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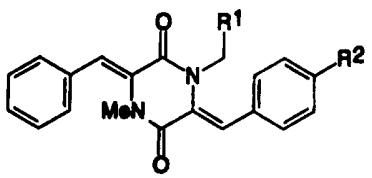
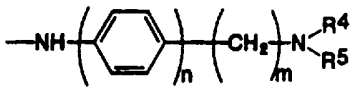
(54) Title: PIPERAZINE-2,5-DIONE DERIVATIVES AS MODULATORS OF MULTI-DRUG RESISTANCE

(57) Abstract

A piperazinedione derivative of formula (I), wherein one of R^1 and R^2 is H and the other is a group $-COR^3$ wherein R^3 is selected from: (i) hydroxy; (ii): (A) wherein n is 0 or 1 and m is 0, 1, 2, 3 or 4, 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, or (b) R^4 and R^5 together with the nitrogen atom to which they are attached, form a heterocyclic group selected from (B1) and (B2), wherein R^6 and R^7, which are the same or different, are each hydrogen or C_1-C_6 alkoxy, or R^6 and R^7 together form a methylenedioxy group; (iii): (C) wherein R^8 is C_1-C_6 alkyl optionally substituted by hydroxy, C_2-C_6 alkenyl or a phenyl ring optionally substituted by a C_1-C_6 alkoxy; and (iv): (D) wherein p is 1, 2 or 3 and R^9 is C_2-C_6 alkenyl or a phenyl ring optionally substituted by C_1-C_6 alkoxy; and pharmaceutically acceptable salts thereof have activity as modulators of multi-drug resistance.


(I)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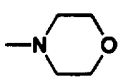
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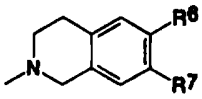
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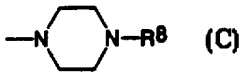
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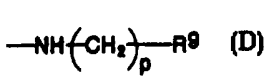
(D)

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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.

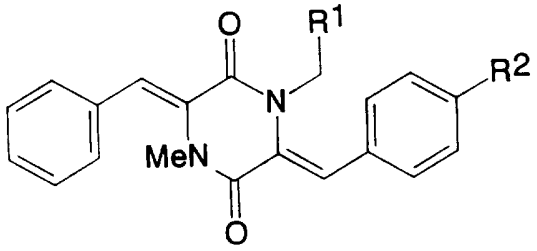
The above phenomena are referred to collectively as multi-drug resistance (MDR). As discussed more fully later on, a plasma membrane glycoprotein (P-gp) is implicated in the mechanism which underlies MDR. P-gp has drug binding properties. Certain agents which have the capacity to

modulate MDR may therefore also be useful in facilitating 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)

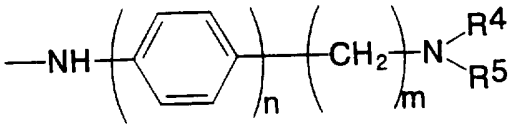


(I)

wherein one of R^1 and R^2 is H and the other is a group $-COR^3$ wherein R^3 is selected from:

(i) hydroxy;

(ii)

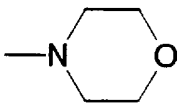


(A)

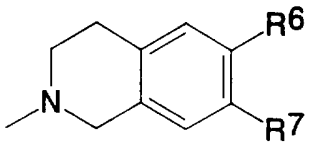
wherein n is 0 or 1 and m is 0, 1, 2, 3 or 4, at least one of n and m being other than 0, and either

(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, or

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



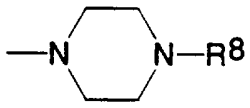
and



(B)

wherein R^6 and R^7, which are the same or different, are each hydrogen or C_1-C_6 alkoxy, or R^6 and R^7 form together a methylenedioxy group;

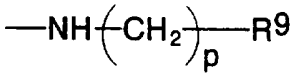
(iii)



(C)

wherein R^8 is C_1-C_6 alkyl optionally substituted by hydroxy, C_2-C_6 alkenyl, or a phenyl group optionally substituted by C_1-C_6 alkoxy; and

(iv)



(D)

wherein p is 1, 2 or 3 and R^9 is C_2-C_6 alkenyl or a phenyl ring optionally substituted by C_1-C_6 alkoxy;

or a pharmaceutically acceptable salt thereof.

An alkyl group may be linear or branched. A C_1-C_6 alkyl group is typically a C_1-C_4 alkyl group, for example a methyl, ethyl, propyl, i-propyl, n-butyl, sec-butyl or tert-butyl

group. A C_1-C_6 alkyl group substituted by hydroxy may be substituted by 1, 2 or 3 hydroxy groups, for instance a C_2-C_6 alkyl group substituted by 1, 2 or 3 hydroxy groups. Preferably it is substituted by one hydroxy group. It is typically substituted on the terminal carbon atom. A preferred example of a C_1-C_6 alkyl group substituted by hydroxy is a 2-hydroxyethyl group.

A C_1-C_6 alkoxy group is typically a C_1-C_4 alkoxy group, for example a methoxy, ethoxy, propoxy, i-propoxy, n-butoxy, sec-butoxy or tert-butoxy group.

When R^3 is a group of formula (A), n is typically 1 and m is 0 or 2, 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 two phenyl rings. For instance, R^5 may be a diphenylmethyl or 2,2-diphenylethyl group. Alternatively, R^4 and R^5 may be as defined under (b). When R^4 and R^5 together form the heterocyclic ring (B), R^6 and R^7 are typically the same, and are preferably hydrogen or methoxy, or together form a methylenedioxy group.

When R^3 is a group of formula (C), R^8 is typically selected from methyl and ethyl optionally substituted by hydroxy, for instance 2-hydroxyethyl; prop-1-enyl and prop-2-enyl; and phenyl monosubstituted at position 2, 3 or 4 by C_1-C_6 alkoxy, for instance methoxy, preferably a 4-methoxyphenyl group.

When R^3 is a group of formula (D) p is preferably 2. R^9 is typically ethenyl, prop-1-enyl or prop-2-enyl, or phenyl substituted by 1 or 2 C_1-C_6 alkoxy groups, for instance methoxy groups. Preferably R^9 is a 3,4-dimethoxyphenyl group.

In a first embodiment of formula (I), R^1 is H, R^2 is a group $-COR^3$ wherein R^3 is a group of formula (A) wherein n is 0 or 1 and m is 2, and R^4 and R^5 form together with the nitrogen to which they are attached a heterocyclic ring (B) as defined above wherein R^6 and R^7 are as defined above. Preferably R^6 and R^7 are both a C_1-C_6 alkoxy group, which may be the same or different. More preferably R^6 and R^7 are both methoxy groups.

In a second embodiment of formula (I), R^2 is H, R^1 is a group $-COR^3$ wherein R^3 is a group of formula (A) in which n is 0 and m is 2, or n is 1 and m is 2, or n is 1 and m is 0, and either

(a) R^4 is C_1-C_6 alkyl and R^5 is unsubstituted C_1-C_6 alkyl or C_1-C_6 alkyl substituted on the terminal C atom by 2 phenyl rings, or

(b) R^4 and R^5 form together with the nitrogen atom to which they are attached a morpholino group or a heterocyclic ring (B) as defined above wherein R^6 and R^7 are both hydrogen or both C_1-C_6 alkoxy.

In this second embodiment C_1-C_6 alkyl is preferably methyl, C_1-C_6 alkyl substituted by two phenyl rings is preferably diphenylmethyl or 2,2-diphenylethyl, and C_1-C_6

alkoxy is preferably methoxy.

In a third embodiment of formula (I), R^2 is H, R^1 is a group $-COR^3$ wherein R^3 is a group of formula (C) as defined above in which R^8 is unsubstituted C_1-C_6 alkyl, or is a 2-hydroxyethyl, ethenyl, prop-1-enyl, prop-2-enyl or 4-methoxyphenyl group.

In a fourth embodiment of formula (I), R^2 is H, R^1 is a group $-COR^3$ wherein R^3 is a group of formula (D) as defined above in which p is 1 or 2 and R^9 is ethenyl, prop-1-enyl, prop-2-enyl or phenyl substituted by one or two C_1-C_6 alkoxy, typically methoxy, groups, for instance 3,4-dimethoxyphenyl.

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

((3Z,6Z)-3,6-Dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetic acid (9005)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide (9020)

N-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide, hydrochloride (9060)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-((3Z,6Z)-3,6-dibenzylidene-4-

methyl-2,5-dioxo-1-piperazinyl)acetamide (9021)

N-(2-Morpholinoethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide, hydrochloride (9055)

N-(2-Dimethylaminoethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide, hydrochloride (9056)

N-(2-Diphenylmethylmethylaminoethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide, hydrochloride (9072)

N-Allyl-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide (9073)

N-(4-Morpholinophenyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide, hydrochloride (9058)

1-((3Z,6Z)-3,6-Dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetyl-4-methylpiperazine, hydrochloride (9057)

1-((3Z,6Z)-3,6-Dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetyl-4-(4-methoxyphenyl)piperazine, hydrochloride (9059)

1-((3Z,6Z)-3,6-Dibenzylidene-4-methyl-2,5-dioxo-1-

piperazinyl)acetyl-4-(2-hydroxyethyl)piperazine (9074)

1-((3Z,6Z)-3,6-Dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetyl-4-allylpiperazine, hydrochloride (9075)

N-(3,4-Dimethoxyphenethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide (9094)

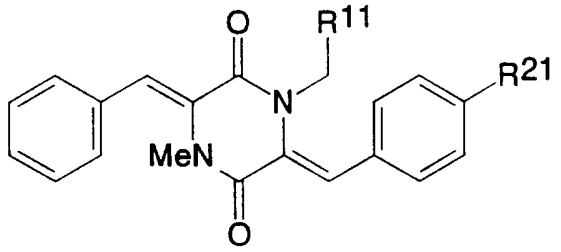
N-(2-(2,2-Diphenylethyl)methylaminoethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide, hydrochloride (9095)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-6-benzylidene-1,4-dimethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9002)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1,4-dimethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9019)

Compounds of formula (I) other than those wherein R^3 is hydroxy are prepared by forming an amide linkage between an amine and a compound of formula (I) wherein R^1 or R^2 is a group $-COR^3$ in which R^3 is hydroxy. The $-COR^3$ group thus denotes -COOH, which may optionally first be suitably activated, for instance by conversion to a corresponding acid halide or to a corresponding mixed anhydride. The

starting compounds may therefore be represented by the formula (II):



(II)

wherein one of R^{11} and R^{21} is hydrogen and the other is -COOH, -COX wherein X is a halogen, or -CO(OCOR') wherein R' is C_1-C_6 alkyl. X may be F, Cl, Br or I, preferably Cl. R' may be any of the examples quoted above for C_1-C_6 alkyl, or may be isobutyl.

The process for producing a compound of formula (I) accordingly comprises treating a compound of formula (II) as defined above with an amine of formula:

$H\text{-}R^3$

wherein R^3 is as defined above for formula (I) excluding hydroxy, in an organic solvent, the reaction being conducted in the presence of a coupling agent when R^{11} or R^{21} is -COOH; and, if desired, converting the resulting compound into a pharmaceutically acceptable salt thereof.

Suitable solvents include dichloromethane at a temperature between -10°C and room temperature. The reaction may optionally be performed in the presence of a base. Suitable bases include trialkylamines such as Et_3N, and pyridine. When R^{11} or R^{21} is -COOH any suitable coupling agent may be used, for instance 1,3-dicyclohexyl-carbodiimide, 1-cyclohexyl-3-(2-

morpholinoethyl)carbodiimide, or 1,1'-carbonyldiimidazole.

The preparation of the starting compounds of formula (II) wherein either R^{11} or R^{21}, as appropriate, is -COOH is described in Reference Example 2 which follows. The optional conversion of either of these compounds to the corresponding acid halide or mixed anhydride derivative is performed by conventional methods which are routine in organic synthesis. For instance, an acid halide derivative may be prepared by treatment of the carboxylic acid with a halogenating agent, for instance a chlorinating agent such as $SOCl_2$, PCl_3, oxalyl chloride or PCl_5. A mixed

anhydride derivative may be prepared by treatment of the carboxylic acid with a C_1-C_6 alkyl haloformate, for instance iBuOCOCl or EtOCOCl, in the presence of a base such as a tertiary amine.

The amines H-R^3 are commercially available products or can be prepared from known starting materials by conventional methods. The synthesis of specific amines of formula H-R^3 is described in Reference Example 3 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 <u>in vitro</u> 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 any 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 <u>58</u>

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 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 are set out in Example 5 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.

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 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.

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 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 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.

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 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 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 multiple drug resistance comprising any one of the present compounds is therefore provided.

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; 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 lecithin, polysorbates, lauryl sulphates. Such preparations may be manufactured in known manners, for example by means of mixing, granulating, tabletting, sugar coating, or film-coating processes.

Liquid dispersions for oral administration may be 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 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.

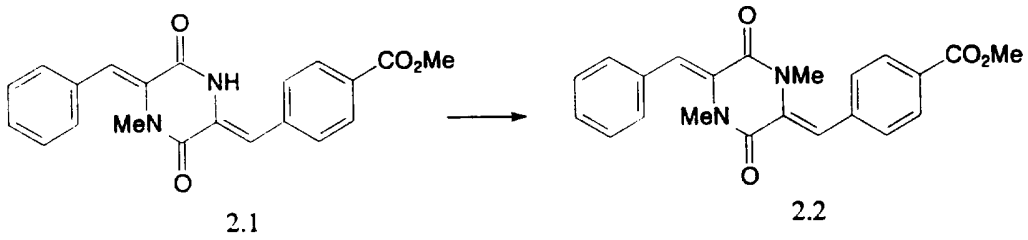
Reference Example 1: 1-acetyl-3-benzylidene-4-methyl-2,5-piperazinedione

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 ($MgSO_4$) 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.

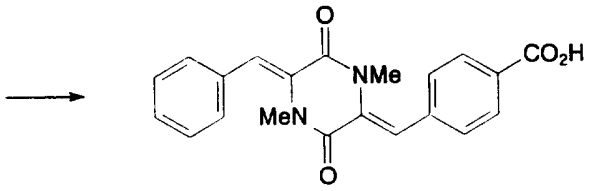
The latter compound was treated with NaH and MeI in DMF: THF (1:5) at a temperature of about 0°C and allowed to warm to room temperature to give the title compound in 57% yield.

Reference Example 2: Preparation of compounds of formula II

Method 1



2.1 2.2



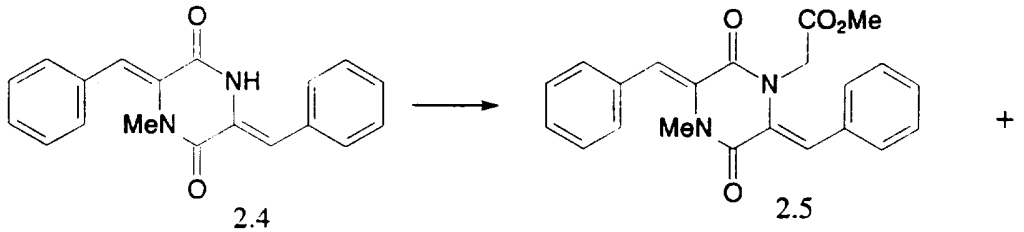
2.3

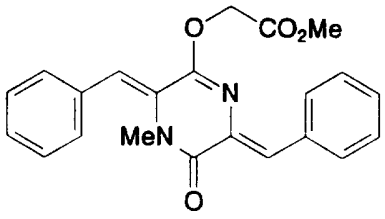
1-Acetyl-3-benzylidene-4-methyl-2,5-piperazinedione, prepared in Reference Example 1, was treated with methyl 4-formylbenzoate in the presence of Cs_2CO_3 in DMF at 90°C for 2 hours to give the starting compound 2.1 in 64% yield.

Compound 2.1 was treated with NaH in THF at 0°C. MeI was added and the solution was then allowed to warm to room temperature, to give 2.2 in 42% yield.

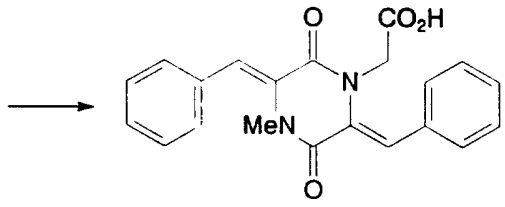
Compound 2.2 was treated with LiOH in aqueous THF to give the final product 2.3.

Method 2





2.6



2.7

1-Acetyl-3-benzylidene-4-methyl-2,5-piperazinedione prepared in Reference Example 1, was treated with benzaldehyde in the presence of Cs_2CO_3 in DMF at 80°C for 5 hours to give starting compound 2.4 in 62% yield.

A solution of Compound 2.4 in DMF was treated first with KOtBu then with $BrCH_2CO_2Me$ at about 0°C and allowed to warm to room temperature to give compound 2.5 in 49% yield. The isomeric O-substitution product, compound 2.6, was also obtained in 37% yield. The two products were separated by chromatography.

Compound 2.5 was then treated with LiOH in aqueous dioxane at room temperature for 3 hours to give the final product 2.7 in 42% yield.

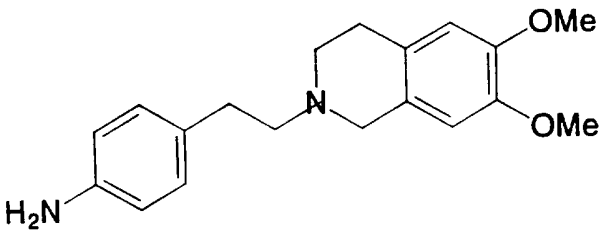
Method 3

The activated acyl chloride derivative of 2.7 prepared by Method 2, denoted compound 2.8, was prepared by treating 2.7 with oxalyl chloride in THF at a temperature of -78°C and allowing the resultant mixture to warm to 0°C.

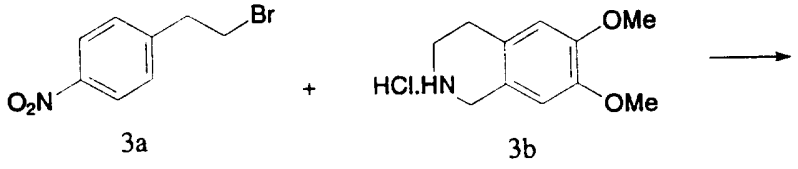
Alternatively, 2.7 was activated by conversion to the corresponding mixed anhydride by treatment with EtOCOCl in CH_2Cl_2 in the presence of Et_3N at 0°C.

Reference Example 3: Preparation of amines H-R^3

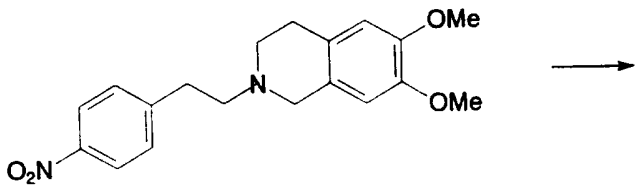
Compound 3.1



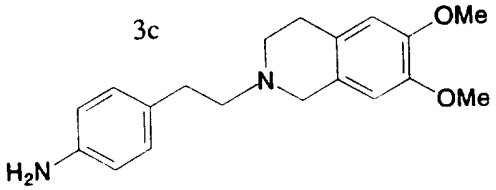
This compound was prepared according to the following scheme:



3a 3b



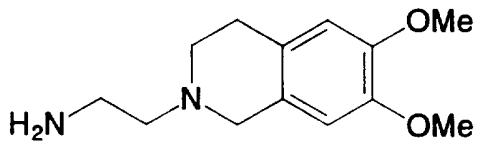
3c



3.1

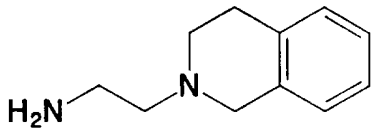
Compound 3a was treated with 3b in the presence of K_2CO_3 in DMF, at a temperature of 100°C for 12 hours, to give 3c in 78% yield. 3c was then reduced with Fe powder in concentrated HCl and MeOH at 80°C for 3 hours to give 3.1 in 51% yield. Alternatively 3c was reduced to 3.1 by catalytic hydrogenation at 30psi over a palladium on carbon catalyst in methanolic HCl for 3 hours, to give 3.1 in quantitative yield.

Compound 3.2



Compound 3b in the scheme above was treated with chloroacetonitrile in acetonitrile in the presence of K_2CO_3 under reflux for 24 hours. The resulting compound was reduced with $LiAlH_4$ in ethylene glycol dimethyl ether at about 0°C and allowed to warm to room temperature over 2 hours to give compound 3.2 in 98% yield.

Compound 3.3:



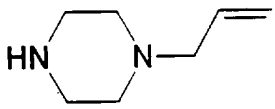
1,2,3,4-Tetrahydroisoquinoline was treated with chloroacetonitrile in the presence of K_2CO_3 in acetonitrile under reflux for 24 hours. The resulting 1,2,3,4-tetrahydro-2-isoquinolyl acetonitrile, obtained in 42%

yield, was treated with $LiAlH_4$ in ethylene glycol dimethyl ether at 0°C for 2 hours, to give 3.3 in 95% yield.

Compound 3.4: $H_2N-CH_2CH_2-N(Me)-CHPh_2$

Diphenylmethylamine was treated with $(CF_3CO)_2O$ in Et_2O at 0°C for 1 hour. The resulting compound $(Ph)_2-CH-NH-COCF_3$ was treated with KH in THF at 0°C followed by MeI in the presence of the crown ether 18-crown-6 at room temperature for 24 hours, to give $(Ph)_2-CH-NMe-COCF_3$ in 78% yield. The latter compound was treated with 2M NaOH in methanol under reflux for 2 hours to give $(Ph)_2-CH-NHMe$ in quantitative yield, which in turn was treated with chloroacetonitrile in the presence of K_2CO_3 in acetonitrile under reflux for 24 hours to give $(Ph)_2-NMe-CH_2CN$ in 31% yield. Reduction of this compound with $LiAlH_4$ in ethylene glycol dimethyl ether at 0°C for 2 hours gave 3.4 in 86% yield.

Compound 3.5:



Piperazine was treated with $CH_2=CH-CH_2Br$ in aqueous THF at 0°C and the resultant mixture allowed to warm to room temperature to yield 3.5 in a single step.

Compound 3.6: $H_2N-(CH_2)_2-NMe-CH_2CHPh_2$

2,2-Diphenylethylamine was treated with $(CF_3CO)_2O$ in Et_2O at 0°C for 1 hour. The resulting compound

$(Ph)_2$-CH-CH_2-$NHCOCF_3$, 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-CH_2-$NMeCOCF_3$ in 91% yield. The latter compound was treated with 2M NaOH in methanol under reflux for 2 hours to give $(Ph)_2$-CH-CH_2NHMe in 81% yield, which in turn was treated with chloroacetonitrile in the presence of K_2CO_3 in acetonitrile under reflux for 24 hours to give $(Ph)_2$-CH-CH_2-NMe-CH_2CN in 83% yield. Reduction of this compound with $LiAlH_4$ in ethylene glycol dimethyl ether at room temperature for 2 hours gave 3.6 in 90% yield.

Example 1: Preparation of compounds 9002 and 9019

1. Compound 2.3, prepared according to Reference Example 2, was treated with amine 3.2, prepared according to Reference Example 3, in the presence of 1-hydroxybenzotriazole and 1-cyclohexyl-3-(2-morpholinoethyl) carbodiimide metho-p-toluenesulphonate at room temperature for 18 hours to give N-(2-(6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-6-benzylidene-1,4-dimethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide.

This compound was then dissolved in THF and HCl gas was bubbled through the solution to form the hydrochloride salt, which is compound 9002.

2. Compound 2.3, prepared according to Reference Example 2, was treated with amine 3.1, prepared according to Reference Example 3, in the presence of 1,1'-

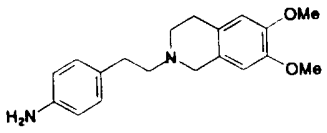
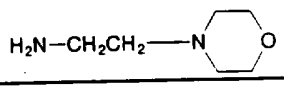
carbonyldiimidazole and 4-dimethylaminopyridine (catalytic amount) at a temperature of 0°C and the resultant mixture allowed to warm to room temperature to give compound 9019.

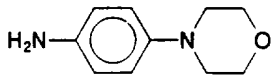
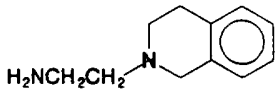
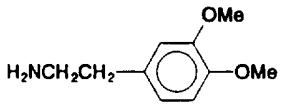
Example 2: Preparation of compound 9020

Compound 2.7, prepared according to Reference Example 2, was treated with EtOCOCl in the presence of triethylamine in CH_2Cl_2 at 0°C. The temperature was maintained at 0°C and amine 3.2, prepared according to Reference Example 3, was then added to the reaction mixture to give compound 9020 in 26% yield.

Under the same reaction conditions, but employing the appropriately substituted amine listed in Table 1 in place of compound 3.2, the following compounds of formula (I) were prepared:

TABLE 1

Compound of formula (I)	Amine H-R^3	Source of Amine
9021		Reference Example 3 (3.1)
9055		Commercial product
9056	$H_2N-CH_2CH_2-NMe_2$	Commercial product

9058		Commercial product
9060		Reference Example 3 (3.3)
9072	$H_2N-CH_2CH_2-N(Me)CHPh_2$	Reference Example 3 (3.4)
9073	$H_2N-CH_2CH=CH_2$	Commercial product
9094		Commercial product
9095	$H_2N-CH_2CH_2-NMe-CH_2CHPh_2$	Reference Example 3 (3.6)

Compounds 9055, 9056, 9058, 9060, 9072 and 9095 were converted in a final step to the corresponding hydrochloride salts, by bubbling gaseous HCl through a solution of each compound in THF.

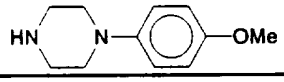
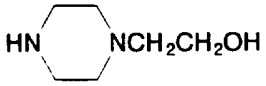
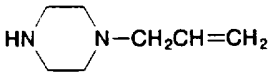
Example 3: Preparation of compound 9057

Compound 2.7, prepared according to Reference Example 2, was treated with oxalyl chloride in THF at a temperature of about 0°C. The resulting acid chloride derivative (a compound of formula II as defined earlier wherein R^{11} is -COCl and R^{21} is H) was then treated with N-methylpiperazine and triethylamine in THF at about -10°C to give compound 9057.

Under the same reaction conditions, but employing the

appropriately substituted amine listed in Table 2 in place of N-methylpiperazine, the following compounds of formula (I) were prepared:

TABLE 2

Compound of Formula I	Amine H-R^3	Source of Amine
9059		Commercial product
9074		Commercial product
9075		Reference Example 3 (3.5)

Compounds 9057, 9059 and 9075 were converted in a final step to the corresponding hydrochloride salts, by treatment with gaseous HCl in THF.

Example 4: Pharmaceutical Composition

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

Composition for 10,000 tablets

compound of the invention (250 g)

lactose (800 g)

corn starch (415 g)

talc powder (30 g)

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 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 5: Testing of compounds (I) as modulators of MDR

Materials and Methods

The EMT6 mouse mammary carcinoma cell line and the MDR resistant subline AR 1.0 were cultured in RPMI 1640 medium containing 10% foetal calf serum and 2mM glutamine at 37°C in 5% CO_2. 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 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, and unlabelled DNR (0.3 μ Ci/ml; 2μM). Compounds of formula I were serially diluted in assay medium over a range of concentrations from 5 nM to 100 μM. The cells were incubated at 37°C for 1 hr before washing and determination of cell associated radioactivity.

Results are expressed as % maximum accumulation where 100% accumulation is that observed in the presence of the known RMA verapamil at a concentration of 100μm or as an IC_{50}.

The results are set out in the following Table 3.

TABLE 3

Compound No.	IC_{50} (μM) Accumulation	Max Accumulation
9002	9	
9005		0%
9019	1	
9020	6	
9021	4	
9055	50	
9056		29%
9057	60	
9058	5	
9059	2	
9060	2	
9072	9	
9073		23%
9074		11%
9075	30	
9094	3.5	
9095	3	

2. Potentiation of Doxorubicin toxicity

Compounds of formula (I) were examined for their 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 (0.86μM) which alone is non-toxic to AR 1.0 cells. After a four day incubation with doxorubicin, proliferation was measured using the colorimetric sulphorhodamine B assay (Skehan et al; J.Natl. Cancer Inst. 82 pp 1107-1112 (1990)).

The results are shown in Table 4.

Compounds which were shown to be able to sensitise AR 1.0 cells to 0.86μM doxorubicin without high innate toxicity were selected for further study. Cells were cultured for four days with concentrations of doxorubicin over the range of 0.01 nM-50 μM in the presence of a fixed concentration of compounds of formula (I). Proliferation was quantified as described by Skehan et al, loc cit. The IC_{50} (concentration required to reduce proliferation to 50% of the untreated controls) for doxorubicin alone and for the compounds of formula (I) were derived and

used to calculate the potentiation index (PI):

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

The results are shown in Table 5:

TABLE 4

Compound No.	Compound toxicity (IC_{50} μM)	Toxicity with cytotoxic agent (IC_{50} μM)
9002	10	1
9019	2	0.01
9020	20	0.80
9021	6	0.3
9055	50	7
9058	40	0.3
9059	10	0.7
9060	6	0.08
9072	8	0.3
9094	25	0.5
9095	15	0.3

TABLE 5

Potentiation Indices	
Compound No.	Potentiation index (RMA at 1 μM)
9002	20
9019	100
9020	2
9021	25
9058	7.5
9059	15
9060	40
9072	9
9094	33
9095	25

Example 6: Characterisation of the present compounds

The compounds and salts prepared in the preceding Examples were characterised by mass spectroscopic and proton NMR techniques. The results are set out in Table 6:

TABLE 6

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9002 (free base)	$C_{34}H_{36}N_4O_5$	581(10), 388(40), 279(50), 208(100), 190(40)	CI	$CDCl_3$/400MHz	2.76-2.92 (6H,m), 2.95 (3H,s), 2.99 (3H,s), 3.63-3.72 (4H,m), 3.83 (2x3H,s), 6.53 (1H,s), 6.63 (1H,s), 7.21 (1H,s), 7.23-7.42 (8H,m), 7.79 (2H,d)
9005	$C_{21}H_{18}N_2O_4$	363(15), 116(100)	CI	$CDCl_3$ + CF_3CO_2H/ 400MHz	3.07 (3H,s), 4.38 (2H,s), 7.30-7.52 (12H,m)
9019	$C_{10}H_{40}N_4O_5$	656(2), 390(100)	EI	$CDCl_3$/400MHz	2.70-3.02 (14H,m), 3.65 (2H,s), 3.83 (2x3H,s), 6.53 (1H,s), 6.60 (1H,s), 7.20-7.95 (16H,m)
9020	$C_{34}H_{36}N_4O_5$	581(100)	ESI	$CDCl_3$/400MHz	2.58-2.90 (6H,m), 2.96 (3H,s), 3.33-3.70 (4H,m), 3.83 (2x3H,s), 4.14 (2H,s), 6.52 (1H,s), 6.59 (1H,s), 7.12-7.43 (13H,m)
9021	$C_{40}H_{40}N_4O_5$	657(9), 345(89), 317(100)	EI	$CDCl_3$/400MHz	2.72-2.98 (8H,m), 3.02 (3H,s), 3.65-3.78 (2H,bs), 3.84 (2x3H,s), 4.29 (2H,s), 6.52 (1H,s), 6.60 (1H,s), 7.10-7.45 (13H,m)

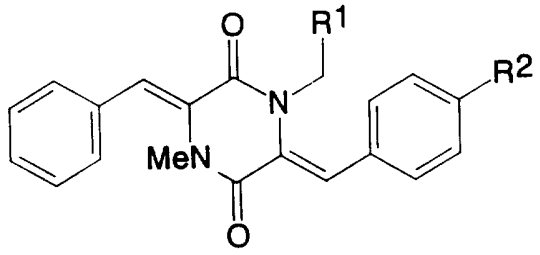
No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9055	$C_{27}H_{30}N_4O_4.HCl$	475(15), 100(20)	CI	$CDCl_3$/300MHz	2.88 (2H,m), 2.99 (3H,s), 3.13 (2H,m), 3.58 (4H,m), 3.94 (2H,m), 4.15 (2H,s), 4.25 (2H,t), 7.09 (1H,s), 7.17 (1H,s), 7.25-7.43 (10H,m), 8.15 (1H,s), 12.1 (1H,bs)
9056	$C_{25}H_{28}N_4O_3.HCl$	433(20), 362(2)	CI	d_6-DMSO/300MHz	2.68 (6H,s), 2.87 (2H,s), 3.01 (2H,m), 3.37 (2H,m), 4.1 (2H,s), 7.15 (1H,s), 7.35 (1H,s), 7.35-7.5 (10H,m), 8.37 (1H,bt) (70°C)
9057	$C_{26}H_{28}N_4O_3.HCl$			d_6-DMSO/300MHz	2.67 (3H,s), 2.87 (3H,s), 2.8-3.5 (8H,m), 4.40 (2H,s), 7.03 (2H,s), 7.34-7.50 (10H,m), 11.55 (1H,bs) (70°C)
9058	$C_{31}H_{30}N_4O_4.HCl$	523(7), 178(100)	CI	d_6-DMSO/300MHz	2.92 (3H,s), 3.20 (4H,t), 3.83 (4H,t), 4.25 (2H,s), 7.06 (1H,s), 7.08 (1H,s), 7.15 (2H,m), 7.3-7.6 (12H,m), 9.89 (1H,s) (70°C)
9059	$C_{32}H_{32}N_4O_4.HCl$	537(20), 235(100)	CI	d_6-DMSO/300MHz	2.90 (3H,s), 2.99 (4H,bs), 3.1-3.7 (4H,m), 3.71 (3H,s), 4.42 (2H,s), 6.89 (1H,s), 6.92 (1H,s), 7.06 (4H,m), 7.3-7.6 (10H,m)
9060	$C_{32}H_{32}N_4O_3.HCl$	522(16), 216(8)	CI	d_6-DMSO/300MHz	2.8-4.6 (10H,m), 2.88 (3H,s), 4.09 (2H,s), 7.03 (1H,s), 7.04 (1H,s), 7.1-7.3 (4H,m), 7.3-7.6 (10H,m), 8.43 (1H,bt)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9072	$C_{31}H_{36}N_4O_3.HCl$	585(80), 283(30), 198(60)	CI	$CDCl_3$/300MHz	2.75 (3H,bs), 3.0 (3H,s), 3.2-3.8 (4H,m), 4.2 (2H,m), 4.95 (1H,bs), 7.18 (1H,s), 7.20 (1H,s), 7.2-7.6 (16H,m), 7.6-7.9 (4H,m), 8.3 (1H,s), 11.9 (1H,s)
9073	$C_{21}H_{23}N_3O_3$	402(100)	CI	$CDCl_3$/300MHz	3.05 (3H,s), 3.82 (2H,t), 4.20 (2H,s), 5.15 (2H,m), 5.50 (1H,bt), 5.75 (1H,m), 7.21 (1H,s), 7.23 (1H,s), 7.25-7.55 (10H,m)
9074	$C_{27}H_{30}N_4O_4.HCl$	475(100)	CI	$CDCl_3$/300MHz	2.7-4.2 (12H,m), 3.0 (3H,s), 4.50 (2H,s), 7.18 (1H,s), 7.22 (1H,s), 7.3-7.6 (10H,m), 11.8 (1H,bs)
9075	$C_{28}H_{30}N_4O_3.HCl$	471(100), 169(85)	CI	$CDCl_3$/300MHz	2.5-4.2 (10H,m), 3.0 (3H,s), 4.6 (2H,s), 5.6 (2H,m), 6.17 (1H,m), 7.19 (1H,s), 7.28 (1H,s), 7.3-7.6 (10H,m), 13.3 (1H,bs)
9094	$C_{31}H_{31}N_3O_5$	543(20), 526(100)	CI	$CDCl_3$/300MHz	2.72 (2H,t), 3.04 (3H,s), 3.45 (2H,m), 3.86 (3H,s), 3.88 (3H,s), 4.12 (2H,s), 5.37 (1H,t), 6.70 (2H,m), 6.81 (1H,m), 7.23 (1H,s), 7.24 (1H,s), 7.35-7.45 (10H,m)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9095	$C_{36}H_{33}N_4O_3$ HCl	599(100), 481(30)	CI	d_6-DMSO/300MHz	2.77 (3H,d), 3.00 (3H,s) 3.0-4.2 (6H,m), 4.18 (2H,s) 4.74 (1H,t), 7.15 (2H,bs) 7.3-7.6 (20H,m), 8.54 (1H,m) 9.87 (1H,bs)

CLAIMS

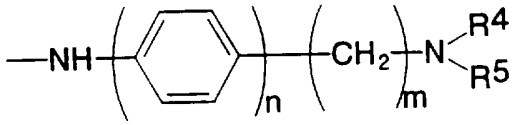
1. A piperazinedione derivative of formula (I):



(I)

wherein one of R^1 and R^2 is H and the other is a group $-COR^3$ wherein R^3 is selected from:

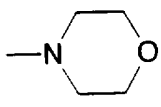
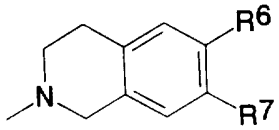
(i) hydroxy;

(ii)  (A)

wherein n is 0 or 1 and m is 0, 1, 2, 3 or 4, 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, or

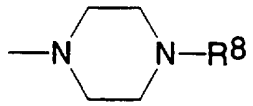
(b) R^4 and R^5, together with the nitrogen atom to which they are attached, form a heterocyclic group selected from

 and  (B)

wherein R^6 and R^7, which are the same or different, are each hydrogen or C_1-C_6 alkoxy, or R^6 and R^7 form

together a methylenedioxy group;

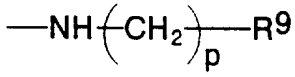
(iii)



(C)

wherein R^8 is C_1-C_6 alkyl optionally substituted by hydroxy, C_2-C_6 alkenyl, or a phenyl group optionally substituted by C_1-C_6 alkoxy; and

(iv)



(D)

wherein p is 1, 2 or 3 and R^9 is C_2-C_6 alkenyl or a phenyl group optionally substituted by C_1-C_6 alkoxy;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 is H, R^2 is a group $-COR^3$ in which R^3 is a group of formula (A) as defined in claim 1 in which n is 0 or 1 and m is 2, and R^4 and R^5 form together with the nitrogen atom to which they are attached a heterocyclic ring selected from morpholino and a group of formula (B) wherein R^6 and R^7 are both hydrogen or C_1-C_6 alkoxy, or together form a methylenedioxy group.

3. A compound according to claim 1 wherein R^2 is H, R^1 is a group $-COR^3$ in which R^3 is a group of formula (A) as defined in claim 1 in which n is 0 and m is 1 or 2, or n is 1 and m is 2, or n is 1 and m is 0, and either

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

alkyl or C_1-C_6 alkyl subsituted on the terminal C atom by 2 phenyl rings; or

(b) R^4 and R^5 form together with the nitrogen atom to which they are attached a morpholino group or a heterocyclic ring (B) as defined in claim 1 wherein R^6 and R^7 are both hydrogen or both C_1-C_6 alkoxy, or together form a methylenedioxy group.

4. A compound according to claim 1 wherein R^2 is H, R^1 is a group $-COR^3$ in which R^3 is a group of formula (C) as defined in claim 1 in which R^8 is unsubstituted C_1-C_6 alkyl, or is a 2-hydroxyethyl, ethenyl, prop-1-enyl or prop-2-enyl group, or a 4-methoxyphenyl group.

5. A compound according to claim 1 wherein R^2 is H, R^1 is a group $-COR^3$ in which R^3 is a group of formula (D) as defined in claim 1 wherein p is 1 or 2 and R^9 is ethenyl, prop-1-enyl, prop-2-enyl or phenyl substituted by one or two C_1-C_6 alkoxy groups.

6. A compound selected from :

((3Z,6Z)-3,6-Dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetic acid (9005)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide (9020)

N-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide, hydrochloride (9060)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide (9021)

N-(2-Morpholinoethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide, hydrochloride (9055)

N-(2-Dimethylaminoethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide, hydrochloride (9056)

N-(2-Diphenylmethylmethylaminoethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide, hydrochloride (9072)

N-Allyl-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide (9073)

N-(4-Morpholinophenyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide, hydrochloride (9058)

1-((3Z,6Z)-3,6-Dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetyl-4-methylpiperazine, hydrochloride (9057)

1-((3Z,6Z)-3,6-Dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetyl-4-(4-methoxyphenyl)piperazine, hydrochloride (9059)

1-((3Z,6Z)-3,6-Dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetyl-4-(2-hydroxyethyl)piperazine (9074)

1-((3Z,6Z)-3,6-Dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetyl-4-allylpiperazine, hydrochloride (9075)

N-(3,4-Dimethoxyphenethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide (9094)

N-(2-(2,2-Diphenylethyl)methylaminoethyl)-((3Z,6Z)-3,6-dibenzylidene-4-methyl-2,5-dioxo-1-piperazinyl)acetamide, hydrochloride (9095)

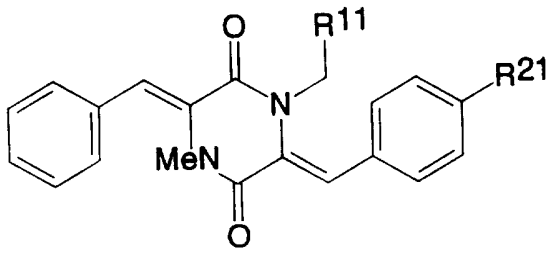
N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-

isoquinolyl)ethyl)-4-((3Z,6Z)-6-benzylidene-1,4-dimethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9002)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1,4-dimethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9019)

7. A pharmaceutical or veterinary composition comprising 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 a compound of formula (II):



(II)

wherein one of R^{11} and R^{21} is hydrogen and the other is -COOH, -COX wherein X is halogen, or -CO(OCOR') wherein R' is C_1-C_6 alkyl, with an amine of formula

$H-R^3$

wherein R^3 is as defined in claim 1 excluding OH, in an organic solvent, the reaction being conducted in the presence of a coupling agent when R^{11} or R^{21} is -COOH; 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.

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/GB 95/03028

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D241/02 C07D401/12 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,94 04513 (XENOVA LTD) 3 March 1994 see claims ---	1,7,9,10
Y	WO,A,94 01408 (GLAXO LAB SA) 20 January 1994 see claims ---	1,7,9,10
A	WO,A,94 04512 (XENOVA LTD) 3 March 1994 see claims -----	1,7,9,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 January 1996	09.02.96

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ual Application No
PCT/GB 95/03028

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		CA-A-	2141939	03-03-94
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		CZ-A-	9500381	13-09-95
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		EP-A-	0672036	20-09-95
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		FI-A-	950617	13-04-95
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