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PHARMACEUTICAL PIPERAZINE COMPOUNDS

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(56) Prior Art Documents
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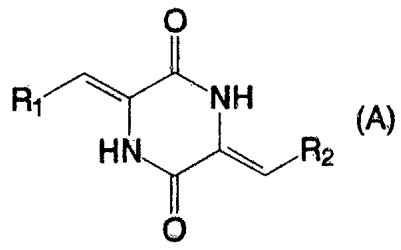
(57) The present invention relates to compounds useful as inhibitors of plasminogen activator inhibitor (PAI), to their preparation and to pharmaceutical and veterinary compositions containing them.

Claim

1. A piperazine of general formula (A):

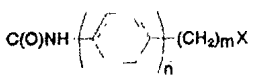


(A)

wherein one or both of R_1 and R_2, which may be the same or different, is:

(I) X, or a phenyl group which is substituted by X, $C(O)X$, $OC(O)CH_2X$, OCH_2CH_2X, CH_2X, $CONH(CH_2)_nX$,

.../2

$O(CH_2)_nCH(OH)(CH_2)_nX$ or 

or which is fused to a group X;

(II) a phenyl group substituted by $CH_2NR_{12}R_{13}$, $OC(O)(CH_2)_nZ$, $CH(OR_{12})(OR_{13})$, $(CH_2)_nNR_{14}C(O)(CH_2)_mNR_{12}R_{13}$, $-CH_2NR_{12}-(CH_2)_nNR_{15}R_{16}$ or $O(CH_2)_nCH(OH)(CH_2)_nN(R_{12}R_{13})$;

(III) a group $CH=C(W)V$; or

(IV) a cyclohexyl group;

and where appropriate, the other of R_1 and R_2 is a phenyl group optionally substituted by one or more groups independently selected from halogen, nitro, methoxy, $NHC(O)R_{12}$, CO_2H, $O(CH_2)_nN(R_{12}R_{13})$, $CH_2Y(CH_2)_nN(R_{12}R_{13})$, C_1-C_4 alkyl and $(CH_2)_nC(O)OR_{12}$;

X is a five- or six-membered saturated or unsaturated heterocyclic group containing one or more heteroatoms, which heteroatoms may be the same or different and are independently selected from O, N and S; the heteroatom(s) when nitrogen being optionally substituted by hydrogen, methyl, oxygen, tertiary-butyloxycarbonyl, $-(CH_2)_nCH_2OH$ or SO_2Me; the heterocyclic ring being optionally substituted by halogen, Me, MeS, phenyl, $O(CH_2)_nNR_{12}R_{13}$, $-N(R_{12})(CH_2)_nN(R_{12}R_{13})$, $-(CH_2)_nN(R_{12}R_{13})$ or $-O(CH_2)_nO(CH_2)_nN(R_{12}R_{13})$, or the heterocyclic ring optionally containing one or more carbonyl groups and being optionally fused to a benzene ring, which benzene ring is optionally substituted by 1 or 2 C_1-C_6 alkoxy groups;

Y is O or S;

Z is a C_3-C_6 cycloalkyl group;

R_{12}, R_{13} and R_{14}, which may be the same or different, are hydrogen or C_1-C_6 alkyl;

R_{15} and R_{16}, which may be the same or different, are hydrogen or C_1-C_6 alkyl, or R_{15} and R_{16} form, together with the atom to which they are attached, a 5- or 6-membered heterocyclic group;

W is hydrogen or a phenyl group;

V is a phenyl group optionally substituted by one or more groups independently selected from nitro, alkoxy, $O(CH_2)_nNR_{12}R_{13}$ and $NR_{12}R_{13}$; and

m and n are each, independently, O or an integer having the value 1, 2, 3 or 4; or a pharmaceutically acceptable salt or ester thereof; with the exception of

3,6-diisonicotinylidenepiperazine-2,5-dione,

3,6-difurfurylidenepiperazine-2,5-dione,

3,6-di-(2-thiophenylidene)piperazine-2,5-dione and

3,6-dicinnamylidene-2,5-piperazinedione.

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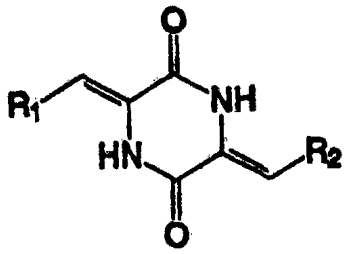
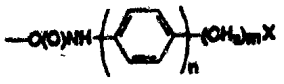
(54) Title: PHARMACEUTICAL PIPERAZINE COMPOUNDS

(57) Abstract

A diketopiperazine of formula (A), wherein one or both of R_1 and R_2, which may be the same or different, is: (I) X, or a phenyl group which is substituted by X, C(O)X, $OC(O)CH_2X$, OCH_2CH_2X, CH_2X, $CONH(CH_2)_nX$, $O(CH_2)_nCH(OH)$ $(CH_2)_nX$ or (a) or which is fused to a group X; (II) a phenyl group substituted by $CH_2NR_{12}R_{13}$, $OC(O)$ $(CH_2)_nZ$, $CH(OR_{12})(OR_{13})$, $(CH_2)_nNR_{14}C(O)$ $(CH_2)_mNR_{12}R_{13}$ or $O(CH_2)_nCH(OH)$ $(CH_2)_nN(R_{12}R_{13})$; (III) a group $CH=C(W)V$; or (IV) a cyclohexyl group; and where appropriate, the other of R_1 and R_2 is a phenyl group optionally substituted by one or more groups independently selected from halogen, nitro, methoxy, $NHC(O)R_{12}$, CO_2H, $O(CH_2)_nN(R_{12}R_{13})$ and $CH_2Y(CH_2)_nN(R_{12}R_{13})$; R_3 is C_1-C_4 alkyl or $(CH_2)_nC(O)OR_{12}$; Y is O or S; Z is a C_3-C_6 cycloalkyl group; W is hydrogen or a phenyl group; and the pharmaceutically acceptable salts and esters thereof having activity as inhibitors of plasminogen activator inhibitor.



(A)



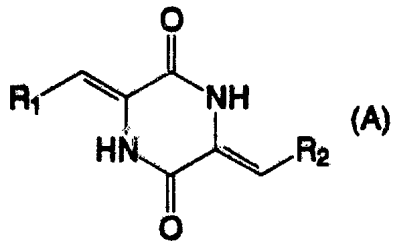
(a)

PHARMACEUTICAL PIPERAZINE COMPOUNDS

The present invention relates to compounds useful as inhibitors of plasminogen activator inhibitor (PAI), to their preparation and to pharmaceutical and veterinary compositions containing them.

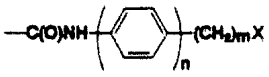
Plasminogen activators (Pas) are serine proteases which control the activation of the zymogen, plasminogen, to the active enzyme plasmin. Plasmin is important in a number of physiological and pathological processes including fibrinolysis, tissue remodelling, tumour growth and metastasis. The glycoprotein plasminogen activator inhibitor (PAI) is an endogenous fast-acting inhibitor of PA activity. PAI is a member of the serpin family and is synthesised by a variety of cells including endothelial cells. An imbalance between PAs and PAI contributes to a number of pathological conditions including haemostasis, inflammation, tumour growth and metastasis.

The present invention provides a diketopiperazine of formula (A):



(A)

wherein one or both of R_1 and R_2, which may be the same or different, is:

(I) X, or a phenyl group which is substituted by X, $C(O)X$, $OC(O)CH_2X$, OCH_2CH_2X, CH_2X, $CONH(CH_2)_nX$, $O(CH_2)_nCH(OH)(CH_2)_nX$ or 

or which is fused to a group X;

(II) a phenyl group substituted by $CH_2NR_{12}R_{13}$, $OC(O)(CH_2)_nZ$, $CH(OR_{12})(OR_{13})$, $(CH_2)_nNR_{14}C(O)(CH_2)_mNR_{12}R_{13}$, $-CH_2NR_{12}-(CH_2)_nNR_{15}R_{16}$ or $O(CH_2)_nCH(OH)(CH_2)_nN(R_{12}R_{13})$;

(III) a group $CH=C(W)V$; or

(IV) a cyclohexyl group;

and where appropriate, the other of R_1 and R_2 is a phenyl group optionally substituted by one or more groups independently selected from halogen, nitro, methoxy, $NHC(O)R_{12}$, CO_2H, $O(CH_2)_nN(R_{12}R_{13})$, $CH_2Y(CH_2)_nN(R_{12}R_{13})$, C_1-C_4 alkyl and $(CH_2)_nC(O)OR_{12}$;

X is a naphthyl group or a five- or six-membered saturated or unsaturated heterocyclic group containing one or more heteroatoms, which heteroatoms may be the same or different and are independently selected from O, N and S; the heteroatom(s) when nitrogen being optionally substituted by hydrogen, methyl, oxygen, tertiary-butyloxycarbonyl, $-(CH_2)_nCH_2OH$ or SO_2Me; the heterocyclic ring being optionally substituted by halogen, Me, MeS, phenyl, $O(CH_2)_nNR_{12}R_{13}$, $-N(R_{12})(CH_2)_nN(R_{12}R_{13})$, $-(CH_2)_nN(R_{12}R_{13})$ or $-O(CH_2)_nO(CH_2)_nN(R_{12}R_{13})$, or the heterocyclic ring optionally containing one or more carbonyl groups and being optionally fused to a benzene ring, which benzene ring is optionally substituted by 1 or 2 C_1-C_6 alkoxy groups;

Y is O or S;

Z is a C_3-C_6 cycloalkyl group;

R_{12}, R_{13} and R_{14}, which may be the same or different, are hydrogen or C_1-C_6 alkyl;

R_{15} and R_{16}, which may be the same or different, are hydrogen or C_1-C_6 alkyl, or R_{15} and R_{16} form, together with the nitrogen atom to which they are attached, a 5- or 6-membered heterocyclic group;

W is hydrogen or a phenyl group;

V is a phenyl group optionally substituted by one or more groups independently selected from nitro, alkoxy, $O(CH_2)_nNR_{12}R_{13}$, and $NR_{12}R_{13}$; and

m and n are each, independently, 0 or an integer having the value 1, 2, 3 or 4;

or a pharmaceutically acceptable salt or ester thereof;

with the exception of

3,6-diisonicotinylidenepiperazine-2,5-dione,

3,6-difurfurylidenepiperazine-2,5-dione,

3,6-di-(2-thiophenylidene)piperazine-2,5-dione and

3,6-dicinnamylidene-2,5-piperazinedione.

A C_1-C_6 alkyl group is, for example, a C_1-C_4 alkyl group, such as a methyl, ethyl, propyl, i-propyl, n-butyl, sec-butyl or tert-butyl group.

A halogen may be F, Cl, Br or I.

In compounds of formula A free rotation may occur at room temperature about the single bonds connecting substituents R_1 and R_2 to the double bonds at positions 3 and 6 of the piperazine-2,5-dione ring.

In one embodiment at least one of R_1 and R_2, which may be the same or different, is chosen from X and a phenyl group which is substituted by X, $C(O)X$, $OC(O)CH_2X$, OCH_2CH_2X, or CH_2X or which is fused to a group X; X is a five- or six-membered saturated or

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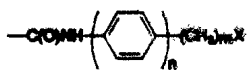
unsaturated heterocyclic group containing one or two heteroatoms, which heteroatoms may be the same or different and are independently selected from O, N and S, the heteroatom(s) when nitrogen being optionally substituted by hydrogen, methyl, oxygen, tertiary-butyloxycarbonyl, $-(CH_2)_nCH_2OH$ or SO_2Me, the heterocyclic ring being optionally substituted by hydrogen, halogen, methyl, MeS, phenyl, $O(CH_2)_nNR_{12}R_{13}$, $O(CH_2)_nN(R_{12}R_{13})$ or $-O(CH_2)_nO(CH_2)_nN(R_{12}R_{13})$; the heterocyclic ring optionally containing one or more carbonyl groups, and being optionally fused to a benzene ring; and the other of R_1 and R_2 is a phenyl group optionally substituted at the 2, 3 or 4-position by $CH_2NR_{12}R_{13}$, $(CH_2)_nNR_{14}C(O)(CH_2)_mNR_{12}R_{13}$, halogen, nitro, $-NHC(O)R_{12}$, $-O(CH_2)_nN(R_{12}R_{13})$ or $-CH_2Y(CH_2)_nN(R_{12}R_{13})$ wherein Y is O or S. In a particularly preferred series of compounds the said other of R_1 and R_2 is a phenyl group substituted at the 4-position by $-O(CH_2)_nN(R_{12}R_{13})$, $-CH_2Y(CH_2)_nN(R_{12}R_{13})$ or $-(CH_2)_nNR_{14}C(O)(CH_2)_mNR_{12}R_{13}$.

In a further embodiment one of R_1 and R_2 is X, a phenyl group substituted by X, $-CH_2X$, $-OCH_2CH_2X$, $O(CH_2)_nCH(OH)CH_2X$ or  ; wherein X is a 5 or 6-membered saturated or unsaturated heterocyclic group as defined above which is optionally substituted and optionally fused to a benzene ring, for instance a pyridyl, imidazolyl, furyl, pyrrolyl, pyrrolidinyl, thienyl, piperazinyl, piperidinyl, morpholinyl, quinolyl, isoquinolyl or indolyl group; and the other of R_1 and R_2 is

a phenyl group optionally substituted at the 4-position by $-O(CH_2)_nN(R_{12}R_{13})$, $-CH_2Y(CH_2)_nN(R_{12}R_{13})$ or $-(CH_2)_nNR_{14}C(O)(CH_2)_mNR_{12}R_{13}$. In this embodiment it is particularly preferred for X to be a furyl, imidazolyl, pyrrolyl, thienyl, morpholinyl, piperidinyl or isoquinolyl group.

In a further embodiment, R_{12} and R_{13}, which may be the same or different, are hydrogen or C_1-C_3 alkyl and n is an integer of value 1 or 2.

In a yet further embodiment one of R_1 and R_2 is a phenyl group which is substituted by X, $CO(X)$, $OCO(O)CH_2X$, OCH_2CH_2X, CH_2X or which is fused to a group X, wherein X is a five- or six-membered heterocyclic ring containing one or two heteroatoms which may be the same or different, independently selected from O, N and S, the heteroatom(s) when nitrogen being optionally substituted by methyl, and the heterocyclic ring being optionally fused to a benzene ring.

In another embodiment one of R_1 and R_2 is a phenyl group substituted by $CH_2NR_{12}R_{13}$, $OC(O)(CH_2)_nZ$, $CH(OR_{12})(OR_{13})$, $(CH_2)_nNR_{14}C(O)(CH_2)_mN(R_{12}R_{13})$; wherein R_{12}, R_{13} and R_{14}, which may be the same or different, are independently selected from hydrogen or C_1-C_3 alkyl; Z is a C_5 or C_6 cycloalkyl group; and m and n are, independently, integers having the values 1, 2 or 3.

In a further embodiment R_{12}, R_{13} and R_{14}, which may be the same or different, are independently selected from hydrogen and C_1-C_2 alkyl; Z is a cyclopentyl group; and

m and n are, independently, integers having the values of 1 or 2.

In a yet further embodiment one of R_1 and R_2 is a phenyl group optionally substituted by one or more groups independently selected from chloro, nitro, methoxy, $NHCOR_{12}$, CO_2H and $O(CH_2)_nNR_{12}R_{13}$; R_{12} and R_{13}, which may be the same or different, are independently selected from hydrogen or methyl and n is an integer having the value 1 or 2.

In another embodiment one of R_1 and R_2 is a group $CH=C(W)V$, W is a phenyl group optionally substituted by one of more groups independently selected from nitro, methoxy and $O(CH_2)_nNMe_2$ and n is an integer having the value 1, 2,3 or 4.

In a further embodiment n is 1 or 2.

In a yet further embodiment one of R_1 and R_2 is a phenyl group optionally substituted by NHAc or methoxy.

In another embodiment one of R_1 and R_2 is cyclohexyl and the other is a phenyl group optionally substituted by $NHC(O)R_{12}$.

In a further embodiment one of R_1 and R_2 is cyclohexyl and the other is a phenyl group optionally substituted by NHC(O)Me.

In a further embodiment R_3 is C_1-C_2 alkyl or $(CH_2)_nC(O)OR_{12}$; R_{12} is hydrogen or C_1-C_2 alkyl and n is an integer of value 1 or 2.

In a yet further embodiment R_3 is methyl or $CH_2C(O)OR_{12}$ and R_{12} is hydrogen or methyl.

Certain diketopiperazines have been disclosed as

having utility as bioactive agents. Yokoi et al in J. Antibiotics vol XLI No. 4, pp 494-501 (1988) describe structure-cytotoxicity relationship studies on a series of diketopiperazines related to neihumicin, a compound obtained from the micro-organism Micromonospora neihuensis. Kamei et al in J. Antibiotics vol XLIII No. 8, 1018-1020 disclose that two diketopiperazines, designated piperafizines A and B, have utility as potentiators of the cytotoxicity of vincristine.

Examples of specific compounds of formula A are as follows. The compound numbering is adhered to in the rest of the specification:

1926 (3Z,6Z)-3-Benzylidene-6-(4-imidazolyl)methylene-2,5-piperazinedione.

1930 (3Z,6Z)-3-Benzylidene-6-(4-(1-imidazolyl)benzylidene)-2,5-piperazinedione.

1929 (3Z,6Z)-3-Benzylidene-6-(4-(1-imidazolylmethyl)benzylidene)-2,5-piperazinedione.

1927 (3Z,6Z)-3-Benzylidene-6-(4-(5-methylimidazolyl))methylene-2,5-piperazinedione.

1921 (3Z,6Z)-3-Benzylidene-6-(4-dimethylaminocinnamylidene)-2,5-piperazinedione.

1976 (3Z,6Z)-3-(4-(3-Dimethylaminopropoxy)benzylidene)-6-(4-(1-imidazolyl)benzylidene-2,5-piperazinedione.

1910 (3Z,6Z)-3-Benzylidene-6-(4-(2-imidazolylethoxy)benzylidene)-2,5-piperazinedione.

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1923 (3Z,6Z)-3-Benzylidene-6-(4-nitrocinnamylidene-2,5-piperazinedione.

1657 (3Z,6Z)-3-(4-Aminomethylbenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione.

1693 (3Z,6Z)-3-(1-methanesulfonyl-3-indolyl)methylene-6-(4-methoxybenzylidene)-2,5-piperazinedione.

1886 (3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-phthalimidoacetoxybenzylidene)-2,5-piperazinedione.

1922 (3Z,6Z)-3-Benzylidene-6-(γ-phenylcinnamylidene)-2,5-piperazinedione.

1618 (3Z,6Z)-3-(1-tert-butoxycarbonyl-3-indolyl)methylene-6-(2-thenylidene)-2,5-piperazinedione.

1560 (3Z,6Z)-3-(2,6-Dichlorobenzylidene)-6-(1-tert-butoxycarbonyl-3-indolyl)methylene-2,5-piperazinedione.

1950 (3Z,6Z)-3-Benzylidene-6-(4-(2-dimethylaminoethoxy)-3-methoxycinnamylidene)-2,5-piperazinedione.

1975 (3Z,6Z)-3-(4-(3-Dimethylaminopropoxy)benzylidene)-6-(4-(1-imidazolylmethyl)benzylidene)-2,5-piperazinedione.

1983 (3Z,6Z)-3-Benzylidene-6-(4-N-methyl-N-(4-(N-methylpiperidinyl))aminomethylbenzylidene-2,5-piperazinedione.

1509 (3Z,6Z)-3-Benzylidene-6-(3-indolylmethylene)-2,5-piperazinedione.

1542 (3Z,6Z)-3-(2,6-Dichlorobenzylidene)-6-(3-furylmethylene)-2,5-piperazinedione.

1545 (3Z,6Z)-3-(3-Indolylmethylene)-6-(4-methoxybenzylidene)-2,5-piperazinedione.

1507 (3Z,6Z)-3-(4-Methoxybenzylidene)-6-(2-(1-

tertbutoxycarbonyl)pyrrolyl)methylene-2,5-piperazinedione.

1506 (3Z,6Z)-3-(4-Methoxybenzylidene)-6-(3-(1-tert-butoxycarbonyl)indolyl)methylene-2,5-piperazinedione.

1471 (3Z,6Z)-3-Benzylidene-6-(3-(1-tert-butoxycarbonyl)indolyl)methylene-2,5-piperazinedione.

1474 (3Z,6Z)-3-(4-Methoxybenzylidene)-6-(2-thienylmethylene)-2,5-piperazinedione.

1476 (3Z,6Z)-3-(4-Methoxybenzylidene)-6-(3-furylmethylene)-2,5-piperazinedione.

1672 (3Z,6Z)-3-(Acetamidobenzylidene)-6-cyclohexylmethylene-2,5-piperazinedione.

1676 (3Z,6Z)-3-(4-Acetamidobenzylidene)-6-cinnamylidene-2,5-piperazinedione.

1891 (3Z,6Z)-3-Benzylidene-6-(diethoxymethylbenzylidene)-2,5-piperazinedione.

1982 (3Z,6Z)-3-Benzylidene-6-(4-(N-methyl-N-(2-dimethylaminoethyl)aminomethylbenzylidene-2,5-piperazinedione hydrochloride.

1884 (3Z,6Z)-3-Benzylidene-6-cyclohexylmethylene-2,5-piperazinedione.

1845 (3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(3,4-methylenedioxybenzylidene)-2,5-piperazinedione.

1950 (3Z,6Z)-3-benzylidene-6-(4-(2-dimethylaminoethoxy)-3-methoxycinnamylidene)-2,5-piperazinedione.

1718 (3Z,6Z)-3-(2-Indolylmethylene)-6-(4-methoxybenzylidene)-2,5-piperazinedione.

1808 (3Z,6Z)-3-Benzylidene-6-(3,4-methylenedioxybenzylidene)-2,5-piperazinedione.

1809 (3Z,6Z)-3-(4-Methoxybenzylidene)-6-(3,4-methylenedioxybenzylidene)-2,5-piperazinedione.

1470 (3Z,6Z)-3-Benzylidene-6-(2-(1-tertbutoxycarbonyl)pyrrolyl)methylene-2,5-piperazinedione.

5023 (3Z,6Z)-3-(4-Dimethylaminomethylbenzylidene)-6-(4-(3-dimethylaminopropoxy)benzylidene-2,5-piperazinedione.

5026 (3Z,6Z)-3-(4-(3-Dimethylaminopropoxy)benzylidene)-6-(4-(1-imidazolyl)methylbenzylidene)-2,5-piperazinedione.

5030 (3Z,6Z)-3-(4-(3-Dimethylaminopropoxy)benzylidene)-6-(4-(1-imidazolyl)benzylidene)-2,5-piperazinedione.

5367 (2-(4-((3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-2,5-dioxo-3-piperazinylidene)methylbenzoyl)-1,2,3,4-tetrahydroisoquinoline.

5386 N-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-6-(4-(3-dimethylaminopropoxy)benzylidene)-2,5-dioxo-3-piperazinylidene)methylbenzamide.

5397 N-(4-(1,2,3,4-Tetrahydro-2-isoquinolyl)butyl)-4-((3Z,6Z)-6-(4-(3-dimethylaminopropoxy)benzylidene)-2,5-dioxo-3-piperazinylidene)methylbenzamide.

5027 (3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene-3-(4-pyridylmethylene)-2,5-piperazinedione.

5028 (3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-(3-pyridylmethylene)-2,5-piperazinedione.

5041 (3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-furfurylidene-2,5-piperazinedione.

5042 (3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-(3-Thenylidene)-2,5-piperazinedione.

5046 (3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-(2-Thenylidene)-2,5-piperazinedione.

5052 (3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-(3-Furylmethylene)-2,5-piperazinedione.

5188 (3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-(2-Naphthylmethylene)-2,5-piperazinedione.

5200 (3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-(1-Naphthylmethylene)-2,5-piperazinedione.

5032 (3Z,6Z)-6-Benzylidene-3-(4-(3-dimethylamino-2-hydroxypropoxy)benzylidene)-2,5-piperazinedione.

5040 (3Z,6Z)-6-Benzylidene-3-(4-(2-hydroxy-3-morpholinopropoxy)benzylidene)-2,5-piperazinedione.

5057 (3Z,6Z)-6-Benzylidene-3-(4-(2-hydroxy-3-(1-imidazolyl)propoxy)benzylidene)-2,5-piperazinedione.

5043 (3Z,6Z)-6-Benzylidene-3-(4-(2-hydroxy-3-(4-(2-hydroxyethyl)-1-piperazinyl)propoxy)benzylidene)-2,5-piperazinedione.

5062 (3Z,6Z)-6-(4-(2-Dimethylaminoethoxy)benzylidene)-3-(3-furylmethylene)-2,5-piperazinedione.

5071 (3Z,6Z)-6-(4-(2-Dimethylaminoethoxy)benzylidene)-3-(3-thenylidene)-2,5-piperazinedione.

5072 (3Z,6Z)-6-(4-(2-Dimethylaminoethoxy)benzylidene)-3-(5-methylthio-2-thenylidene)-2,5-piperazinedione.

5054 (3Z,6Z)-6-Benzylidene-3-(4-(2-

morpholinoethoxy)benzylidene)-2,5-piperazinedione.

5055 (3Z,6Z)-6-Benzylidene-3-(4-(2-(1-imidazolyl)ethoxy)benzylidene)2,5-piperazinedione.

5053 (3Z,6Z)-6-Benzylidene-3-(4-(2-(1-pyrrolidinyl)ethoxy)benzylidene)2,5-piperazinedione.

5069 (3Z,6Z)-6-(4-(2-Dimethylaminoethoxymethyl)benzylidene)-3-(3-thenylidene)-2,5-piperazinedione.

5077 (3Z,6Z)-6-(4-(2-Dimethylaminoethoxymethyl)benzylidene)-3-(3-furylmethylene)-2,5-piperazinedione.

5074 (3Z,6Z)-6-(4-Dimethylaminoacetamidomethyl benzylidene)-3-(3-thenylidene)-2,5-piperazinedione.

5079 (3Z,6Z)-3-(2-Bromobenzylidene)-6-(4-dimethylaminoacetamidomethylbenzylidene)-2,5-piperazinedione.

5081 (3Z,6Z)-6-(4-Dimethylaminoacetamidomethylbenzylidene)-3-(3-furylmethylene)-2,5-piperazinedione.

5061 (3Z,6Z)-6-Benzylidene-3-(4-dimethylaminoacetamidomethylbenzylidene)-2,5-piperazinedione.

5073 (3Z,6Z)-6-(4-(2-Dimethylaminoethylthiomethyl)benzylidene)-3-(3-furylmethylene)-2,5-piperazinedione.

5078 (3Z,6Z)-6-(4-(2-Dimethylaminoethylthiomethyl)benzylidene)-3-(3-thenylidene)-2,5-piperazinedione.

1912 (3Z,6Z)-6-Benzylidene-3-(4-

dimethylaminoacetamidoaminomethylbenzylidene)-2,5-piperazinedione.

5324 (3Z,6Z)-6-Benzylidene-3-(5-(2-dimethylaminoethoxy)-2-thienylmethylene)-2,5-piperazinedione.

5327 (3Z,6Z)-6-Benzylidene-3-(4-(2-dimethylaminoethoxy)-2-thienylmethylene)-2,5-piperazinedione.

5335 (3Z,6Z)-6-Benzylidene-3-(5-(2-dimethylaminoethyl)-2-thienylmethylene)-2,5-piperazinedione.

5388 (3Z,6Z)-6-Benzylidene-3-(5-(2-(2-dimethylaminoethoxy)ethoxy)-2-thienylmethylene)-2,5-piperazinedione.

5389 (3Z,6Z)-6-Benzylidene-3-(5-(6-dimethylaminohexyloxy)-2-thienylmethylene)-2,5-piperazinedione.

5299 (3Z,6Z)-6-Benzylidene-3-(5-(2-dimethylaminoethyl)methylamino-2-thienylmethylene)-2,5-piperazinedione.

5075 (3Z,6Z)-3-(2,5-Dichloro-3-thenylidene)-6-benzylidene-2,5-piperazinedione.

5371 N-(4-(1,2,3,4-Tetrahydro-2-isoquinolyl)butyl)-4-((3Z,6Z)-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide.

5391 N-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide.

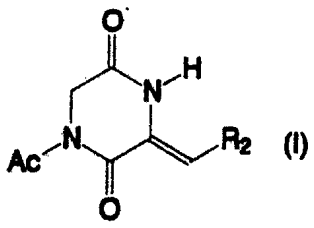
5394 N-(3-(1,2,3,4-Tetrahydro-2-isoquinolyl)propyl)-4-((3Z,6Z)-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide.

5393 N-(4-(2-(1,2,3,4-Tetrahydro-2-

isoquinolyl)ethyl)phenyl-4-((3Z,6Z)-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide.

5402 N-(4-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-2,5-dioxo-6-(4-nitrobenzylidene)-3-piperazinylidene)methylbenzamide.

Compounds of formula A, may be prepared by a process which comprises either (i) condensing compound of formula (I)

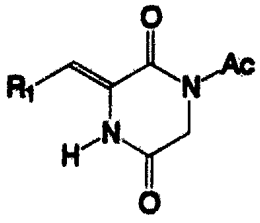


(I)

wherein R_2 is as defined above and is optionally protected, with a compound of formula (II):

$$R_1—CHO \quad (II)$$

wherein R_1 is as defined above and is optionally protected, in the presence of a base in an organic solvent; or (ii) condensing a compound of formula (I'):



(I')

wherein R_1 is as defined above and is optionally protected, with a compound of formula (III):

$$R_2—CHO \quad (III)$$

wherein R_2 is as defined above and is optionally protected,

in the presence of a base in an organic solvent; and, in either case (i) or (ii), if required, removing optionally present protecting groups and/or, if desired, converting one compound of formula A into another compound of formula A, and/or, if desired, converting a compound of formula A into a pharmaceutically acceptable salt or ester thereof, and/or, if desired, converting a salt or ester into a free compound, and/or, if desired, separating a mixture of isomers of compounds of formula A into the single isomers.

A compound of formula A produced directly by the condensation reaction between (I) and (II) or (I') and (III) may be modified, if desired, by converting R_1 into a different R_1 group. These optional conversions may be carried out by methods known in themselves. For example, a compound of formula A in which R_1 comprises an ester group may be converted to a compound of formula A wherein the corresponding substituent is a free -COOH or OH group, by acid or alkaline hydrolysis at a suitable temperature, for example from ambient temperature to 100°C.

A compound of formula A in which either or both of R_1 and R_2 includes an -OH group may be converted into a compound of formula A wherein the corresponding substituent is esterified, for example by treating with a suitable carboxylic acid in the presence of an appropriate coupling agent, acid anhydride or acid chloride in an inert solvent.

A compound of formula A in which either or both of R_1 and R_2 includes a $-CO_2H$ group may be converted into a

compound of formula A wherein the corresponding substituent is esterified, for example by treating the carboxylic acid with a suitable C_1-C_6 alkyl alcohol in the presence of 1,3-dicyclohexylcarbodiimide in an inert solvent.

A compound of formula A in which either or both of R_1 and R_2 includes a free $-CO_2H$ group may be converted into a compound of formula A in which the corresponding substituent is a group $-CON(R_{11}R_{12})$, wherein R_{11} and R_{12} are as defined above, for example by treatment with ammonia or an amine in the presence of 1,3-dicyclohexylcarbodiimide in an inert solvent.

A compound of formula A in which either or both of R_1 and R_2 includes a free $-CO_2H$ group may be converted into a compound of formula A wherein the corresponding substituent is a $-CH_2OH$ group by reduction, for example using borane in a suitable solvent such as tetrahydrofuran.

A compound of formula A in which either or both of R_1 and R_2 is a nitro group may be converted into a compound of formula A in which the corresponding substituent is an amino group by reduction under standard conditions, for example by catalytic hydrogenation.

Protecting groups for substituents on R_1 and/or R_2 in any of the compounds of formulae (I), (I'), (II) and (III) are optionally introduced prior to step (i) or step (ii) when either or both R_1 and R_2 include one or more groups which are sensitive to the condensation reaction conditions or incompatible with the condensation reaction, for example a -COOH, $-CH_2OH$ or amino group. The protecting groups are

then removed at the end of the process. Any conventional protecting group suitable for the group R_1 and/or R_2 in question may be employed, and may be introduced and subsequently removed by well-known standard methods.

The condensation reaction between compounds (I) and (II) or (I') and (III) is suitably performed in the presence of a base which is potassium t-butoxide, sodium hydride, potassium carbonate, sodium carbonate, caesium carbonate, sodium acetate, potassium fluoride on alumina, or triethylamine in a solvent such as dimethylformamide, potassium t-butoxide in t-butanol, or a mixture of t-butanol and dimethylformamide (DMF). The reaction is typically performed at a temperature from 0°C to the reflux temperature of the solvent.

The compounds of formula (I) may be prepared by a process comprising reacting 1,4-diacetyl-2,5-piperazinedione with a compound of formula (III) as defined above, in the presence of a base in an organic solvent. Similarly, the compounds of formula (I') may be prepared by a process which comprises reacting 1,4-diacetyl-2,5-piperazinedione with a compound of formula (II) as defined above, in the presence of a base in an organic solvent.

If necessary, the resulting compound of formula (I) or (I') can be separated from other reaction products by chromatography.

The reaction of 1,4-diacetyl-2,5-piperazinedione with the compound of formula (III) or (II) is suitably performed under the same conditions as described above for the

condensation between compounds (I) and (II), or (I') and (III).

The substituted aldehydes of formulae (II) and (III) are known compounds or can be prepared from readily available starting materials by conventional methods. The 1,4-diacetyl-2,5-piperazinedione used as a starting material in the preparation of compounds of formula (I) may be prepared by treating 2,5-piperazinedione (glycine anhydride) with an acetylating agent. The acetylation may be performed using any conventional acetylating agent, for example acetic anhydride under reflux or, alternatively, acetic anhydride at a temperature below reflux in the presence of 4-dimethylaminopyridine.

Compounds of formula (I) may also be prepared by the microwave irradiation of a mixture comprising 1,4-diacetyl-2,5-piperazinedione, a compound of formula (III) and potassium fluoride on alumina (as base) in the absence of solvent.

Compounds of formula (I) may alternatively be prepared directly from 2,5-piperazinedione (glycine anhydride) by a process which comprises treating the 2,5-piperazinedione with a mixture comprising a compound of formula (III), sodium acetate and acetic anhydride at an elevated temperature, for example under reflux.

Compounds of formula (I') may be prepared by analogous processes, replacing compound (III) in each case by a compound of formula (II).

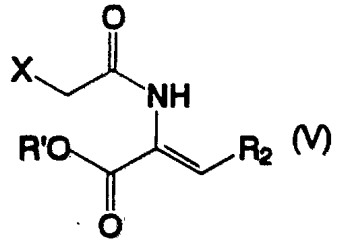
Compounds of formula A may also be prepared by a

process comprising the microwave irradiation of (i) a mixture comprising a compound of formula (I) as defined above, a compound of formula (II) and potassium fluoride on alumina, or (ii) a mixture comprising a compound of formula (I') a compound of formula (III) and potassium fluoride on alumina, or (iii) a mixture comprising 1,4-diacetyl-2,5-piperazinedione, a compound of formula (II), a compound of formula (III) and potassium fluoride on alumina. The irradiation is performed in the absence of a solvent.

Compounds of formula (A) may also be obtained directly by a process which comprises condensing together 1,4-diacetyl-2,5-piperazinedione, a compound of formula (II) and a compound of formula (III) in the presence of a base in an organic solvent. Suitable bases, solvents and reaction conditions are as described above for the condensation reaction between, for example, compounds (I) and (II).

An alternative direct process for the preparation of compounds of formula (A) comprises condensing together 2,5-piperazinedione, a compound of formula (II) and a compound of formula (III) in the presence of sodium acetate and acetic anhydride at elevated temperature, for example under reflux.

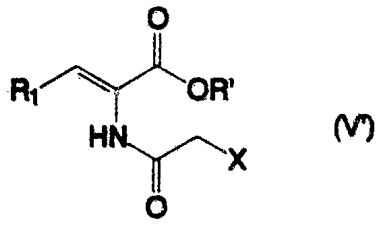
An alternative process for the preparation of compounds of formula (I) comprises treating a compound of formula (V):



(V)

wherein R_6 to R_{10} are as defined above, X is a halogen and R' is a C_1-C_6 alkyl group, with ammonia followed by acetic anhydride.

Compounds of formula (I') may be prepared by an analogous process which comprises treating a compound of formula (V'):



(V')

wherein R_1 to R_5, X and R' are as defined above, with ammonia followed by acetic anhydride.

X in formula (V) or (V') is typically iodine. R' is, for example, a C_1-C_4 alkyl group such as a methyl, ethyl, propyl, i-propyl, butyl, sec-butyl or tert-butyl group.

A review of synthetic approaches to unsaturated 3-monosubstituted and 3,6-disubstituted-2,5-piperazinediones is provided in Heterocycles, 1983, 20, 1407 (C.Shin).

Compounds of formula (A) may be optionally washed after any of the above preparative procedures with one or more of the following: water, ethanol, ethyl acetate and diethyl ether.

Where appropriate compounds of formula (A) may be

optionally recrystallised from a suitable solvent such as methanol or acetic acid.

Compounds of formula (A) 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 or bases. Examples of inorganic bases include ammonia and carbonates, hydroxides and hydrogen carbonates of group I and group II metals such as sodium, potassium, magnesium and calcium. Examples of organic bases include aliphatic and aromatic amines such as methylamine, triethylamine, benzylamine, dibenzylamine or α- or ß-phenylethylamine, and heterocyclic bases such as piperidine, 1-methylpiperidine and morpholine. Examples of inorganic acids include hydrochloric acid, sulphuric acid and orthophosphoric acid. Examples of organic acids include p-toluenesulphonic acid, methansulphonic acid, mucic acid and succinic acid.

Compounds of formula (A) may also be converted into pharmaceutically acceptable esters. Suitable esters include branched or unbranched, saturated or unsaturated C_1-C_6 alkyl esters, for example methyl, ethyl and vinyl esters.

The diketopiperazines of formula (A), both novel and known and their pharmaceutically acceptable salts and esters (referred to hereinafter as the "present compounds") have utility as inhibitors of PAI. Elevated levels of PAI-1, by reducing the net endogenous fibrinolytic capacity,

can contribute to the pathogenesis of various thrombotic disorders including myocardial infarction, deep vein thrombosis and disseminated intravascular coagulation. The present compounds therefore can act as inhibitors of the tPA/PAI-1 interaction. The present compounds can be used in the treatment of haemostatic disorders. A human or animal, e.g. a mammal, can therefore be treated by a method comprising administration of a therapeutically effective amount of a diketopiperazine of formula (A) or a pharmaceutically or veterinarily acceptable salt thereof.

Tissue plasminogen activator (tPA) is used as a fibrinolytic agent in the treatment of thrombotic disorders. The efficacy of the tPA in this role may be enhanced if it is administered together with a PAI inhibitor. A human or animal, e.g. a mammal, can therefore be treated by a method comprising the combined administration of a therapeutically effective amount of tPA and a therapeutically effective amount of any one of the present compounds. The present invention also provides products containing a diketopiperazine of formula (A) or a pharmaceutically acceptable salt or ester thereof and tPA as a combined preparation for simultaneous, separate or sequential use in the treatment of thrombotic disorders, for example where there is inappropriate PAI activity. In such products the present compound is formulated for oral or parenteral (intravenous, intramuscular or subcutaneous) administration and the tPA is formulated for intravenous administration.

As one example, during acute myocardial infarction (MI) one of the present compounds may be administered to a patient together with tPA to enhance the efficacy of the tPA treatment. As a further example, early re-occlusion following treatment of a patient with tPA may be prevented by the post-MI administration of one of the present compounds.

The compounds of formula (A) have been tested in a PAI functional assay. In this assay, a compound is incubated with PAI-1 prior to addition to the tPA assay system. Inhibition of PAI-1 results in the production of plasmin from plasminogen. In turn, plasmin cleaves the chromogenic substrate S2251 (Kabi Vitrum) producing pNA (p-nitroaniline) which is detected spectrophotometrically at 405 nm (K.Nilsson et al, Fibrinolysis (1987) 1, 163-168). The results of the assay are reported below.

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

10 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.

When one of the present compounds is administered in combination with tPA to adult humans, the dosage adopted for each route of administration is typically from 0.001 to 10 mg, more typically 0.01 to 5 mg per kg body weight for a compound of the invention and from 5 to 500mg administered intravenously for the tPA. A suitable dosage regimen for the tPA is 100 mg given intravenously over 3 hours as follows: 10% of the total dose as an i.v. bolus over 1-2 minutes, 50% of the total dose as an infusion over 1 hour, 40% of the total dose as an infusion over the subsequent 2 hours.

A diketopiperazine of formula (A) or a pharmaceutically acceptable salt or ester 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 an inhibitor of PAI 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. A compound may be encapsulated within liposomes.

TESTING OF THE PRESENT COMPOUNDS AS PAI INHIBITORS

Compounds of formula (A) were tested in a PAI chromogenic substrate assay. In the assay (K.Nilsson, Fibrinolysis (1987) 1, 163-168) each compound was incubated with PAI-1 prior to addition to the tPA assay system. Inhibition of PAI-1 by the compound of formula (A) resulted in the production of plasmin from plasminogen. In turn, the plasmin cleaved the chromogenic substrate S2251 (Kabi-Vitrum) producing pNA (p-nitroaniline) which was detected spectrophotometrically at 405 nm.

The degrees of inhibition observed in the chromogenic substrate assay at various concentrations, and/or IC_{50} values, of compounds of formula (A) are presented in Table 1. IC_{50} values for some compounds, not shown in Table 1, are listed in Table 2 which follows Table 1.

TABLE 1: INHIBITION OF PAI-1 IN THE S2251 CHROMOGENIC SUBSTRATE ASSAY

Compound No.	Concentration in μm				
	100	50	25	12.5	6.25
1470	70	20	2	0	0
1471	80	60	20	6	0
1474	64	52	28		
1476	68	48	18		
1506	75	58	26	4	2
1507	78	62	45	1	1

1509	58	35	1	1	1
1542	75	41	9	1	1
1545	87	64	39	5	1
1560	50	48	46	34	13
1618	51	32	3	1	
1649	34	0	1	0	
1657	53	60	46	2	
1672	70	44	13	4	1
1676	29	51	52	12	1
1693	89	2	1	0	
1718	62	1	0	0	1
1808	76	48	73	2	1
1809	81	76	84	7	1
1845	14	30	49	60	53
1884	40	14	0	0	0
1886	42	40	18	6	0
1891	28	36	17	3	3
1910	27	36	50	61	63
1912	30	55	29	22	17
1921	65	43	25	14	16
1922	13	11	26	13	14
1923	38	31	20	12	13
1926	36	35	12	6	10
1927	33	39	20	22	14
1928	67	60	47	24	19
1929	27	45	59	48	16
1930	54	61	79	38	30
1975	7	0	0	0	0
1976	3	0	0	0	0
1950	19	3	2	2	1
1982	48	49	28	6	1
1983	34	14	0	0	0

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Compound No.	Concentration in μM			IC_{50}
	100μM	50μM	20μM	
5023			1	
5026	34		10	
5027	12	8	8	
5028	11	4	4	
5030	20	7	6	
5032	65	62	63	25.0-12.0
5040	0	1	0	
5041	1	0	0	
5042	77	64	42	20.0-10.0
5043	21	15	1	
5048	55	19	11	100.0-50.0
5052	77	76	86	12.0-6.0
5053	68	64	56	25.0-12.0
5054	5	57	48	50.0-25.0
5055	69	69	70	6.0-3.0
5057	44	29	37	
5061	43	48	60	25.0-12.0
5062	78	81	87	12.0-6.0
5069	70	71	75	10.0-5.0
5071	80	82	73	10.0-5.0
5072	60	61	61	10.0-5.0
5073	63	70	14	20.0-10.0
5074	47	57	26	20.0-10.0
5075	88	88	52	25.0-12.0
5077	34	46	42	
5078	60	67	11	20.0-10.0
5079	44	58	14	20.0-10.0
5081	25	34	50	6.0-3.0
5188	90		94	3.50
5200	10		10	
5205	56		33	100.0

5206	72		78	3.0
5299				7.00
5324				9.00
5327			17	
5335				22.0
5367				18.00
5371				12.00
5376				12.00
5379			65	15.00
5386				18.00
5388			58	9.00
5388.HCl			60	12.00
5389			55	2.50
5389.HCl			57	2.50
5391			64	6.50
5391.HCl			100	3.50
5393			76	14.00
5393.HCl			58	20.00
5394			59	16.00
5394.HCl			62	17.00
5397			42	
5397.HCl			21	
5402			37	
5402.HCl			37	

TABLE 2

Compound No.	IC50 (μm)
1470	50.0 - 100.0
1471	25.0 - 50.0
1474	25.0 - 50.0
1476	50.0 - 100.0
1506	25.0 - 50.0
1507	25.0 - 50.0

1509	50.0 - 100.0
1542	50.0 - 100.0
1560	50.0 - 100.0
1618	50.0 - 100.0
1652	25.0 - 50.0
1657	25.0 - 50.0
1672	50.0 - 100.0
1676	12.0 - 25.0
1693	50.0 - 100.0
1718	50.0 - 100.0
1808	25.0 - 12.0
1809	25.0 - 12.0
1845	10.0 - 5.0
1888	50.0 - 100.0
1910	5.0 - 10.0
1912	25.0 - 50.0
1921	100.0 - 50.0
1928	25.0 - 50.0
1929	25.0 - 12.0
1930	25.0 - 12.0
1982	50.0 - 25.0

Reference Example 1: Preparation of (3Z)-1-acetyl-3-benzylidene-2,5-piperazinedione

1,4-Diacetyl-2,5-piperazinedione (25.0g, 126 mmol), which is compound (8) mentioned in Reference Example 3, was heated at 120-130°C in DMF (200 ml) with triethylamine (17.6 ml, 126 mmol) and benzaldehyde (13.0 ml, 126 mmol). After 4 h the mixture was cooled to room temperature and

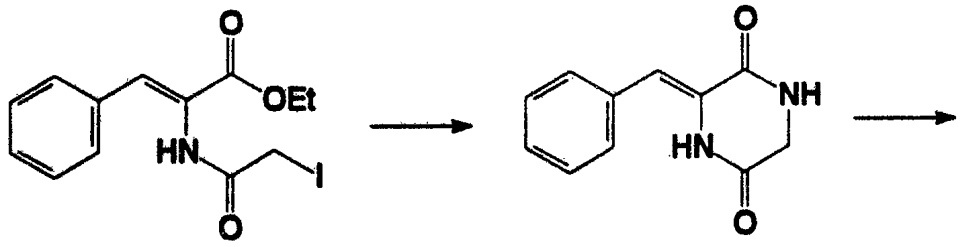
poured into EtOAc (1000 ml), and washed three times with brine. Any solid formed at this stage was filtered off. The filtrate was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was recrystallised from EtOAc:Hexane to give 11.78 g (38%) of the title compound as a yellow solid.

^1H NMR ($CDCl_3$ 400 MHz) δ=2.69 (3H, s) 4.54 (2H, s) 7.20 (1H, s) 7.40 (3H, m), 7.48 (2H, m), 7.93 (1H, br.s)

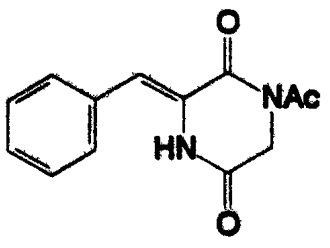
MS(DCI,NH_3): 262 (MNH_4^+, 20%), 245 (MH^+, 53%), 220 (52%), 204 (100%), 203 (100%)

Microanalysis	C	H	N
Calc	63.93	4.95	11.47
Found	64.11	5.02	11.41
Found	64.05	4.90	11.44

Alternatively (3Z)-1-acetyl-3-benzylidene-2,5-piperazinedione can be produced as follows:



(16) (17)



(18)

Compound 16 is treated with ammonia and subsequently with acetic anhydride to yield the title compound.

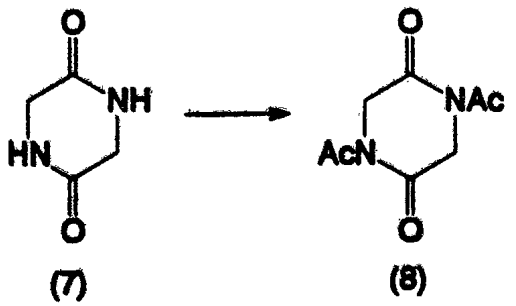
Reference Example 2: Preparation of (3Z)-1-acetyl-3-(4-acetamidobenzylidene)-2,5-piperazinedione

1,4-Diacetyl-2,5-piperazinedione (10.0g, 50 mmol), prepared by the published procedure mentioned in Example 3, was stirred in DMF (40 ml) with 4-acetamidobenzaldehyde (8.24 g, 50 mmol) and triethylamine (7 ml, 50 mmol) and heated to 120°C. After 2½ h the mixture was cooled to room temperature, diluted with EtOAc (100 ml) and stirred overnight. The solid formed was collected, washed with EtOAc and dried to give 8.46 g (56%) of a yellow solid.

^{1}H NMR ($CDCl_3$+TFA, 400 MHz) δ=2.32 (3H, s) 2.72 (3H, s) 4.68 (2H, s) 7.36 (1H, s) 7.45 (2H, d, J=8Hz) 7.60 (2H, d, J=8Hz)

Microanalysis	C	H	N
Calc	59.80	5.02	13.95
Found	60.08	5.09	13.89
	60.11	5.07	13.86

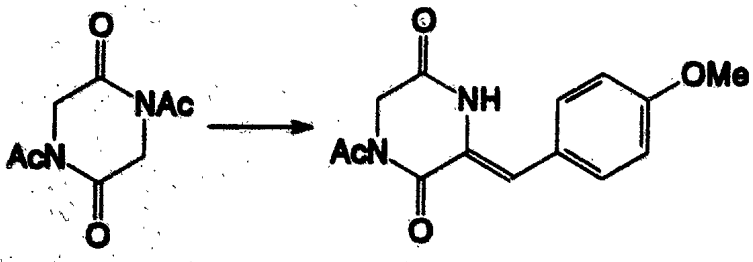
Reference Example 3: Preparation of 1,4-Diacetyl-2,5-piperazinedione



(7) (8)

1,4-Diacetyl-2,5-piperazine dione (8) was prepared by the published procedure (S.M. Marcuccio and J.A. Elix, Aust. J. Chem., 1984, 37, 1791).

Reference Example 4: (3Z)-1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione



(3Z)-1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (9) was prepared by the published procedure (T. Yokoi, L-M. Yang, T. Yokoi, R-Y. Wu, and K-H. Lee, J. Antibiot., 1988, 41, 494).

Reference Example 5: Preparation of (3Z)-1-acetyl-3-(2,6-dichlorobenzylidene)-2,5-piperazinedione

1,4-Diacetyl-2,5-piperazinedione prepared by the published procedure mentioned in Reference Example 3, was stirred in DMF with 2,6-dichlorobenzaldehyde and triethylamine and heated to 120-130°C for 1-3h. The title compound was obtained with a yield of 40%.

Reference Example 6: Preparation of (3Z)-1-acetyl-3-(4-(3-dimethylamino)propoxybenzylidene)-2,5-piperazinedione

1,4-Diacetyl-2,5-piperazinedione, prepared by the published procedure mentioned in Reference Example 3, was stirred in DMF with 4-(3-dimethylamino)propoxybenzaldehyde and triethylamine and heated to 120-130°C for 2-4h to give the title compound.

By the same method, using 4-(2-dimethylamino)ethoxybenzaldehyde in place of the above-mentioned aldehyde, (3Z)-1-acetyl-3-(4-(2-dimethylamino)ethoxybenzylidene)-2,5-piperazinedione was prepared.

Reference Example 7: (3Z,6Z)-3-(4-Hydroxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione

(3Z,6Z)-3-(4-Acetoxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione was treated with aqueous sodium hydroxide in THF at room temperature for 8 hrs to give the title compound (1519) in 30% yield.

Example 1: Preparation of 1470

3(Z)-1-Acetyl-3-benzylidene-2,5-piperazinedione (one equivalent), which is compound 18 prepared according to Reference Example 1, was treated with 1-tert-butoxycarbonylpyrrole-2-carboxaldehyde in the presence of

Cs_2CO_3 (1-1.1 equivalents) in DMF at 80-100°C for 1-6 hours. The title compound was obtained in 24% yield.

The crude product was optionally, washed with water, methanol, ethyl acetate or diethylether and optionally recrystallised from methanol as appropriate.

By the same method, but replacing 1-tert-butoxycarbonylpyrrole-2-carboxaldehyde by the appropriately substituted aldehyde or benzaldehyde, the following compounds were prepared:

Compound	Yield (%)
1471	52
1652	37
1983	45
1921	54
1922	43
1924	44
1910	31
1926	27
1927	26
1928	20
1929	-
1930	-
1912	33
5032	50
5040	45
5043	24
5053	44
5054	22
5057	43
5058	16

Example 2: Preparation of 1474

3(Z)-1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione prepared according to Reference Example 4, was treated with 2-thiophenecarboxaldehyde in the presence of Cs_2CO_3 (1-1.1 equivalents) in DMF at 80-100°C for 1-6 hours. The title compound was obtained in 76% yield.

By the same method, but replacing 2-thiophenecarboxaldehyde by the appropriately substituted aldehyde, the following compounds were prepared:

Compound	Yield (%)
1476	54
1479	84
1506	67
1507	7

The crude product was optionally washed with water, methanol, ethyl acetate and diethylether and optionally recrystallised from acetic acid or methanol as appropriate.

Example 3: Preparation of 1884

3(Z)-1-Acetyl-3-benzylidene-2,5-piperazinedione (1 equivalent), prepared according to Reference Example 1, was treated with cyclohexanecarboxaldehyde (4 equivalents) in the presence of 0.5M potassium tert-butoxide in tertiary butanol (2 equivalents) in DMF at 0-100°C for 2 hours. The title compound was obtained with a yield of 58%. Purification was effected by recrystallisation from acetic acid.

1672 was prepared as above but replacing the 3(Z)-1-

acetyl-3-benzylidene-2,5-piperazinedione with 3(Z)-1-acetyl-3-(4-acetamidobenzylidene)-2,5-piperazinedione. The reaction was maintained for 18 hours. A low yield was obtained.

Example 4: Preparation of 1676

1-Acetyl-3-(4-acetamidobenzylidene)-2,5-piperazinedione (one equivalent), prepared according to Reference Example 2, was treated with cinnamaldehyde in the presence of Cs_2CO_3 (1-1.1 equivalents) in DMF at 80-100°C for 1-6 hours. The title compound was obtained in 46% yield.

Example 5: Preparation of 1618

1,4-Diacetyl-2,5-piperazinedione, prepared by the published procedure mentioned in Reference Example 3, was stirred in DMF with 2-thiophenecarboxaldehyde (1 equivalent) and triethylamine (1 equivalent) at 120°C for 2-4h. (3Z)-1-Acetyl-3-(2-thenylidene)-2,5-piperazinedione was obtained with a yield of 36%.

(3Z)-1-Acetyl-3-(2-thenylidene)-2,5-piperazinedione (1 equivalent) was stirred in DMF with 3-1-tert-butoxycarbonylindole-3-carboxyaldehye (1 equivalent) in the presence of Cs_2CO_3 (1-1.1 equivalents) at 80-100°C for 2-3h. The title compound was obtained with a yield of 14%.

Example 6: Preparation of 1542

3(Z)-1-Acetyl-3-(2,6-dichlorobenzylidene)-2,5-piperazinedione (1 equivalent), prepared according to Reference Example 5 was treated with 3-furaldehyde (1 equivalent) in the presence of Cs_2CO_3 (1-1.1 equivalents) in DMF at 80-100°C for 2-5 hours. The title compound was obtained in 46% yield.

By the same method, but replacing 3-furaldehyde by the appropriately substituted aldehyde, 1560 was obtained with a yield of 39%.

Example 7: Preparation of 1982

3(Z)-1-Acetyl-3-benzylidene-2,5-piperazinedione (1 equivalent), as prepared in Reference Example 1, was treated with 4-(N-(3-dimethylaminoethyl)-N-methyl)aminomethylbenzaldehyde in the presence of Cs_2CO_3 (1-1.1 equivalents) in DMF at 80-100°C for 1-6h to give (3Z,6Z)-3-Benzylidene-6-(4-(N-dimethylaminoethyl)-N-methyl)aminomethylbenzylidene)-2,5-piperazinedione in a yield of 50%.

Compound 1982, the hydrochloride salt of (3Z,6Z)-3-Benzylidene-6-(4-(N-(3-dimethylaminoethyl)-N-methyl)aminomethylbenzylidene)-2,5-piperazinedione, was prepared by bubbling HCl gas through a solution of the corresponding free base in THF, followed by evaporation to dryness. The yield was 45%.

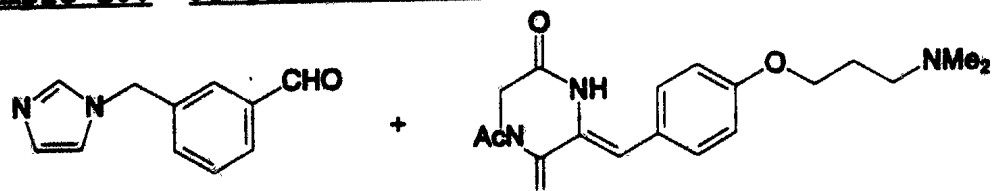
Example 8: Preparation of 1976

3(Z)-1-Acetyl-3-(4-(3-dimethylamino)propoxybenzylidene)-2,5-piperazinedione (1 equivalent), prepared according to Reference Example 6 was treated with 3-(imidazol-1-yl)benzaldehyde (1 equivalent) in the presence of Cs_2CO_3 (1-1.1 equivalent) in DMF at 80-90°C for 2-4 hours. The title compound was obtained in 52% yield.

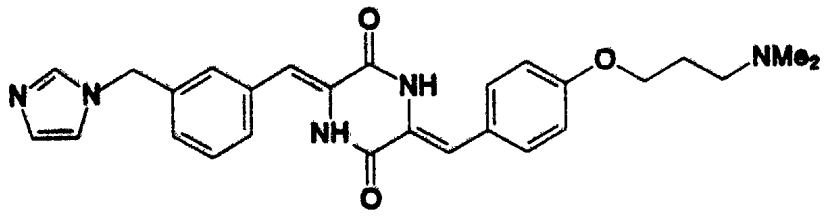
Example 9: Preparation of 1886

1519 (1 equivalent), prepared in Reference Example 7, was treated in DMF with sodium hydride (1 equivalent) and N-phthaloylglycyl chloride (1 equivalent) in DMF at room temperature for 4h. The title compound was obtained with a yield of 30%.

Example 10: Preparation of 5026



10.1



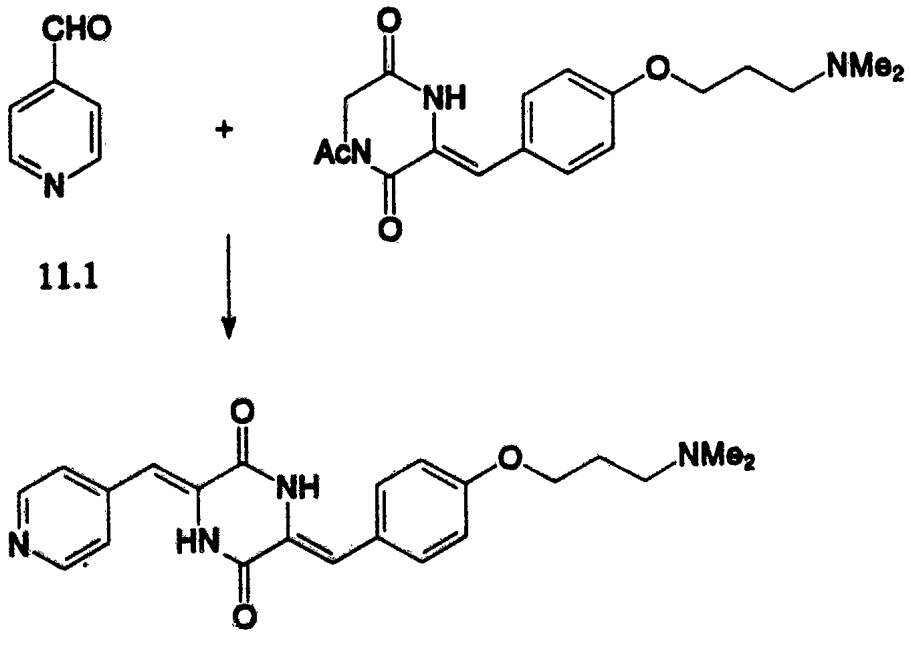
5026

(3Z)-1-acetyl-3-(4-(3-dimethylamino)propoxy-benzylidene)-2,5-piperazinedione, prepared as in Reference Example 6, was treated with compound 10.1 in dimethylformamide (DMF) in the presence of Cs_2CO_3 at a temperature of 80°C-90°C for 2-4 hours. Compound 5026 was obtained in 95% yield.

By an analogous process, using the appropriately substituted benzaldehyde in place of compound 10.1, the following compounds were prepared:

Compound No.	Yield %
5030	30
5048	72
5188	70

Example 11: Preparation of 5027



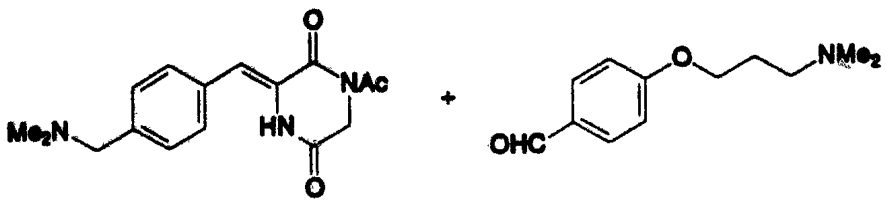
5027

(3Z)-1-acetyl-3-(4-(3-dimethylamino)propoxybenzylidene)-2,5-piperazinedione, prepared as in Reference Example 6, was treated with compound 11.1 in DMF in the presence of Cs_2CO_3 at 80°C-90°C for 2-4 hours. Compound 5027 was produced in 33% yield.

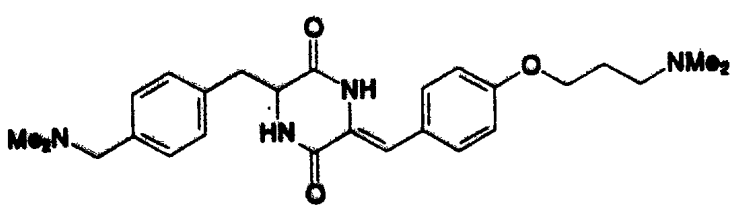
By the same method, but replacing 11.1 by the appropriately substituted aldehyde, the following compounds were prepared:

Compound No.	Yield (%)
5028	44
5029	25
5041	39
5042	39
5046	37
5052	58

Example 12: Preparation of 5023



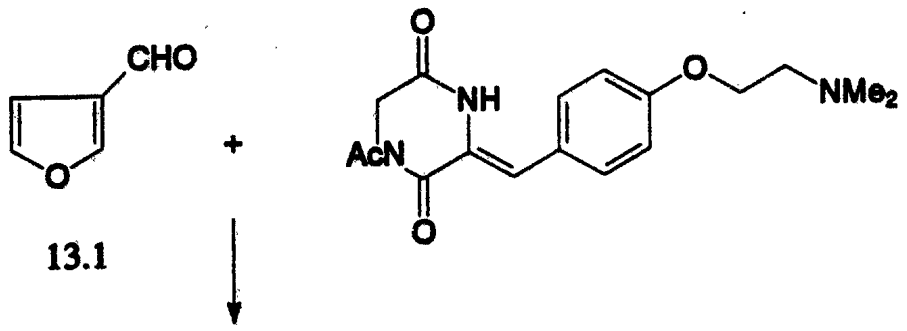
12.1



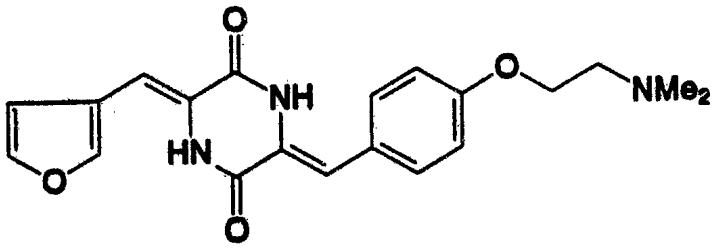
5023

Compound 12.1 was treated with 4-(3-dimethylamino)propoxybenzaldehyde in DMF in the presence of Cs_2CO_3 at a temperature of 80°C-90°C for 2-4 hours. Compound 5023 was obtained in 36% yield.

Example 13: Preparation of 5062



13.1



5062

(3Z)-1-acetyl-3-(4-(2-dimethylamino)ethoxybenzylidene)-2,5-piperazinedione, prepared as in Reference Example 6, was treated with compound 13.1 in DMF in the presence of Cs_2CO_3 at a temperature of 80°C-90°C for 2-4 hours. Compound 5062 was obtained in 12% yield.

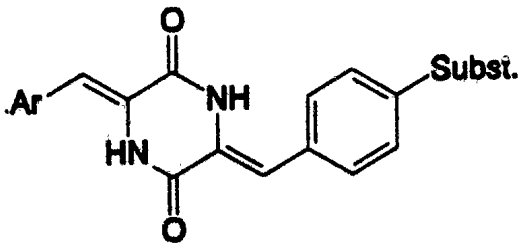
By the same method, but using the appropriately substituted aldehyde in place of compound 13.1, the following compounds were prepared:

Compound No.	Yield (%)
5071	41
5072	86

Example 14: Preparation of compounds of formula (I)



14.1 14.2

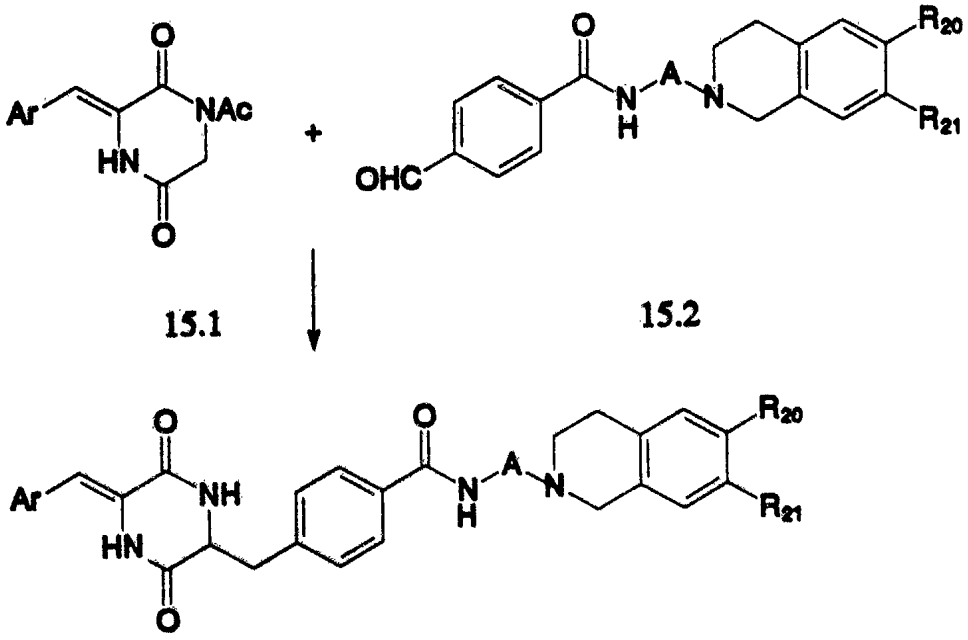


Compound (I)

The 2,5-piperazinedione derivative 14.1 was treated with the aldehyde 14.2, the groups Ar and Subst. being as specified below, in DMF in the presence of Cs_2CO_3 at 80°C-90°C for 2-4 hours. The compounds of formula (I) listed below were prepared:

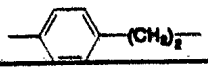
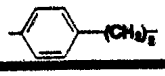
Ar	Subst.	Compound of formula (I)	Yield (%)
Phenyl	$-CH_2S(CH_2)_2NMe_2$	5058	16
3-furyl	$-CH_2S(CH_2)_2NMe_2$	5073	33
3-thienyl	$-CH_2S(CH_2)_2NMe_2$	5078	38
3-thienyl	$-CH_2NHC(O)CH_2NMe_2$	5074	83
2-bromophenyl	$-CH_2NHC(O)CH_2NMe_2$	5079	28
3-furyl	$-CH_2NHC(O)CH_2NMe_2$	5081	68
3-thienyl	$-CH_2O(CH_2)_2NMe_2$	5069	29
3-furyl	$-CH_2O(CH_2)_2NMe_2$	5077	20

Example 15: Preparation of compounds of formula (I)

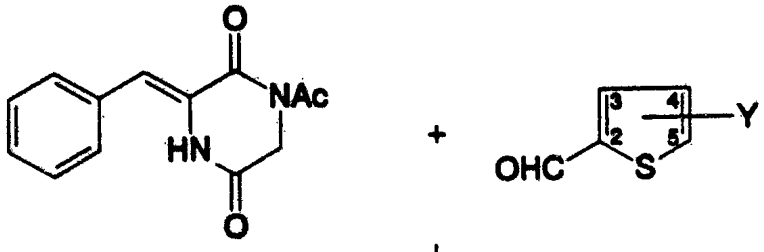


Compound (I)

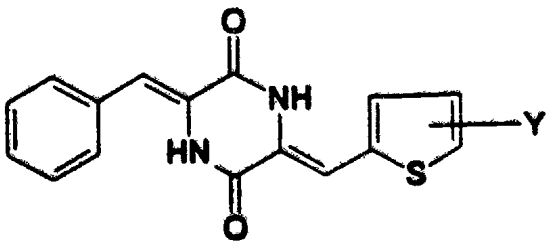
The 2,5-piperazinedione derivative 15.1 was treated with the aldehyde 15.2 in which R_{20} and R_{21} are both H or are both OMe, the substituent Ar and linking group A being as specified below, in DMF in the presence of Cs_2CO_3 at 80°C to 90°C for 2-4 hours. The compounds of formula (I) listed below were prepared. In 5391, 5394 and 5371 R_{20} and R_{21} are both H. In 5393 and 5402 R_{20} and R_{21} are OMe.

Ar	A	Compound of Formula (I)	Yield (%)
Phenyl	$-(CH_2)_2-$	5391	21
Phenyl	$-(CH_2)_3-$	5394	47
Phenyl	$-(CH_2)_4-$	5371	56
Phenyl		5393	44
4-nitrophenyl		5402	62

Example 16: Preparation of compounds of formula (I)



18 16.1



(3Z)-1-acetyl-3-benzylidene-2,5-dione prepared as in Reference Example 1 (compound 18), was treated with the aldehyde 16.1 in which substituent Y was as indicated below, in DMF in the presence of Cs_2CO_3 at 80°C-90°C for 2-4 hours. The compounds of formula (I) listed below were prepared:

Y	Compound of formula (I)	Yield %)
5-$O(CH_2)_2NMe_2$	5324	34
4-$O(CH_2)_2NMe_2$	5327	51
5-$(CH_2)_2NMe_2$	5335	45
5-$O(CH_2)_2O(CH_2)_2NMe_2$	5388	12
5-$O(CH_2)_6NMe_2$	5389	35
5-$N(Me)(CH_2)_2NMe_2$	5299	2

By the same method, but using 2,5-dichlorothiophene-4-carboxaldehyde in place of compound 16.1, 5075 was prepared in 31% yield.

Example 17: Preparation of salts

1. Hydrochloride salts of the following compounds of formula (I) were prepared by bubbling HCl gas through a solution of the corresponding free base in tetrahydrofuran (THF) at room temperature. The salt was recovered in the yield indicated.

Compound of formula (I)	Hydrochloride salt	Yield (%)
1975	5026	95
1976	5030	30
5048	5048.HCl	72
5188	5206	24
5200	5205	31
5367	5376	47
5397	5397.2HCl	36
5041	5041.HCl	63
5042	5042.HCl	51
5046	5046.HCl	32
5052	5052.HCl	58
5023	1988	50
5062	5062.HCl	-
5071	5071.HCl	-
5072	5072.HCl	-
1910	5055	57
1912	5061	47
5032	5032.HCl	39
5053	5053.HCl	90
5054	5053.HCl	88
5073	5073.HCl	76
5078	5078.HCl	78
1912	5061	47
5074	5074.HCl	51
5079	5079.HCl	73
5081	5081.HCl	76
5069	5069.HCl	-
5077	5077.HCl	-
5324	5324.HCl	68
5336	5336.HCl	74
5335	5335.HCl	-

5388	5388.HCl	79
5389	5389.HCl	75
5391	5391.HCl	-
5394	5394.HCl	75
5371	5379	65

2. Hydrochloride salts of the following compounds of formula (I) were prepared by bubbling HCl gas through a solution of the corresponding free base in hot DMF. The salt was recovered in the yield indicated.

Compound of formula (I)	Hydrochloride salt	Yield
5386	5386.2HCl	79
5393	5393.HCl	60
5402	5402.HCl	52

3. Hydrochloride salts of the following compounds of formula (I) were prepared by treating the free base with 2M HCl:

Compound of formula (I)	Hydrochloride salt	Yield (%)
5027	5027.HCl	67
5028	5028.HCl	92
5029	5029.HCl	76
5040	5040.HCl	90

4. 5043.HCl, the hydrochloride salt of 5043, was prepared by bubbling HCl gas through a solution of 5043 in MeOH. 5057.HCl, the salt of 5057, was prepared by bubbling HCl gas through a solution of 5057 in THF following by recrystallisation from MeOH.

Example 18: 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 19: **Characterisation of compounds of formula A**

The compounds prepared in the preceding Examples, were characterised by mass spectroscopic, microanalytical, proton nuclear magnetic resonance and, in some cases, infra-red techniques. The results are set out in the Tables which follow:

No.	Mol. Formula	Mass spec. data		^{1}H nmr data	
		mass (intensity)	mode	solvent (field)	δ
1910	$C_{23}H_{28}N_4O_3$	401(100)	CI	d_6-DMSO/400MHz	4.28-4.32 (2H,t), 4.35-4.40 (2H,t), 6.75-7.70 (14H,m), 10.15 (2H,brs).
5023	$C_{26}H_{32}N_4O_3$	449(100)	EI	$CDCl_3$/400MHz	2.00 (2H,m), 2.25 (12H,s), 2.46 (2H,t), 3.45 (2H,s), 4.05 (2H,t), 6.95-7.42 (10H,m), 8.15 (2H,brs).
5026	$C_{27}H_{29}N_5O_3.2HCl$			d_6-DMSO/400MHz	2.12 (2H,m), 2.73 (6H,s), .21 (2H,m), 4.11 (2H,t), 5.48 (2H,s), 6.76 (2H,s), 7.00 (2H,d), 7.47 (2H,d), 7.50 (2H,d), 7.55 (2H,d), 7.65 (1H,s), 7.77 (1H,s), 9.21 (1H,s), 10.12 (2H,brs), 10.45 (1H,brs).
5027	$C_{22}H_{24}N_4O_3.2HCl$			$CDCl_3$+CF_3CO_2H/400 MHZ	2.00 (2H,t), 3.00 (6H,s), 3.45 (2H,m), 3.90 (2H,t), 7.00 (2H,d), 7.15 (1H,s), 7.35 (1H,s), 7.45 (2H,d), 8.00 (2H,d), 8.95 (2H,d).
5028	$C_{22}H_{24}N_4O_3.2HCl$			$CDCl_3$+CF_3CO_2D/400MHz	2.35 (2H,m), 3.00 (6H,s), 3.45 (2H,t), 4.15 (2H,t), 7.00 (2H,d), 7.15 (1H,s), 7.30 (1H,s) 7.45 (2H,d), 8.10 (1H,t), 8.50 (1H,d), 8.95 (1H,d), 9.15 (1H,s).
5030				d_6-DMSO/400MHz	2.18 (2H,m), 2.77 (6H,s), 3.20 (2H,m), 4.10 (2H,t), 6.77 (1H,s), 6.81 (1H,s), 7.00 (2H,d), 7.51 (2H,d), 7.65 (2H,m), 7.71 (1H,m), 7.85 (1H,s), 7.96 (1H,s), 8.29 (1H,s), 9.60 (1H,s), 10.21 (1H,brs), 10.50 (1H,brs), 10.61 (1H,brs).

SUBSTITUTE SHEET (RULE 26)

No.	Mol. Formula	Mass spec. data		^{1}H nmr data	
		mass (intensity)	mode	solvent (field)	δ
5032	$C_{23}H_{25}N_3O_4.HCl$	408(20), 306(30)	CI	d_6-DMSO/400MHz	2.83 (6H,s), 3.23 (2H,m), 4.02 (2H,d), 4.30 (1H,m), 5.96 (1H,brd), 6.77 (1H,s), 6.78 (1H,s), 7.02 (2H,d), 7.33 (1H,m), 7.42 (2H,m), 7.55 (4H,m), 9.70 (1H,brs), 10.12 (2H,br).
5040	$C_{25}H_{27}N_3O_5.HCl$	450(10)	CI	d_6-DMSO/400MHz	3.20-3.55 (6H,m), 3.75-4.00 (4H,m), 4.02 (2H,d), 4.39 (1H,m), 5.99 (1H,brs), 6.77 (1H,s), 6.78 (1H,s), 7.02 (2H,d), 7.33 (1H,m), 7.45 (2H,m), 7.55 (4H,m), 10.20 (3H,br)
5041	$C_{21}H_{23}N_3O_4.HCl$	382(100)	EI	d_6-DMSO/400MHz	2.09 (2H,m), 2.80 (6H,s), 3.20 (2H,m), 4.09 (2H,t), 6.63 (1H,s), 6.64 (1H,m), 6.78 (1H,s), 6.89 (1H,m) 7.0 (2H,d), 7.54 (2H,d), 7.90 (1H,s), 9.45 (1H,brs), 9.75 (1H,brs), 10.14 (1H,brs)
5042	$C_{21}H_{23}N_3O_3S.HCl$	398(35)	EI	d_6-DMSO/400MHz	2.09 (2H,m), 2.79 (6H,s), 3.18 (2H,m), 4.10 (2H,t), 6.76 (1H,s), 6.85 (1H,s), 7.00 (2H,d), 7.41 (1H,m), 7.51 (2H,d), 7.62 (1H,m), 7.94 (1H,m), 9.89 (1H,brs), 9.92 (1H,brs), 10.10 (1H,brs).
5043	$C_{27}H_{32}N_4O_5.HCl$	493(100)	CI	d_6-DMSO/400MHz	3.10-3.85 (14H,m), 4.02 (2H,d), 4.40 (1H,brs), 6.77 (1H,s), 6.78 (1H,s), 7.02 (2H,d), 7.32 (1H,m), 7.42 (2H,m), 7.55 (4H,m), 10.20 (2H,s).
5046	$C_{21}H_{23}N_3O_3S.HCl$	398(23), 169(100)	EI	d_6-DMSO/400MHz	2.09 (2H,m), 7.28 (6H,s), 3.12 (2H,m), 4.10 (2H,t), 6.78 (1H,s), 6.94 (1H,s), 7.00 (2H,d), 7.18 (1H,m), 7.54 (2H,d), 7.58 (1H,m), 7.76 (1H,m), 9.75 (1H,brs), 10.16 (1H,brs).

SUBSTITUTE SHEET (RULE 26)

No.	Mol. Formula	Mass spec. data		^{1}H nmr data	
		mass (intensity)	mode	solvent (field)	δ
5048	$C_{25}H_{28}N_4O_4.HCl$	485 (100)	EI	d_6-DMSO/400MHz	2.05 (2H,s), 2.14 (2H,m), 2.79 (6H,d), 3.20 (2H,m), 4.13 (2H,t), 6.70 (1H,s), 6.75 (1H,s), 7.0 (2H,d), 7.48 (2H,d), 7.51 (2H,d), 7.62 (2H,d), 9.94 (1H,brs), 10.15 (1H,brs), 10.20 (1H,brs).
5052				d_6-DMSO/400MHz	2.15 (2H,m), 2.28 (6H,s), 3.20 (2H,m), 4.10 (2H,t), 6.68 (1H,s), 6.75 (1H,s), 6.94 (1H,s), 7.00 (2H,d), 7.54 (2H,d), 7.76 (1H,s), 8.23 (1H,s).
5053	$C_{24}H_{25}N_3O_3.HCl$			$CDCl_3$+CF_3CO_2D/400MHz	2.20 (4H,m), 3.20 (2H,m), 3.70 (2H,m), 4.00 (2H,m), 4.45 (2H,m), 7.00 (2H,d), 7.23 (1H,s), 7.39 (1H,s), 7.45 (7H,m).
5054	$C_{24}H_{25}N_3O_4.HCl$			$CDCl_3$+CF_3CO_2D/400MHz	3.25 (2H,m), 3.67 (2H,m), 3.85 (2H,m), 4.05-4.20 (4H,m), 4.47 (2H,m), 6.97 (2H,d) 7.20 (1H,s), 7.26 (1H,s), 7.39-7.51 (7H,m).
5055	$C_{23}H_{20}N_4O_3.HCl$	401(100)	ESI	d_6-DMSO/400MHz	4.40 (2H,t), 4.60 (2H,t), 6.73 (1H,s), 6.75 (1H,s), 6.99 (2H,d), 7.30 -7.55 (7H,m), 7.65 (1H,s), 7.90 (1H,s), 9.10 (1H,s), 10.10 (1H,s), 10.15 (1H,s), 10.20 (1H,brs)
5057	$C_{24}H_{22}N_4O_4.HCl$			d_6-DMSO/400MHz	4.00-4.05 (2H,m), 4.20-4.32 (2H,m), 4.48 (1H,m), 6.77 (1H,s), 6.78 (1H,s), 7.03 (2H,d), 7.32 (2H,m), 7.42 (2H,m), 7.55 (4H,m), 7.71 (1H,m), 7.77 (1H,m), 9.12 (1H,s), 10.20 (2H,brs).

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No.	Mol. Formula	Mass spec. data		^{1}H nmr data	
		mass (intensity)	mode	solvent (field)	δ
5058.HCl	$C_{23}H_{25}N_3O_2S.HCl$	409(15)	CI	d_6-DMSO/400MHz	2.70-2.75 (8H,m), 3.20-3.25 (2H,m), 3.85 (2H,s), 6.78 (2H,s), 7.32-7.55 (9H,m), 9.68 (1H,brs), 10.22 (1H,s), 10.24 (1H,s)
5061	$C_{23}H_{24}N_4O_3.HCl$			d_6-DMSO/400MHz	2.84 (6H,s), 3.95 (2H,s), 4.40 (2H,d), 6.75 (1H,s), 6.77 (1H,s), 7.33-7.55 (9H,m), 9.15 (1H,t), 9.85 (1H,brs), 10.20 (1H,brs), 10.25 (1H,brs).
5062	$C_{20}H_{21}N_3O_4.HCl$			d_6-DMSO/400MHz	2.76 (6H,d), 3.51 (2H,m), 4.38 (2H,t), 6.66 (1H,s), 6.75 (1H,s), 6.91 (1H,s), 7.05 (2H,d), 7.55 (2H,d), 7.74 (1H,s), 8.22 (1H,s), 9.76 (1H,s).
5069	$C_{21}H_{23}N_3O_3S.HCl$	397(10)	CI	d_6-DMSO/400MHz	2.80 (6H,s), 3.30 (2H,t), 3.76 (2H,t), 4.58 (2H,s), 6.82 (1H,s), 6.87 (1H,s), 7.45 (2H,m), 7.58 (2H,d), 7.65 (1H,m), 8.00 (1H,s), 9.78 (1H,s), 10.02 (1H,s), 10.18 (1H,s).
5071	$C_{20}H_{21}N_3O_3S.HCl$			d_6-DMSO/400MHz	2.86 (6H,d), 3.53 (2H,m), 4.38 (2H,t), 6.78 (1H,s), 6.84 (1H,s), 7.07 (2H,d), 7.43 (1H,m), 7.58 (2H,d), 7.65 (1H,m), 7.96 (1H,m), 9.55 (1H,s), 10.05 (1H,brs), 10.13 (1H,brs).
5072	$C_{21}H_{23}N_3O_3S_2.HCl$			d_6-DMSO/400MHz	2.58 (3H,s), 2.78 (6H,s), 3.44 (2H,m), 4.36 (2H,t), 6.77 (1H,s), 6.85 (1H,s), 7.05 (2H,d), 7.12 (1H,d), 7.52 (1H,d), 7.58 (2H,d), 10.20 (1H,s).

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No.	Mol. Formula	Mass spec. data		^{1}H nmr data	
		mass (intensity)	mode	solvent (field)	δ
5073	$C_{21}H_{23}N_3O_3S$	398(15), 293(100)	EI	$CDCl_3$+CF_3CO_2D/400MHz	2.75 (2H,t), 2.90 (6H,s), 3.25 (2H,t), 3.78 (2H,s), 6.70 (1H,s), 7.10 (1H,s), 7.40 (4H,s), 7.60 (1H,s), 7.85 (1H,s).
5073.HCl	$C_{21}H_{23}N_3O_3S$.HCl			d_6-DMSO/400MHz	2.75 (6H,s), 2.75-2.80 (2H,m), 3.20 (2H,m), 3.84 (2H,s), 6.70 (1H,s), 6.77 (1H,s), 6.90 (1H,s), 7.40 (2H,d), 7.52 (2H,d), 7.75 (1H,s), 8.20 (1H,s), 9.78 (1H,brs), 10.00 (1H,brs), 10.10 (1H,brs)
5074				d_6-DMSO/400MHz	2.82 (6H,s), 4.00 (2H,s), 4.41 (2H,d), 6.81 (1H,s), 6.88 (1H,s), 7.98 (2H,m), 9.15 (1H,brs), 9.90 (1H,brs), 10.04 (1H,brs), 10.18 (1H,brs).
5075	$C_{16}H_{10}Cl_2N_2O_2S$			d_6-DMSO/400MHz	6.50 (1H,s), 6.80 (1H,s), 7.35 (1H,t), 7.39-7.45 (3H,m), 7.55 (2H,d).
5077	$C_{21}H_{23}N_3O_4$.HCl			d_6-DMSO/400MHz	2.55 (2H,t), 2.80 (6H,s), 3.80 (2H,t), 4.55 (2H,s), 6.70 (1H,s), 6.80 (1H,s), 6.95 (1H,s), 7.45 (2H,d), 7.60 (2H,d), 7.85 (1H,s), 8.30 (1H,s), 9.90 (1H,s), 10.01 (1H,s).
5078	$C_{21}H_{23}N_3O_2S_2$	414(15), 309(100)	EI	$CDCl_3$+CF_3CO_2D/400MHz	2.75 (2H,t), 2.88 (6H,s), 3.25 (2H,t), 3.88 (2H,s), 7.22-7.28 (3H,m), 7.45 (4H,s), 7.50-7.54 (1H,m), 7.64 (-7.66 (1H,s).

SUBSTITUTE SHEET (RULE 26)

No.	Mol. Formula	Mass spec. data		^{1}H nmr data	
		mass (intensity)	mode	solvent (field)	δ
5078.HCl	$C_{21}H_{23}N_3O_2S_2$.HCl			d_6-DMSO/400MHz	2.72-2.78 (2H,m), 2.75 (6H,s), 3.20-3.25 (2H,m), 3.84 (2H,s), 6.75 (1H,s), 6.85 (1H,s), 7.40-7.45 (3H,m), 7.55 (2H,d), 7.64-7.67 (1H,m), 7.96-7.99 (1H,m), 9.85 (1H,brs), 10.05 (1H,brs), 10.18 (1H,brs).
5079	$C_{23}H_{23}BrN_4O_3$.HCl			d_6-DMSO/400MHz	2.82 (6H,s), 4.00 (2H,s), 4.41 (2H,d), 6.74 (1H,s), 6.80 (1H,s), 7.30 (1H,m), 7.36 (2H,d), 7.45 (1H,m), 7.54 (2H,d), 7.60 (1H,d), 7.68 (1H,d) 9.56 (1H,brt), 9.90 (1H,brs), 10.36 (1H,brs), 10.48 (1H,brs).
5081	$C_{21}H_{22}N_4O_4$.HCl			d_6-DMSO/400MHz	2.83 (6H,s), 4.01 (2H,s), 4.39 (2H,d), 6.68 (1H,s), 6.79 (1H,s), 6.94 (1H,s), 7.35 (2H,d), 7.54 (2H,d), 7.76 (1H,s), 8.22 (1H,s), 9.12 (1H,brt), 9.82 (2H,brs) 10.12 (1H,brs).
5188	$C_{27}H_{27}N_3O_3$	442(100)	ESI	d_6-DMSO/400MHz	1.8-1.9 (2H,m), 2.15 (6H,s), 2.38 (2H,t), 4.05 (2H,t), 6.78 (1H,s), 6.90 (1H,s), 6.99 (2H,d), 7.50-7.58 (4H,m), 7.61-7.65 (1H,m), 7.39-7.98 (3H,m), 8.11 (1H,s), 10.28 (2H,brs).
5200	$C_{27}H_{27}N_3O_3$	442(100)	ESI	d_6-DMSO/400MHz	1.81-1.91 (2H,m), 2.15 (6H,s), 2.35 (2H,t), 4.09 (2H,t), 6.75 (1H,s), 6.96 (2H,d), 7.21 (1H,s), 7.5-7.65 (7H,m), 7.94 (2H,d), 10.15 (2H,brs).

SUBSTITUTE SHEET (RULE 26)

No.	Mol. Formula	Mass spec. data		^{1}H nmr data	
		mass (intensity)	mode	solvent (field)	δ
5205	$C_{27}H_{27}N_3O_3.HCl$	442(40)	CI	d_6-DMSO/400MHz	2.12-2.20 (2H,m), 2.80(6H,s), 3.20-3.25 (2H,m), 4.10 (2H,t), 6.75 (1H,s), 7.01 (2H,d), 7.24 (1H,s), 7.51 -7.67 (6H,m), 7.92 (2H,d), 7.98-8.01 (1H,m), 10.1 (2H,brs), 10.25 (1H,brs).
5206	$C_{27}H_{27}N_3O_3.HCl$			d_6-DMSO/400MHz	2.11-2.21 (2H,m), 2.60 (6H,s), 2.85-2.98 (2H,m), 4.09 (2H,t), 6.78 (1H,s), 6.94 (1H,s), 7.0 (2H,d), 7.50-7.59 (4H,m), 7.64 (1H,d), 7.90-7.99 (3H,m), 8.12 (1H,m), 10.21 (1H,brs), 10.43 (1H,brs).
5324	$C_{20}H_{21}N_3O_3S.HCl$	384(100)	CI	d_6-DMSO/400MHz	2.85 (6H,s), 3.52 (2H,t), 4.50 (2H,t), 6.52 (1H,d), 6.78 (1H,s), 6.81 (1H,s), 7.31 (1H,d), 7.32 (1H,m), 7.45 (2H,m) 7.57 (2H,d), 9.70 (1H,s), 10.15 (1H,s), 10.41 (1H,brs).
5327	$C_{20}H_{21}N_3O_3S$	384(20)	CI	d_6-DMSO/400MHz	2.22 (6H,s), 2.63 (2H,t), 4.05 (2H,t), 6.76 (1H,s), 6.82 (2x1H,s), 7.30 (1H,s), 7.33 (1H,m), 7.42 (2H,m), 7.55 (2H,d).
5335	$C_{20}H_{21}N_3O_2S.HCl$	368(20)	CI	d_6-DMSO/400MHz	2.78 (6H,s), 3.28 (4H,m), 6.78 (1H,s), 6.89 (1H,s), 7.02 (1H,d), 7.38-7.45 (4H,m), 7.55 (2H,d), 9.68 (1H,brs), 10.40 (1H,br).
5336	$C_{20}H_{21}N_3O_3S.HCl$	384(10)	CI	d_6-DMSO/400MHz	2.82 (6H,s), 3.49 (2H,t), 4.38 (2H,t), 6.78 (1H,s), 6.80 (1H,s), 6.94 (1H,s), 7.31 (1H,s), 7.32 (1H,m), 7.42 (2H,m), 7.55 (2H,d), 9.78 (1H,s), 10.25 (1H,s), 10.45 (1H,brs).

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No.	Mol. Formula	Mass spec. data		^{1}H nmr data	
		mass (intensity)	mode	solvent (field)	δ
5367	$C_{33}H_{34}N_4O_4$	551(100)	CI	$CDCl_3$+CF_3CO_2D/400MHz	1.72 (2H,m), 1.95-2.01 (2H,m), 2.24 (6H,m), 2.48 (2H,t), 2.96 (2H,m), 3.70 (1H,m), 4.07 (2H,t), 4.89 (1H,m), 7.0 (2H,d), 7.01 ((2H,s), 7.15-7.25 (4H,m), 7.35 (2H,d), 7.48 (2H,d), 7.57 (2H,d), 8.17 (2H,brs).
5371	$C_{32}H_{32}N_4O_3$	521(100)	CI	$CDCl_3$/400MHz	1.75-1.80 (4H,m), 2.55-2.60 (2H,m), 2.75 (2H,t), 2.88 (2H,t), 3.50-3.55 (2H,m), 3.65 (2H,s), 6.95 (1H,s), 6.98-7.02 (1H,m), 7.05-7.10 (4H,m), 7.15-7.20 (2H,m) 7.38-7.50 (5H,m), 7.65 (2H,d), 7.85 (1H,brs), 8.00 (1H,brs), 8.15 (1H,brs).
5379	$C_{32}H_{32}N_4O_3$.HCl			d_6-DMSO/400MHz	1.60-1.68 (2H,m), 1.80-1.88 (2H,m), 3.00-3.06 (1H,m), 3.15-3.35 (6H,m), 3.65 -3.75 (1H,m), 4.25-4.55 (2H,m), 6.80 (2H,brs), 7.18-7.45 (7H,m), 7.55-7.65 (4H,m), 7.89 (2H,d), 8.57 (1H,brs), 10.29 (2H,brs), 10.36 (1H,brs).
5386	$C_{35}H_{39}N_5O_4$	594(100), 97(50)	ESI	d_6-DMSO/400MHz	1.81-1.90 (2H,m), 2.15 (6H,s), 2.35 (2H,t), 2.62-2.70 (2H,m), 2.79-2.83 (2H,m), 3.46-3.53 (2H,m), 4.02 (2H,t), 6.73 (1H,s), 6.75 (1H,s), 6.73 (1H,s), 6.75 (1H,s), 6.98 (2H,d), 7.02-7.11 (4H,m) 7.50 (2H,d), 7.60 (2H,d), 7.78 (2H,d), 8.41-8.48 (1H,m), 10.22 (1H,brs)

SUBSTITUTE SHEET (RULE 26)

No.	Mol. Formula	Mass spec. data		^{1}H nmr data	
		mass (intensity)	mode	solvent (field)	δ
5386.2HCl	$C_{35}H_{39}N_5O_4.2HCl$	594(100), 297(58)	ESI	d_6-DMSO/400MHz	2.12-2.21 (2H,m), 2.72 (6H,s), 3.1-3.25 (4H,m), 3.76-3.82 (2H,m), 4.12 (2H,t), 4.41 (2H,brs), 6.78 (1H,s), 6.79 (1H,s), 7.02 (2H,d), 9.05 (1H,brs), 10.19 (1H,brs), 10.35 (1H,brs).
5388	$C_{22}H_{25}N_3O_4S$			d_6-DMSO/400MHz	2.16 (6H,s), 2.42 (2H,t), 3.55 (2H,t), 3.75 (2H,t), 4.23 (2H,t), 6.43 (1H,d), 6.72 (1H,s), 6.78 (1H,s), 7.22 (1H,d), 7.32 (1H,m), 7.42 (2H,m), 7.53 (2H,d).
5388.HCl	$C_{22}H_{25}N_3O_4S.HCl$	428(5)	CI	d_6-DMSO/400MHz	2.72 (6H,s), 3.25 (2H,t), 3.81 (4H,m), 4.32 (2H,t), 6.47 (1H,d), 6.76 (1H,s), 6.81 (1H,s), 7.27 (1H,d), 7.32 (1H,m), 7.42 (2H,m), 7.55 (2H,d), 10.15 (1H,brs).
5389	$C_{24}H_{29}N_3O_3S$	440(5)	CI	d_6-dMSO/400MHz	1.28-1.45 (6H,m), 1.57 (2H,m), 2.12 (6H,s), 2.20 (2H,t), 4.13 (2H,t), 6.41 (1H,d), 6.75 (1H,s), 6.79 (1H,s), 7.23 (1H,d), 7.32 (1H,m), 7.42 (2H,m), 7.55 (2H,d).
5389.HCl	$C_{24}H_{29}N_3O_3S.HCl$	440(5)	CI	d_6-DMSO/400MHz	1.36 (2H,m), 1.45 (2H,m), 1.66 (2H,m), 1.76 (2H,m), 2.72 (6H,s), 30.. (2H,t), 4.13 (2H,t), 6.42 (1H,d), 6.75 (1H,s), 6.80 (1H,s), 7.25 (1H,d), 7.32 (1H,m), 7.41 (2H,m), 7.55 (2H,d), 10.06 (3H,brs).

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No.	Mol. Formula	Mass spec. data		^{1}H nmr data	
		mass (intensity)	mode	solvent (field)	δ
5391	$C_{30}H_{28}N_4O_3$	493(100), 489(50)	ESI	$CDCl_3$+CF_3CO_2D/430MHz	3.15-3.25 (1H,m), 3.28-3.40 (1H,m), 3.48-3.57 (1H,m), 3.60-3.68 (2H,m), 3.92-4.02 (3H,m), 4.33 (2H,d), 4.77 (1H,d), 7.11 (1H,d), 7.22-7.56 (12H,m), 7.85 (2H,d).
5391.HCl	$C_{30}H_{28}N_4O_3$.HCl	493(100)	ESI	d_6-DMSO/400MHZ	3.01-3.10 (1H,m), 3.38-3.45 (4H,m), 3.80-3.85 (3H,m), 4.32-4.41 (1H,m), 4.61-4.70 (1H,m), 6.80 (2H,s), 7.18-7.36 (5H,m), 7.41 (2H,t), 7.58 (2H,d), 7.67 (2H,d), 7.99 (2H,d), 9.02 (1H,t), 10.29 (1H,brs), 10.39 (1H,brs), 10.99 (1H,brs).
5393	$C_{38}H_{36}N_4O_5$			d_6-DMSO/400MHz	2.70 (6H,m), 2.80 (2H,m), 3.55 (2H,s), 3.70 (6H,s), 6.63 (1H,s), 6.65 (1H,s), 6.80 (1H,s), 6.83 (1H,s), 7.22 (2H,d), 7.32 (1H,m), 7.42 (2H,m), 7.55 (2H,d), 7.68 (4H,d), 7.99 (2H,d), 10.15 (1H,s), 10.35 (2H,br).
5393.HCl	$C_{38}H_{36}N_4O_5$.HCl	629(100)	CI	d_6-DMSO/400MHz	2.95-3.45 (8H,m), 3.75 (2x3H,s), 4.25-4.50 (2H,m), 6.79 (1H,s), 6.80 (1H,s), 6.82 (1H,s), 6.83 (1H,s), 7.30 (2H,d), 7.32 (1H,m), 7.41 (2H,m), 7.55 (2H,d), 7.68 (2H,d), 7.77 (2H,d), 8.01 (2H,d), 10.28 (2H,s), 10.40 (1H,s), 10.80 (1H,brs).
5394	$C_{31}H_{30}N_4O_3$	507(15)	CI	d_6-DMSO/400MHz	1.75-1.85 (2H,m), 2.52-2.57 (2H,m), 2.67 (2H,t), 2.84 (2H,t), 3.34-3.40 (2H,m), 3.57 (2H,s), 6.75 (1H,s), 6.80 (1H,s), 7.05-7.10 (4H,m), 7.30-7.55 (7H,m), 7.84 (2H,d), 8.57 (1H,brt), 10.25 (2H,brs).

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No.	Mol. Formula	Mass spec. data		^{1}H nmr data	
		mass (intensity)	mode	solvent (field)	δ
5394.HCl	$C_{31}H_{30}N_4O_3.HCl$			d_6-DMSO/400MHz	2.02-2.10 (2H,m), 2.95-3.01 (1H,m), 3.18-3.43 (6H,m), 3.65-3.70 (1H,m), 4.23-4.53 (2H,m), 6.79 (1H,s), 6.81 (1H,s), 7.20-7.45 (7H,m) 7.55 (2H,d), 7.65 (2H,d), 7.90 (2H,d), 8.70 (1H,t), 10.25 (1H,s), 10.35 (1H,s), 10.60 (1H,brs).
5397	$C_{37}H_{43}N_5O_4$	622(80)	CI	$CDCl_3$/400MHz	1.75-1.83 (4H,m), 1.95-2.00 (2H,m), 2.25 (6H,s), 2.45 (2H,t), 2.58-2.61 (2H,m), 2.75 (2H,t), 2.85-2.90 (2H,m), 3.47-3.52 (2H,m), 3.62 (2H,s), 4.05 (2H,t), 6.90 (1H,s), 6.95-7.20 (10H,m), 7.35 (2H,d), 7.65 (1H,d), 7.83 (1H,brs), 8.15 (1H,brs).
5397.2HCl	$C_{37}H_{43}N_5O_4.2HCl$			d_6-DMSO/400MHz	1.60-1.65 (2H,m), 1.82-1.90 (2H,m), 2.12-2.20 (2H,m), 2.79 (6H,d), 3.00-3.15 (1H,m), 3.25-3.35 (8H,m), 3.65-3.75 (1H,m), 4.13 (2H,t), 4.25-4.55 (2H,m), 6.75 (1H,s), 6.78 (1H,s), 7.00 (2H,d), 8.60 (1H,brt), 10.20 (1H,brs), 10.30 (1H,brs).
5402	$C_{38}H_{35}N_5O_7$			d_6-DMSO/400MHz	2.70 (6H,m), 2.80 (2H,m), 3.55 (2H,s), 3.70 (6H,s), 6.61 (1H,s), 6.63 (1H,s), 6.80 (1H,s), 6.82 (1H,s), 7.22 (2H,d), 7.68 (4H,d), 7.82 (2H,d), 7.98 (2H,d), 8.22 (2H,d), 10.15 (1H,s), 10.55 (1H,brs).

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No.	Mol. Formula	Mass spec. data		^{1}H nmr data	
		mass (intensity)	mode	solvent (field)	δ
5402.HCl	$C_{30}H_{35}N_5O_2$.HCl	674(80)	ESI	d_6-DMSO/400MHz	3.00-3.50 (8H,m), 3.73 (2x3H,s), 4.25 (2H,m), 6.75 (1H,s), 6.79 (1H,s), 6.86 (1H,s), 6.88 (1H,s), 7.29 (2H,d), 7.69 (2H,d), 7.77 (4H,m), 8.00 (2H,d), 8.25 (2H,d), 10.25 (1H,s), 10.55 (1H,brs), 10.70 (1H,brs).
5376	$C_{33}H_{34}N_4O_4$.HCl	551(100)	ESI	d_6-DMSO/400MHz	2.11-2.20 (2H,m), 2.78 (6H,s), 2.83-2.82 (2H,m), 3.20 (2H,m), 3.62 (2H,brs), 4.09 (2H,t), 4.75 (2H,brs), 6.77 (1H,s), 6.79 (1H,s), 7.00 (2H,d), 7.19 (4H,brs), 7.50 (2H,d), 7.55 (2H,d), 7.60 (2H,d), 10.19 (1H,brs), 10.32 (1H,brs), 10.55 (1H,brs).
5299	$C_{21}H_{24}N_4O_2S$			d_6-DMSO/400MHz	2.18 (6H,s), 2.47 (2H,t), 3.01 (3H,s), 3.40 (2H,d), 5.98 (1H,d), 6.71 (1H,s), 6.85 (1H,s), 7.26 (1H,d), 7.31 (1H,m), 7.41 (2H,m), 7.52 (2H,d), 9.85 (1H,brs).
1912	$C_{23}H_{24}N_4O_3$	404(55)	EI	d_6-DMSO/400MHz	2.25 (6H,s), 2.93 (2H,s), 4.30 (2H,d), 6.74 (1H,s), 6.76 (1H,s), 7.28-7.55 (9H,m), 8.25 (1H,t), 10.20 (2H,brs).

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No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
		m/z, mass intensity (mode)	Solvent δ all 400 MHz	Calc		Found	
1927	$C_{16}H_{14}N_4O_2$ 294	291, 30%; 295, MH^+ 100% (DCI, NH_3)	$CDCl_3$ + TFA 2.45 (3H,s), 6.85 (1H,s), 7.38 (1H,s), 7.48 (5H,m), 8.95 (1H,s).				
1926	$C_{15}H_{12}N_4O_2$ 280	281 MH, 100% (DCI, NH_3)	$CDCl_3$ + TFA 7.20 (1H,s), 7.45 (8H,m).				
1545	$C_{21}H_{17}N_3O_3$ 359	192, 20%; 292, 10%, MH^+ 360 (DCI NH_3)	$CDCl_3$ + CF_3CO_2D 7.82 (1H,d), 7.75 (1H,d), 7.65 (1H,), 7.48 (3H,m), 7.35 (2H,m), 7.25 (1H,s), 7.06 (2H,d), 3.98 (3H,s).				
1542	$C_{16}H_{10}N_2O_3Cl_2$ 348	349, 351, 353, 100%; 366, 368, 370, 50%; 313, 39%. (DCI NH_3)	$CDCl_3$/TFA 6.72 (1H,s), 7.18 (2H,2xs), 7.34 (1H,t), 7.43 (2H,d), 7.59 (1H,s).				

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No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
		m/z, mass intensity (mode)	Solvent δ all 400 MHz	Calc		Found	
1509	$C_{20}H_{15}N_3O_2$	347 MNH_4^+, 1%; 330 MH^+, 100% (DCI NH_3)	$CDCl_3$/TFA 7.22-7.40 (3H,m), 7.40-7.52 (6H,m), 7.60 (1H,s), 7.78 (1H,d, J=7Hz), 7.81 (1H,s), 8.10 (1H,s).				
1507	$C_{22}H_{23}N_3O_5$ 407	310, 100%; 336, 20%; 351, 20%; MH^+ 410, 5% MNH_4^+, 427, 2% (DCI NH_3)	$CDCl_3$ + CF_3CO_2D 7.65 (1H,s), 7.48 (1H,brs), 7.42 (2H,d), 7.22 (1H,s), 7.00 (2H,d), 6.72 (1H,brd), 6.39 (1H,brd), 3.90 (3H,s), 1.65 (9H,s).	C H N	64.54 5.66 10.26	64.45 5.61 10.46	64.39 5.62 10.43
1506	$C_{26}H_{25}N_3O_5$ 459	360, 100%; MH^+ 460, MNH_4^+ 477, 2% (DCI NH_3)	$CDCl_3$ + CF_3CO_2D 8.27 (1H,d) 8.05 (1H,s) 7.70 (1H,d), 7.47 (3H,m), 7.38 (2H,pt), 7.25 (1H,s), 7.05 (2H,d), 3.90 (3H,s), 1.65 (9H,s).	C H N	67.96 5.48 9.14	67.54 5.35 9.21	67.63 5.30 9.22

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No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
		m/z, mass intensity (mode)	Solvent δ all 400 MHz	Calc		Found	
1476	$C_{17}H_{14}N_2O_4$ 310	279, 15%; MH$^+$, 311; MNH_4^+, 328, 2% (DCI NH_3)	$CDCl_3$ + CF_3CO_2D 7.85 (1H,s), 7.60 (1H,brs), 7.42 (2H,d), 7.21 (1H,s), 7.08 (1H,s), 7.02 (2H,d), 6.72 (1H,brs), 3.90 (3H,s).	C H N	65.80 4.55 9.03	65.87 4.44 9.03	65.68 4.54 8.98
1474	$C_{17}H_{14}N_2O_3$ 326	279, 10%; MH+, 327 (DCI NH_3)	$CDCl_3$ + CF_3CO_2D 7.60 (1H,d), 7.45 (3H,m), 7.35 (1H,s), 7.23 (2H,m), 7.05 (2H,d), 3.90 (3H,s).	C H N	62.56 4.32 8.58	62.41 4.41 8.57	62.39 4.46 8.55
1950	$C_{25}H_{27}N_3O_4$ 433	MH+ (100%) 434 CI/NH_3	$CDCl_3$ CF_3CO_2D 400 MHZ 7.50-7.42 (m,5H), 7.25-7.15 (m,4H), 7.00 (d,1H), 6.96 (d,1H), 6.90 (d,1H), 4.41 (t,2H), 3.90 (2,3H), 3.67 (t,2H), 3.12 (s,6H).	C H N	69.57 6.28 9.69	68.98 6.25 9.59	69.06 6.25 9.60

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No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
		m/z, mass intensity (mode)	Solvent δ all 400 MHz	Calc		Found	
1718	$C_{21}H_{17}N_3O_3$ 359	MH^+ 360, 100% (DCI NH_3)	DMSO 11.4 (1H,s), 10.08 (1H,s), 9.82 (1H,s), 7.55 (3H,m), 7.39 (1H,d), 7.18 (1H,t), 7.01 (4H,m) 6.85 (1H,s), 6.78 (1H,s), 3.80 (3H,s).				
1693	$C_{22}H_{19}N_3O_5S$ 437	360, 85%; 402, 25%, MH^+438 (DCI NH_3)	7.98 (1H,d), 7.88 (1H,s), 7.75 (1H,d), 7.45 (5H,m), 7.35 (1H,s), 7.02 (2H,d), 3.90 (3H,s), 3.30 (2.33H,s).				
1618	$C_{23}H_{21}N_3O_4S$ 435	436, 100%; 336, 82%	$CDCl_3$ TFA 1.75 (9H,s), 7.22-7.28 (overlapping solvent & sample signals), 7.36-7.50 (6H, overlapping signals), 7.61 (2H, overlapping signals), 8.10 (1H,s).				

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No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
				Calc		Found	
		m/z, mass intensity (mode)	Solvent δ all 400 MHz				
1560	$C_{25}H_{21}N_3O_4Cl_2$ 497	498/500/502 (100/69/15)% 398/400/402 (49/31/7)%	DMSO-D6 1.68 (9H,s). 6.66 (1H,s). 6.92 (1H,s). 7.30-7.44 (3H,c). 7.49 (2H,d). 7.68 (1H,d). 8.08 (1H,d). 8.17 (1H,s).				
1470	$C_{21}H_{21}N_3O_4$	397. MNH_4. 4%: 380. MH^+. 13%. 280. 100% (DCI NH_3)	$CDCl_3$ 1.64 (9H,s). 6.33 (1H,br.s). 6.57 (1H,br.s). 7.00 (1H,s). 7.35-7.50 (7H,m). 8.10 (1H,br.s). 8.18 (1H,br.s)				
1471	$C_{25}H_{23}N_3O_4$	447. MNH_4^+. 17%: 430. MH^+. 100%: 330. 82%	$CDCl_3$ 1.72 (9H,s). 7.07 (1H,s). 7.14 (1H,s). 7.30-7.50 (7H,m). 7.66 (1H,d, J=7Hz). 7.84 (1H,s). 8.03 (1H,br.s). 8.18 (2H,m)				

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No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
		m/z, mass intensity (mode)	Solvent δ all 400 MHz	Calc		Found	
1729	$C_{23}H_{19}N_3O_5$	435, MNH_4^+, 23%; 418, MH^+, 100% (DCI NH_3)	$CDCl_3$ 3.09 (4H,s), 3.92 (3H,s), 7.07 (2H,d, J=7Hz), 7.28 (1H,s), 7.30 (1H,s), 7.39 (2H,d, J=6Hz), 7.45 (2H,d, J=7Hz), 7.60 (2H,d, J=6Hz)				
1647	$C_{23}H_{21}N_3O_3$ 387	405, M^+NH_4, 7%; 388, M^+H, 100%; 317, 43%; 459, 29% DCI NH_3	$CDCl_3$ 1.84-2.00 (4H,m), 3.13 (2H,t), 3.64 (2H,t), 6.98 (1H,s), 7.03 (1H,s), 7.32-7.50 (9H,m), 8.10 (1H,brs), 8.32 (1H,brs)				
1845	$C_{21}H_{17}N_3O_5$ 391	409, M^+NH_4, 35%; 392, MH^+, 100% (DCI NH_3)	$CDCl_3$ + TFA 2.35 (3H,s,Ac), 6.05 (2H,s, OCH_2O), 6.85-7.60 (9H,m)	C H N	64.45 4.38 10.74	63.99 4.42 10.99	63.94 4.37 11.01
1809	$C_{20}H_{16}N_2O_5$ 364	382, M^++NH_4, 5%; 365, MH^+, 100% (DCI NH_3)	$CDCl_3$ + TFA 3.85 (3H,s,OMe), 6.05 (2H,s,OCH_2O), 6.90-7.45 (9H,m)	C H N	65.93 4.43 7.69	65.85 4.38 7.60	65.96 4.37 7.65

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No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
		m/z, mass intensity (mode)	Solvent δ all 400 MHz	Calc		Found	
1808	$C_{19}H_{14}N_2O_4$ 334	335, M$^+$+1, 100%	$CDCl_3$ + TFA 6.05 (2H,s,OCH_2O), 6.90-7.50 (10H,m)	C H N	68.26 4.22 8.38	68.07 4.15 8.35	68.00 4.17 8.35
1929	$C_{22}H_{18}N_4O_2$ 370	MH$^+$, 371 (DCI NH_3)	$CDCl_3$ + TFA 5.45 (2H,s), 7.18 (1H,s), 7.26 (1H,s), 7.30 (1H,s), 7.45 (10H,m), 8.88 (1H,s)				
1930		MH$^+$, 357, 100% (DCI NH_3)	$CDCl_3$ + TFA 7.27 (1H,s), 7.30 (1H,s), 7.50 (5H,m), 7.65 (5H,m), 7.75 (1H,t), 9.10 (1H,s).				

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No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
		m/z, mass intensity (mode)	Solvent δ all 400 MHz	Calc		Found	
1975	$C_{27}H_{29}N_5O_3$	236. 25%: 257. 100%: 376. 20%: MH^+. 472. 20%. DCI NH_3	$CDCl_3$ + TFA 2.35 (2H,m). 3.01 (6H,s). 3.45 (2H,t). 4.18 (2H,t). 5.40 (2H,s). 6.95 (2H,d). 7.20 (1H,m). 7.25 (1H,s). 7.40 (3H,m). 7.50 (3H,m).				
1976	$C_{26}H_{27}N_5O_3$ 457	230. 100%: 247. 60%: MH^+. 458. 90%. DCI NH_3	$CDCl_3$ + TFA 2.30 (2H,m). 2.05 (6H,s). 3.45 (2H,t). 4.18 (2H,t). 6.98 (2H,d). 7.25 (2H,d). 7.45 (2H,d). 7.55 (3H,m). 7.75 (3H,m). 9.18 (1H,s).				

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No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
		m/z, mass intensity (mode)	Solvent δ all 400 MHz	Calc		Found	
1982	$C_{24}H_{28}N_4O_3.2HCl$ 404+73	405. 100%. MH$^+$ EI$^+$	D_2O 2.98 (3H,s). 3.09 (6H,s). 3.75 (4H,brs). 4.50 (2H,s). 7.09 (1H,s). 7.13 (1H,s). 7.52-7.68 (5H,c). 7.67-7.77 (4H,overlapping signals).				
1983	$C_{26}H_{30}N_4O_2$	431. 25%. MH$^+$: 332. 30%: 303. 18%: 84. 92%: 118. 100%. EI$^+$	DMSO-D6 1.53 (2H,m). 1.71 (2H,d). 1.83 (2H,t). 2.12 (3H,s). 2.14 (3H,s). 2.35 (1H,m). 2.80 (2H,d). 3.57 (2H,s). 6.78 (2H,overlapping signals). 7.34 (3H,overlapping signals). 7.43 (2H,t). 7.50 (2H,d). 7.57 (2H,d).				

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No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
		m/z, mass intensity (mode)	Solvent δ all 400 MHz	Calc		Found	
1886	$C_{29}H_{21}N_3O_7$		$CDCl_3$ / TFA 3.90 (3H,s), 4.79 (2H,s), 7.01 (2H,d,J=8Hz), 7.21 (1H,s), 7.24 (1H,s), 7.27 (2H,d),J=8Hz), 7.41 (2H,d, J=8Hz), 7.47 (2H,d, J=8Hz), 7.82 (2H,m), 7.97 (2H,m).				
1657	$C_{20}H_{19}N_3O_3$ 349	MH^+, 350, 12%; M^+, 349, 13%; 333, 100%. CI NH_3	$CDCl_3$ / TFA 3.92 (3H,s), 4.32 (2H,s), 7.05 (2H,d), 7.24 (2H,d), 7.45 (2H,d), 7.52 (4H,s).				
1891	$C_{23}H_{24}N_2O_4$ 392	392, M^+, 25%; 347, M^+-OCH_2CH_3, 100% EI	DMSO 1.15 (6H,t, J=6Hz, CH_3), 3.45-3.60 (4H,m, $\underline{CH_2}CH_3$), 5.50 (1H,s, O_2CH), 6.75 (2H,s), 7.28-7.55 (9H,m,Ar), 10.25 (2H,br.s,NH)	C H N	70.39 6.16 7.14	70.31 6.16 7.03	70.03 6.16 7.09

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No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
		m/z, mass intensity (mode)	Solvent δ all 400 MHz	Calc		Found	
1912	$C_{23}H_{24}N_4O_3$ 404	404, M^+, 55%; 303, M^+-NHC(O)CH_2NMe_2, 30%; EI	DMSO 2.25 (6H,s, 2xMe), 2.95 (2H,s), 4.30 (2H,d,J=6Hz), 6.74 (1H,s), 6.76 (1H,s), 7.28-7.55 (9H,m), 8.24-8.27 (1H,br,m,NH), 10.20 (2H,br,s, 2xNH)				
1676	$C_{22}H_{19}O_3N_3$ 373	MH^+, 100%, 374 (DCI/NH_3)	$CDCl_3$, CF_3CO_2D 7.65 (2H,d), 7.58 (2H,d), 7.48 (2H,d), 7.41-7.35 (4H,m), 7.24 (1H,s), 7.12-7.07 (2H,m), 2.36+2.23 (3H,s, rotamers).				

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AUSTRALIAN PATENT OFFICE

No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
		m/z, mass intensity (mode)	Solvent δ all 400 MHz	Calc		Found	
1921	$C_{22}H_{21}N_3O_2$ 359	MH^+, 100%, 360 CI/NH_3	$CDCl_3$ + CF_3CO_2D 7.81 (2H,d), 7.52 (2H,d), 7.40-7.50 (6H, m), 7.24 (1H,s), 6.98 (1H,d), 6.96 (1H,d), 3.33 (6H,s),	C H N	73.52 5.89 11.69	73.24 5.82 11.50	73.11 5.77 11.52
1922	$C_{26}H_{20}N_2O_2$ 392	MH^+, 393, 100%, MNH^+, 410, 10% CI/NH_3	d_6-DMSO 11.15 (1H, brs), 10.00 (1H, brs), 7.66 (1H,d), 7.51-7.30 (13H,m), 7.20 (2H,m), 6.78 (1H,s), 6.83 (1H,d),				

No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
		m/z, mass intensity (mode)	Solvent δ all 400 MHz	Calc		Found	
1923	$C_{20}H_{15}N_3O_4$ 361	MH^+, 362, 100% (DCI NH_3)	$CDCl_3$ CF_3CO_2D 8.25 (2H,d), 7.83 (2H,d), 7.63 (1H,dd), 7.55-7.45 (5H,m), 7.35 (1H,s), 7.12 (1H,d), 7.08 (1H,d).	C H N	66.48 4.18 11.63	66.61 4.23 11.40	66.54 4.26 11.48
1672	$C_{20}H_{23}N_3O_3$ 353	MH^+, 354, 100%; MNH^+, 371, 10%; 271, 10%; 260, 10% (DCI NH_3)	$CDCl_3$,CF_3CO_2D 7.59 (2H,d), 7.45 (2H,d), 7.18 (1H,s), 6.29 (1H,d), 2.55-2.47 (1H,m), 2.36-2.22 (3H,s,rotamers), 1.82-1.70 (5H,s), 1.51-1.40 (2H,m), 1.32-1.20 (3H,m).				
1884	$C_{18}H_{20}N_2O_2$ 296	MH^+, 297, 100%; MNH^+, 315, 10% (DCI NH_3)	$CDCl_3$,CF_3CO_2D 7.48-7.38 (5H,m), 7.21 (1H,s), 6.26 (1H,d), 2.48 (1H,m), 1.83-1.70 (1H,m), 1.35 (2H,m), 1.30-1.19 (3H,m).				

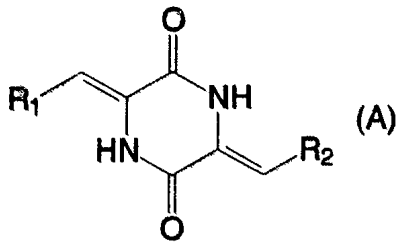
SUBSTITUTE SHEET (RULE 26)

No.	Mol. Formula (M. Wt)	Mass spec	^{1}H nmr	Microanalysis			
		m/z, mass intensity (mode)	Solvent δ all 400 MHz	Calc		Found	
1570	$C_{17}H_{14}N_2O_2S$ 310	311, M$^+$H, 100% DCI-NH_3	$CDCl_3$ 4.13 (3H,s), 6.59 (1H,s), 7.10 (1H,m), 7.30-7.60 (8H,m), 8.09 (1H,brs).	C H N	65.79 4.55 9.03	65.24 4.53 8.73	65.20 4.49 8.79

SUBSTITUTE SHEET (RULE 26)

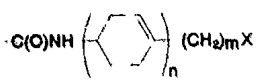
CLAIMS

1. A piperazine of general formula (A):



(A)

wherein one or both of R_1 and R_2, which may be the same or different, is:

(I) X, or a phenyl group which is substituted by X, $C(O)X$, $OC(O)CH_2X$, OCH_2CH_2X, CH_2X, $CONH(CH_2)_nX$, $O(CH_2)_nCH(OH)(CH_2)_nX$ or 

or which is fused to a group X;

(II) a phenyl group substituted by $CH_2NR_{12}R_{13}$, $OC(O)(CH_2)_nZ$, $CH(OR_{12})(OR_{13})$, $(CH_2)_nNR_{14}C(O)(CH_2)_mNR_{12}R_{13}$, $-CH_2NR_{12}-(CH_2)_nNR_{15}R_{16}$ or $O(CH_2)_nCH(OH)(CH_2)_nN(R_{12}R_{13})$;

(III) a group $CH=C(W)V$; or

(IV) a cyclohexyl group;

and where appropriate, the other of R_1 and R_2 is a phenyl group optionally substituted by one or more groups independently selected from halogen, nitro, methoxy, $NHC(O)R_{12}$, CO_2H, $O(CH_2)_nN(R_{12}R_{13})$, $CH_2Y(CH_2)_nN(R_{12}R_{13})$, C_1-C_4 alkyl and $(CH_2)_nC(O)OR_{12}$;

X is a five- or six-membered saturated or unsaturated heterocyclic group containing one or more heteroatoms, which heteroatoms may be the same or different and are

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independently selected from O, N and S; the heteroatom(s) when nitrogen being optionally substituted by hydrogen, methyl, oxygen, tertiary-butyloxycarbonyl, $-(CH_2)_nCH_2OH$ or SO_2Me; the heterocyclic ring being optionally substituted by halogen, Me, MeS, phenyl, $O(CH_2)_nNR_{12}R_{13}$, $-N(R_{12})(CH_2)_nN(R_{12}R_{13})$, $-(CH_2)_nN(R_{12}R_{13})$ or $-O(CH_2)_nO(CH_2)_nN(R_{12}R_{13})$, or the heterocyclic ring optionally containing one or more carbonyl groups and being optionally fused to a benzene ring, which benzene ring is optionally substituted by 1 or 2 C_1-C_6 alkoxy groups;

Y is O or S;

Z is a C_3-C_6 cycloalkyl group;

R_{12}, R_{13} and R_{14}, which may be the same or different, are hydrogen or C_1-C_6 alkyl;

R_{15} and R_{16}, which may be the same or different, are hydrogen or C_1-C_6 alkyl, or R_{15} and R_{16} form, together with the atom to which they are attached, a 5- or 6-membered heterocyclic group;

W is hydrogen or a phenyl group;

V is a phenyl group optionally substituted by one or more groups independently selected from nitro, alkoxy, $O(CH_2)_nNR_{12}R_{13}$ and $NR_{12}R_{13}$; and

m and n are each, independently, O or an integer having the value 1, 2, 3 or 4; or a pharmaceutically acceptable salt or ester thereof; with the exception of

3,6-diisonicotinylidenepiperazine-2,5-dione,

3,6-difurfurylidenepiperazine-2,5-dione,

3,6-di-(2-thiophenylidene)piperazine-2,5-dione and

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3,6-dicinnamylidene-2,5-piperazinedione.

2. A compound according to claim 1, wherein one or both of R_1 and R_2, which may be the same or different, is chosen from X and a phenyl group substituted by X, $C(O)X$, $OC(O)CH_2X$, OCH_2CH_2X, CH_2X or which is fused to a group X; X is a five- or six-membered saturated or unsaturated heterocyclic ring containing one or two heteroatoms, which heteroatoms may be the same or different and are independently selected from O, N and S, the heteroatoms(s) when nitrogen being optionally substituted by hydrogen, methyl, oxygen, tertiary-butyloxycarbonyl, $-(CH_2)_nCH_2OH$ or SO_2Me, the heterocyclic ring being optionally substituted by hydrogen, halogen, methyl, MeS, phenyl, $O(CH_2)_nN(R_{12}R_{13})$, $O(CH_2)_nN(R_{12}R_{13})$ or $-O(CH_2)_nO(CH_2)_nN(R_{12}R_{13})$, the heterocyclic ring optionally containing one or more carbonyl groups and being optionally fused to a benzene ring, and the other of R_1 and R_2 is a phenyl group optionally substituted at the 2,3 or 4-position by $CH_2NR_{12}R_{13}$, $(CH_2)_nNR_{14}C(O)(CH_2)_mNR_{12}R_{13}$, halogen, nitro, $-NHC(O)R_{12}$, $-O(CH_2)_nN(R_{12}R_{13})$ or $-CH_2Y(CH_2)_nN(R_{12}R_{13})$; and Y, R_{12}, R_{13} and n are as defined in claim 1.

3. A compound according to claim 1 or 2, wherein R_{12} and R_{13}, which may be the same or different, are hydrogen or C_1-C_3 alkyl and n is an integer of value 1 or 2.

4. A compound according to claim 1, 2, or 3 wherein one of R_1 and R_2 is a phenyl group which is substituted by X, $C(O)X$, $OC(O)CH_2X$, OCH_2CH_2X, CH_2X or which

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is fused to a group X; wherein X is a five- or six-membered heterocyclic ring containing one or two heteroatoms which may be the same or different, independently selected from O, N and S, the heteroatoms(s) when nitrogen being optionally substituted by methyl, the heterocyclic ring being optionally fused to a benzene ring.

5. A compound according to claim 1, wherein one of R_1 and R_2 is a phenyl group substituted by $CH_2NR_{12}R_{13}$, $OC(O)(CH_2)_nZ$, $CH(OR_{12})(OR_{13})$, $(CH_2)_n NR_{14}C(O)(CH_2)_mNR_{12}R_{13}$; wherein R_{12}, R_{13} and R_{14}, which may be the same or different, are independently selected from hydrogen or C_1-C_3 alkyl;
Z is a C_5 or C_6 cycloalkyl group;
and m and n are, independently, integers having the values 1, 2 or 3.

6. A compound according to claim 1 or 5, wherein R_{12}, R_{13} and R_{14}, which may be the same or different, are independently selected from hydrogen and C_1-C_2 alkyl;
Z is a cyclopentyl group; and
m and n are, independently, integers having the values of 1 or 2.

7. A compound selected from
(3Z,6Z)-3-Benzylidene-6-(4-imidazolyl)methylene-2,5-piperazinedione.
(3Z,6Z)-3-Benzylidene-6-(4-(1-imidazolyl)benzylidene)-2,5-piperazinedione.
(3Z,6Z)-3-Benzylidene-6-(4-(1-imidazolylmethyl)benzylidene)-2,5-piperazinedione.
(3Z,6Z)-3-Benzylidene-6-(4-(5-methylimidazolyl))methylene-

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2,5-piperazinedione.

(3Z,6Z)-3-Benzylidene-6-(4-dimethylaminocinnamylidene)-2,5-piperazinedione.

(3Z,6Z)-3-(4-(3-Dimethylaminopropoxy)benzylidene)-6-(4-(1-imidazolyl)benzylidene-2,5-piperazinedione.

(3Z,6Z)-3-Benzylidene-6-(4-(2-imidazolylethoxy)benzylidene)-2,5-piperazinedione.

(3Z,6Z)-3-Benzylidene-6-(4-nitrocinnamylidene-2,5-piperazinedione.

(3Z,6Z)-3-(4-Aminomethylbenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione.

(3Z,6Z)-3-(1-methanesulfonyl-3-indolyl)methylene-6-(4-methoxybenzylidene)-2,5-piperazinedione.

(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-phthalimidoacetoxybenzylidene)-2,5-piperazinedione.

(3Z,6Z)-3-Benzylidene-6-(γ-phenylcinnamylidene)-2,5-piperazinedione.

(3Z,6Z)-3-(1-tert-butoxycarbonyl-3-indolyl)methylene-6-(2-thenylidene)-2,5-piperazinedione.

(3Z,6Z)-3-(2,6-Dichlorobenzylidene)-6-(1-tert-butoxycarbonyl-3-indolyl)methylene-2,5-piperazinedione.

(3Z,6Z)-3-Benzylidene-6-(4-(2-dimethylaminoethoxy)-3-methoxycinnamylidene)-2,5-piperazinedione.

(3Z,6Z)-3-(4-(3-Dimethylaminopropoxy)benzylidene)-6-(4-(1-imidazolylmethyl)benzylidene)-2,5-piperazinedione.

(3Z,6Z)-3-Benzylidene-6-(4-N-methyl-N-(4-(N-methylpiperidinyl))aminomethylbenzylidene-2,5-piperazinedione.

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((3Z,6Z)-3-Benzylidene-6-(3-indolylmethylene)-2,5-piperazinedione.

(3Z,6Z)-3-(2,6-Dichlorobenzylidene)-6-(3-furylmethylene)-2,5-piperazinedione.

(3Z,6Z)-3-(3-Indolylmethylene)-6-(4-methoxybenzylidene)-2,5-piperazinedione.

(3Z,6Z)-3-(2,6-Dichlorobenzylidene)-6-(3-(1-tertbutoxycarbonyl)indolyl)methylene-2,5-piperazinedione.

(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(2-(1-tertbutoxycarbonyl)pyrrolyl)methylene-2,5-piperazinedione.

(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(3-(1-tertbutoxycarbonyl)indolyl)methylene-2,5-piperazinedione.

(3Z,6Z)-3-Benzylidene-6-(3-(1-tertbutoxycarbonyl)indolyl)methylene-2,5-piperazinedione.

(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(2-thienylmethylene)-2,5-piperazinedione.

(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(3-furylmethylene)-2,5-piperazinedione.

(3Z,6Z)-3-(Acetamidobenzylidene)-6-cyclohexylmethylene-2,5-piperazinedione.

(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-cinnamylidene-2,5-piperazinedione.

(3Z,6Z)-3-Benzylidene-6-(diethoxymethylbenzylidene)-2,5-piperazinedione.

(3Z,6Z)-3-Benzylidene-6-(4-(N-methyl-N-(2-dimethylaminoethyl)aminoethylbenzylidene-2,5-piperazinedione hydrochloride.

(3Z,6Z)-3-Benzylidene-6-cyclohexylmethylene-2,5-piperazinedione.

(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(3,4-methylenedioxybenzylidene)-2,5-piperazinedione.

(3Z,6Z)-3-(2-Indolylmethylene)-6-(4-methoxybenzylidene)-2,5-piperazinedione.

(3Z,6Z)-3-Benzylidene-6-(3,4-methylenedioxybenzylidene)-2,5-piperazinedione.

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(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(3,4-methylenedioxybenzylidene)-2,5-piperazinedione.

(3Z,6Z)-3-Benzylidene-6-(2-(1-tertbutoxycarbonyl)pyrrolyl)methylene-2,5-piperazinedione.

(3Z,6Z)-3-(4-Dimethylaminomethylbenzylidene)-6-(4-(3-dimethylaminopropoxy)benzylidene-2,5-piperazinedione.

(3Z,6Z)-3-(4-(3-Dimethylaminopropoxy)benzylidene)-6-(4-(1-imidazolyl)methylbenzylidene)-2,5-piperazinedione.

(3Z,6Z)-3-(4-(3-Dimethylaminopropoxy)benzylidene)-6-(4-(1-imidazolyl)benzylidene.

(2-(4-((3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-2,5-dioxo-3-piperazinylidene)methylbenzoyl)-1,2,3,4-tetrahydroisoquinoline.

N-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-6-(4-(3-dimethylaminopropoxy)benzylidene)-2,5-dioxo-3-piperazinylidene)methylbenzamide.

N-(4-(1,2,3,4-Tetrahydro-2-isoquinolyl)butyl)-4-((3Z,6Z)-6-(4-(3-dimethylaminopropoxy)benzylidene)-2,5-dioxo-3-piperazinylidene)methylbenzamide.

(3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene-3-(4-pyridylmethylene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-(3-pyridylmethylene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-furfurylidene-2,5-piperazinedione.

(3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-(3-Thenylidene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-(2-

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AMENDED SHEET

Thenylidene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-(3-Furylmethylene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-(2-Naphthylmethylene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-(3-Dimethylaminopropoxy)benzylidene)-3-(1-Naphthylmethylene)-2,5-piperazinedione.

(3Z,6Z)-6-Benzylidene-3-(4-(3-dimethylamino-2-hydroxypropoxy)benzylidene)-2,5-piperazinedione.

(3Z,6Z)-6-Benzylidene-3-(4-(2-hydroxy-3-morpholinopropoxy)benzylidene)-2,5-piperazinedione.

(3Z,6Z)-6-Benzylidene-3-(4-(2-hydroxy-3-(1-imidazolyl)propoxy)benzylidene)-2,5-piperazinedione.

(3Z,6Z)-6-Benzylidene-3-(4-(2-hydroxy-3-(4-(2-hydroxyethyl)-1-piperazinyl)propoxy)benzylidene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-(2-Dimethylaminoethoxy)benzylidene)-3-(3-Furylmethylene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-(2-Dimethylaminoethoxy)benzylidene)-3-(3-thenylidene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-(2-Dimethylaminoethoxy)benzylidene)-3-(5-methylthio-2-thenylidene)-2,5-piperazinedione.

(3Z,6Z)-6-Benzylidene-3-(4-(2-morpholinoethoxy)benzylidene)-2,5-piperazinedione.

(3Z,6Z)-6-Benzylidene-3-(4-(2-(1-imidazolyl)ethoxy)benzylidene)2,5-piperazinedione.

(3Z,6Z)-6-Benzylidene-3-(4-(2-(1-pyrrolidinyl)ethoxy)benzylidene)2,5-piperazinedione.

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(3Z,6Z)-6-(4-(2-Dimethylaminoethoxymethyl)benzylidene)-3-(3-thenylidene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-(2-Dimethylaminoethoxymethyl)benzylidene)-3-(3-furylmethylene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-Dimethylaminoacetamidomethyl benzylidene)-3-(3-thenylidene)-2,5-piperazinedione.

(3Z,6Z)-3-(2-Bromobenzylidene)-6-(4-dimethylaminoacetamidomethylbenzylidene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-Dimethylaminoacetamidomethylbenzylidene)-3-(3-furylmethylene)-2,5-piperazinedione.

(3Z,6Z)-6-Benzylidene-3-(4-dimethylaminoacetamidomethylbenzylidene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-(2-Dimethylaminoethylthiomethyl)benzylidene)-3-(3-furylmethylene)-2,5-piperazinedione.

(3Z,6Z)-6-(4-(2-Dimethylaminoethylthiomethyl)benzylidene)-3-(3-thenylidene)-2,5-piperazinedione.

(3Z,6Z)-6-Benzylidene-3-(4-dimethylaminoacetamidoaminomethylbenzylidene)-2,5-piperazinedione.

(3Z,6Z)-6-Benzylidene-3-(5-(2-dimethylaminoethoxy)-2-thienylmethylene)-2,5-piperazinedione.

(3Z,6Z)-6-Benzylidene-3-(4-(2-dimethylaminoethoxy)-2-thienylmethylene)-2,5-piperazinedione.

(3Z,6Z)-6-Benzylidene-3-(5-(2-dimethylaminoethyl)-2-thienylmethylene)-2,5-piperazinedione.

(3Z,6Z)-6-Benzylidene-3-(5-(2-(2-

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dimethylaminoethoxy)ethoxy)-2-thienylmethylene)-2,5-piperazinedione.
(3Z,6Z)-6-Benzylidene-3-(5-(6-dimethylaminohexyloxy)-2-thienylmethylene)-2,5-piperazinedione.
(3Z,6Z)-6-Benzylidene-3-(5-(2-dimethylaminoethyl)methylamino-2-thienylmethylene)-2,5-piperazinedione.
(3Z,6Z)-3-(2,5-Dichloro-3-thenylidene)-6-benzylidene-2,5-piperazinedione.
N-(4-(1,2,3,4-Tetrahydro-2-isoquinolyl)butyl)-4-((3Z,6Z)-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide.
N-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide.
N-(3-(1,2,3,4-Tetrahydro-2-isoquinolyl)propoyl)-4-((3Z,6Z)-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide.
N-(4-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)phenyl-4-((3Z,6Z)-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide.
N-(4-(2-(1,2,3,4-Tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-2,5-dioxo-6-(4-nitrobenzylidene)-3-piperazinylidene)methylbenzamide.

8. A 3,6-dimethylene piperazine-2,5-dioxo derivative, substantially as hereinbefore described with reference to any one of the Examples.

9. A pharmaceutical or veterinary composition comprising a pharmaceutically or veterinarily acceptable carrier or diluent and, as an active principle, a compound as defined in any one of claims 1 to 8.

10. A process for preparing a compound of formula (A) as defined in claim 1, the process comprising:

(a) condensing a compound of formula (I):

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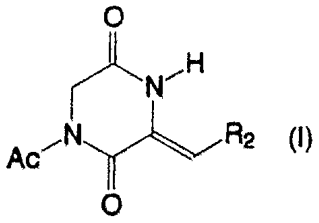


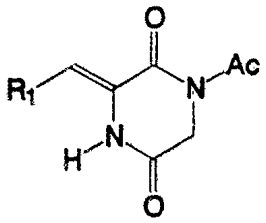
(I)

wherein R_2 is as defined in claim 1 and is optionally protected, with a compound of formula (II):

$$R_1—CHO \quad (II)$$

wherein R_1 is as defined in claim 1 and is optionally protected, in the presence of a base in an organic solvent; or

(b) condensing a compound of formula (I'):



(I')

wherein R_1 is as defined in claim 1 and is optionally protected with a compound of formula (III):

$$R_2—CHO \quad (III)$$

wherein R_2 is as defined in claim 1 and is optionally protected, in the presence of a base in an organic solvent; and

(c) if required, removing optionally present protecting groups, and/or, if desired, converting one

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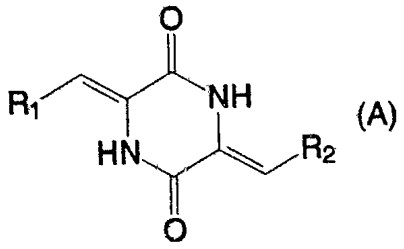
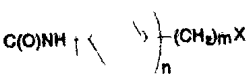
compound of formula A into another compound of formula A, and/or, if desired, converting a compound of formula A into a pharmaceutically acceptable salt or ester thereof, and/or, if desired, converting a salt or ester into a free compound, and/or, if desired, separating a mixture of isomers into the single isomers.

11. A method for the treatment or prophylaxis of a condition indicating the administration of an inhibitor of plasminogen activator inhibitor in a mammal requiring said treatment or prophylaxis, which method comprises adminstering to said mammal an effective amount of at least one compound which is diketopiperazine of formula (A):



(A)

wherein one or both of R_1 and R_2, which may be the same or different, is:

(I) X, or a phenyl group which is substituted by X, $C(O)X$, $OC(O)CH_2X$, OCH_2CH_2X, CH_2X, $CONH(CH_2)_nX$, $O(CH_2)_nCH(OH)(CH_2)_nX$ or 

or which is fused to a group X;

(II) a phenyl group substituted by $CH_2NR_{12}R_{13}$, $OC(O)(CH_2)_nZ$, $CH(OR_{12})(OR_{13})$, $(CH_2)_nNR_{14}C(O)(CH_2)_mNR_{12}R_{13}$, $-CH_2NR_{12}(CH_2)_nNR_{15}R_{16}$ or $O(CH_2)_nCH(OH)(CH_2)_nN(R_{12}R_{13})$;

(III) a group $CH=C(W)V$; or

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(IV) a cyclohexyl group;

and where appropriate, the other of R_1 and R_2 is a phenyl group optionally substituted by one or more groups independently selected from halogen, nitro, methoxy, $NHC(O)R_{12}$, CO_2H, $O(CH_2)_nN(R_{12}R_{13})$ and $CH_2Y(CH_2)_nN(R_{12}R_{13})$;

X is a five- or six-membered saturated or unsaturated heterocyclic group containing one or more heteroatoms, which heteroatoms may be the same or different and are independently selected from O, N and S; the heteroatom(s) when nitrogen being optionally substituted by hydrogen, methyl, oxygen, tertiary-butyloxycarbonyl, $-(CH_2)_nCH_2OH$ or SO_2Me; the heterocyclic ring being optionally substituted by halogen, Me, MeS, phenyl, $O(CH_2)_nNR_{12}R_{13}$, $-N(R_{12})(CH_2)_nN(R_{12}R_{13})$, $-(CH_2)_nN(R_{12}R_{13})$ or $-O(CH_2)_nO(CH_2)_nN(R_{12}R_{13})$, or the heterocyclic ring optionally containing one or more carbonyl groups and being optionally fused to a benzene ring, which benzene ring is optionally substituted by 1 or 2 C_1-C_6 alkoxy groups;

Y is O or S;

Z is a C_3-C_6 cycloalkyl group;

R_{12}, R_{13} and R_{14}, which may be the same or different, are hydrogen or C_1-C_6 alkyl;

W is hydrogen or a phenyl group;

V is a phenyl group optionally substituted by one or more groups independently selected from nitro, alkoxy, $O(CH_2)_nNR_{12}R_{13}$ and $NR_{12}R_{13}$; and

m and n are each, independently, O or an integer having the value 1, 2, 3 or 4;

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or a pharmaceutically acceptable salt thereof.

12. A process for the preparation of a 3,6-dimethylene piperazine-2,5-dioxo derivative, substantially as hereinbefore described with reference to any one of the Examples.

Dated 17 . pril, 1998
Xenova Limited

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

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INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/GB 95/00302

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D241/02 C07D401/06 C07D405/06 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.
A	DE,C,621 862 (I. G. WERK) 14 November 1935 see claims; example 5	1
P,A	WO,A,94 04512 (XENOVA) 3 March 1994 see the whole document	1-10
A	CHEMICAL ABSTRACTS, vol. 97, no. 6, 1982, Columbus, Ohio, US; abstract no. 40323s, page 70 ; see abstract	1
A	& JP,A,8 247 357 (RICOH) 18 March 1982	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 April 1995	11. 04. 95

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	Francois, J

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INTERNATIONAL SEARCH REPORT

Inter ..al Application No
PCT/GB 95/00302

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 98, no. 28, 1983, Columbus, Ohio, US; abstract no. 160674z, M.L. BARON ET AL. 'THE REACTION OF PIPERAZINE-2,5-DIONE WITH 2-FORMYLBENZOIC ACID.' page 511 ; see abstract	1,9
A	& AUST.J. CHEM., vol.35, no.12, 1982, AUSTRALIA pages 2567 - 2569 -----	1,9

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/GB 95/00302

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DE-C-621862		NONE		
WO-A-9404512	03-03-94	AU-B-	4726493	15-03-94
		AU-B-	4726593	15-03-94
		WO-A-	9404513	03-03-94
JP-A-8247357		NONE		