

PHARMACEUTICAL COMPOUNDS

The present invention relates to compounds useful as modulators of multi-drug resistance (MDR), to their preparation and to pharmaceutical and veterinary

5 compositions containing them.

The resistance of tumours to treatment with certain cytotoxic agents is an obstacle to the successful chemotherapeutic treatment of cancer patients. A tumour may acquire resistance to a cytotoxic agent used in a previous
10 treatment. A tumour may also manifest intrinsic resistance, or cross-resistance, to a cytotoxic agent to which it has not previously been exposed, that agent being unrelated by structure or mechanism of action to any agent used in previous treatments of the tumour.

15 Analogously, certain pathogens may acquire resistance to pharmaceutical agents used in previous treatments of the diseases or disorders to which those pathogens give rise. Pathogens may also manifest intrinsic resistance, or cross resistance, to pharmaceutical agents to which they have not
20 previously been exposed. Examples of this effect include multi-drug resistant forms of malaria, tuberculosis, leishmaniasis and amoebic dysentery.

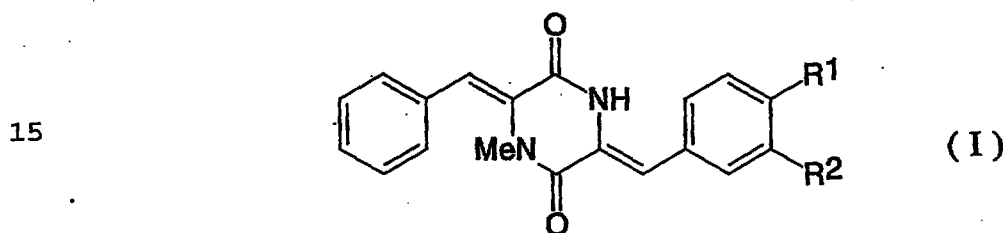
The above phenomena are referred to collectively as multi-drug resistance (MDR). As discussed more fully later
25 on, a plasma membrane glycoprotein (P-gp) is implicated in the mechanism which underlies MDR. P-gp has drug binding properties. Certain agents which have the capacity to modulate MDR may therefore also be useful in facilitating



the delivery of drugs across the blood-brain barrier and in treating AIDS and AIDS-related complex.

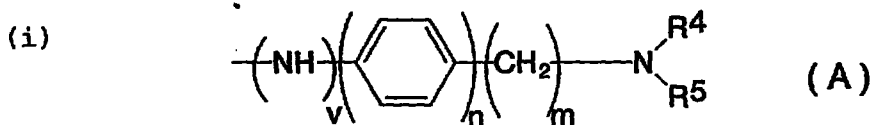
Disadvantages of drugs which have so far been used to modulate MDR, termed resistance modifying agents or RMAs, are that they frequently possess a poor pharmacokinetic profile and/or are toxic at the concentrations required for MDR modulation.

It has now been found that a series of piperazinedione derivatives have activity as modulators of multi-drug resistance. The present invention therefore provides a piperazinedione derivative of formula (I):



wherein R¹ is selected from:

- hydrogen;
- 20 - a group of formula $-(NH)_t-COR^3$ wherein t is 0 or 1 and R³ is selected from:

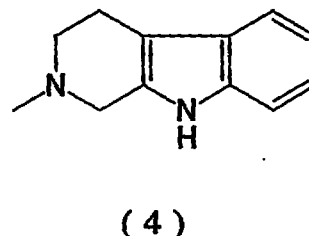
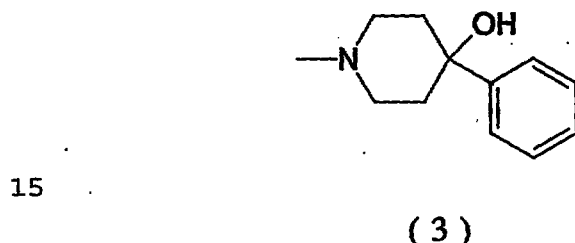
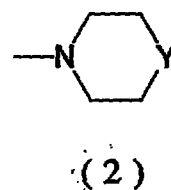
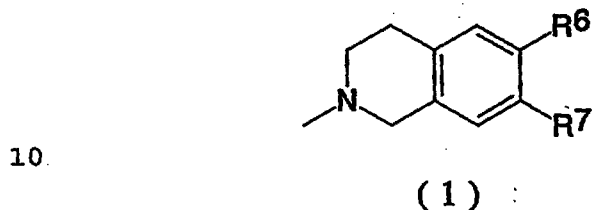


25

wherein v is 0 when t is 1 and v is 1 when t is 0; and wherein n is 0 or 1 and m is 0, 1, 2 or 3, at least one of n and m being other than 0, and either:

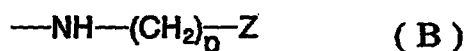
(a) R^4 is H or C_1-C_6 alkyl and R^5 is C_1-C_6 alkyl optionally substituted by one or two phenyl groups, the phenyl group or groups being optionally substituted by one or two C_1-C_6 alkoxy groups; or

5 (b) R^4 and R^5 , together with the nitrogen atom to which they are attached, form a heterocyclic group selected from (1) to (4):



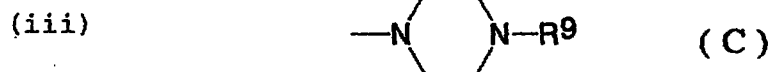
wherein R^6 and R^7 , which are the same or different, are H or C_1-C_6 alkoxy or R^6 and R^7 form together a methylenedioxy group; Y is O or $-NR^8$ wherein R^8 is C_1-C_6 alkyl or a phenyl group optionally substituted by CF_3 ;

(ii)



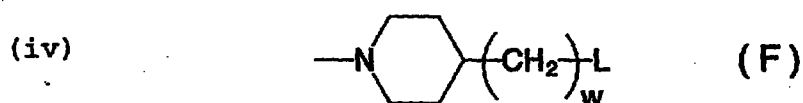
wherein p is 1 or 2 and Z is C_2-C_6 alkenyl or a phenyl group optionally substituted by C_1-C_6 alkoxy; and

25



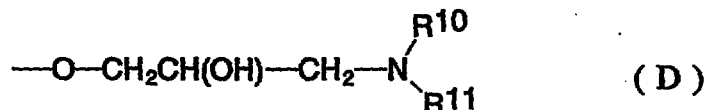
wherein R^9 is C_1-C_6 alkyl, pyrimidinyl or a phenyl group

optionally substituted by C₁-C₆ alkoxy; and



5 wherein w is 1, 2 or 3 and L is a heterocyclic group of formula (1) as defined above;

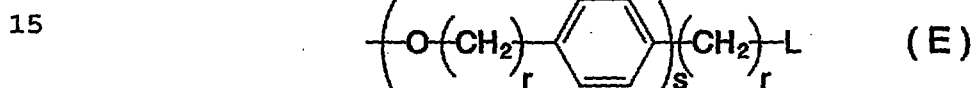
- a group of the formula (D):



10

wherein each of R¹⁰ and R¹¹, which may be the same or different, is C₁-C₆ alkyl; and

- a group of formula (E):



wherein s is 0 or 1 and each r, which may be the same or different, is 1, 2 or 3 and L is a heterocyclic group of formula (1) as defined above;

20 and R² is hydrogen or a group of formula -COR³ as defined above provided that one of R¹ and R² is hydrogen and the other is not hydrogen; or a pharmaceutically acceptable salt thereof.

25 An alkyl group may be linear or branched. A C₁-C₆ alkyl group is typically a C₁-C₄ alkyl group, for example a methyl, ethyl, propyl, i-propyl, n-butyl, sec-butyl or tert-butyl group. A C₁-C₆ alkoxy group is typically a C₁-C₄ alkoxy group, for example a methoxy, ethoxy, propoxy, i-propoxy, n-

butoxy, sec-butoxy or tert-butoxy group.

When R^1 is a group of formula $-(NH)_t-COR^3$, t may be 0 in which case the group has the formula $-COR^3$. The integer v in formula (A) is then 1. When R^3 is a group of formula (A), n is typically 1 and m is 0, 1, 2 or 3, or n is 0 and m is 2. R^4 and R^5 may be as defined under (a), in which case R^4 is preferably C_1-C_6 alkyl, for instance methyl. R^5 is preferably C_1-C_6 alkyl, for instance methyl or ethyl, either unsubstituted or substituted on the terminal carbon atom by one or two phenyl groups. These phenyl groups are in turn unsubstituted or substituted by one or two methoxy groups. For instance, R^5 may be a diphenylmethyl, 2-2-diphenylethyl or 3,4-dimethoxyphenethyl group. Alternatively, R^4 and R^5 may be as defined under (b). When R^4 and R^5 together form the heterocyclic ring (1), R^6 and R^7 are typically the same, and are preferably hydrogen or methoxy, or together form a methylenedioxy group. When R^4 and R^5 together form the heterocyclic ring (2), Y is O or $-NR^8$ wherein R^8 is preferably methyl, phenyl or 3-trifluoromethylphenyl.

When R^3 is a group of formula (B), Z is preferably ethenyl, prop-1-enyl or prop-2-enyl, or a phenyl group substituted by one or two C_1-C_6 alkoxy groups, preferably methoxy groups. Preferably the phenyl ring is 3,4-disubstituted by methoxy groups.

When R^3 is a group of formula (C), R^9 is preferably selected from methyl, ethyl, pyrimidinyl and phenyl, the phenyl being monosubstituted at position 2, 3 or 4 by C_1-C_6 alkoxy, for instance methoxy, and more preferably being a 4-

methoxyphenyl group.

When R^1 is a group of formula (D) R^{10} , and R^{11} are typically the same and are preferably both methyl. When R^1 is a group of formula (E), s may be 0 in which case the group has the formula $-(CH_2)_r-L$. In formula (E) the substituents R^6 and R^7 in the heterocyclic ring are typically the same and are preferably both H or methoxy, or together form a methylenedioxy group.

In a first embodiment of formula (I) in which $t = 1$ and $v = 0$, R^1 is hydrogen and R^2 is a group of formula $-COR^3$ as defined above in which R^3 is a group of formula A.

In a second embodiment of formula (I) R^2 is hydrogen and R^1 is a group of formula $-COR^3$ as defined above in which R^3 is a group of formula (A), a group of formula (B) wherein Z is ethenyl or phenyl substituted by two C_1-C_6 alkoxy groups, or a group of formula (C) wherein R^2 is methyl, pyrimidinyl or phenyl. Phenyl substituted by two C_1-C_6 alkoxy groups is preferably 3,4-dimethoxyphenyl.

In formula (A) in the first and second embodiments described above it is preferred that n is 0 and m is 2, or n is 1 and $m=0, 1$ or 2, and either:

(a) R^4 is C_1-C_6 alkyl and R^5 is C_1-C_6 alkyl substituted on the terminal C atom by 2 unsubstituted phenyl groups or by one phenyl group which is disubstituted by C_1-C_6 alkoxy groups; or

(b) R^4 and R^5 form together with the nitrogen atom to which they are attached a heterocyclic group selected from groups of formulae (1) wherein R^6 and R^7 are both H or both

C₁-C₆ alkoxy, or wherein R⁶ and R⁷ together form a methylenedioxy group; (2) wherein Y is O or -NR⁸ wherein R⁸ is methyl, phenyl or trifluoromethylphenyl; (3); and (4).

Preferably R⁴ is methyl and R⁵ is diphenylmethyl or 2-
5 (3,4-dimethoxyphenyl)ethyl, or R⁴ and R⁵ together form instead heterocyclic ring (1) in which R⁶ and R⁷ are both H or both OMe, or together form a methylenedioxy group.

Examples of preferred compounds of formula (I) are as follows:

10 1-(4-((3Z,6Z)-6-Benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzoyl)-4-(2-pyrimidyl)piperazine (9022)

15 1-(4-((3Z,6Z)-6-Benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzoyl)-4-methylpiperazine, hydrochloride (9052)

20 1-(4-((3Z,6Z)-6-Benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzoyl)-4-(4-methoxyphenyl)piperazine, hydrochloride (9071)

N-Allyl-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9070)

25 N-(2-Diphenylmethylethylmethylaminoethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9076)

N-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9116)

- 5 N-(3,4-Dimethoxyphenethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9117)

- N-(4-(4-Phenyl-1-piperaziny)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9104)
- 10

N-(2-(4-Methyl-1-piperaziny)ethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9007)

15

N-(2-Morpholinoethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9053)

- 20 N-(4-Morpholinophenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9054)

- N-(4-(2-(1,2,3,4-Tetrahydro- β -carbolin-2-yl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9080)
- 25

N-(4-(1,2,3,4-Tetrahydro- β -carbolin-2-yl)methylphenyl)-4-

((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9096)

5 N-(4-(2-(4-Phenyl-1-piperaziny)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9103)

10 N-(4-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9065)

15 N-(4-(2-(4-(3-Trifluoromethylphenyl)-1-piperaziny)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9049)

N-(4-(2-(4-(4-Chlorophenyl)-4-hydroxypiperidino)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9079)

20 N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9006)

25 N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9008)

N-(4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-

isoquinolyl)methylphenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-
2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride
(9064)

5 (3Z,6Z)-6-Benzylidene-3-(4-(3-dimethylamino-2-
hydroxypropoxy)benzylidene)-1-methyl-2,5-piperazinedione
(9023)

(3Z,6Z)-6-Benzylidene-3-(4-(2-(6,7-dimethoxy-1,2,3,4-
10 tetrahydro-2-isoquinolyl)ethyl)benzylidene)-1-methyl-2,5-
piperazinedione (9115)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-
isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-methyl-
15 2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride
(9051)

N-(4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-
isoquinolyl)methylphenyl)-3-((3Z,6Z)-6-benzylidene-1-methyl-
20 2,5-dioxo-3-piperazinylidene)methylbenzamide (9128)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-
3-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-
piperazinylidene)methylbenzamide (9136)

25 N-(2-(3,4-Dimethoxyphenethyl)methylamino)ethyl)-3-((3Z,6Z)-
6-benzylidene-1-methyl-2,5-dioxo-3-
piperazinylidene)methylbenzamide (9137)

N-(4-(2-(3,4-Dimethoxyphenethyl)methylamino)ethyl)phenyl)-3-
((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-
piperazinylidene)methylbenzamide (9138)

5 N-(4-(2-(4-Phenyl-1-piperaziny)ethyl)phenyl)-3-((3Z,6Z)-6-
benzylidene-1-methyl-2,5-dioxo-3-
piperazinylidene)methylbenzamide (9083)

10 N-(4-(3-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-
isoquinolyl)propyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-
methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide,
hydrochloride (9161)

15 N-(2-(2,2-Diphenylethyl)methylaminoethyl)-3-((3Z,6Z)-6-
benzylidene-1-methyl-2,5-dioxo-3-
piperazinylidene)methylbenzamide (9163)

20 (3Z,6Z)-6-Benzylidene-3-(4-(4-(2-(6,7-dimethoxy-1,2,3,4-
tetrahydro-2-isoquinolyl)ethyl)benzyloxy)benzylidene)-1-
methyl-2,5-piperazinedione (9176)

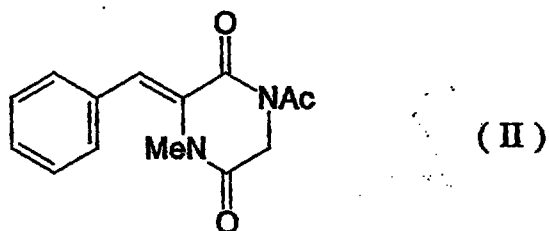
25 (3Z,6Z)-6-Benzylidene-3-(3-(4-(2-(6,7-dimethoxy-1,2,3,4-
tetrahydro-2-isoquinolyl)ethyl)benzyloxy)benzylidene)-1-
methyl-2,5-piperazinedione (9177)

N-(4-((3Z,6Z)-6-Benzylidene-1-methyl-2,5-dioxo-3-
piperazinylidene)methylphenyl)-4-(2-(6,7-dimethoxy-1,2,3,4-
tetrahydro-2-isoquinolyl)ethyl)benzamide (9190)

1- (4- ((3Z,6Z)-6-Benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzoyl)-4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)methylpiperidine (9200)

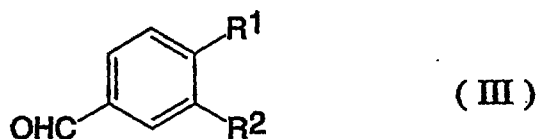
5 Compounds of formula (I) are produced by a process which comprises treating 1-acetyl-3-benzylidene-4-methyl-2,5-piperazinedione, which has the formula (II):

10



with an aldehyde of the following formula (III):

15



wherein R¹ and R² are as defined for formula (I), in an organic solvent in the presence of a base; and, if desired, converting the resulting compound into a pharmaceutically acceptable salt thereof.

20 Suitable bases include caesium carbonate, sodium carbonate, potassium carbonate, sodium hydride, potassium t-butoxide and triethylamine.

25 Suitable organic solvents include dimethylformamide (DMF), tetrahydrofuran (THF) and in the case of potassium t-butoxide, t-butanol and mixtures thereof.

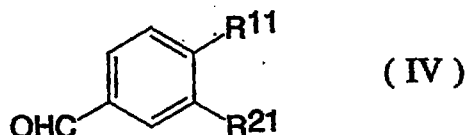
When DMF is used as solvent the temperature is

typically between 0°C and reflux temperature, for example from 80°C to 95°C when caesium carbonate is used as base.

When sodium hydride or potassium t-butoxide is used as the base the reaction mixture is typically warmed from 0°C to room temperature or to 40°C.

The duration of the reaction may be from 1 to 4 hours, for example from 2 to 3 hours.

The compound of formula (II) may be prepared as described in Reference Example 1 which follows. Compounds of formula (III) may be prepared from commercially available starting materials by conventional methods, the particular starting material and method employed depending upon the identity of the aldehyde. For instance, an aldehyde of formula (III) wherein one of R¹ and R² is hydrogen and the other is a group of formula -COR³ as defined above may be prepared by a process which comprises treating a compound of formula (IV):



wherein one or R¹¹ and R²¹ is hydrogen and the other is -COOH, -COX wherein X is a halogen, or -CO(OCOR') wherein R' is C₁-C₆ alkyl, with an amine of formula



wherein R³ is as defined above, in an inert organic solvent; the reaction being performed in the presence of a coupling agent when R¹¹ or R²¹ is -COOH.

Suitable coupling agents for use when R¹¹ or R¹² is -COOH

include 1,3-dicyclohexylcarbodiimide, 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulphonate and 2-chloro-1-methylpyridinium iodide.

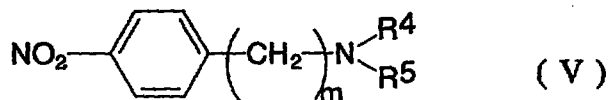
When R^{11} or R^{21} is a group $-COX$ or $-CO(OCOR')$ as defined
5 above, the reaction is optionally conducted in the presence of a base, for instance a tertiary amine such as Et_3N , or pyridine. The solvent is then suitably dichloromethane.

The activated compounds of formula (IV) wherein R^{11} or R^{21} is $-COX$ or $-CO(OCOR')$ may be prepared from the
10 correspondingly compound of formula (IV) wherein R^{11} or R^{21} , respectively, is the carboxy group $-COOH$ by conventional methods which are routine in organic synthesis.

For instance, compounds wherein R^{11} or R^{21} is $-COX$ may be prepared by treating the carboxy compound with a
15 halogenating agent, for example a chlorinating agent such as $SOCl_2$, PCl_3 , oxalyl chloride or PCl_5 .

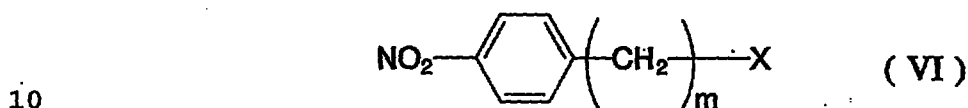
Compounds wherein R^{11} or R^{21} is $-CO(OCOR')$ may be prepared by treating the carboxy compound with a C_1-C_6 alkyl haloformate in the presence of a tertiary amine, for
20 instance $EtOCOC l$ or $iBuOCOC l$ in the presence of Et_3N . In this case it is generally convenient to treat the resulting mixture directly with the amine $H-R^3$.

When R^3 is a group of formula (A) as defined above in which n is 1 and v is 1, the amine $H-R^3$ may be prepared by
25 reducing the corresponding nitro compound of formula (V):

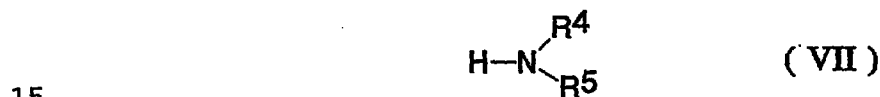


wherein m, R⁴ and R⁵ are as defined above for formula (A).
The reduction may suitably be performed using iron powder
and concentrated hydrochloric acid in methanol, typically
under reflux. Alternatively, the reduction may be performed
5 using hydrogen over a palladium on carbon catalyst.

A compound of formula (V) may be prepared by treating a
compound of the following formula (VI):

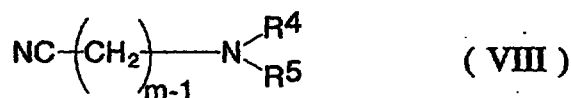


wherein m is as defined in formula (V) and X is a halogen,
with an amine of formula (VII):



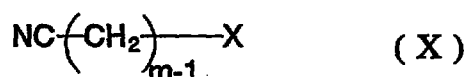
wherein R⁴ and R⁵ are as defined above for formula (A), in an
organic solvent in the presence of base. The organic
solvent is typically DMF or acetonitrile, and the base is
typically K₂CO₃. The temperature is typically from room
20 temperature to 100°C, for instance from 60°C to 80°C. The
duration of the reaction is usually from 1 to 30 hours, for
instance 2 to 24 hours, typically from about 8 hours to
about 12 hours.

When R³ is a group of formula (A) as defined above in
25 which n is 0 and v is 1, the amine H-R³ may be prepared by
reducing the corresponding nitrile of formula (VIII):



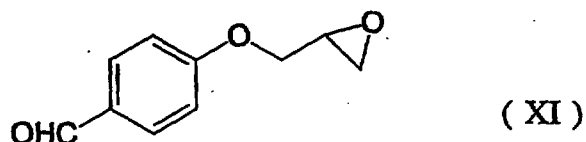
wherein m is 1, 2 or 3 and R⁴ and R⁵ are as defined above for formula (A). The reduction may suitably be performed with LiAlH₄ in ethylene glycol dimethyl ether, at a temperature between 0°C and 40°C, typically warming from 0°C to room temperature, for instance from 0°C to 20°C. Other amines H-R³ may be prepared by analogous methods using known starting materials, or are commercially available products.

A nitrile of formula (VIII) may be prepared by treating a compound of formula (VII) as defined above with a compound of formula (X):



wherein X is a halogen and m is as defined for formula (VIII), in an organic solvent in the presence of a base. The solvent is suitably acetonitrile. The base may be, for example, K₂CO₃. The reaction is typically carried out at the reflux temperature of the solvent for a period of from 1 hour to 30 hours, for instance from 1 hour to 20 hours.

An aldehyde of formula (III) wherein R¹ is a group of formula (D) may be prepared by treating the compound of formula (XI):



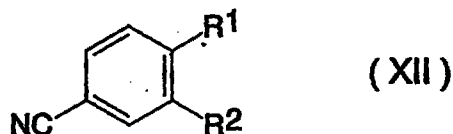
with an amine of formula H-N(R¹⁰)(R¹¹) wherein R¹⁰ and R¹¹ are

as defined for formula (D), in a suitable solvent. Such solvents include aqueous THF. The compound of formula (XI) may in turn be prepared by treatment of 4-hydroxybenzaldehyde with 1.5M sodium hydroxide followed by epichlorohydrin. This reaction is typically performed at about 50°C for about 5 hours.

The aldehyde of formula (III) wherein R¹ is a group of formula (E) in which r is 2 (compound 5.1) may be prepared as described in Reference Example 5 which follows.

Corresponding aldehydes in which r in formula (E) is 1 or 3 may be prepared by an analogous process, replacing the 4-(2-bromoethyl)benzoic acid used as starting material by 4-bromomethylbenzoic acid or 4-(3-bromopropyl)benzoic acid, respectively.

An aldehyde of formula (III) may also be prepared by treating the corresponding nitrile of formula (XII)



with formic acid and Raney nickel, for instance as described in Reference Example 7 which follows.

Compounds of formula (I) may be converted into pharmaceutically acceptable salts, and salts may be converted into the free compound, by conventional methods.

Suitable salts include salts with pharmaceutically acceptable inorganic or organic acids. Examples of inorganic acids include hydrochloric acid, sulphuric acid and orthophosphoric acid. Examples of organic acids include

p-toluenesulphonic acid, methanesulphonic acid, mucic acid and succinic acid.

Cancer cells which exhibit multi-drug resistance, referred to as MDR cells, display a reduction in intracellular drug accumulation compared with the corresponding drug-sensitive cells. Studies using in vitro derived MDR cell lines have shown that MDR is often associated with increased expression of a plasma membrane glycoprotein (P-gp) which has drug binding properties. P-gp is thought to function as an efflux pump for many hydrophobic compounds, and transfection studies using cloned P-gp have shown that its overexpression can confer the MDR phenotype on cells: see, for example, Ann. Rev. Biochem 58 137-171 (1989).

A major function of P-gp in normal tissues is to export intracellular toxins from the cell. There is evidence to suggest that overexpression of P-gp may play a clinical role in multi-drug resistance. Increased levels of P-gp mRNA or protein have been detected in many forms of human cancers - leukaemias, lymphomas, sarcomas and carcinomas. Indeed, in some cases P-gp levels have been found to be increased in tumour biopsies obtained after relapse from chemotherapy.

Inhibition of P-gp function in P-gp mediated MDR has been shown to lead to a net accumulation of anti-cancer agent in the cells. For example, Verapamil a known calcium channel blocker was shown to sensitise MDR cells to Vinca alkaloids in vitro and in vivo: Cancer Res., 41, 1967-1972 (1981). The proposed mechanism of action involves

competition with the anti-cancer agent for binding to the P-gp. A range of structurally unrelated resistance-modifying agents acting by this mechanism have been described such as tamoxifen (Nolvadex:ICI) and related compounds, and
5 cyclosporin A and derivatives.

Compounds of formula I and their pharmaceutically acceptable salts (hereinafter referred to as "the present compounds") have been found in biological tests to have activity in modulating multi-drug resistance. The results
10 are set out in Example 3 which follows. The present compounds may therefore be used as multi-drug resistance modifying agents, also termed resistance-modifying agents, or RMAs. The present compounds can modulate, e.g. reduce, or eliminate multi-drug resistance.

15 The present compounds can therefore be used in a method of potentiating the cytotoxicity of an agent which is cytotoxic to a tumour cell. Such a method comprises, for instance, administering one of the present compounds to the tumour cell whilst the tumour cell is exposed to the
20 cytotoxic agent in question. The therapeutic effect of a chemotherapeutic, or antineoplastic, agent may thus be enhanced. The multi-drug resistance of a tumour cell to a cytotoxic agent during chemotherapy may be reduced or eliminated.

25 The present compounds can also be used in a method of treating a disease in which the pathogen concerned exhibits multi-drug resistance, for instance multi-drug resistant forms of malaria (Plasmodium falciparum), tuberculosis,

leishmaniasis and amoebic dysentery. Such a method comprises, for instance, administering one of the present compounds with (separately, simultaneously or sequentially) the drug to which the pathogen concerned exhibits multi-drug resistance. The therapeutic effect of the drug may thus be enhanced.

A human or animal patient harbouring a tumour may be treated for resistance to a chemotherapeutic agent by a method comprising the administration thereto of one of the present compounds. The present compound is administered in an amount effective to potentiate the cytotoxicity of the said chemotherapeutic agent. Examples of chemotherapeutic or antineoplastic agents which are preferred in the context of the present invention include Vinca alkaloids such as vincristine and vinblastine; anthracycline antibiotics such as daunorubicin and doxorubicin; mitoxantrone; actinomycin D; taxanes e.g. taxol; epipodophyllotoxins e.g. etoposide and plicamycin.

In addition, a human or animal patient suffering from a disease in which the responsible pathogen exhibits multi-drug resistance may be treated for resistance to a therapeutic agent by a method comprising the administration thereto of one of the present compounds.

Examples of such disease include multi-drug resistant forms of malaria (Plasmodium falciparum), tuberculosis, leishmaniasis and amoebic dysentery.

MDR modulators also have utility in the delivery of drugs across the blood-brain barrier, and in the treatment

of AIDS and AIDS-related complex. The present compounds can therefore be used in a method of facilitating the delivery of drugs across the blood brain barrier, and in the treatment of AIDS or AIDS-related complex. A human or
5 animal patient in need of such treatment may be treated by a method comprising the administration thereto of one of the present compounds.

The present compounds can be administered in a variety of dosage forms, for example orally such as in the form of
10 tablets, capsules, sugar- or film-coated tablets, liquid solutions or suspensions or parenterally, for example intramuscularly, intravenously or subcutaneously. The present compounds may therefore be given by injection or infusion.

15 The dosage depends on a variety of factors including the age, weight and condition of the patient and the route of administration. Typically, however, the dosage adopted for each route of administration when a compound of the invention is administered alone to adult humans is 0.001 to
20 50 mg/kg, most commonly in the range of 0.01 to 5 mg/kg, body weight. Such a dosage may be given, for example, from 1 to 5 times daily by bolus infusion, infusion over several hours and/or repeated administration.

A piperazinedione derivative of formula (I) or, a
25 pharmaceutically acceptable salt thereof is formulated for use as a pharmaceutical or veterinary composition also comprising a pharmaceutically or veterinarily acceptable carrier or diluent. The compositions are typically prepared

following conventional methods and are administered in a pharmaceutically or veterinarily suitable form. An agent for use as a modulator of multi-drug resistance comprising any one of the present compounds is therefore provided.

5 For example, the solid oral forms may contain, together with the active compound, diluents such as lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants such as silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; 10 binding agents such as starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose, or polyvinyl pyrrolidone; disintegrating agents such as starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs, sweeteners; wetting agents such as 15 lecithin, polysorbates, lauryl sulphates. Such preparations may be manufactured in known manners, for example by means of mixing, granulating, tableting, sugar coating, or film-coating processes.

 Liquid dispersions for oral administration may be 20 syrups, emulsions and suspensions. The syrups may contain as carrier, for example, saccharose or saccharose with glycerol and/or mannitol and/or sorbitol. In particular, a syrup for diabetic patients can contain as carriers only products, for example sorbitol, which do not metabolise to 25 glucose or which only metabolise a very small amount to glucose. The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose or polyvinyl

alcohol.

Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier such as sterile water, olive oil, ethyl oleate, glycols such as propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. Some of the present compounds are insoluble in water. Such compounds may be encapsulated within liposomes.

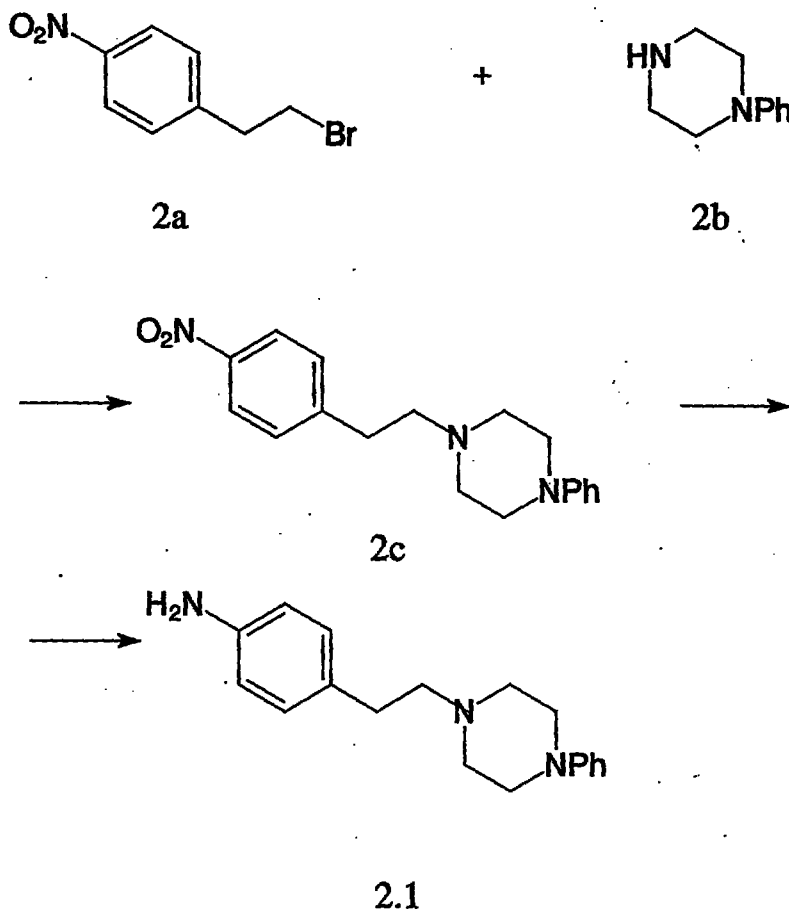
The invention will be further illustrated in the Examples which follow.

Reference Example 1: 1-acetyl-3-benzylidene-4-methyl-2,5-piperazinedione

1,4-Diacetyl-2,5-piperazinedione (described by Marcuccio and Elix in Aust. J. Chem, 1984, 37, 1791) (25.0g, 126 mmol) was treated at 130°C in DMF (200ml) with triethylamine (17.6ml, 126 mmol) and benzaldehyde (13.0 ml, 126 mmol). After 4 hours the mixture was cooled to room temperature and poured into EtOAc (1000 ml) and washed 3 times with brine. Any solid formed at this stage was filtered off. The filtrate was dried (MgSO₄) and the solvent removed in vacuo. The residue was recrystallised from EtOAc:Hexane to give 11.78g (38%) of 1-acetyl-3-benzylidene-2,5-piperazinedione.

The latter compound was treated with NaH and MeI in DMF: THF (1:5) at a temperature of 0°C and allowed to warm to room temperature to give the title compound in 57% yield.

Reference Example 2: Preparation of amines H-R³ via substituted nitrobenzene

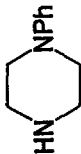
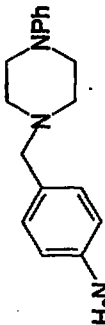
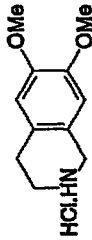
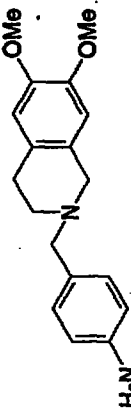
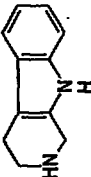
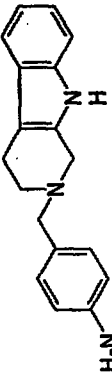
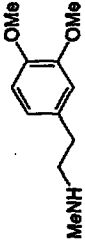
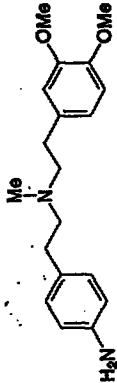
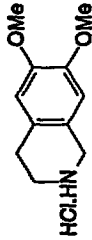
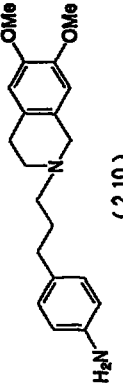


4-Bromoethyl nitrobenzene (2a) was treated with 1-phenylpiperazine (2b) in the presence of K₂CO₃ in DMF at 80°C for 8 hours. Compound 2c was obtained in 58% yield. 2c was then reduced by treatment with iron powder and concentrated HCl in MeOH under reflux for 3 hours. The desired amine 2.1 was obtained in 40% yield.

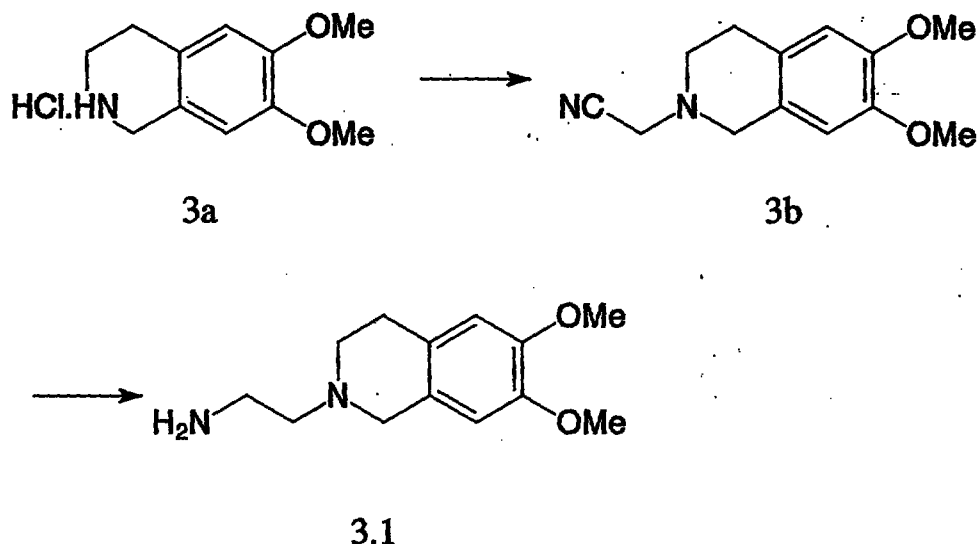
Following an analogous synthetic route, but using where necessary 4-bromomethylnitrobenzene or 4-(3-bromopropyl)nitrobenzene in place of 4-(2-bromoethyl)nitrobenzene (2a), and replacing 4-

phenylpiperazine (2b) by the appropriate compound of formula (VII), further amines H-R³ were prepared as shown in Table 1. The conditions employed at each stage in the preparation of these further amines were as described above for amine 2.1, 5 except for amine 2.9 where the reduction step was conducted using hydrogen at 50 p.s.i. over palladium on carbon, in ethanol. This reduction was performed for 2.5 hours at room temperature. In the case of amine 2.4, reduction of the 10 nitro group was accompanied by hydrogenolysis of the 4-chlorophenyl group to give the amine 2.4.

TABLE 1 continued

1		 (2.6)
1	 HCl.HN	 (2.7)
1		 (2.8)
2	 MeNH	 (2.9)
3	 HCl.HN	 (2.10)

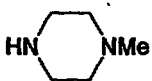
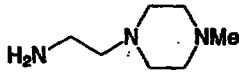
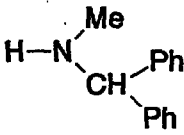
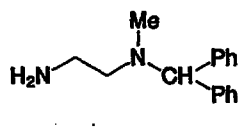
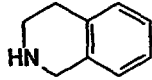
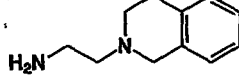
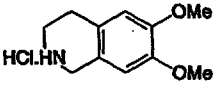
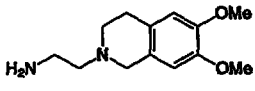
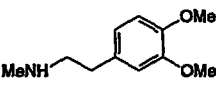
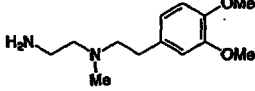
Reference Example 3: Preparation of amines H-R³ via substituted nitrile



6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (3a) was treated with chloroacetonitrile in the presence of K₂CO₃ in acetonitrile under reflux for 24 hours. Compound 3b was obtained in 92% yield. 3b was then treated with LiAlH₄ in ethylene glycol dimethyl ether at room temperature overnight. The temperature was then raised to 40°C and the reaction continued for 30 minutes. The desired amine 3.1 was obtained in 98% yield.

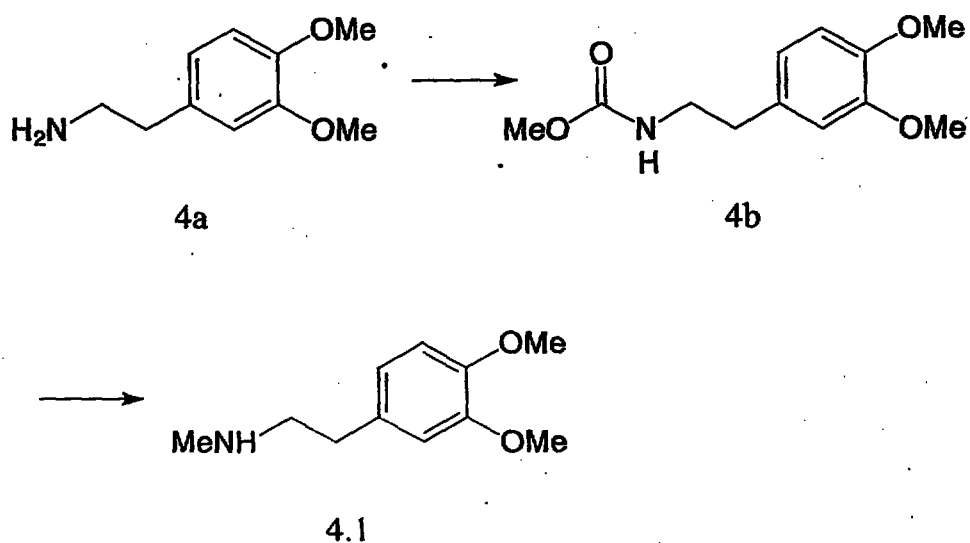
Following an analogous synthetic route, but modifying the conditions of the first step where necessary and replacing compound 3a by the appropriate compound of formula VII, the further amines H-R³ listed in Table 2 were prepared:

TABLE 2

Compound of formula VII	Conditions of first step	Amine H-R ³ (No)
	K ₂ CO ₃ , ClCH ₂ CN, CH ₃ CN reflux 20h	 (3.2)
	K ₂ CO ₃ , ClCH ₂ CN, CH ₃ CN reflux, 24h	 (3.3)
	K ₂ CO ₃ , ClCH ₂ CN, CH ₃ CN reflux 24h	 (3.4)
	K ₂ CO ₃ , ClCH ₂ CN, CH ₃ CN reflux 24h	 (3.5)
	K ₂ CO ₃ , ClCH ₂ CN CH ₃ CN reflux 4h	 (3.6)

Reference Example 4: Preparation of further amines H-R³

1. **(3,4-Dimethoxyphenethyl)methylamine**

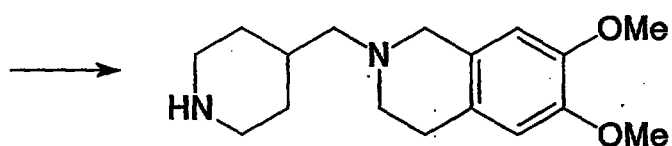
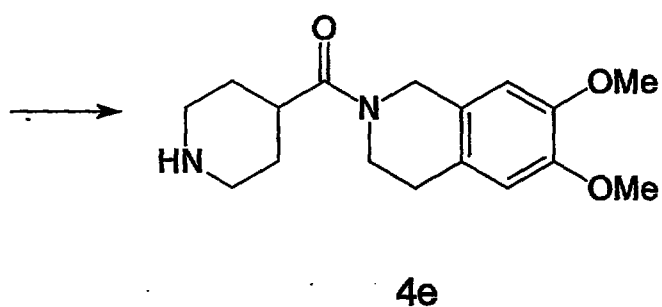
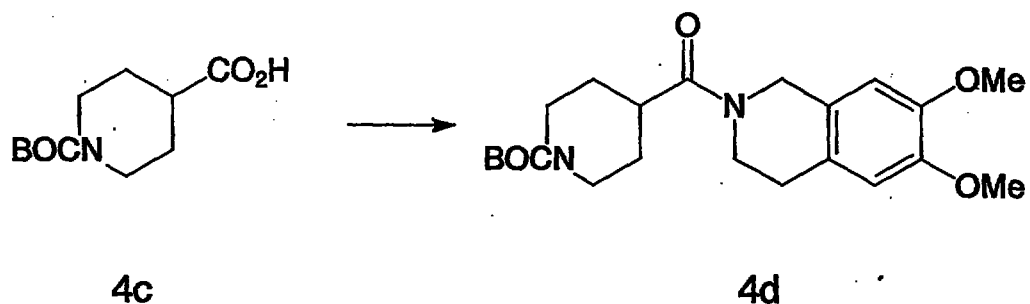


2-(3,4-Dimethoxyphenyl)ethylamine (4a) was treated with MeOCOCl in the presence of triethylamine in CH₂Cl₂ at -78°C and allowed to warm to 0°C overnight. Compound 4b was obtained in 9% yield. 4b was treated with LiAlH₄ in THF at a temperature of 0°C and allowed to warm to room temperature overnight. Compound 4.1, which is the starting amine used to prepare compound 2.9 in Reference Example 2, was obtained in 91% yield.

10 2. H₂N-(CH₂)₂-NMe-CH₂CHPh₂

2,2-Diphenylethylamine was treated with (CF₃CO)₂O in Et₂O at 0°C for 1 hour. The resulting compound (Ph)₂-CH-CH₂-NHCOCF₃, obtained in quantitative yield, was treated with KH in THF at 0°C followed by MeI and 18-crown-6 at room temperature for 24 hours to give (Ph)₂-CH-CH₂-NMeCOCF₃ in 91% yield. The latter compound was treated with 2M NaOH in methanol under reflux for 2 hours to give (Ph)₂-CH-CH₂NHMe in 81% yield, which in turn was treated with chloroacetonitrile in the presence of K₂CO₃ in acetonitrile under reflux for 24 hours to give (Ph)₂-CH-CH₂-NMe-CH₂CN in 83% yield. Reduction of this compound with LiAlH₄ in ethylene glycol dimethyl ether at room temperature for 2 hours gave the title amine, which is compound 4.2, in 90% yield.

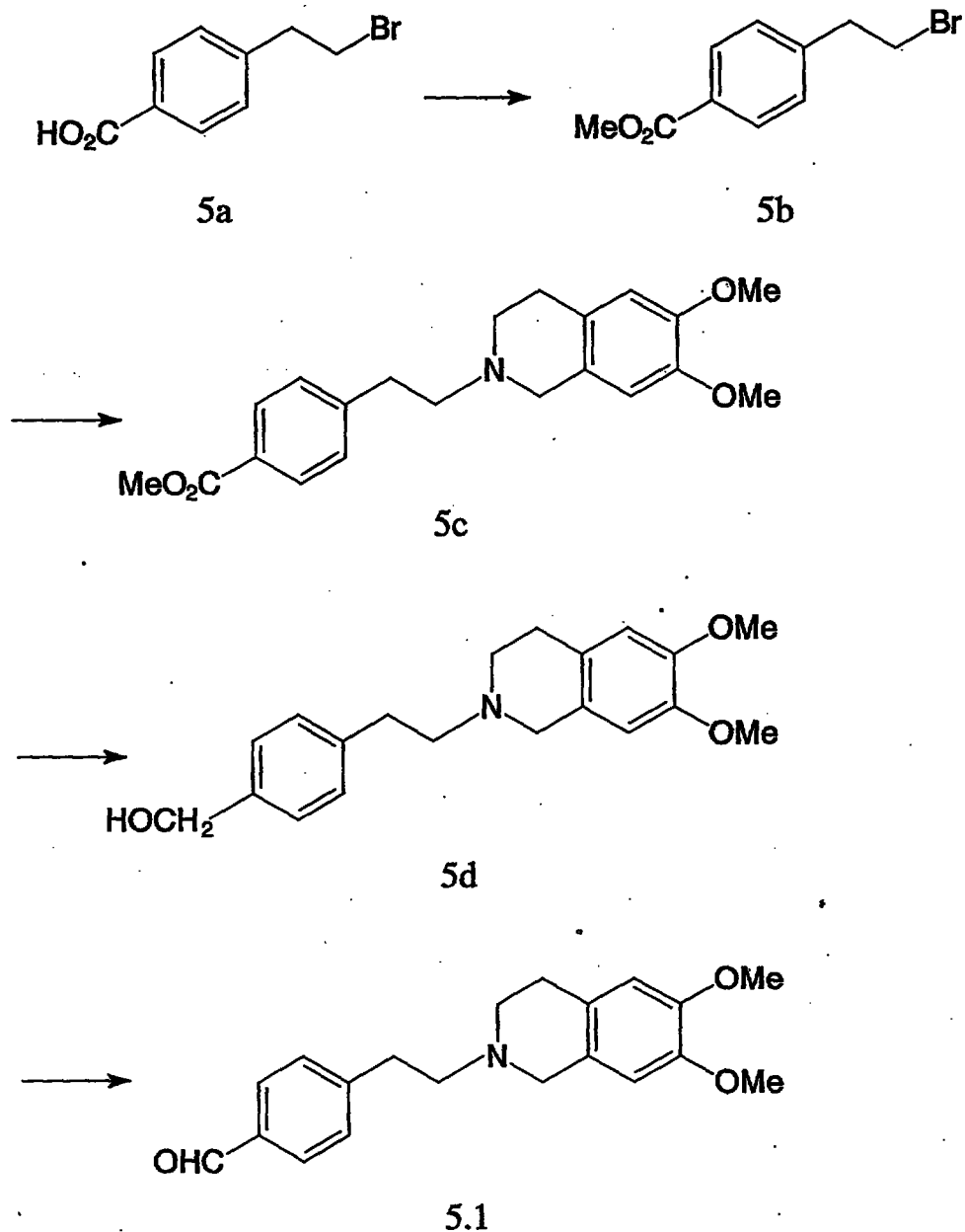
3. Amine 4.3



Compound 4c was treated with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline in CH_2Cl_2 at 0°C in the presence of 2-chloro-1-methylpyridinium iodide and triethylamine. The solution was allowed to warm to room temperature overnight. Compound 4d, which was obtained in 93% yield, was treated with trifluoroacetic acid in dichloromethane at room temperature for 30 minutes. Compound 4e was obtained in 10% yield after trituration with acetone. Compound 4e was treated with LiAlH_4 in THF at 10°C and left overnight to

warm to room temperature. Compound 4.3 was obtained in 75% yield.

Reference Example 5: Preparation of aldehyde 5.1



Compound 5a was treated with excess CH_2N_2 in THF at 0°C for 7 hours. 5b was obtained in 98% yield. Compound 5b was then treated with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride in DMF in the presence

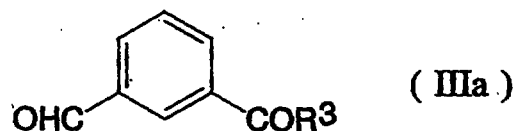
of K_2CO_3 at room temperature for 5 days to give 5c in 56% yield. Compound 5c was reduced by treatment with $LiAlH_4$ in THF at room temperature for 1 hour to give 5d (80% yield), which in turn was treated with pyridinium chlorochromate (PCC) buffered with NaOAc in CH_2Cl_2 at room temperature for 16 hours. Compound 5.1 was obtained in 25% yield.

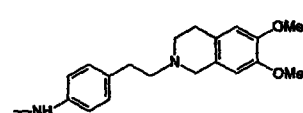
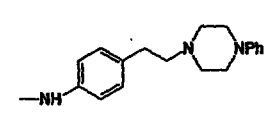
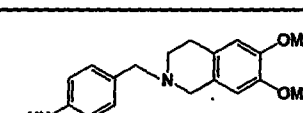
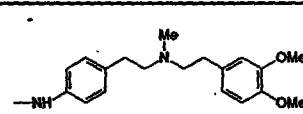
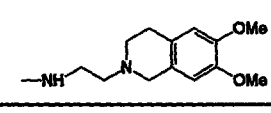
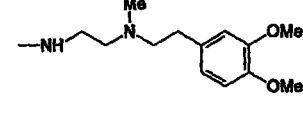
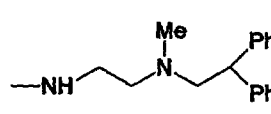
Reference Example 6: Preparation of aldehydes of
formula (III)

10 Method 1

The aldehydes of formula IIIa listed in Table 3 below were prepared by treating 3-formylbenzoic acid with the appropriate amine $H-R^3$ (a compound prepared in one of Reference Examples 2 and 3) in CH_2Cl_2 in the presence of 2-chloro-1-methylpyridinium iodide at $0^\circ C$. The reaction was 15 allowed to warm to room temperature overnight.

TABLE 3: Aldehydes of formula IIIa



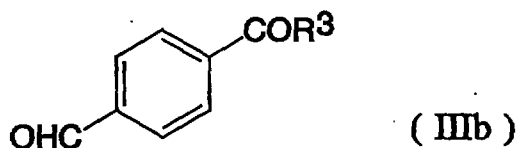
Aldehyde No.	R ³	Corresponding amine H-R ³
6.1		2.2
6.2		2.1
6.3		2.7
6.4		2.9
6.5		3.5
6.6		3.6
6.29		4.2

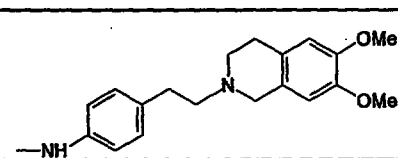
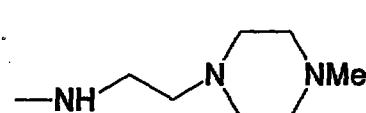
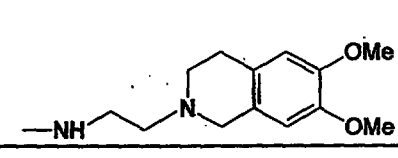
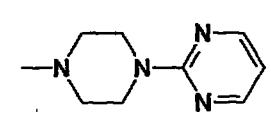
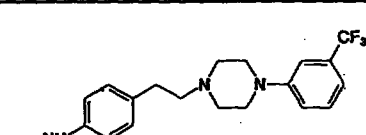
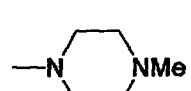
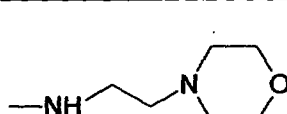
Method 2

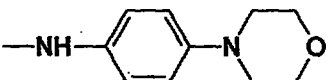
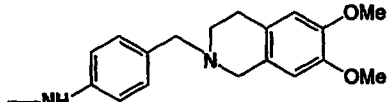
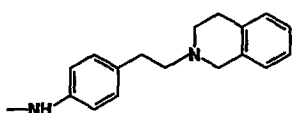
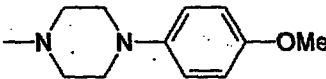
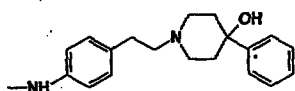
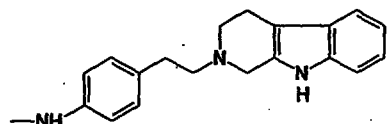
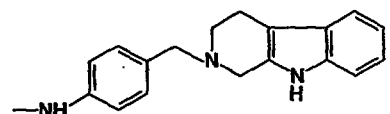
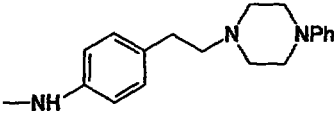
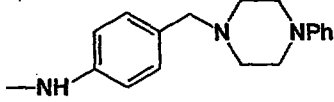
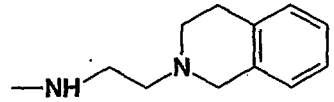
The aldehydes of formula IIIb listed in Table 4 below were prepared by treating 4-formylbenzoyl chloride with the appropriate amine H-R³ in CH₂Cl₂ in the presence of triethylamine at 0°C. In the case of aldehyde 6.32, 4-carboxybenzaldehyde was used in place of 4-formylbenzoyl

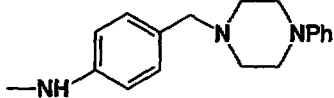
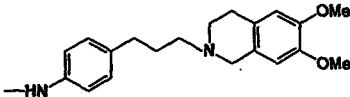
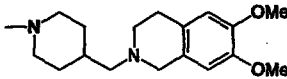
chloride and 2-chloro-1-pyridinium iodide was additionally present in the reaction mixture. The reaction was allowed to warm to room temperature overnight. Each amine was either a compound prepared in one of Reference Examples 2 and 3, or a commercially available product.

TABLE 4: Aldehydes of formula IIIb



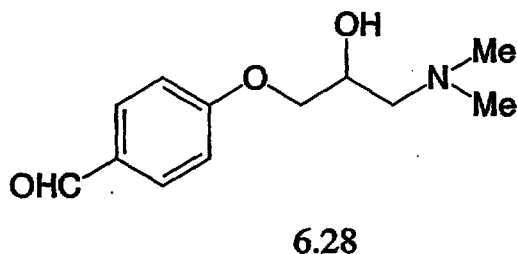
Aldehyde No.	R ³	Corresponding amine H-R ³
6.7		2.2
6.8		3.2
6.9		3.1
6.10		Commercial product
6.11		Commercial product
6.12		Commercial product
6.13		Commercial product

6.14		Commercial product
6.15		2.7
6.16		2.3
6.17	$\text{—NH—CH}_2\text{CH=CH}_2$	Commercial product
6.18		Commercial product
6.19	$\text{—NH—CH}_2\text{CH}_2\text{—N(CH}_3\text{)CHPh}_2$	3.3
6.20		2.4
6.21		2.5
6.22		2.8
6.23		2.1
6.24		2.6
6.25		3.4

6.26		Commercial product
6.27		2.10
6.32		4.3

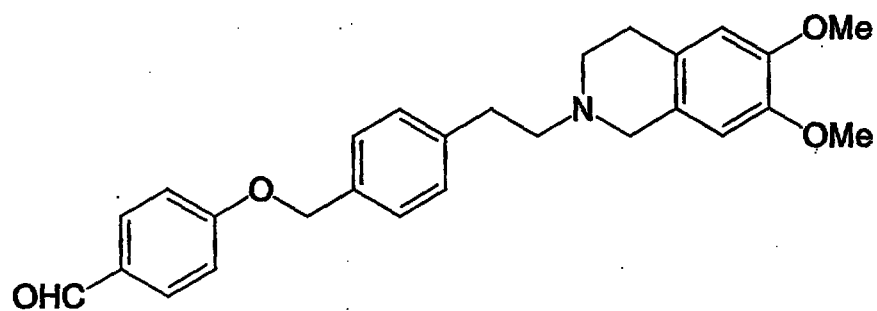
Method 3

By treating the compound of formula (XI) defined above in THF with aqueous HNMe_2 at room temperature for about 2 hours, the following aldehyde of formula (III) was produced in 91% yield:

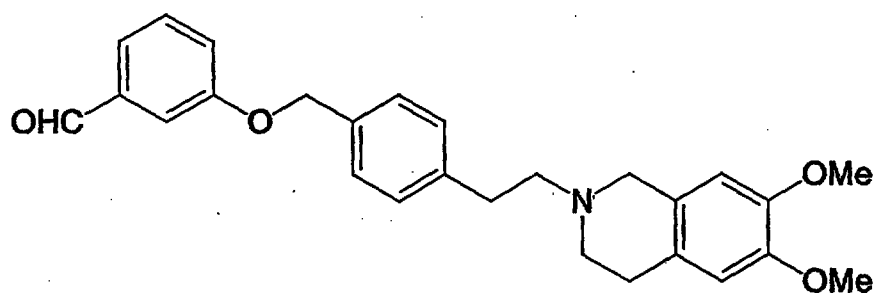


Method 4

Compound 5d, described in Reference Example 5, was treated with 4-hydroxybenzaldehyde in THF at 0°C in the presence of triphenylphosphine and diethyl azidocarboxylate to give the following aldehyde of formula (III) in 40% yield:



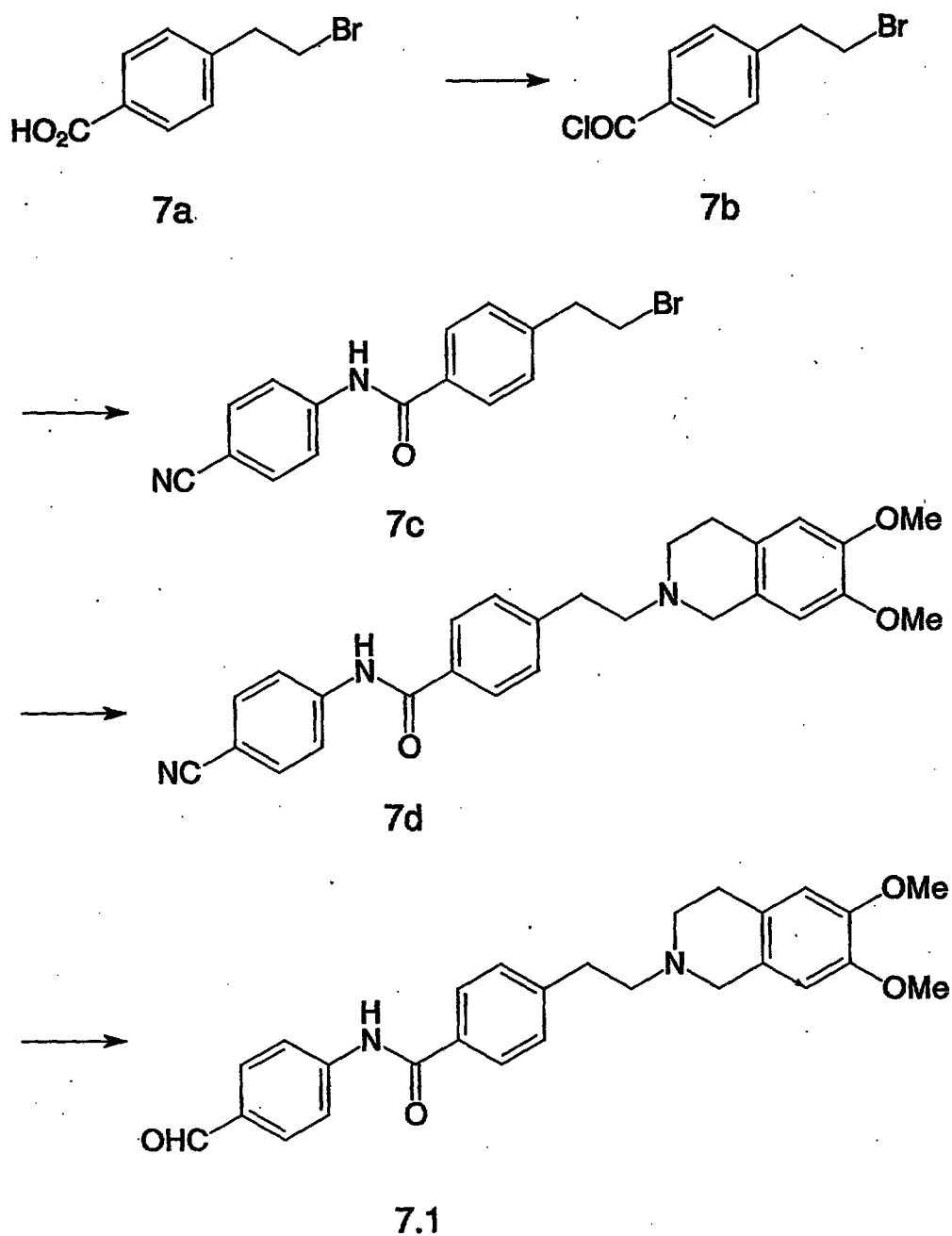
The above process was repeated, but using 3-hydroxybenzaldehyde in place of 4-hydroxybenzaldehyde. The following aldehyde of formula (III) was produced in 50% yield:



6.31

Reference Example 7:

Preparation of aldehyde 7.1



7a was treated with an excess of SOCl_2 and a catalytic amount of DMF in toluene under reflux for 4 hours. The resulting compound 7b was treated with 4-aminobenzonitrile in CH_2Cl_2 in the presence of triethylamine at 0°C . The reaction mixture was warmed to room temperature overnight. Flash

chromatography (1:1 hexane:ethyl acetate) gave 7c in 39% yield, which was treated with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline in the presence of K_2CO_3 in acetonitrile under reflux for 18 hours. Flash

5 chromatography (10% methanol in ethyl acetate) gave 7d in 25% yield. 7d was treated with formic acid and a 50% slurry in water of Raney nickel under reflux for 2 hours. The aldehyde 7.1 was obtained in 71% yield.

10 Example 1: Preparation of compounds of formula (I)

By treating 1-acetyl-3-benzylidene-4-methyl-2,5-piperazinedione, as described in Reference Example 1, with an aldehyde prepared in one of Reference Examples 5, 6 or 7 in DMF in the presence of Cs_2CO_3 , at a temperature of between
15 80 and 90°C, the compounds of formula I listed in Table 5 were prepared:

TABLE 5

Aldehyde N°	Compound of formula I
6.7	9006
6.8	9007
6.9	9008
6.10	9022
6.28	9023
6.11	9049
6.1	9051
6.12	9052
6.13	9053
6.14	9054
6.15	9064
6.16	9065
6.17	9070
6.18	9071
6.19	9076
6.20	9079
6.21	9080
6.2	9083
6.22	9096
6.23	9103
6.24	9104
5.1	9115
6.25	9116
6.26	9117
6.3	9128
6.5	9136
6.6	9137
6.4	9138
6.27	9161
6.29	9163
6.30	9176

6.31	9177
7.1	9190
6.32	9200

5 Compounds 9052, 9071, 9076, 9116, 9104, 9053, 9054,
9064 and 9051 were converted in a final step to their
hydrochloride salts, by bubbling gaseous HCl through a
solution of each compound in THF. (For these compounds the
hydrochloride salt rather than the free base was used in the
10 biological testing described in Example 3).

Example 2: Pharmaceutical Composition

Tablets, each weighing 0.15 g and containing 25 mg of a
compound of the invention can be manufactured as follows:

15 Composition for 10,000 tablets

compound of the invention (250 g)
lactose (800 g)
corn starch (415 g)
talc powder (30 g)
20 magnesium stearate (5 g)

The compound of the invention, lactose and half of the
corn starch are mixed. The mixture is then forced through a
sieve 0.5 mm mesh size. Corn starch (10 g) is suspended in
warm water (90 ml). The resulting paste is used to
25 granulate the powder. The granulate is dried and broken up
into small fragments on a sieve of 1.4 mm mesh size. The
remaining quantity of starch, talc and magnesium stearate is
added, carefully mixed and processed into tablets.

Example 3: Testing of compounds (I) as modulators of

MDR

Materials and Methods

The EMT6 mouse mammary carcinoma cell line and the MDR
5 resistant subline AR 1.0 were cultured in RPMI 1640 medium
containing 10% foetal calf serum and 2mM glutamine at 37°C in
5% CO₂. Cells were passaged between 1 in 200 and 1 in 2000
in the case of the parental cell line and between 1 in 20
and 1 in 200 in the case of the MDR resistant subline, after
10 trypsinisation (0.25% trypsin, 0.2gl⁻¹, EDTA).

1. Drug accumulation assay

AR 1.0 cells were seeded into 96 well opaque culture
plates (Canberra Packard). The assay medium contained a
mixture of tritiated Daunorubicin (DNR), a cytotoxic agent,
15 and unlabelled DNR (0.3 μ Ci/ml; 2 μ M). Compounds of formula
I were serially diluted in assay medium over a range of
concentrations from 5 nM to 100 μ M. The cells were
incubated at 37°C for 1 hr before washing and determination
of cell associated radioactivity. Results were expressed as
20 % maximum accumulation where 100% accumulation is that
observed in the presence of the known RMA verapamil at
100 μ M. Where possible an IC₅₀ was determined.

The results are set out in the following Table 6.

TABLE 6

Compound No.	IC ₅₀ (μM) Accumulation	Max Accumulation
9006	0.4	
9007		30%
9008	3.0	
9022	7.0	
9023		30%
9049		20%
9051	0.15	
9052	100	
9053	50	
9054		32%
9064	0.3	
9065	6	
9070	5	
9071	6	
9076		44%
9079	80	
9080		18%
9083	2	
9096		20%
9103		20%
9104	5	
9115	5	
9116	4	
9117	5	
9128	3	
9136	0.9	
9137	2	
9138	0.8	
9161		20%
9163	2.0	

9176	1.000	
9177	1.750	
9190	0.350	
9200	1.700	

5

2. Potentiation of Doxorubicin toxicity

Compounds of formula (I) were examined for their
10 ability to potentiate the toxicity of doxorubicin in AR 1.0
cells. In initial proliferation assays compounds were
titrated against a fixed concentration of doxorubicin (0.86
 μM) which alone is non-toxic to AR 1.0 cells. After a four
day incubation with doxorubicin proliferation was measured
15 using the colorimetric sulphorhodamine B assay (Skehan et
al; J.Natl. Cancer Inst. 82 pp 1107-1112 (1990)). The
results are shown in Table 7.

Compounds which were shown to be able to sensitise AR
1.0 cells to 0.86 μM doxorubicin without high innate
20 toxicity were selected for further study. Cells were
cultured for four days with a titration of doxorubicin (0.01
nm - 50 μM) in the presence of a fixed concentration of each
compound. Proliferation was quantified as described by
Skehan et al, loc cit. The IC_{50} (concentration required to
25 reduce proliferation to 50% of the untreated controls) for
doxorubicin alone and with each compound were derived and
used to calculate the potentiation index (PI):

$$\text{PI} = \frac{\text{IC}_{50} \text{ for Doxorubicin alone}}{\text{IC}_{50} \text{ for Doxorubicin plus RMA}}$$

The results are shown in Table 8:

TABLE 7

Compound No.	Compound toxicity (IC ₅₀ μ M)	Toxicity with cytotoxic agent (IC ₅₀ μ M)
9006	2	0.04
9008	10	2.0
9022	35	0.8
9023	10	5.0
9049	2	0.2
9051	2	0.01
9053	40	4.0
9054	50	30
9064	2	0.01
9065	2	0.2
9070	40	4.0
9071	6	0.2
9079	2	1.7
9083	3	0.1
9104	40	0.05
9115	60	2.0
9116	8	1
9117	8	3
9128	10	2
9136	13	2
9137	12	4.5
9138	8	1.0
9163	10	0.5
9176	10	0.2
9177	15	0.5
9190	15	0.05
9200	13	0.8

TABLE 8

Potentialiation Indices	
<u>Compound No.</u>	<u>Potentialiation index</u> (RMA at 1 μ M)
9006	1000
9022	5
9049	15
9051	2000
9064	750
9065	15
9071	4
9079	3
9104	17
9136	25
9138	333
9163	6.7
9176	300.0
9177	75.0
9190	75.0 (measured at 0.3 μ M)
	10.0 (measured at 0.1 μ M)
	3.3 (measured at 0.03 μ M)
	1.4 (measured at 0.01 μ M)

Example 4: Characterisation of the present compounds

The compounds and salts prepared in the preceding Examples were characterised by mass spectroscopic, microanalytical and proton nmr techniques. The results are set out in Tables 9 and 10:

TABLE 9

No.	Mol. Formula	Mass spec data		¹ H nmr data		Microanalysis		
		mass (intensity)	mode	solvent/ field	δ	Calc	Found	
9023	C ₂₃ H ₂₇ N ₃ O ₄	422(100)	ESI	CDCl ₃ / 400MHz	2.35 (6H,s), 2.41 (1H,dd), 2.57 (1H,dd), 2.99 (3H,s), 4.02 (2H,m), 4.08 (1H,m), 7.00-7.03 (3H,m), 7.28- 7.42 (8H,m), 7.95 (1H,b)	C 68.39 H 6.46 N 9.97	68.09 6.44 9.81	68.26 6.42 9.81
9052	C ₂₅ H ₂₆ N ₄ O ₃ HCl	431(100), 331(50)	FAB+	d ₆ -DMSO/ 300MHz	2.75 (3H,s), 2.88 (3H,s), 3.10-3.30 (4H,bs), 3.35 (4H,bs), 6.85 (1H,s), 7.12 (1H,s), 7.32-7.40 (5H,m), 7.48 (2H,d), 7.65 (2H,d), 10.30 (1H,bs)	C 64.3 H 5.85 N 12.0	64.3 5.80 11.6	
9054	C ₃₀ H ₂₈ N ₄ O ₄ HCl	509(40), 508(45), 331(35), 178(100)	CI	d ₆ -DMSO/ 300MHz	2.96 (3H,s), 3.40 (4H,bs), 3.99 (4H,bs), 6.98 (1H,s), 7.20 (1H,s), 7.43-7.56 (7H,m), 7.82 (2H,d), 7.89 (2H,d), 8.12 (2H,d), 10.43 (1H,s), 10.83 (1H,s)	C 66.1 H 5.35 N 10.3	66.0 5.30 10.3	

TABLE 10

No.	Mol. Formula	Mass spec data		¹ H nmr data	
		mass (intensity)	mode	solvent/field	δ
9006	C ₃₉ H ₃₈ N ₂ O ₅	643(100)	ESI	d ₆ -DMSO/400MHz	2.87 (3H,s), 2.89-3.23 (8H,m), 3.73 (2x3H,s), 4.20-4.54 (2H,m), 6.78 (1H,s), 6.82 (1H,s), 6.88 (1H,s), 7.09 (1H,s), 7.20-8.07 (13H,m), 10.30 (1H,s), 10.62 (1H,s), 11.01 (1H,bs)
9007	C ₂₇ H ₃₁ N ₅ O ₃	474(100)	ESI	CDCl ₃ /400MHz	2.35 (3H,s), 2.49-2.73 (10H,m), 3.02 (3H,s), 3.59 (2H,m), 7.07 (1H,s), 7.28-7.44 (6H,m), 7.50 (2H,d), 7.86 (2H,d)
9008	C ₃₃ H ₃₄ N ₄ O ₅	567(100)	ESI	CDCl ₃ /400MHz	2.76-2.90 (6H,m), 3.02 (3H,s), 3.61-3.70 (4H,m), 3.85 (2x3H,s), 6.55 (1H,s), 6.64 (1H,s), 6.94 (1H,bs), 7.07 (1H,s), 7.27-7.43 (6H,m), 7.47 (2H,d), 7.85 (2H,d)
9022	C ₂₈ H ₂₆ N ₆ O ₃	495 (20), 331(100)	ESI	CDCl ₃ /400MHz	3.02 (3H,s), 3.35-4.07 (8H,m), 6.56 (1H,t), 7.08 (1H,s), 7.29-7.43 (6H,m), 7.50 (2H,d), 7.55 (2H,d), 8.83 (2H,d)
9049	C ₃₉ H ₃₆ F ₃ N ₅ O ₃	680(100)	ESI	CDCl ₃ /400MHz	2.64-2.75 (6H,m), 2.87 (2H,m), 3.04 (3H,s), 3.23-3.31 (4H,m), 7.04-7.10 (3H,m), 7.12 (1H,s), 7.23-7.42 (9H,m), 7.55 (2H,d), 7.59 (2H,d), 7.78 (1H,s), 7.96 (2H,d)
9051	C ₃₉ H ₃₈ N ₄ O ₅ .HCl	643(22), 348(30), 206(100)	CI	d ₆ -DMSO/400MHz	2.86 (3H,s), 2.92-3.18 (6H,m), 3.36-3.48 (2H,m), 3.73 (2x3H,s), 4.22-4.55 (2H,m), 6.78 (1H,s), 6.82 (1H,s), 6.89 (1H,s), 7.09 (1H,s), 7.28-8.14 (13H,m) 10.29 (1H,s), 10.69 (2H,bs)

No.	Mol. Formula	Mass spec data		¹ H nmr data	
		mass (intensity)	mode	solvent/field	δ
9053	C ₃₆ H ₂₈ N ₄ O ₄ .HCl	461(100), 331(10)	FAB+	d ₆ -DMSO/ 300MHz	2.82 (3H,s), 3.05-3.20 (2H,bs), 3.45-3.62 (2H,bs), 3.68-3.78 (4H,bs), 3.80-3.90 (2H,bs), 3.90-4.00 (2H,bs), 6.82 (1H,s), 7.07 (1H,s), 7.33-7.48 (5H,m), 7.66 (2H,d), 7.96 (2H,d), 8.80-9.05 (1H,bs), 10.15 (1H,s), 10.95-11.15 (1H,bs)
9064	C ₃₈ H ₃₆ N ₄ O ₅ .HCl	629(100)	ESI	d ₆ -DMSO/ 400MHz	2.87 (3H,s), 2.90-3.40 (4H,m), 3.70 (2x3H,s), 4.10-4.52 (4H,m), 6.80 (2x1H,s), 6.89 (1H,s), 7.11 (1H,s), 7.30-7.45 (5H,m), 7.59 (2H,d), 7.73 (2H,d), 7.91 (2H,d), 8.02 (2H,d), 10.46 (1H,s), 10.64 (2H,bs)
9065	C ₃₇ H ₃₄ N ₄ O ₃	582(10), 449(30), 331(100)	CI	CDCl ₃ /400MHz	2.65-3.10 (11H,m), 3.74 (2H,s), 6.95-8.10 (21H,m)
9070	C ₂₃ H ₂₁ N ₃ O ₃	388(100)	CI	CDCl ₃ /300MHz	3.05 (3H,s), 4.15 (2H,t), 5.35 (2H,m), 5.95 (1H,m), 6.24 (1H,bs), 7.10 (1H,s), 7.32-7.46 (6H,m), 7.53 (2H,d), 7.90 (2H,d), 8.05 (1H,bs)
9071	C ₃₁ H ₃₀ N ₄ O ₄ .HCl	523(100), 162(60) 331(75)	FAB+	d ₆ -DMSO/300MHz	2.88 (3H,s), 3.12 (4H,m), 3.69 (4H,m), 3.72 (3H,s), 6.86-6.89 (3H,m), 7.02 (2H,d), 7.11 (1H,s), 7.35-7.52 (7H,m), 7.63 (2H,d), 10.36 (1H,bs) (70°C)
9076	C ₃₆ H ₃₄ N ₄ O ₃ .HCl	571(35), 196(50), 167(100), 108(80)	CI	CDCl ₃ /300MHz	2.7-4.3 (4H,m), 2.90 (3H,s), 3.05 (3H,s), 4.95 (1H,bs), 7.0-8.5 (21H,m), 9.35 (1H,bs), 11.95 (1H,bs)

No.	Mol. Formula	Mass spec data		¹ H nmr data	
		mass (intensity)	mode	solvent/field	δ
9079	C ₃₉ H ₃₈ N ₄ O ₄	627(5), 156(36), 85(100)	CI	d ₆ -DMSO/400MHz	1.62 (2H,m), 1.88-2.04 (2H,m), 2.40-2.82 (8H,m), 2.89 (3H,s), 4.77 (1H,s), 6.87 (1H,s), 7.09 (1H,s), 7.17-7.80 (17H,m), 8.02 (2H,d), 10.19 (1H,s)
9080	C ₃₉ H ₃₅ N ₅ O ₃	622(100)	ESI	d ₆ -DMSO/400MHz	2.64-2.90 (8H,m), 2.86 (3H,s), 3.68 (2H,s), 6.88 (1H,s), 6.90-7.04 (2H,m), 7.10 (1H,s), 7.22-7.48 (9H,m), 7.72 (4H,m), 8.00 (2H,d), 10.19 (1H,s), 10.67 (1H,s)
9096	C ₃₈ H ₃₃ N ₅ O ₃	608(15), 291(100)	CI	d ₆ -DMSO/400MHz	2.74 (3H,s), 2.70 (2H,m), 2.80 (2H,m), 3.58 (2H,s), 3.70 (2H,s), 6.88 (1H,s), 6.90-7.05 (2H,m), 7.10 (1H,s), 7.20-7.50 (9H,m), 7.65-7.80 (4H,m), 8.00 (2H,d), 10.27 (1H,s), 10.62 (1H,s)
9103	C ₃₈ H ₃₇ N ₅ O ₃	612(87), 175(100)	CI	d ₆ -DMSO/400MHz	2.5-2.6 (6H,m), 2.75 (2H,m), 2.85 (3H,s), 3.11 (4H,m), 6.75 (1H,t), 6.88 (1H,s), 6.90 (2H,d), 7.1 (1H,s), 7.2 (3H,m), 7.28-7.49 (7H,m), 7.75 (3H,m), 8.1 (2H,d), 10.15 (1H,s), 10.6 (1H,bs)
9104	C ₃₇ H ₃₅ N ₅ O ₃ .HCl	598(100)	CI	d ₆ -DMSO/400MHz	2.5 (4H,m), 2.85 (3H,s), 3.11 (4H,m), 3.5 (2H,s), 6.75 (1H,t), 6.88 (1H,s), 6.90 (2H,d), 7.1 (1H,s), 7.2 (3H,m), 7.28-7.49 (7H,m), 7.75 (3H,m), 8.1 (2H,d)
9116	C ₃₁ H ₃₀ N ₄ O ₃ .HCl	507(100)	CI	CDCl ₃ /300MHz	2.90 (3H,s), 3.0-4.8 (10H,m), 6.86 (1H,s), 7.11 (1H,s), 7.15-7.50 (9H,m), 7.68 (2H,d), 7.96 (2H,d), 8.77 (1H,bs), 10.34 (1H,bs), 10.42 (1H,b)

No.	Mol. Formula	Mass spec data		¹ H nmr data	
		mass (intensity)	mode	solvent/field	δ
9117	C ₃₀ H ₂₉ N ₃ O ₅	529(5), 512(100), 275(10), 118(20)	CI	CDCl ₃ /300MHz	2.93 (2H, t); 3.05 (3H, s), 3.76 (2H, q), 3.90 (3H, s), 3.92 (3H, s), 6.20 (1H, bt), 6.81-6.90 (3H, m), 7.08 (1H, s), 7.30-7.47 (6H, m), 7.51 (2H, d), 7.81 (2H, d), 8.04 (1H, bs)
9115	C ₃₂ H ₃₃ N ₃ O ₄	524(95), 190(100)	CI	d ₆ -DMSO/400MHz	2.63-2.72 (4H, m), 2.7 (3H, s), 2.84 (4H, bs), 3.52 (2H, s), 3.69 (6H, s), 6.61 (1H, s), 6.65 (1H, s), 6.8 (1H, s), 6.98 (1H, s), 7.07 (1H, s), 7.28-7.51 (9H, m)
9161	C ₄₀ H ₄₀ N ₄ O ₅	657(7)	CI	CDCl ₃ /400MHz	1.92 (2H, m), 2.47-2.85 (8H, m), 2.99 (3H, s), 3.57 (2H, s), 3.85 (2x3H, s), 6.52 (1H, s), 6.59 (1H, s), 7.10 (1H, s), 7.15-7.60 (13H, m), 7.85 (1H, m), 7.98 (1H, s), 8.08 (1H, s)
9083	C ₃₈ H ₃₇ N ₃ O ₃	612(100)	ESI	CDCl ₃ /400MHz	2.62-2.72 (6H, m), 2.82-2.89 (2H, m), 2.99 (3H, s), 3.25 (4H, m), 6.88 (1H, t), 6.96 (2H, d), 7.09 (1H, s), 7.20-7.29 (6H, m), 7.32-7.42 (4H, m), 7.53-7.61 (4H, m), 7.85 (1H, m), 7.97 (1H, s), 8.05 (1H, s), 8.53 (1H, bs)
9128	C ₃₈ H ₃₆ O ₅ N ₄	629(100)	ESI	CDCl ₃ /400MHz	2.74 (m, 2H), 2.83 (m, 2H), 3.01 (s, 3H), 3.55 (s, 2H), 3.69 (s, 2H), 3.82 (s, 3H), 3.85 (s, 3H), 6.49 (s, 1H), 6.58 (s, 1H), 7.09 (s, 1H), 7.25-7.44 (10H, m), 7.58-7.64 (4H, m), 7.92 (1H, s), 7.96 (1H, s)
9136	C ₃₃ H ₃₄ N ₄ O ₅	567(100)	CI	CDCl ₃ /400MHz	2.75-2.90 (6H, m), 3.00 (3H, s), 3.60-3.72 (4H, m), 3.84 (6H, s), 6.54 (1H, s), 6.60 (1H, s), 7.03-7.11 (2H, m), 7.24-7.78 (10H, m), 7.84 (1H, s)

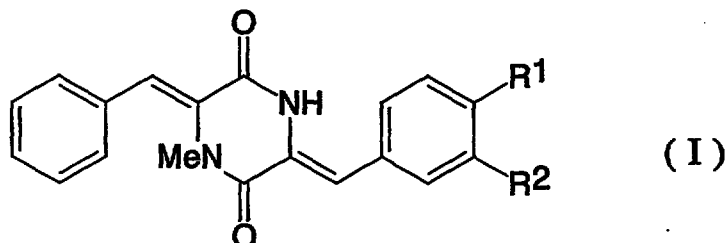
No.	Mol. Formula	Mass spec data		¹ H nmr data	
		mass (intensity)	mode	solvent/field	δ
9137	C ₃₃ H ₃₆ N ₄ O ₅	569(95), 357(100)	CI	CDCl ₃ /400MHz	2.38 (3H,s), 2.62-2.80 (6H,m), 3.2 (3H,s), 3.46-3.54 (2H,m), 3.75 (3H,s), 3.81 (3H,s), 6.60-6.85 (5H,m), 7.6 (1H,s), 7.25-7.55 (9H,m) 7.79 (1H,s)
9138	C ₃₉ H ₄₀ N ₄ O ₅	645(71), 106(100)	CI	CDCl ₃ /400MHz	2.38 (3H,s), 2.60-2.82 (8H,m), 2.96 (3H,s), 3.85 (2x3H,s), 6.68-6.82 (3H,m), 7.04-7.60 (14H,m), 7.81 (1H,d), 7.97 (1H,s), 8.07 (1H,s)
9155	C ₃₇ H ₃₆ N ₄ O ₅ S	649(100)	ESI	CDCl ₃ /400MHz	2.72-2.93 (8H,m), 3.19 (3H,s), 3.65 (2H,s), 3.85 (2x3H,s), 6.54 (1H,s), 6.60 (1H,s), 7.04 (1H,m), 7.08-7.10 (2H,m), 7.22-7.29 (3H,m), 7.45 (1H,m), 7.52-7.60 (4H,m), 7.81 (1H,m), 7.95 (2H,s) 8.38 (1H,s)
9163	C ₃₇ H ₃₆ N ₄ O ₃	585(100)	ESI	CDCl ₃ /400MHz	2.36 (3H,s), 2.65 (2H,t), 2.95-3.10 (5H,m), 3.45 (2H,d), 4.20 (1H,t), 6.38 (1H,brs), 7.05-8.20 (22H,m)
9176				CDCl ₃ /400MHz	2.70-2.98 (8H,m), 3.00 (3H,s), 3.65 (2H,s), 3.82 (2x3H,s), 5.09 (2H,s), 6.53 (1H,s), 6.61 (1H,s), 7.00-7.10 (4H,m), 7.21-7.58 (7H,m), 7.82 (2H,d), 7.91 (1H,br s)
9177				CDCl ₃ /400MHz	2.62-2.89 (8H,m), 2.91 (3H,s), 3.57 (2H,s), 3.76 (2x3H,s), 4.97 (2H,s), 6.45 (1H,s), 6.51 (1H,s), 6.82-6.95 (3H,m), 7.12-7.38 (12H,m), 8.05 (1H,br s)
9190	C ₃₉ H ₃₈ N ₄ O ₃	643(3)	CI	CDCl ₃ /400MHz	2.70-3.04 (11H,m), 3.65 (2H,s), 3.85 (2x3H,s), 6.53 (1H,s), 6.60 (1H,s), 7.03 (1H,s), 7.15-7.50 (11H,m), 7.68-7.92 (5H,m)

No.	Mol. Formula	Mass spec data		¹ H nmr data	
		mass (intensity)	mode	solvent/field	δ
9200	C ₃₇ H ₄₀ N ₄ O ₅	620 (32)	EI	CDCl ₃ /400MHz	1.05-2.00 (9H,m), 2.35-2.45 (2H,d), 2.62-2.84 (4H,m), 3.2 (3H,s), 3.55 (2H,s), 3.84 (2x3H,s), 6.52 (1H,s), 6.60 (1H,s), 7.06 (1H,s), 7.20-7.55 (11H,m)



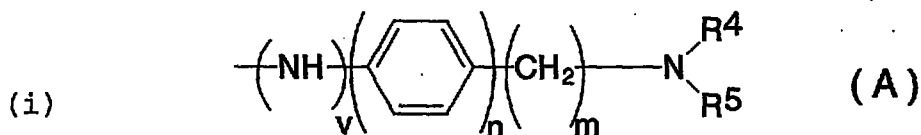
CLAIMS

1. A piperazinedione of general formula (I):



wherein R^1 is selected from:

- hydrogen;
- a group of formula $-(NH)_t-COR^3$ wherein t is 0 or 1 and R^3 is selected from:



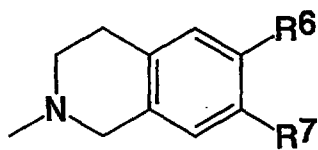
wherein v is 0 when t is 1 and v is 1 when t is 0; and

wherein n is 0 or 1 and m is 0, 1, 2 or 3, at least one of n and m being other than 0, and either

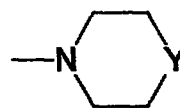
(a) R^4 is H or C_1-C_6 alkyl and R^5 is C_1-C_6 alkyl optionally substituted by one or two phenyl groups; the phenyl groups or groups being optionally substituted by one or two C_1-C_6 alkoxy groups; or

(b) R^4 and R^5 , together with the nitrogen atom to which

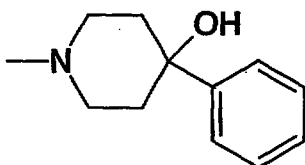
they are attached, form a heterocyclic group selected from (1) to (4):



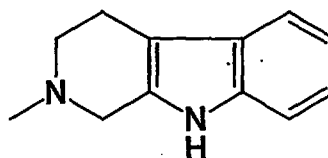
(1)



(2)

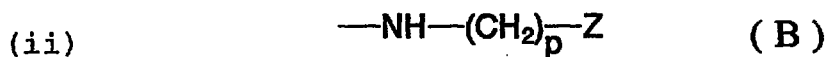


(3)

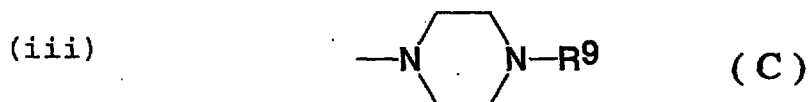


(4)

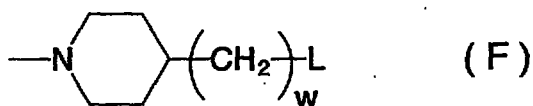
wherein R^6 and R^7 , which are the same or different, are H or C_1 - C_6 alkoxy, or R^6 and R^7 together form a methylenedioxy group; Y is O or $-NR^8$ wherein R^8 is C_1 - C_6 alkyl or a phenyl group optionally substituted by CF_3 ;



wherein p is 1 or 2 and Z is C_2 - C_6 alkenyl or a phenyl group optionally substituted by C_1 - C_6 alkoxy; and



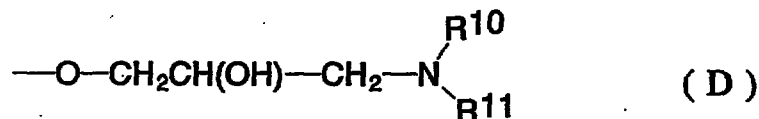
wherein R^9 is C_1 - C_6 alkyl, pyrimidinyl or a phenyl group optionally substituted by C_1 - C_6 alkoxy; and





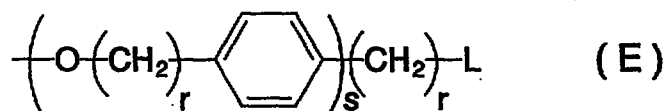
wherein w is 1, 2 or 3 and L is a heterocyclic group of formula (1) as defined above;

- a group of the formula (D):



wherein each of R^{10} and R^{11} , which may be the same or different, is $\text{C}_1\text{--C}_6$ alkyl; and

- a group of formula (E):



wherein S is 0 or 1 and each r, which may be the same or different, is 1, 2 or 3 and L is a heterocyclic group of formula (1) as defined above;

and R^2 is hydrogen or a group of formula ---COR^3 as defined above, provided that one of R^1 and R^2 is hydrogen and the other is not hydrogen; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 is hydrogen and R^2 is a group of formula ---COR^3 as defined in claim 1 in which R^3 is a group of formula A.

3. A compound according to claim 1, wherein R^2 is hydrogen and R^1 is a group of formula ---COR^3 as defined in claim 1 in which R^3 is a group of formula (A), a group of formula (B) wherein Z is ethenyl or phenyl substituted by two $\text{C}_1\text{--C}_6$ alkoxy groups, or a group of formula (C) wherein R^2 is methyl, pyrimidinyl or phenyl.



4. A compound according to any one of the preceding claim, wherein, in formula (A), n is 0 and m is 2, or n is 1 and m is 0, 1, 2 or 3, or n is 1 and m is 0, and either

(a) R^4 is C_1-C_6 alkyl and R^5 is C_1-C_6 alkyl substituted on

the terminal C atom by 2 unsubstituted phenyl groups or by one phenyl group which is disubstituted by C_1-C_6 alkoxy groups; or

(b) R^4 and R^5 form together with the nitrogen atom to which they are attached a heterocyclic group selected from groups of formulae (1) wherein R^6 and R^7 are both H or both C_1-C_6 alkoxy, or together form a methylenedioxy group; (2) wherein Y is O or $-NR^8$ wherein R^8 is methyl, phenyl or trifluoromethylphenyl; (3); and (4).

5. A compound according to claim 1 wherein R^2 is hydrogen and R^1 is a group of formula (D) or (E) as defined in claim 1

6. A compound selected from:

1-(4-((3Z,6Z)-6-Benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzoyl)-4-(2-pyrimidyl)piperazine (9022)

1-(4-((3Z,6Z)-6-Benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzoyl)-4-methylpiperazine, hydrochloride (9052)

1-(4-((3Z,6Z)-6-Benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzoyl)-4-(4-



methoxyphenyl)piperazine, hydrochloride (9071)

N-Allyl-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9070)

N-(2-Diphenylmethyldimethylaminoethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9076)

N-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9116)

N-(3,4-Dimethoxyphenethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9117)

N-(4-(4-Phenyl-1-piperazinyl)methylphenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9104)

N-(2-(4-Methyl-1-piperazinyl)ethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9007)

N-(2-Morpholinoethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9053)



N-(4-Morpholinophenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9054)

N-(4-(2-(1,2,3,4-Tetrahydro- β -carbolin-2-yl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9080)

N-(4-(1,2,3,4-Tetrahydro- β -carbolin-2-yl)methylphenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9096)

N-(4-(2-(4-Phenyl-1-piperaziny)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9103)

N-(4-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9065)

N-(4-(2-(4-(3-Trifluoromethylphenyl)-1-piperaziny)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9049)

N-(4-(2-(4-(4-Chlorophenyl)-4-hydroxypiperidino)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9079)



N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9006)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9008)

N-(4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)methylphenyl)-4-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9064)

(3Z,6Z)-6-Benzylidene-3-(4-(3-dimethylamino-2-hydroxypropoxy)benzylidene)-1-methyl-2,5-piperazinedione (9023)

(3Z,6Z)-6-Benzylidene-3-(4-(2-(6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)benzylidene)-1-methyl-2,5-piperazinedione (9115)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9051)

N-(4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)methylphenyl)-3-((3Z,6Z)-6-benzylidene-1-



methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9128)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-3-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9136)

N-(2-(3,4-Dimethoxyphenethyl)methylamino)ethyl)-3-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9137)

N-(4-(2-((3,4-Dimethoxyphenethyl)methylamino)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9138)

N-(4-(2-(4-Phenyl-1-piperazinyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9083)

N-(4-(3-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)propyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9161)

N-(2-(2,2-Diphenylethyl)methylaminoethyl)-3-((3Z,6Z)-6-benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9163)



(3Z,6Z)-6-Benzylidene-3-(4-(4-(2-(6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)benzyloxy)benzylidene)-1-methyl-2,5-piperazinedione (9176)

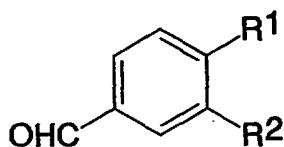
(3Z,6Z)-6-Benzylidene-3-(3-(4-(2-(6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)benzyloxy)benzylidene)-1-methyl-2,5-piperazinedione (9177)

N-(4-((3Z,6Z)-6-Benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylphenyl)-4-(2-(6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)benzamide (9190)

1-(4-((3Z,6Z)-6-Benzylidene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzoyl)-4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)methylpiperidine (9200)

7. A pharmaceutical or veterinary composition which comprises a pharmaceutically or veterinarily acceptable carrier or diluent and, as an active principal, a compound as claimed in any one of the preceding claims.

8. A process for producing a compound as defined in claim 1, which process comprises treating 1-acetyl-3-benzylidene-4-methyl-2,5-piperazinedione with an aldehyde of formula (III):



(III)

wherein R¹ and R² are as defined in claim 1, in an organic



THIS SHEET HAS BEEN
REPLACED

- 65 -

solvent in the presence of a base; and, if desired, converting the resulting compound into a pharmaceutically acceptable salt thereof.

9. A compound as defined in any one of claims 1 to 6 for use as a modulator of multi-drug resistance.

10. Use of a compound as defined in any one of claims 1 to 6 in the manufacture of a medicament for use as a modulator of multi-drug resistance.

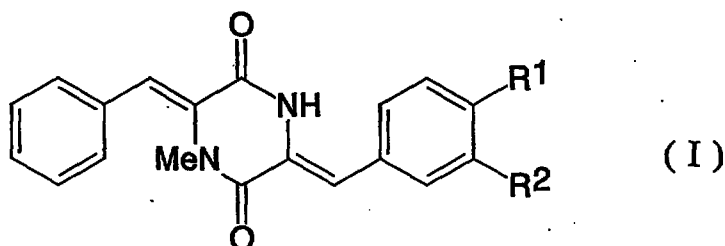
This Sheet Has Been Replaced



- 66 -

ABSTRACTPHARMACEUTICAL COMPOUNDS

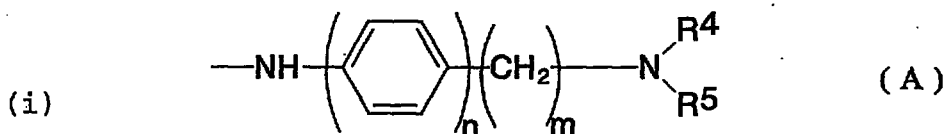
A piperazinedione of general formula (I):



wherein R^1 is selected from:

- hydrogen;

- a group of formula $-\text{COR}^3 - (\text{NH})_t - \text{COR}^3$ wherein t is 0 or 1 and R^3 is selected from:



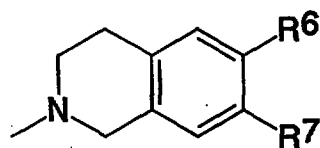
wherein v is 0 or 1 when t is 1 and v is 1 when t is 0; and wherein n is 0, 1, 2, or 3 at least one of n and m being other than 0, and either:

(a) R^4 is H or $\text{C}_1\text{-C}_6$ alkyl and R^5 is $\text{C}_1\text{-C}_6$ alkyl optionally substituted by one or two phenyl groups, the phenyl group or groups being optionally substituted by one or two $\text{C}_1\text{-C}_6$ alkoxy groups; or

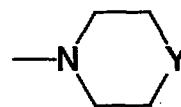
(b) R^4 and R^5 , together with the nitrogen atom to which

they are attached, form a heterocyclic group selected from (1) to (4):

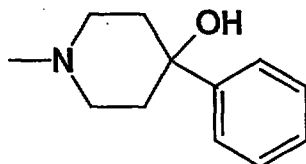




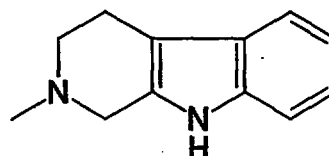
(1)



(2)

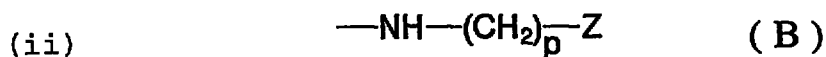


(3)

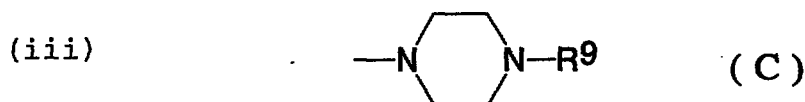


(4)

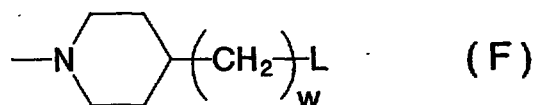
wherein R^6 and R^7 , which are the same or different, are H or C_1-C_6 alkoxy, or R^6 and R^7 together form a methylenedioxy group; Y is O or $-NR^8$ wherein R^8 is C_1-C_6 alkyl or a phenyl group optionally substituted by CF_3 ;



wherein p is 1 or 2 and Z is C_2-C_6 alkenyl or a phenyl group optionally substituted by C_1-C_6 alkoxy; and



wherein R^9 is C_1-C_6 alkyl, pyrimidinyl or a phenyl group optionally substituted by C_1-C_6 alkoxy; and



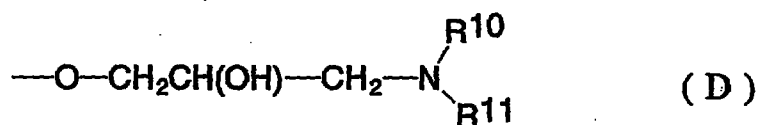
wherein w is 1, 2 or 3 and L is a heterocyclic group of



- 68 -

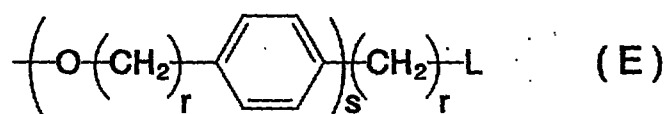
formula (1) as defined above;

- a group of the formula (D):



wherein each of R^{10} and R^{11} , which may be the same or different, is $\text{C}_1\text{--C}_6$ alkyl; and

- a group of formula (E):



wherein s is 0 or 1 and each r , which may be the same or different, is 1, 2 or 3 and L is a heterocyclic group of formula (1) as defined above;

and R^2 is hydrogen or a group of formula ---COR^3 as defined above, provided that one of R^1 and R^2 is hydrogen and the other is not hydrogen; and the pharmaceutically acceptable salts thereof have activity as modulators of multi-drug resistance.

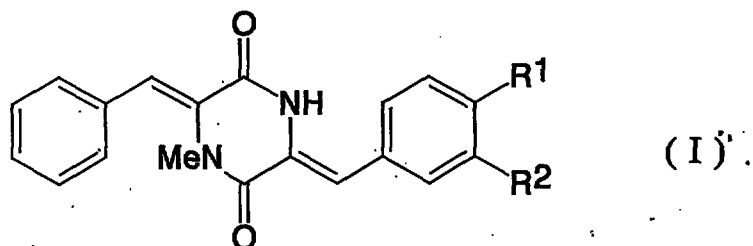
17 APR 1996

Date

- 66 -

ABSTRACTPHARMACEUTICAL COMPOUNDS

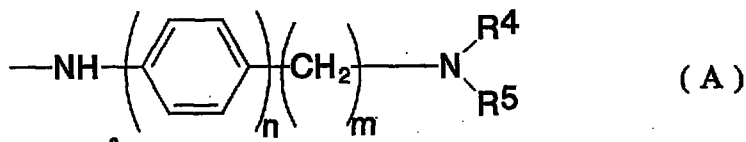
A piperazinedione of general formula (I):



wherein R^1 is selected from:

- hydrogen;
- a group of formula $-\text{COR}^3 - (\text{NH})_t - \text{COR}^3$ wherein t is 0 or 1 and R^3 is selected from:

(i)

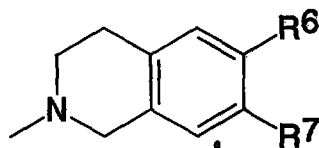


wherein either:

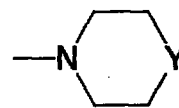
- (a) R^4 is H or $\text{C}_1\text{-C}_6$ alkyl and R^5 is $\text{C}_1\text{-C}_6$ alkyl optionally substituted by one or two phenyl groups, or
- (b) R^4 and R^5 , together with the nitrogen atom to which they are attached, form a heterocyclic group selected from (1) to (4):



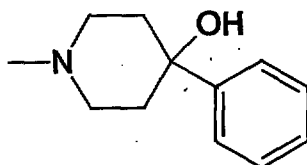
- 67 -



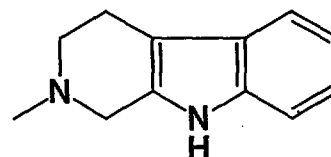
(1)



(2)

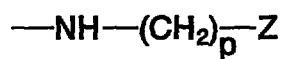


(3)



(4)

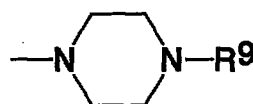
(ii)



(B)

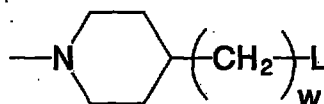
wherein p is 1 or 2 and Z is $\text{C}_2\text{—C}_6$ alkenyl or phenyl; and

(iii)



(C)

wherein R^9 is $\text{C}_1\text{—C}_6$ alkyl, pyrimidinyl or phenyl; and



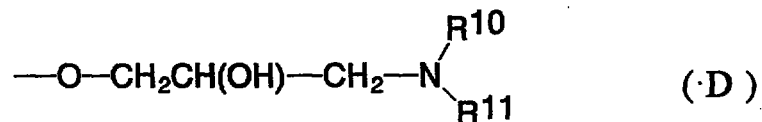
(F)

wherein w is 1, 2 or 3 and L is a heterocyclic group of

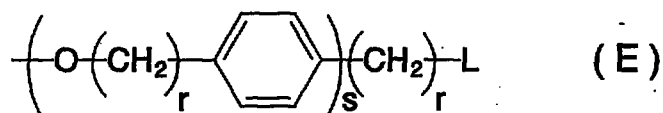


- 68 -

formula (1) as defined above;



wherein R^{10} and R^{11} are $\text{C}_1\text{--C}_6$ alkyl; and



wherein L is a heterocyclic group of formula (1) as defined above;

and R^2 is hydrogen or a group of formula ---COR^3 as defined above; and the pharmaceutically acceptable salts thereof have activity as modulators of multi-drug resistance.

- 1 -

PIPERAZINE-2, 5-DIONE DERIVATIVES AS
MODULATORS OF MULTI-DRUG RESISTANCE

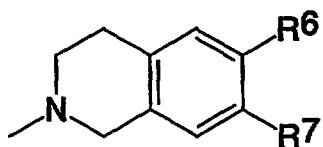
The present invention relates to compounds useful as modulators of multi-drug resistance (MDR), to their preparation and to pharmaceutical and veterinary compositions containing them.

The resistance of tumours to treatment with certain cytotoxic agents is an obstacle to the successful chemotherapeutic treatment of cancer patients. A tumour may acquire resistance to a cytotoxic agent used in a previous treatment. A tumour may also manifest intrinsic resistance, or cross-resistance, to a cytotoxic agent to which it has not previously been exposed, that agent being unrelated by structure or mechanism of action to any agent used in previous treatments of the tumour.

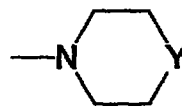
Analogously, certain pathogens may acquire resistance to pharmaceutical agents used in previous treatments of the diseases or disorders to which those pathogens give rise. Pathogens may also manifest intrinsic resistance, or cross resistance, to pharmaceutical agents to which they have not previously been exposed. Examples of this effect include multi-drug resistant forms of malaria, tuberculosis, leishmaniasis and amoebic dysentery.

The above phenomena are referred to collectively as multi-drug resistance (MDR). As discussed more fully later on, a plasma membrane glycoprotein (P-gp) is implicated in the mechanism which underlies MDR. P-gp has drug binding properties. Certain agents which have the capacity to modulate MDR may therefore also be useful in facilitating

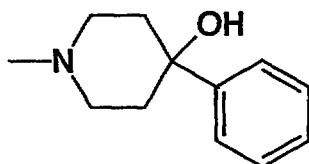
- 57 -



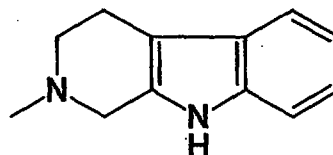
(1)



(2)

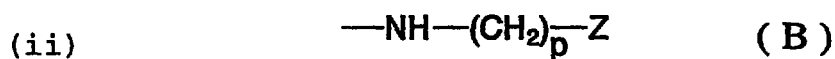


(3)

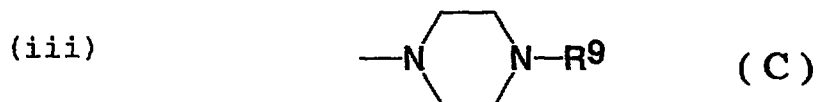


(4)

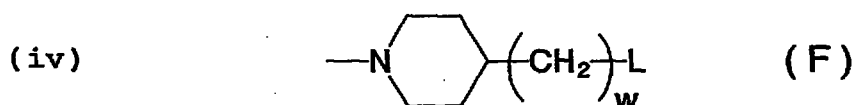
wherein R^6 and R^7 , which are the same or different, are H or C_1-C_6 alkoxy, or R^6 and R^7 together form a methylenedioxy group; Y is O or $-NR^8$ wherein R^8 is C_1-C_6 alkyl or a phenyl group optionally substituted by CF_3 ;



wherein p is 1 or 2 and Z is C_2-C_6 alkenyl or a phenyl group optionally substituted by C_1-C_6 alkoxy; and



wherein R^9 is C_1-C_6 alkyl, pyrimidinyl or a phenyl group optionally substituted by C_1-C_6 alkoxy; and





REPLACEMENT SHEET

Date **04 OCT 1996**

- 65 -

solvent in the presence of a base; and, if desired, converting the resulting compound into a pharmaceutically acceptable salt thereof.

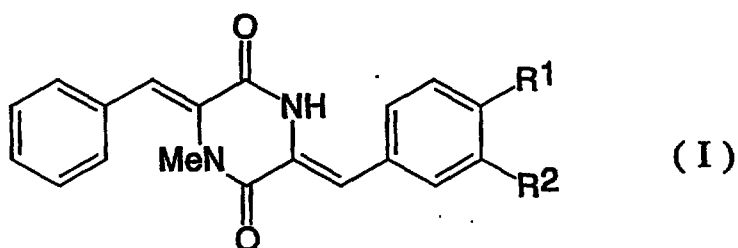
9. A compound as defined in any one of claims 1 to 6 when used as a modulator of multi-drug resistance.

10. Use of a compound as defined in any one of claims 1 to 6 in the manufacture of a medicament for use as a modulator of multi-drug resistance.

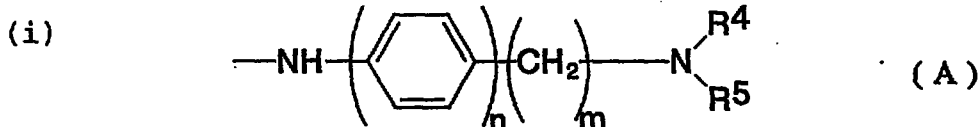
- 66 -

ABSTRACTPIPERAZINE-2, 5-DIONE DERIVATIVES AS
MODULATORS OF MULTI-DRUG RESISTANCE

A piperazinedione of general formula (I):

wherein R^1 is selected from:

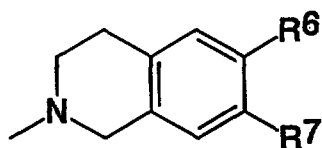
- hydrogen;
- a group of formula $-\text{COR}^3 - (\text{NH})_t - \text{COR}^3$ wherein t is 0 or 1 and R^3 is selected from:



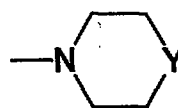
wherein either:

- (a) R^4 is H or $\text{C}_1\text{-C}_6$ alkyl and R^5 is $\text{C}_1\text{-C}_6$ alkyl optionally substituted by one or two phenyl groups, or
- (b) R^4 and R^5 , together with the nitrogen atom to which they are attached, form a heterocyclic group selected from (1) to (4):

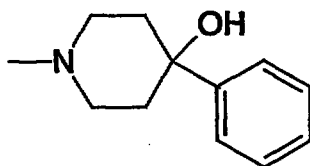
- 67 -



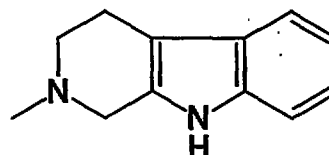
(1)



(2)

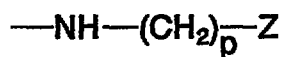


(3)



(4)

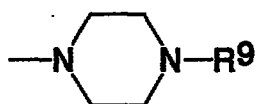
(ii)



(B)

wherein p is 1 or 2 and Z is $\text{C}_2\text{-C}_6$ alkenyl or phenyl; and

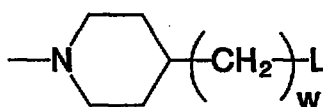
(iii)



(C)

wherein R^9 is $\text{C}_1\text{-C}_6$ alkyl, pyrimidinyl or phenyl; and

(iv)



(F)

wherein w is 1, 2 or 3 and L is a heterocyclic group of