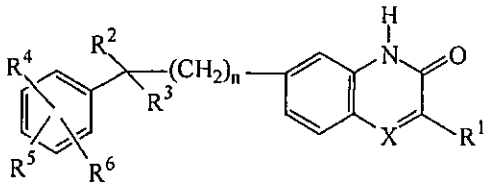
CLAIMS

1. A compound of formula (I),



(I)

the *N*-oxide forms, the addition salts and the stereo-chemically isomeric forms thereof, wherein

n is 0, 1 or 2;

X is N or CR^7, wherein R^7 is hydrogen or taken together with R^1 may form a bivalent radical of formula -CH=CH-CH=CH-;

R^1 is C_{1-6}alkyl or thienyl;

R^2 is hydrogen, hydroxy, C_{1-6}alkyl, C_{3-6}alkynyl or taken together with R^3 may form =O;

R^3 is a radical selected from

$-(CH_2)_s-NR^8R^9$	(a-1),
-O-H	(a-2),
$-O-R^{10}$	(a-3),
$-S-R^{11}$	(a-4), or
$-C\equiv N$	(a-5),

wherein

s is 0, 1, 2 or 3;

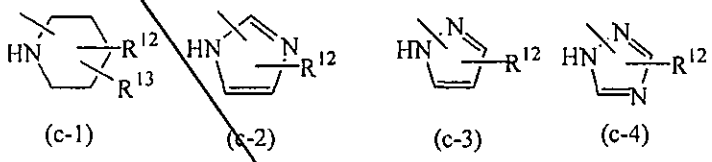
R^8 is –CHO, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, piperidinylC_{1-6}alkyl, piperidinylC_{1-6}alkylaminocarbonyl, C_{1-6}alkyloxy, thienylC_{1-6}alkyl, pyrrolylC_{1-6}alkyl, arylC_{1-6}alkylpiperidinyl, arylcarbonylC_{1-6}alkyl, arylcarbonylpiperidinylC_{1-6}alkyl, haloindozolylpiperidinylC_{1-6}alkyl, or arylC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl;

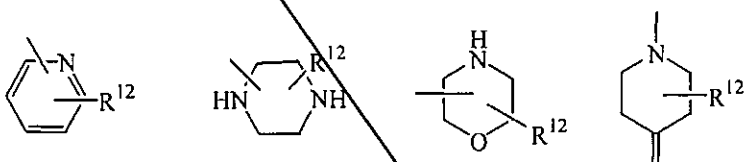
R^9 is hydrogen or C_{1-6}alkyl;

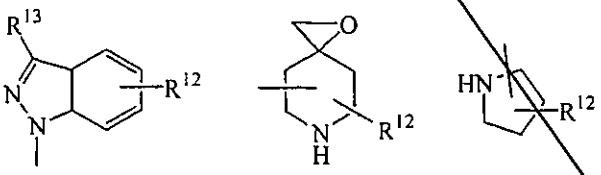
R^{10} is C_{1-6}alkyl, C_{1-6}alkylcarbonyl or di(C_{1-6}alkyl)aminoC_{1-6}alkyl; and
R^{11} is di(C_{1-6}alkyl)aminoC_{1-6}alkyl;
or R^3 is a group of formula

$$-(CH_2)_t-Z- \qquad (b\text{-}1),$$

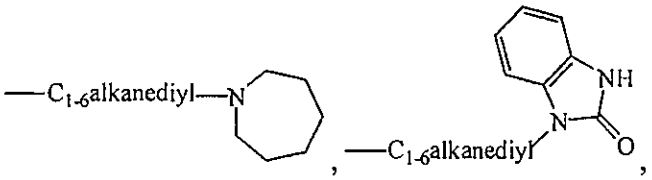
wherein
t is 0, 1, 2 or 3;
Z is a heterocyclic ring system selected from


(c-1) (c-2) (c-3) (c-4)


(c-5) (c-6) (c-7) (c-8)


(c-9) (c-10) (c-11)

wherein each R^{12} independently is hydrogen, C_{1-6}alkyl, aminocarbonyl, hydroxy,


, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkylamino, di(phenylC_{2-6}alkenyl), piperidinylC_{1-6}alkyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkylC_{1-6}alkyl, aryloxy(hydroxy)C_{1-6}alkyl, haloindazolyl, arylC_{1-6}alkyl, arylC_{2-6}alkenyl, morpholino, C_{1-6}alkylimidazolyl, or pyridinylC_{1-6}alkylamino; and
each R^{13} independently is hydrogen, piperidinyl or aryl;

R^4, R^5 and R^6 are each independently selected from hydrogen, halo, trihalomethyl, trihalomethoxy, C_{1-6}alkyl, C_{1-6}alkyloxy, di(C_{1-6}alkyl)amino, di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy or C_{1-6}alkyloxycarbonyl; or

when R^5 and R^6 are on adjacent positions they may taken together form a bivalent radical of formula

$-O-CH_2-O$ (d-1),

$-O-(CH_2)_2-O-$ (d-2),

$-CH=CH-CH=CH-$ (d-3), or

$-NH-C(O)-NR^{14}=CH-$ (d-4),

wherein R^{14} is C_{1-6}alkyl;

aryl is phenyl or phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy;

with the proviso that when

n is 0, X is N, R^1 is C_{1-6}alkyl, R^2 is hydrogen, R^3 is a group of formula (b-1), t is 0, Z is the heterocyclic ring system (c-2) wherein said heterocyclic ring system Z is attached to the rest of the molecule with a nitrogen atom, and R^{12} is hydrogen; then at least one of the substituents R^4, R^5 or R^6 is other than hydrogen, halo, C_{1-6}alkyl or C_{1-6}alkyloxy; and

with the proviso that 7-benzoyl-3-methyl-2(1H)-quinoxalinone is excluded.

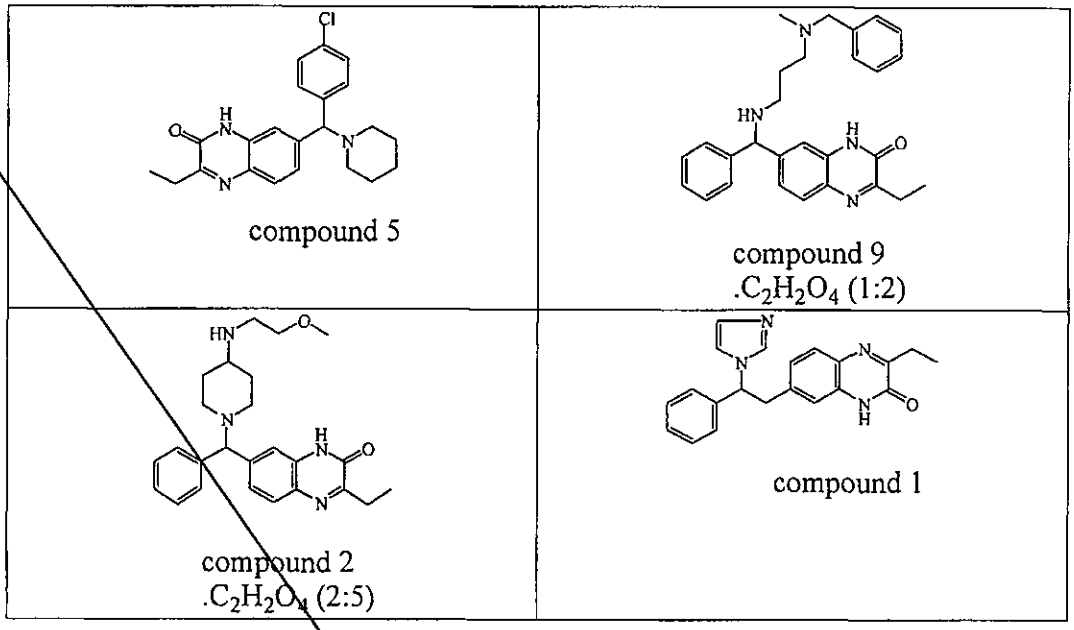
2. A compound as claimed in claim 1 wherein

n is 0 or 1; X is N or CR^7, wherein R^7 is hydrogen; R^1 is C_{1-6}alkyl; R^2 is hydrogen; R^3 is a radical selected from (a-1) or (a-2) or is group of formula (b-1); s is 0, 1 or 2; R^8 is C_{1-6}alkyl or arylC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl; t is 0, 1 or 2; Z is a heterocyclic ring system selected from (c-1), (c-2), (c-3), (c-4), (c-5) or (c-11); each R^{12} independently is hydrogen or C_{1-6}alkyloxyC_{1-6}alkylamino; each R^{13} independently is hydrogen; and R^4, R^5 and R^6 are each independently selected from hydrogen, halo or C_{1-6}alkyl.

3. A compound according to claim 1 and 2 wherein

n is 0 or 1; X is N; R^1 is C_{1-6}alkyl; R^2 is hydrogen; R^3 is a radical of formula (a-1) or is a group of formula (b-1); s is 0; R^8 is arylC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl; t is 0; Z is a heterocyclic ring system selected from (c-1) or (c-2); each R^{12} independently is hydrogen or C_{1-6}alkyloxyC_{1-6}alkylamino; each R^{13} independently is hydrogen; and R^4, R^5 and R^6 are each independently selected from hydrogen or halo.

4. A compound according to claim 1, 2 and 3 selected from compound No 5, compound No 9, compound No 2 and compound No 1.



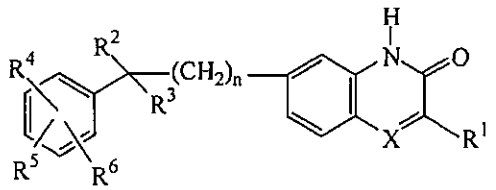
5. A compound according to claim 1 wherein R^3 is a radical selected from (a-1) or (a-2).

6. A compound according to claim 1 wherein Z is a heterocyclic ring system other than the heterocyclic ring system of formula (c-2) or (c-4).

7. A compound as claimed in any of claims 1 to 6 for use as a medicine.

8. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in claim 1 to 6.

9. Use of a compound for the manufacture of a medicament for chemosensitization or radiosensitization, wherein said compound is a compound of formula (I)



(I)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

n is 0, 1 or 2;

X is N or CR^7, wherein R^7 is hydrogen or taken together with R^1 may form a bivalent radical of formula -CH=CH-CH=CH-;

R^1 is C_{1-6}alkyl or thienyl;

R^2 is hydrogen, hydroxy, C_{1-6}alkyl, C_{3-6}alkynyl or taken together with R^3 may form =O;

R^3 is a radical selected from

$-(CH_2)_s-NR^8R^9$ (a-1),

-O-H (a-2),

$-O-R^{10}$ (a-3),

$-S-R^{11}$ (a-4), or

—C≡N (a-5),

wherein

s is 0, 1, 2 or 3;

R^8 is –CHO, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, piperidinylC_{1-6}alkyl, piperidinylC_{1-6}alkylaminocarbonyl, C_{1-6}alkyloxy, thienylC_{1-6}alkyl, pyrrolylC_{1-6}alkyl, arylC_{1-6}alkylpiperidinyl, arylcarbonylC_{1-6}alkyl, arylcarbonylpiperidinylC_{1-6}alkyl, haloindozolylpiperidinylC_{1-6}alkyl, or arylC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl;

R^9 is hydrogen or C_{1-6}alkyl;

R^{10} is C_{1-6}alkyl, C_{1-6}alkylcarbonyl or di(C_{1-6}alkyl)aminoC_{1-6}alkyl; and

R^{11} is di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

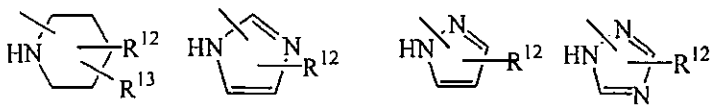
or R^3 is a group of formula

$-(CH_2)_t-Z-$ (b-1),

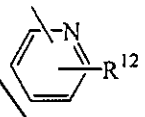
wherein

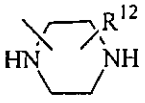
t is 0, 1, 2 or 3;

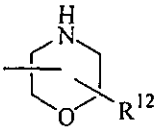
Z is a heterocyclic ring system selected from

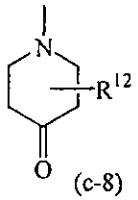


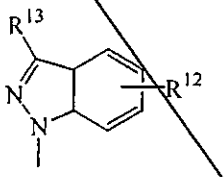
(c-1) (c-2) (c-3) (c-4)

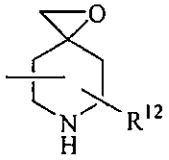

(c-5)

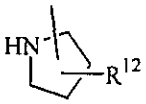

(c-6)


(c-7)

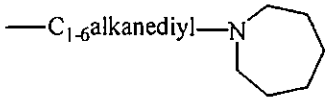
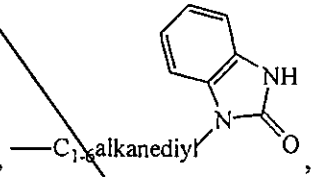

(c-8)


(c-9)


(c-10)


(c-11)

wherein each R^{12} independently is hydrogen, C_{1-6}alkyl, aminocarbonyl, hydroxy,


, 
,

C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkylamino, di(phenylC_{2-6}alkenyl), piperidinylC_{1-6}alkyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkylC_{1-6}alkyl, aryloxy(hydroxy)C_{1-6}alkyl, haloindazolyl, arylC_{1-6}alkyl, arylC_{2-6}alkenyl, morpholino, C_{1-6}alkylimidazolyl, or pyridinylC_{1-6}alkylamino; and

each R^{13} independently is hydrogen, piperidinyl or aryl;

R^4, R^5 and R^6 are each independently selected from hydrogen, halo, trihalomethyl, trihalomethoxy, C_{1-6}alkyl, C_{1-6}alkyloxy, di(C_{1-6}alkyl)amino, di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy or C_{1-6}alkyloxycarbonyl; or

when R^5 and R^6 are on adjacent positions they may taken together form a bivalent radical of formula

-O-CH_2-O (d-1),

-O-$(CH_2)_2$-O- (d-2),

-CH=CH-CH=CH- (d-3), or

-NH-C(O)-NR^{14}=CH- (d-4),

wherein R^{14} is C_{1-6}alkyl;

aryl is phenyl or phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy.

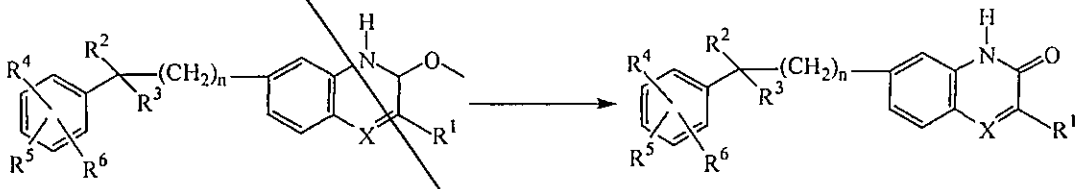
10. Use according to claim 9 wherein the medicament is for chemosensitization.

11. Use according to claim 9 wherein the medicament is for radiosensitization.

12. A combination of a compound as claimed in any one of claims 1 to 6 with a chemotherapeutic agent.

13. A process for preparing a compound as claimed in claim 1, characterized by

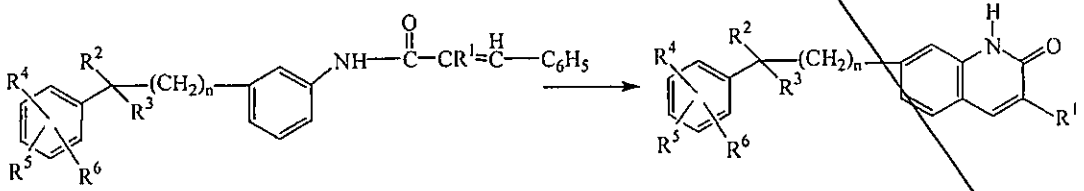
a) the hydrolysis of intermediates of formula (VIII), according to art-known methods, by submitting the intermediates of formula (VIII) to appropriate reagents, such as, tinchloride, acetic acid and hydrochloric acid, in the presence of a reaction inert solvent, e.g. tetrahydrofuran.



(VIII) (I)

wherein R^1 to R^6, n and X are as defined in claim 1;

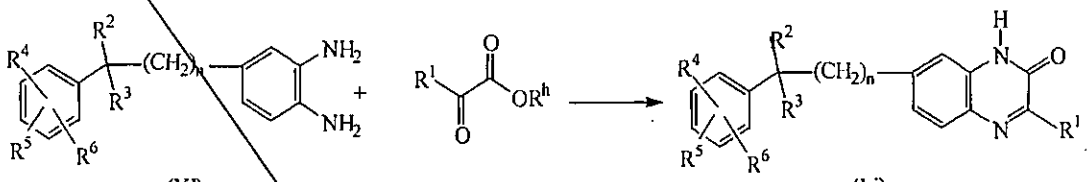
b) the cyclization of intermediates of formula (X), according to art-known cyclizing procedures into compounds of formula (I) wherein X is CH, herein referred to as compounds of formula (I-j), preferably in the presence of a suitable Lewis Acid, e.g. aluminum chloride either neat or in a suitable solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, chlorobenzene, methylbenzene and the like; halogenated hydrocarbons, e.g. trichloromethane, tetrachloromethane and the like; an ether, e.g. tetrahydrofuran, 1,4-dioxane and the like or mixtures of such solvents.



(X) (I-j)

wherein R^1 to R^6 and n are as defined in claim 1;

c) the condensation of an appropriate ortho-benzenediamine of formula (XI) with an ester of formula (XII) wherein R^h is C_{1-6}alkyl, into compounds of formula (I), wherein X is N, herein referred to as compounds of formula (I-i), in the presence of a carboxylic acid, e.g. acetic acid and the like, a mineral acid such as, for example hydrochloric acid, sulfuric acid, or a sulfonic acid such as, for example, methanesulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid and the like.



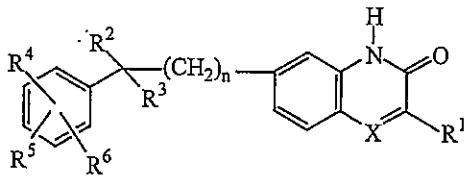
(XI) (XII) (I-i)

wherein R^1 to R^6 and n are as defined in claim 1 and wherein R^h is C_{1-6}alkyl;

14. Use of a compound according to claim 5 or 6 for the manufacture of a medicament for the treatment of cancer.

CLAIMS

1. A compound of formula (I),



(I)

a *N*-oxide form, an addition salt or a stereo-chemically isomeric form thereof, wherein

n is 0, 1 or 2;

X is N or CR^7, wherein R^7 is hydrogen or taken together with R^1 may form a bivalent radical of formula -CH=CH-CH=CH-;

R^1 is C_{1-6}alkyl or thienyl;

R^2 is hydrogen, hydroxy, C_{1-6}alkyl, C_{3-6}alkynyl or taken together with R^3 may form =O;

R^3 is a radical selected from

$-(CH_2)_s-NR^8R^9$ (a-1), and

-O-H (a-2),

wherein

s is 0, 1, 2 or 3;

R^8 is –CHO, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, piperidinylC_{1-6}alkyl, piperidinylC_{1-6}alkylaminocarbonyl, C_{1-6}alkyloxy, thienylC_{1-6}alkyl, pyrrolylC_{1-6}alkyl, arylC_{1-6}alkylpiperidinyl, arylcarbonylC_{1-6}alkyl, arylcarbonylpiperidinylC_{1-6}alkyl, haloindozolylpiperidinylC_{1-6}alkyl, or arylC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl;

R^9 is hydrogen or C_{1-6}alkyl;

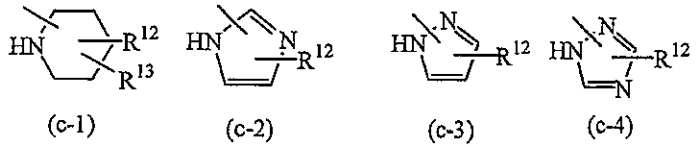
or R^3 is a group of formula

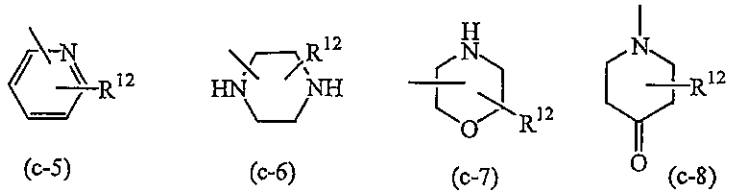
$-(CH_2)_t-Z-$ (b-1),

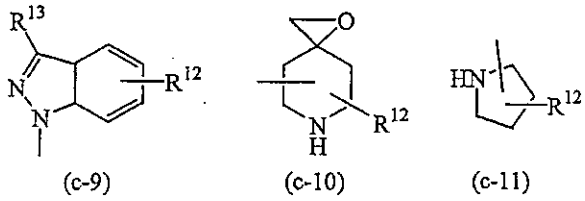
wherein

t is 0, 1, 2 or 3;

Z is a heterocyclic ring system selected from


(c-1) (c-2) (c-3) (c-4)


(c-5) (c-6) (c-7) (c-8)


(c-9) (c-10) (c-11)

wherein each R^{12} independently is hydrogen or C_{1-6}alkyloxyC_{1-6}alkylamino; and each R^{13} independently is hydrogen, piperidinyl or aryl;

R^4, R^5 and R^6 are each independently selected from hydrogen, halo, trihalomethyl, trihalomethoxy, C_{1-6}alkyl, C_{1-6}alkyloxy, di(C_{1-6}alkyl)amino, di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy and C_{1-6}alkyloxycarbonyl; or

when R^5 and R^6 are on adjacent positions they may taken together form a bivalent radical of formula

-O-CH_2-O (d-1),

-O-$(CH_2)_2$-O- (d-2),

-CH=CH-CH=CH- (d-3), or

-NH-C(O)-NR^{14}=CH- (d-4),

wherein R^{14} is C_{1-6}alkyl;

aryl is phenyl or phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy;

with the proviso that when

n is 0, X is N, R^1 is C_{1-6}alkyl, R^2 is hydrogen, R^3 is a group of formula (b-1), t is 0, Z is the heterocyclic ring system (c-2) wherein said heterocyclic ring system Z is attached to the rest of the molecule with a nitrogen atom, and R^{12} is hydrogen; then

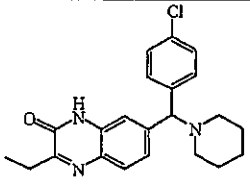
at least one of the substituents R^4, R^5 or R^6 is other than hydrogen, halo, C_{1-6}alkyl or

C_{1-6}alkyloxy; and with the proviso that 7-benzoyl-3-methyl-2(1H)-quinoxalinone is excluded.

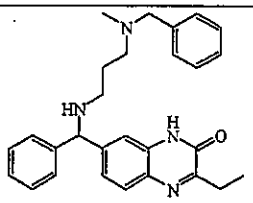
2. The compound according to claim 1 wherein
n is 0 or 1; X is N or CR^7, wherein R^7 is hydrogen; R^1 is C_{1-6}alkyl; R^2 is hydrogen; R^3 is a radical selected from (a-1) and (a-2) or is group of formula (b-1); s is 0, 1 or 2; R^8 is C_{1-6}alkyl or arylC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl; t is 0, 1 or 2; Z is a heterocyclic ring system selected from (c-1), (c-2), (c-3), (c-4), (c-5) and (c-11); each R^{13} independently is hydrogen; and R^4, R^5 and R^6 are each independently selected from hydrogen, halo and C_{1-6}alkyl.

3. The compound according to claim 1 or 2 wherein
n is 0 or 1; X is N; R^1 is C_{1-6}alkyl; R^2 is hydrogen; R^3 is a radical of formula (a-1) or is a group of formula (b-1); s is 0; R^8 is arylC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl; t is 0; Z is a heterocyclic ring system selected from (c-1) and (c-2); each R^{13} independently is hydrogen; and R^4, R^5 and R^6 are each independently selected from hydrogen and halo.

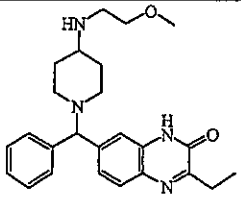
4. The compound according to any one of claims 1 to 3 selected from compound 5, compound 9, compound 2 and compound 1 as defined below



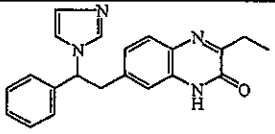
compound 5



compound 9
$.C_2H_2O_4$ (1:2)



compound 2
$.C_2H_2O_4$ (2:5)



compound 1

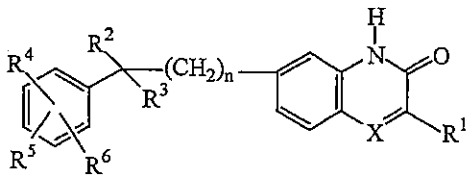
5. The compound according to claim 1 wherein R^3 is a radical selected from (a-1) and (a-2).

6. The compound according to claim 1 wherein Z is a heterocyclic ring system other than the heterocyclic ring system of formula (c-2) or (c-4).

7. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as the active ingredient the compound according to any one of claims 1 to 6.

8. A process of preparing a pharmaceutical composition according to claim 7 wherein the pharmaceutically acceptable carriers and the compound according to any one of claims 1 to 6 are intimately mixed.

9. Use of a compound for the manufacture of a medicament for chemosensitization or radiosensitization, wherein said compound is a compound of formula (I)



(I)

a *N*-oxide form, a pharmaceutically acceptable addition salt or a stereo-chemically isomeric form thereof, wherein

n is 0, 1 or 2;

X is N or CR^7, wherein R^7 is hydrogen or taken together with R^1 may form a bivalent radical of formula -CH=CH-CH=CH-;

R^1 is C_{1-6}alkyl or thienyl;

R^2 is hydrogen, hydroxy, C_{1-6}alkyl, C_{3-6}alkynyl or taken together with R^3 may form =O;

R^3 is a radical selected from

$-(CH_2)_s-NR^8R^9$ (a-1), and

-O-H (a-2),

wherein

s is 0, 1, 2 or 3;

R^8 is –CHO, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, piperidinylC_{1-6}alkyl, piperidinylC_{1-6}alkylaminocarbonyl, C_{1-6}alkyloxy,

thienylC_{1-6}alkyl, pyrrolylC_{1-6}alkyl, arylC_{1-6}alkylpiperidinyl, arylcarbonylC_{1-6}alkyl, arylcarbonylpiperidinylC_{1-6}alkyl, haloindozolylpiperidinylC_{1-6}alkyl, or arylC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl;

R^9 is hydrogen or C_{1-6}alkyl;

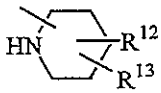
or R^3 is a group of formula

$-(CH_2)_t-Z-$ (b-1),

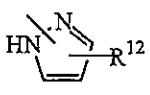
wherein

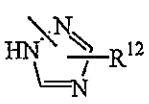
t is 0, 1, 2 or 3;

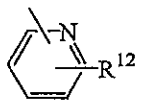
Z is a heterocyclic ring system selected from

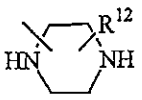

(c-1)

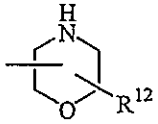

(c-2)

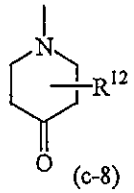

(c-3)

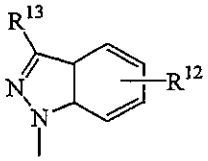

(c-4)

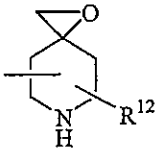

(c-5)

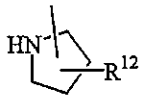

(c-6)


(c-7)


(c-8)


(c-9)


(c-10)


(c-11)

wherein each R^{12} independently is hydrogen or C_{1-6}alkyloxyC_{1-6}alkylamino; and each R^{13} independently is hydrogen, piperidinyl or aryl;

R^4, R^5 and R^6 are each independently selected from hydrogen, halo, trihalomethyl, trihalomethoxy, C_{1-6}alkyl, C_{1-6}alkyloxy, di(C_{1-6}alkyl)amino, di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy and C_{1-6}alkyloxycarbonyl; or

when R^5 and R^6 are on adjacent positions they may taken together form a bivalent radical of formula

$-O-CH_2-O$ (d-1),

$-O-(CH_2)_2-O-$ (d-2),

$-CH=CH-CH=CH-$ (d-3), or

$-NH-C(O)-NR^{14}=CH-$ (d-4),

wherein R^{14} is C_{1-6}alkyl;

aryl is phenyl or phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy.

10. The use according to claim 9 wherein the treatment involves chemosensitization.

11. The use according to claim 9 wherein the treatment involves radiosensitization.

12. A combination of the compound according to any one of claims 1 to 6 with a chemotherapeutic agent.