl, pyridyl, furyl, pyrrolyl or thienyl either unsubstituted or substituted at one or more ring carbon atoms with R^4 wherein R^4 is independently selected from the group consisting of halo, (1-4C)alkyl, NO_2, CN, (C1-3)perfluoroalkyl, OH, OCF_3, (2-4C)alkenyl, (2-4C)alkynyl, O(1-4C)alkyl, NR'R", $SO_2NR'R"$, or SO_mR', a heterocyclic group, NR'COR", COR", $NR'CO_2R"$, CO_2R', CONR'R";

R^1 is:

phenyl or benz derivatives thereof and is either unsubstituted or substituted with 1, 2, 3 or 4 groups chosen from -O-(1-4C)alkyl, -O-(2-4C)alkenyl, -O-(2-4C)alkynyl, -O(C0-C6alkyl)phenyl, -OH, halo, $-NO_2$, -CN, $-CF_3$, -(1-4C)alkylCF_3, -NH(CO)R', -(1-4C)alkyl, -NR'R", $-CO_2R'$, -CONR'R", $-SO_mR'$, $-SO_2NR'R"$, (C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy-, oxy(1-6C)alkyloxy which may form a cyclic ring attached to the phenyl ring in an ortho manner, aryloxy(1-4C)alkyloxy(1-4C)alkyl, (C1-C6)alkyloxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, hydroxy(C1-C6)alkyloxy(C1-C6)alkyloxy-, -O(C1-C6alkyl)NR'R", -NR'(C1-C6alkyl)NR'R", -(C1-C6alkyl)NR'R", -O-(1-4C)perfluoroalkyl,

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-(1-4C)perfluoroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy), -(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', -(CH)$_n$NR'R"COOR' wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', -NR'(CH$_2$)$_n$COOR', -S(O)$_m$(C1-4alkyl)oxy(C1-4alkyl), -S(O)$_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole or isothiazole (and oxidized versions thereof selected from S(O)$_m$ wherein m is 1-2), pyridazine, pyrimidine, pyrazine or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or triazine, or those groups containing four heteroatoms such as tetrazole, wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to the pyridazine ring of formula (I) via a carbon atom or a heteroatom on the heteroaryl group;

R is selected from H or (1-4C)alkyl;

R' and R" are independently selected from H, (1-4C)alkyl wherein alkyl includes alkenyl(C2-C4) and alkynyl(C2-C4); (3-6C)cycloalkyl, Phenyl(0-4C)alkyl-, heterocycle(0-4C)alkyl- or heteroaryl(0-4C)alkyl- wherein phenyl or heteroaryl is as defined above and heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1, 2, or 3 heteroatoms chosen from O, N, or S, or aryl or heteroaryl benz derivative thereof, and any of the above is optionally substituted at one or more carbon atoms with halo, H, (1-4C)alkyl, (3-6C)cycloalkyl, phenyl, NO_2, CN, CF_3, OH, O-(1-4C)alkyl, NR'R" S(O)$_m$R' or SO_2NR'R" wherein NR'R" may optionally form an N-alkyl(C1-3)oxyalkyl(C2-3) ring with N;

m is chosen from 0-2.

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thereof selected from C1-C6alkyl or phenyl; or benz or heteroaryl benz heterocyclic derivatives selected from -1-phthalimide, orthobenzoicsulfimide, isatoic anhyrdride or 3,4-dicarboximide;

heteroaryl selected from thiophene, imidazole, triazole, tetrazole furan or pyridine; and n is 0-2. Advantageously, for the compounds of formula II, n is equal to zero and L is selected from: phenyl, 4-methoxyphenyl, 4-hydroxyphenyl, 4-chlorophenyl, 4-methylphenyl, 4-isopropylphenyl, napthyl, 4-flourophenyl, 4-bromophenyl, 2-methoxyphenyl, 2-hydroxyphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 4-triflouromethoxyphenyl, 3-chloro,4-methoxyphenyl, 5-methoxy-3-pyridyl, 4-$S(O)_m$R'phenyl wherein m is 0-2 and R' is methyl; 3-chlorophenyl, 3-chloro-4-hydroxyphenyl, 2-methyl-4-chlorophenyl, 3-methylphenyl, 2-methylphenyl, 3-flourophenyl, 2,4-diflourophenyl, 3,5-triflouromethylphenyl, 3-nitrophenyl, 2-flourophenyl, 2,4-dimethylphenyl, 3-chloro-4-methylphenyl, 4-triflouromethylphenyl, 4-iodophenyl, 3,4-dimethylphenyl, 3,4-dimethoxyphenyl, 2-methyl-4-methoxyphenyl, 2-methoxy,4-bromophenyl, 2-methyl,4-hydroxyphenyl, 4-ethylphenyl, 2,3-dimethylphenyl, 3,4-dihydroxyphenyl, 2,4-dimethoxyphenyl, 2,4-dichlorophenyl, 4-nitrophenyl, 2,5-dimethoxyphenyl, 2,5-dimethylphenyl, 4-oxybenzylphenyl, 2,5-dihydroxyphenyl, 4-vinylphenyl, 2,5-diflourophenyl, 2-methyl-4-flourophenyl, 3,5-dimethoxyphenyl, 4-carboxyphenyl, 4-caboxamidophenyl, 4-(N,N-diethylcarboxamido)phenyl, 4-cyanophenyl, or 4-tetrazolephenyl. Advantageously, the present invention also relates to compounds of formula II wherein n is equal to 1 and L is selected from any of the members identified above for n equal to zero and, more particularly to groups selected from 1-flourophenyl, 4-cyanophenyl, 4-triflouromethylphenyl, 4-methylphenyl, pentaflourophenyl or 3,5-ditriflouromethylphenyl or to compounds of formula II wherein n is equal to three and L is selected from any group designated for n equal to zero or one, but more

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REPLACEMENT SHEETS SG
☑ Description : paged 17.. to paged ....
☑ Claim(s) : paged 151, 168 to paged ....
☐ Drawing(s) : paged ..... to paged .....
☐ Abstract : paged ..... to paged .....
DATE OF RECEIPT 4/10/99

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-S(O)$_m$(C1-4alkyl)oxy(C1-4alkyl), -S(O)$_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole, isothiazole, or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or those groups containing 4 heteroatoms such as tetrazole wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to the pyridazine ring of formula (II) via a carbon atom or a heteroatom on the heteroaryl group;

R is selected from H or (1-4C)alkyl;

R' and R" are independently selected from H, (1-4C)alkyl wherein alkyl includes alkenyl(C2-C4) and alkynyl(C2-C4); (3-6C)cycloalkyl, Phenyl(0-4C)alkyl-, heterocycle(0-4C)alkyl- or heteroaryl(0-4C)alkyl- wherein phenyl or heteroaryl is as defined above and heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1, 2 or 3 heteroatoms chosen from O, N or S or aryl or heteroaryl benz derivatives thereof, and any of the above is optionally substituted at one or more carbon atoms with halo, H, (1-4C)alkyl, (3-6C)cycloalkyl, phenyl, NO_2, CN, CF_3, OH, O-(1-4C)alkyl, NR'R" S(O)$_m$R' or SO_2NR'R" wherein NR'R" may optionally form an N-alkyl(C1-3)oxyalkyl(C2-3) ring with N;

m is chosen from 0-2.

2. A compound according to claim 1 wherein R^1 is selected from:
phenyl, 4-methoxyphenyl, 4-hydroxyphenyl, 4-chlorophenyl, 4-methylphenyl, 4-isopropyl-phenyl, naphthyl, 4-fluorophenyl, 4-bromophenyl, 2-methoxyphenyl, 2-hydroxyphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 4-trifluoromethoxyphenyl, 3-chloro-4-methoxyphenyl, 5-methoxy-3-pyridyl, 4-S(O)$_m$R'phenyl wherein m is 0-2 and R' is methyl; 3-chlorophenyl, 3-chloro-4-hydroxyphenyl, 2-methyl-4-chlorophenyl, 3-methylphenyl, 2-methylphenyl, 3-

-(1-4C)perfluoroalkyl, -NR'(C1-C6alkyloxy), -NR'(C1-C6alkylhydroxy), -(C1-4alkyl)oxy(C1-4alkyl), -O(C1-4alkyl)COOR', -$(CH)_n$NR'R"COOR' wherein n is 1-4, -(C1-4alkyl)NR'R", -(C1-4alkyl)OR', -NR'$(CH_2)_n$COOR', -$S(O)_m$(C1-4alkyl)oxy(C1-4alkyl), -$S(O)_m$(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl), -NR'(C1-4alkyl)oxy(C1-4alkyl)oxy(C1-4alkyl);

heteroaryl wherein heteroaryl is selected from unsubstituted or substituted aromatic species and benz derivatives thereof including pyridyl, thienyl, furanyl, or those groups containing two heteroatoms selected from N, O or S such as pyrazole, imidazole, isoxazole, oxazole, thiazole or isothiazole (and oxidized versions thereof selected from $S(O)_m$ wherein m is 1-2), pyridazine, pyrimidine, pyrazine or those groups containing three heteroatoms chosen from N, O or S such as triazole or oxadiazole or triazine, or those groups containing four heteroatoms such as tetrazole, wherein the N on the heteroaryl group is optionally substituted with R and the substituted aromatic substituents include typical aromatic substituents selected from hydroxy, alkoxy, halo or cyano and the heteroaryl group is attached to the nitrogen of formula **(XIX)** or **(X)** via a carbon atom or a heteroatom on the heteroaryl group;

R is selected from H or (1-4C)alkyl;

R' and R" are independently selected from H, (1-4C)alkyl wherein alkyl includes alkenyl(C2-C4) and alkynyl(C2-C4); (3-6C)cycloalkyl, Phenyl(0-4C)alkyl-, heterocycle(0-4C)alkyl- or heteroaryl(0-4C)alkyl- wherein phenyl or heteroaryl is as defined above and heterocycle is selected from a five- and/or six- and/or seven-membered heterocyclic ring containing 1, 2, or 3 heteroatoms chosen from O, N, or S, or aryl or heteroaryl benz derivative thereof, and any of the above is optionally substituted at one or more carbon atoms with halo, H, (1-4C)alkyl, (3-6C)cycloalkyl, phenyl, NO_2, CN, CF_3, OH, O-(1-4C)alkyl, NR'R" $S(O)_m$R' or SO_2NR'R" wherein NR'R" may optionally form an N-alkyl(C1-3)oxyalkyl(C2-3) ring with N;

m is chosen from 0-2.

REPLACEMENT SHEET
04 OCT 1999