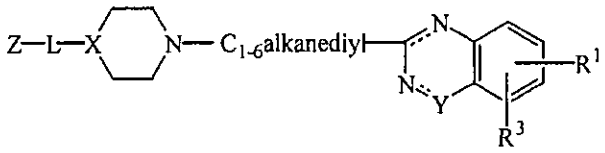
CLAIMS

1. A compound of formula (I)



(I)

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

the dotted lines represent optional bonds;

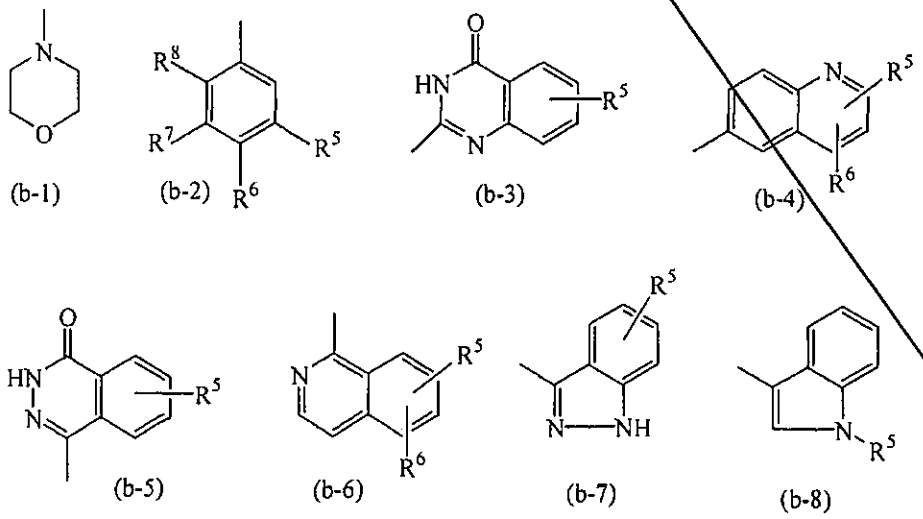
X is >N- , >CH- or >CR^2- wherein R^2 is aminocarbonyl;

—N⋯Y— is –N-C(O)- or -N=CR^4-, wherein R^4 is hydroxy;

R^1 is hydrogen, halo, C$_{1-6}$alkyloxy or C$_{1-6}$alkyl;

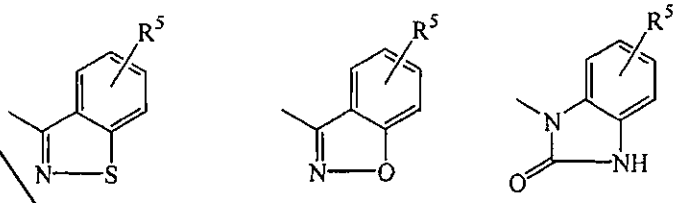
R^3 is hydrogen, or C$_{1-6}$alkyloxy;

Z is a radical selected from



(b-1) (b-2) (b-3) (b-4)

(b-5) (b-6) (b-7) (b-8)



(b-9) (b-10) (b-11)

wherein each R^5, R^6, R^7 and R^8 is independently selected from hydrogen, halo, amino, C_{1-6}alkyl or C_{1-6}alkyloxy; or

R^7 and R^8 taken together may form a bivalent radical of formula

- CH_2-CR^9_2-O- (c-1),
-$(CH_2)_3$-O- (c-2),
-O-$(CH_2)_2$-O- (c-3) or
-CH=CH-CH=CH- (c-4)

wherein each R^9 is independently selected from hydrogen or C_{1-6}alkyl; and

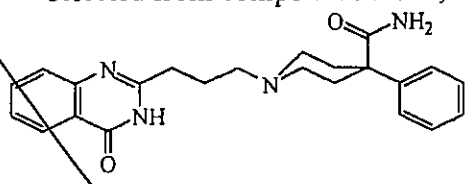
L is a bivalent radical selected from -C(O)-NH-, -C(O)-C_{1-6}alkanediyl- or -C(O)-O-C_{1-6}alkanediyl-; or

L can be a direct bond when X is >CR^2- or when Z is a radical of formula (b-11).

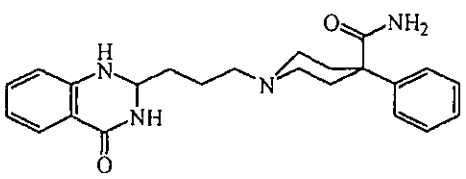
2. A compound as claimed in claim 1 wherein X is >CH- or >CR^2- wherein R^2 is aminocarbonyl; R^1 is hydrogen; R^3 is hydrogen; Z is a radical of formula (b-1), (b-2) or (b-11), each R^5, R^6, R^7 and R^8 is independently selected from hydrogen or halo; L is a bivalent radical selected from -C(O)-NH- or -C(O)-C_{1-6}alkanediyl-; and L can be a direct bond when X is >CR^2- or when Z is a radical of formula (b-11).

3. A compound as claimed in claim 1 or 2 wherein X is >CH- or >CR^2- wherein R^2 is aminocarbonyl; R^1 is hydrogen; R^3 is hydrogen; Z is a radical of formula (b-1) or (b-2); each R^5, R^6, R^7 and R^8 is independently selected from hydrogen or halo; L is -C(O)-NH- and L can be a direct bond when X is >CR^2-.

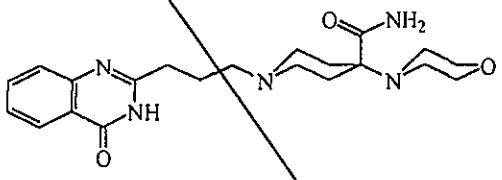
4. A compound as claimed in any one of claims 1, 2 or 3 wherein the compound is selected from compounds No. 4, No. 5, No. 11 and No. 12.



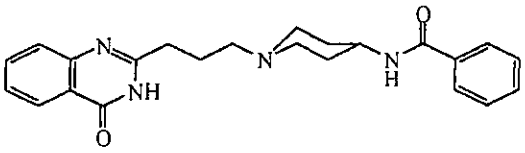
Compound 4



Compound 5



Compound 11



Compound 12

5. A compound as claimed in any of claims 1 to 4 for use as a medicine.

6. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 4.

7. Use of a compound as claimed in any one of claims 1 to 4 for the manufacture of a medicament for the treatment of a PARP mediated disorder.

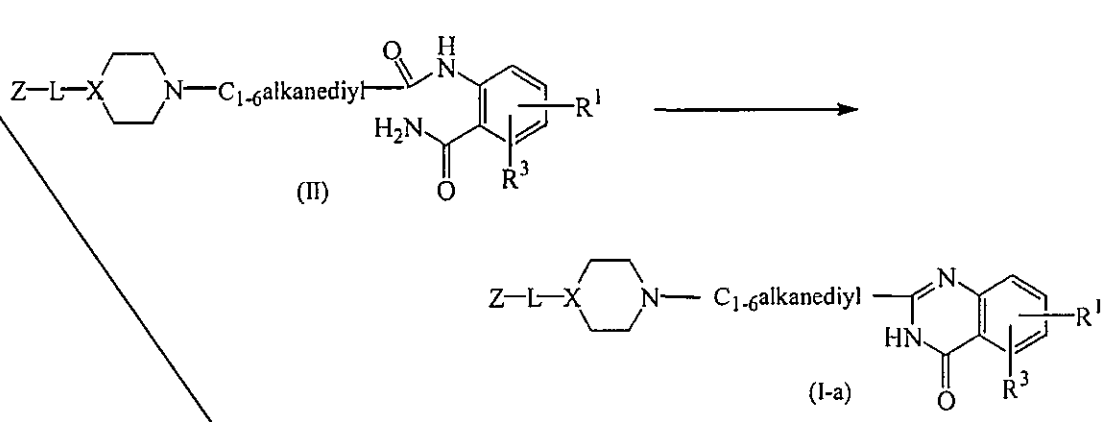
8. Use as claimed in claim 7 for the manufacture of a medicament for the treatment of a PARP-1 mediated disorder.

9. Use as claimed in claim 7 or 8 wherein the treatment involves chemosensitization.

10. Use as claimed in claim 7 or 8 wherein the treatment involves radiosensitization.

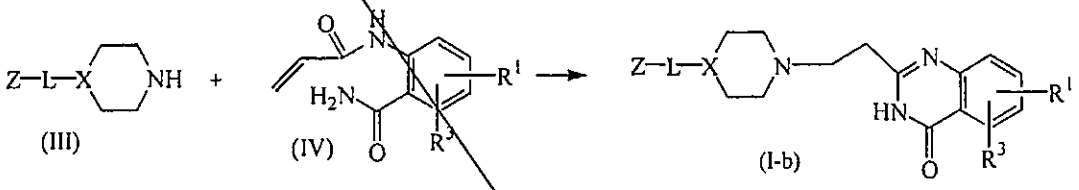
11. A combination of a compound as claimed in any one of claims 1 to 4 with a chemotherapeutic agent.

12. A process for preparing a compound as claimed in claim 1, characterized by a) cyclizing an appropriate substituted 2-aminocarbonylbenzamide of formula (II) into compounds of formula (I-a), wherein both dotted lines can be a bond,



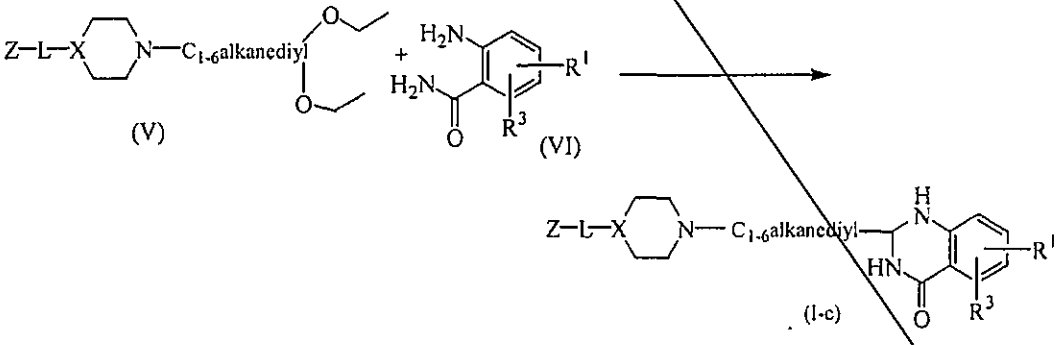
wherein the variables are as defined in claim 1;

b) cyclizing an appropriate substituted 2-aminocarbonylbenzamide of formula (VI) with an intermediate of formula (III) into compounds of formula (I-b), wherein $-C_{1-6}$alkanediyl- is $-CH_2-CH_2-$ and both dotted lines can be a bond, or



wherein the variables are as defined in claim 1;

c) cyclizing an appropriate substituted 2-aminobenzamide of formula (V) with an intermediate of formula (VI) into compounds of formula (I-c), wherein only one of the dotted lines can be a bond.

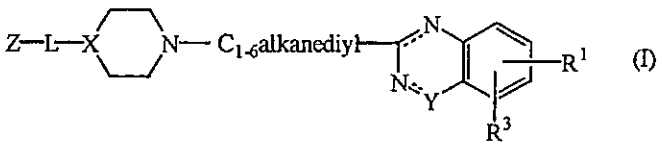


wherein the variables are as defined in claim 1.

13. Use of a compound as claimed in any one of claims 1 to 4 for the manufacture of a medicament for the treatment of cancer.

CLAIMS

1. A compound of formula (I)



(I)

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

the dotted lines represent optional bonds;

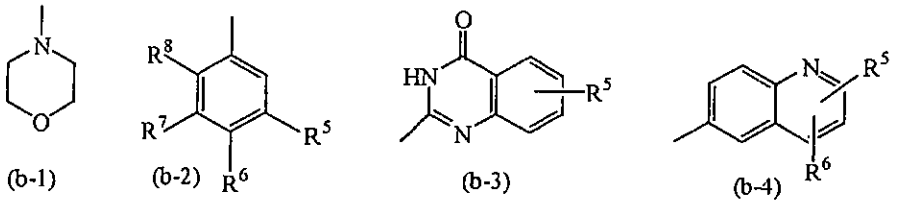
X is >N- , >CH- or >CR^2- wherein R^2 is aminocarbonyl;

-N=Y- is -NH-C(O)- or -N=CR^4-, wherein R^4 is hydroxy;

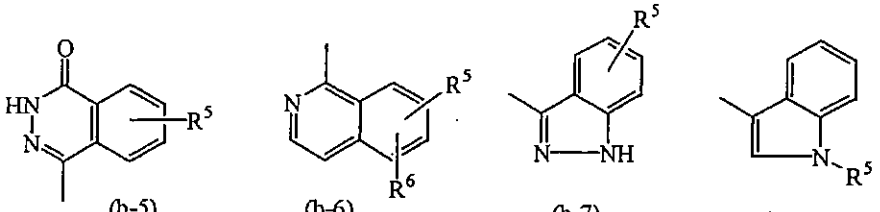
R^1 is hydrogen, halo, C_{1-6}alkyloxy or C_{1-6}alkyl;

R^3 is hydrogen, or C_{1-6}alkyloxy;

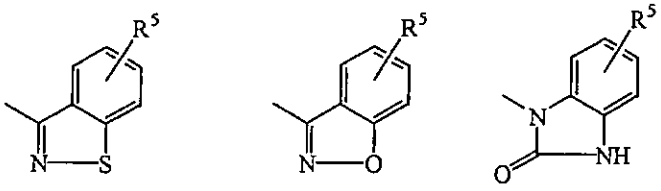
Z is a radical selected from



(b-1) (b-2) (b-3) (b-4)



(b-5) (b-6) (b-7) (b-8)



(b-9) (b-10) (b-11)

wherein each R^5, R^6, R^7 and R^8 is independently selected from hydrogen, halo, amino, C_{1-6}alkyl or C_{1-6}alkyloxy; or R^7 and R^8 taken together may form a bivalent radical of formula

- CH_2-CR^9_2-O- (c-1),

-$(CH_2)_3$-O- (c-2),

-O-$(CH_2)_2$-O- (c-3)

or

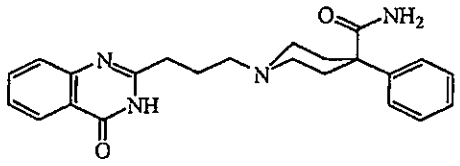
-CH=CH-CH=CH- (c-4)

wherein each R^9 is independently selected from hydrogen or C_{1-6}alkyl; and
L is a bivalent radical selected from -C(O)-NH-, -C(O)-C_{1-6}alkanediyl- or -C(O)-O-C_{1-6}alkanediyl-; or
L can be a direct bond when X is >CR^2- or when Z is a radical of formula (b-11).

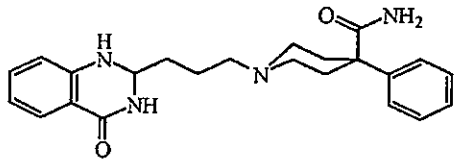
2. A compound according to claim 1 wherein
X is >CH- or >CR^2- wherein R^2 is aminocarbonyl; R^1 is hydrogen; R^3 is hydrogen;
Z is a radical of formula (b-1), (b-2) or (b-11); each R^5, R^6, R^7 and R^8 is independently selected from hydrogen or halo; L is a bivalent radical selected from -C(O)-NH- or -C(O)-C_{1-6}alkanediyl-; and L can be a direct bond when X is >CR^2- or when Z is a radical of formula (b-11).

3. A compound according to claim 1 or 2 wherein
X is >CH- or >CR^2- wherein R^2 is aminocarbonyl; R^1 is hydrogen; R^3 is hydrogen;
Z is a radical of formula (b-1) or (b-2); each R^5, R^6, R^7 and R^8 is independently selected from hydrogen or halo; L is -C(O)-NH- and L can be a direct bond when X is >CR^2-.

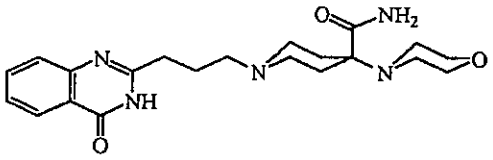
4. A compound according to claim 1, 2 and 3 wherein the compound is selected from compounds No. 4, No. 5, No. 11 and No. 12.



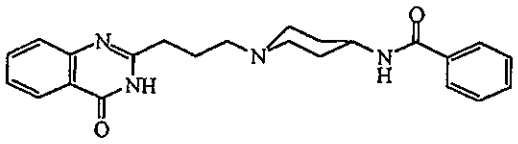
Compound 4



Compound 5



Compound 11



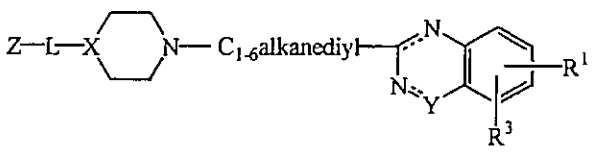
Compound 12

5. A compound as claimed in any of claims 1 to 4 for use as a medicine.

6. 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 5.

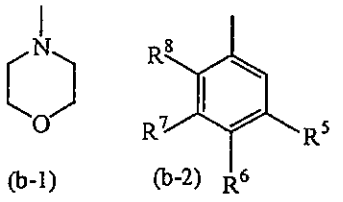
7. A process of preparing a pharmaceutical composition as claimed in claim 6 wherein the pharmaceutically acceptable carriers and a compound as claimed in claim 1 to 4 are intimately mixed.

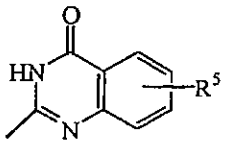
8. Use of a compound for the manufacture of a medicament for the treatment of a PARP mediated disorder, wherein the compound is a compound of formula (I)

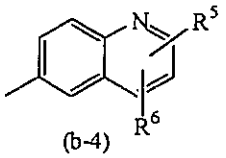


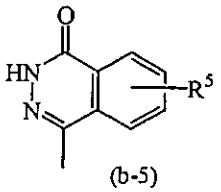
(I)

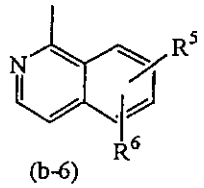
the N-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein
the dotted lines represent optional bonds;
X is >N- , >CH- or >CR^2- wherein R^2 is aminocarbonyl;
-N=Y- is -NH-C(O)- or -N=CR^4-, wherein R^4 is hydroxy;
R^1 is hydrogen, halo, C_{1-6}alkyloxy or C_{1-6}alkyl;
R^3 is hydrogen, or C_{1-6}alkyloxy;
Z is a radical selected from

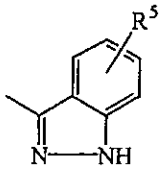

(b-1) (b-2)

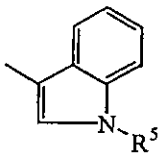

(b-3)

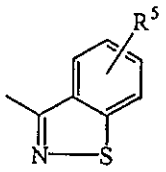

(b-4)

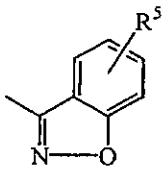

(b-5)

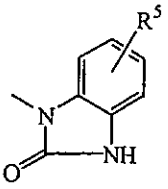

(b-6)


(b-7)


(b-8)


(b-9)


(b-10)


(b-11)

wherein each R^5, R^6, R^7 and R^8 is independently selected from hydrogen, halo, amino, C_{1-6}alkyl or C_{1-6}alkyloxy; or R^7 and R^8 taken together may form a bivalent radical of formula

- CH_2-CR^9_2-O- (c-1),

-$(CH_2)_3$-O- (c-2),

-O-$(CH_2)_2$-O- (c-3)

or

-CH=CH-CH=CH- (c-4)

wherein each R^9 is independently selected from hydrogen or C_{1-6}alkyl; and
L is a bivalent radical selected from -C(O)-NH-, -C(O)-C_{1-6}alkanediyl- or -C(O)-O-C_{1-6}alkanediyl-; or
L can be a direct bond when X is >CR^2- or when Z is a radical of formula (b-11).

9. Use according to claim 8 of a PARP inhibitor of formula (I) for the manufacture of a medicament for the treatment of a PARP-1 mediated disorder.

10. Use according to claim 8 and 9 wherein the treatment involves chemosensitization.

11. Use according to claims 8 and 9 wherein the treatment involves radiosensitization.

12. A combination of a compound of formula (I) as claimed in claim 1 with a chemotherapeutic agent.