SUBSTITUTED DIKETOPIPERAZINES AS OXYTOCIN ANTAGONISTS

This invention relates to the use of a class of diketopiperazine derivatives as potent and selective antagonists of oxytocin, to novel compounds within that class and to processes for their preparation.

USP5817751 describes combinatorial and solid phase methods for the synthesis of diverse diketopiperazine derivatives and the use of these methods to create libraries of diverse diketopiperazine derivatives.

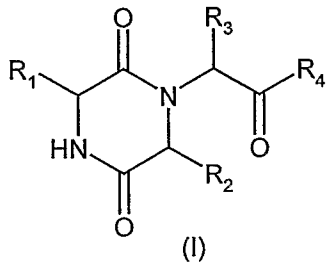
WO99/47549 describes diketopiperazine derivatives including 3-benzyl-2,5 diketopiperazine derivatives as inhibitors of fructose 1,6-bisphospate (FBPase).
WO99/38844 describes a method for preparing N-[aliphatic or aromatic) carbonyl]-2-aminoacetamide compounds and their cyclisation to give inter alia diketopiperazine derivatives.

WO99/37304 describes oxaheterocyclyl compounds including oxapiperazinyl compounds that are inhibitors of Factor Xa.

The hormone oxytocin is potent contractor of the uterus and is used for the induction or augmentation of labour. Also the density of uterine oxytocin receptors increases significantly by >100 fold during pregnancy and peaks in labour (pre-term and term). Pre-term births/labour (between 24 and 37 weeks) causes about 60% of infant mortality/morbidity and thus a compound which inhibits the uterine actions of oxytocin e.g. oxytocin antagonists, should be useful for the prevention or control of pre-term labour.

We have found a class of diketopiperazine derivatives which exhibit a particularly useful level of activity as selective antagonists at the oxytocin receptor.

The present invention thus a method of treating or preventing diseases or conditions mediated through the action of oxytocin which comprises administering to a mammal in need thereof of an effective amount of a compound of the formula (I)



(I)

and/or a physiologically acceptable derivative thereof, wherein:

R_1 represents aryl (C_{1-4}) alkyl or a 5-7 membered cycloalkyl group optionally substituted with one or more hydroxyl groups which is fused to an optionally substituted benzene ring;

R_2 represents C_{1-6}alkyl (optionally substituted by a C_{1-2}alkoxy, C_{1-2}alklthio, di(C_{1-2}alkyl) amino or a C_{3-6} cycloalkyl group) or C_{3-6}cycloalkyl, or 5-6 membered heterocyclic group containing a single hetero atom selected from O, S or N, which nitrogen atom carries a hydrogen atom or a methyl or ethyl group;

R_3 represents optionally substituted phenyl, a 5 or 6 membered hetero aryl group or a fused bicyclic ring system containing 9-10 ring members which may be a carbocyclic group or it may contain up to 3 heteroatoms selected from O, S or N and one of the fused rings is benzene;

R_4 represents OH or OC_{1-4} alkyl (optionally substituted with C_{1-4}alkylcarbonyloxy) or NR_5R_6;

R_5 represents hydrogen, C_{1-6}alkyl (optionally substituted with C_{1-4}alkoxy) or C_{3-7}cycloalkyl;

R_6 represents hydrogen, C_{1-4}alkoxy, C_{3-7}cycloalkyl, C_{1-4}alkyl [optionally substituted with one or more groups selected from, carboxyl, C_{1-4}alkylsulphonyl, or C_{1-4}alkoxycarbonyl], C_{2-4}alkyl [optionally substituted with one or more groups selected from halogen, hydroxy, C_{1-4}alkoxy or NR_7R_8 wherein R_7 and R_8 independently represent hydrogen or C_{1-4}alkyl or together with the nitrogen atom to which they are attached to form a 3-7 membered saturated heterocyclic ring which may contain an additional heteroatom selected from O, S or N (and which heterocyclic group may be substituted by 1 to 3 groups selected from C_{1-3}alkyl, hydroxy, C_{1-3} alkoxy (optionally substituted by C $_{3-6}$ cycloalkyl or optionally subtituted phenyl), C $_{3-6}$cycloalkyl or NR_cR_d wherein R_c and R_d each independently represent a group selected from C $_{1-3}$alkyl (optionally substituted by C $_{3-6}$ cycloalkyl or optionally substituted phenyl) or C $_{3-6}$ cycloalkyl)] or R_6 represents a phenyl or benzyl group (optionally substituted by one or more methoxy or benzyloxy groups) or an optionally substituted heteroarylmethyl group or a heteroaryl group or C_{3-7} cycloalkyl or the group $CH_2CONR_9R_{10}$ wherein R_9 represents hydrogen or C_{1-4}alkyl, R_{10} represents hydrogen, C_{1-4}alkyl optionally substituted by a 5 or 6 membered heteroaryl group or R_9, R_{10} and the nitrogen atom to which they are attached together form a 5 or 6 membered saturated heterocyclic ring and wherein the 6 membered heterocyclic group may contain an additional heteroatom selected from oxygen, sulphur or nitrogen and the additional nitrogen atom either carries a hydrogen atom or a C_{1-4}alkyl or C_{1-4}alkanoyl group; or R_5 and R_6 together with the nitrogen atom to which they are attached form a 3 to 7 membered saturated heterocyclic ring which heterocycle may contain an additional heteroatom selected from oxygen, sulphur and nitrogen and wherein the sulphur atom may be in an oxidised form e.g. SO_2 and the additional nitrogen atom either carries a hydrogen atom or a C_{1-4}alkyl or **a** C_{1-4}alkanoyl group or a C_{1-4}alkylsulphonyl group or a C_{1-3} alkoxyC_{2-4} alkyl [and which heterocyclic groups may be substituted by one or more halogen atoms or a group selected from C_{1-3}alkyl, hydroxy, oxo, C $_{3-6}$cycloalkyl or NR_eR_f

wherein R_e and R_f each independently represent a group selected from C_{1-3}alkyl (optionally substituted by C_{3-6} cycloalkyl or optionally substituted phenyl) or C_{3-6} cycloalkyl].

The invention also provides novel compounds of formula (I). A particularly useful class of novel compounds of formula (I) are those wherein R_1 is 2-indanyl optionally substituted by hydroxyl and more particularly a 2-indanyl group and R_2, R_3 and R_4 have the meanings defined above and/or physiologically acceptable derivatives thereof. A further useful class of novel compounds of formula (I) are those wherein R_1 is a 2-phenethyl and R_2, R_3 and R_4 have the meanings defined above and/or physiologically acceptable derivatives thereof.

The compounds of formula (I) contain at least three centers of asymmetry, namely the carbon atoms carrying the substituents R_1, R_2 and R_3 respectively and it is to be understood that formula (I) includes all possible stereoisomers and mixtures thereof. The substituent R_3 may exist in more than one tautomeric form and it is to be all understood that formula (I) includes all possible tautomeric forms and mixtures thereof.

The compounds of formula (I) wherein at least one of the groups R_1, R_2,R_3 or R_4 contains a basic or acidic grouping may form salts with physiologically acceptable acids or bases and reference to compounds of formula (I) herein includes such salts.

As used herein, the terms "physiologically acceptable derivative" or " pharmaceutically acceptable derivative", mean any pharmaceutically acceptable salt, solvate, or prodrug e.g. ester or carbamate, or salt or solvate of such a prodrug, of a compound of formula (I), which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I), or an active metabolite or residue thereof. Preferred pharmaceutically acceptable derivatives are salts and solvates.

As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference. Esters may be active in their own right and /or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. Examples of such esters include alkyl and 1-(acetyloxy)ethyl esters.

The term alkyl as a group or part of a group refers to a straight or branched alkyl group e.g. methyl, ethyl, propyl, isopropyl, n-butyl, 1-methylpropyl, 2-methylpropyl, t-butyl, pentyl or hexyl.

The term C $_{3-6}$ cycloalkyl as a group or part of a group includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. The term C_{3-7}cycloalkyl also includes cycloheptyl.

The term halogen refers to fluorine, chlorine, bromine or iodine.

Unless otherwise specified the term optionally substituted phenyl refers to a phenyl group which may be substituted by 1 to 3 substituents which may be the same or different and selected from halogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1-3 halogen atomsor NR_gR_h [wherein R_g is hydrogen or C_{1-4} alkyl, R_h is hydrogen, C_{1-4} alkyl, or R_g and R_h together with the nitrogen atom to which they are attached to form a 5 to 7 membered ring, which ring is saturated and may contain an additional heteroatom selected from nitrogen, oxygen or sulphur]), C_{1-4} alkylsulphonyl, carboxyl, C_{1-4} alkoxycarbonyl, di(C_{1-4}alkyl)aminocarbonyloxy, C_{1-4}alkoxy (optionally substituted by 1-3 halogen atoms, amino, C_{1-4} alkylamino or di-(C_{1-4}alkyl) amino), phenyl (optionally substituted by halogen or alkylaminosulphonyl), C_{1-4}alkoxy, NR_aR_b [wherein R_a is hydrogen or C_{1-4} alkyl, R_b is hydrogen, C_{1-4} alkyl, C_{1-4} alkanoyl or C_{1-4} alkylsulphonyl or R_a and R_b together with the nitrogen atom to which they are attached to form a 5 to 7 membered ring, which ring is saturated and may be substituted by hydroxyl or 1 or 2 C_{1-4}alkyl groups or may be spiro-fused to a dioxalane ring or may contain an additional heteroatom selected from nitrogen, oxygen or sulphur and may be substituted by 1 or 2 C_{1-4}alkyl groups, or which ring is unsaturated and contains 1-3 additional nitrogen atoms], a 5 or 6 membered heteroaryl group, an optionally N-substituted aminocarbonyl or aminosulphonyl group (wherein the substituents may be 1 or 2 C_{1-4} alkyl groups) or a dihydroxyboryl group).

The term 5 membered heteroaryl refers to a 5 membered ring which contains a heteroatom selected from oxygen, sulphur or nitrogen and which may also contain from 1 to 3 additional nitrogen atoms and which groups may be substituted by 1 or more groups selected from halogen, trifluoromethyl, C_{1-4} alkyl , cycloalkyl, heteroaryl, saturated heterocyclic, or phenyl groups. Examples of such 5 membered heteroaryl groups include furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl or tetrazolyl and these heterocycles may be substituted as described above.

The term 6-membered heteroaryl group refers to a 6-membered unsaturated ring which contains from 1 to 3 nitrogen atoms and which may be substituted by 1 to 3 C_{1-4} alkyl groups, or trifluoromethyl, or alkoxy groups. Examples of such groups include pyridyl, methylpyridyl, trifluoromethylpyridyl, pyrimidinyl and triazinyl.

When R_3 is a 5 or 6 membered heteroaryl group this is linked to the rest of the molecule via a carbon atom in the ring.

When R_3 is a fused bicyclic carbocyclic ring system this may be for example a naphthyl, tetrahydronaphthyl, indanyl or indenyl group.

When R_3 is a fused bicylic system containing up to 3 heteroatoms which may be the same or different, this is conveniently a 6,5 or 6,6 ring system wherein the heterocycle may be partially saturated or together with the benzene ring to which it is fused to form a heteroaryl group and the heterocycle may be substituted by 1 or 2 groups selected from C_{1-4} alkyl or halogen or haloalkyl and or may contain a carbonyl group. The said R_3 group may be linked to the rest of the molecule via a carbon atom in the benzene ring or a carbon atom in the heterocyclic group.

When R_3 is a fused 6,6 heteroaryl group the hetero ring contains from 1 to 3 nitrogen atoms and examples of such heteroaryl groups include quinolinyl, isoquinolinyl, phthalazinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,2,3 benzotriazinyl or 1,2,4 benzotriazinyl.

When R_3 is a 6,5 bicyclic heteroaryl group the 5 membered heterocycle contains a hetero atom selected from O, S or N and may in addition also contain a further 1 or 2 nitrogen atoms and the heterocyclic ring may also be substituted by 1 or 2 C_{1-4} alkyl or halogen or haloalkyl and or may contain a carbonyl group. Examples of such 6, 5 bicyclic heteroaryl groups include benzofuranyl, benzothienyl, indolyl, benzo-oxadiazolyl, benzothiadiazolyl, benzo-oxazolyl, benzothiazolyl, benzoisothiazolyl, benzoisoxazolyl, benzimidazolyl, indazolyl or benzotriazolyl and these groups may be substituted as described above.

When R_3 is a 6,6 or 6,5 bicyclic heterocyclic group and the hererocycle is partially saturated, this may contain 1 or 2 heteroatoms selected from O, S or N. Examples of such groups include indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, 1,3-benzodioxolyl, benzopyrrolyl, 1,3-benzodithiolyl 1,4-benzodioxanyl, phthalyl, thiophthalyl, chromanyl or chromenyl and the groups may be substituted by one or more halogen or C_{1-4} alkyl groups, haloalkyl, or may contain a carbonyl group.

When R_3 is a fused bicyclic heteroaryl linked via the benzene ring therein then suitable examples of such a group include 6-quinolinyl, 4-isoindolinyl, 4-(N-methyl-isoindolinyl, benzimidazolyl, benzothiazolyl, benzofuranyl, benzothienyl, benzimidazolyl benzoxazolyl, 2 methyl-benzo-oxazolyl, benzothiadiazolyl, benzotriazolyl and 1-methyl benzotriazolyl.

When R_3 is a fused bicyclic heteroaryl group linked via the heteroaryl ring this may be for example a 2-benzofuranyl, 2-benzothienyl or 2-N-methylindolyl group .
When R_3 is a 6,6 or 6,5 heterocyclic group wherein the heterocycle is partially saturated this is conveniently linked via the benzene ring therein and suitable examples include dihydrobenzofuran, dihydrobenzopyrrole, 1,3-benzodioxolyl, 2,2-difluoro-1,3-benzodioxolyl, and 1,4-benzodioxanyl.

When R_3 is a substituted phenyl group the said group conveniently carries from 1 to 3 substituents which may be the same or different selected from fluorine, chlorine, bromine C_{1-3}alkyl(methyl), C_{1-3}haloalkyl (trifluoromethyl), C_{1-3}alkoxy (methoxy, ethoxy), haloalkoxy (trifluoromethoxy), aminoethoxy e.g. dimethylaminoethoxy, C_{1-3}alkoxycarbonyl, carboxy, hydroxy, phenyl or phenyl (substituted by halogen or alkylaminosulphonyl), NR_aR_b [wherein R_a is hydrogen or C_{1-2}alkyl and R_b is C_{1-2}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-3}alkylaminocarbonyl] or NR_aR_b represents a pyrrolidino or piperidino ring, which ring may be substituted by a C_{1-2}alkyl, hydroxyl or a 2,2-1,3-dioxolane group or NR_aR_b represents a morpholino or a piperazino group which groups may be substituted by 1 or 2 C_{1-2}alkyl groups or NR_aR_b represents a 5 or 6 membered heteroaryl group containing from 1 to 4 nitrogen atoms (such as a 1-imidazolyl, 1,2-pyrazolyl, 1,2,3-triazolyl or 1,2,4-triazolyl substitutent), C_{1-3}alkylsulphonyl, C_{1-3}alkylaminocarbonyl, C_{1-3}alkylaminosulphonyl, dihydroxyboryl or a 5 or 6 membered atom heteroaryl group containing from 1 to 4 nitrogen atoms and which is linked to the phenyl group via a carbon atom in the heteroaryl group (for example pyridyl, pyrazolyl, imidazolyl or tetrazol 5-yl, which heteroaryl groups may be substituted by 1 or more C_{1-4} alkyl groups.

Examples of suitable R_3 groups wherein R_3 is optionally substituted phenyl include phenyl, halophenyl such as 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2-chloro-4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2 fluoro-4-bromophenyl, 4-chloro-3-fluorophenyl 2,3,4-trifluorophenyl 2,4,5-trifluorophenyl or 2,4,6-trifluorophenyl, 2-fluoro-4,5-dimethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-fluoro-4 methoxyphenyl, 2- fluoro-4 hydroxyphenyl, 2-fluoro-4-dimethylaminomethylphenyl, 2-fluoro-4-hydroxymethylphenyl, 3-fluoro-4-(4-morpholino)phenyl, 3-fluoro-4-carboxymethyloxyphenyl, 3-fluoro-4-t-butyloxycarbonylmethyloxyphenyl, 3-fluoro-4-dimethylaminocarbonyloxyphenyl, 3-chloro-4 trifluoromethoxyphenyl, 2,3-difluoro-4-methyl-phenyl, 4-trifluoromethoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-methoxycarbonylphenyl, 3-methoxycarbonyphenyl, 4-methylsulphonylphenyl, 4-methylaminocarbonylphenyl, 4- aminocarbonylphenyl, 4-methylaminosulphonylphenyl, 3-(3-pyrazyolyl)phenyl, 4-(3-pyrazolyl)phenyl, 4-(4-pyrazolyl)phenyl, 4-(3-pyridyl)phenyl, 4-(2-pyridylphenyl), 4-(2-imidazolyl)phenyl, 3-(2-imidazolyl)phenyl, 4-

(1-t-butyl-tetrazol-5-yl)phenyl, 4-methylaminophenyl, 4-dimethylaminophenyl, 4-diethylaminophenyl, 4-acetylaminophenyl, 3-acetylaminophenyl, 4-hydroxy-3-acetylaminophenyl, 4-methylsulphonylaminophenyl, 4-N-methylpiperazinophenyl, 4-N-pyrrolidinophenyl, 2-fluoro-4-(4-morpholino)phenyl, 4-(4-morpholino)phenyl, 4-(4-hydroxypiperidino)phenyl, 2-fluoro-4-(4-hydroxypiperidino)phenyl, 3-(1-pyrazolyl)phenyl, 4-(1-pyrazolyl)phenyl, , 4-(1-3,5 di-t-butylpyrazolyl)phenyl, 3-(1-imidazolyl)phenyl, 4-(1-imidazolyl)phenyl, 4-(1-1,2,4-triazolyl)phenyl, 4-(1-1,2,3-triazolyl)phenyl, 4-(2-4,-t-butylthiazolyl)phenyl, 4-(5- 2-t-butyltetrazolyl)phenyl, 4-(4 spiro-1,3-dioxolanyl)piperidinophenyl, 4-(4-fluorophenyl)phenyl, 4-(4-ethylaminosulphonylphenyl)phenyl, 4-dimethylaminoethoxyphenyl or 3-(dihydroxyboryl)phenyl.

When R_3 is a 5 or 6 membered heteroaryl group suitable examples of such groups include 2-furanyl, 3-thienyl, 3-furanyl, 2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-chloro-2-thienyl, 3-fluoro-5-methyl-2-thienyl, 5-fluoro-2-thienyl, 5-methyl-2-thienyl, 5-methyl-2-furanyl, 5-bromo-2-furanyl, 4,5-dimethyl-2-furanyl, 2,3-dimethyl-5-thienyl, 5-trifluoromethyl-2-furanyl, 2-furanyl-4-carboxylic acid methylamide, 2-furanyl-5-carboxylic acid methylamide, 2-pyridyl, 6-methyl-2-pyridyl, 6-methyl-3-pyridyl, 6-hydroxy-3-pyridyl, 6-methoxy-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 3-pyridyl, 4-pyridyl, 3,5-pyrimidinyl, 2-thiazolyl, 4-oxazolyl, 4-thiazolyl, 2-methyl-4-oxazolyl, 2-ethyl-4-oxazolyl, 2-cyclopropyl-4-oxazolyl, 2-trifluoromethyl-4-oxazolyl, 2,5-dimethyl-4-oxazolyl, 4-thiazolyl, 2-methyl-4-thiazolyl, 2-trifluoromethyl-4-thiazolyl, 2-trifluoromethyl-5-thiazolyl, 4-isoxazolyl, 1-methyl-4-pyrazolyl, 1,3-dimethyl-5-pyrazolyl, 5-(2-pyridyl)-2-thienyl, 2-(4-morpholino)-5-thiazolyl or 2-(4-methyl-1-piperazino)-5-thiazolyl.

When R_3 is an optionally substituted fused bicyclic ring system examples of suitable groups include 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 1H-1,2,3-benzotriazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,3-benzothiazol-6-yl, 1-methyl-1H-1,2,3-benzotriazol-5-yl, 1-methyl-1H-1,2,3-benzotriazol-6-yl, 1,2,3-benzothiadiazol-6-yl, 2-methyl-1,3-benzoxazol-5-yl, 2-methyl-1,3-benzoxazol-6-yl, 1-benzofuran-5-yl, 1-methyl-1H-lindol-5-yl, 1-benzothien-5-yl, 1-benzofuran-6-yl, 1H-indol-6-yl, 1-methyl-1H-benzimidazol-6-yl, 1-methyl-1H-benzimidazol-5-yl, 3-methyl-1,2-benzoisoxazol-5-yl, 2-fluoro-1-benzofuran-5-yl, 1H-indol-5-yl, 2-methyl-1H-benzofuran-5-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1-benzofuran-2-yl or 1-methyl-1H-benzimidazol-2-yl.

When the group R_1 is a 5-7 membered cycloalkyl group which is fused to an optionally substituted benzene ring the optional substituents may be from 1 to 3 groups which may be the same or different and selected from halogen, alkyl, alkoxy, hydroxy, trifluoromethyl, nitro, carboxyl, alkoxycarbonyl or carboxamido.

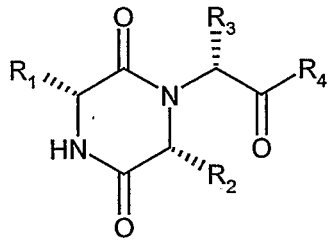
When the group R_1 is aralkyl the aryl moiety is phenyl optionally substituted by 1 to 3 groups which may be the same or different and selected from halogen, alkyl, alkoxy, hydroxy, trifluoromethyl, nitro, carboxyl, alkoxycarbonyl or carboxamido.

Examples of suitable R_1 groups include phenethyl or indanyl optionally substituted by hydroxyl e.g. 2-indanyl, 1-hydroxy -2-indanyl, 5-hydroxy –2-indanyl.
Examples of suitable R_2 groups include C_{3-4}alkyl e.g. isopropyl, 1-methylpropyl or 2-methylpropyl ,C_{3-6} cycloalkyl e.g cyclopentyl.

Conveniently R_4 is hydroxy , C_{1-4} alkoxy e.g. methoxy, propoxy, t-butoxy , 1-acetyloxyethoxy or NR_5R_6.

A preferred class of compounds of formula (I) are those wherein R_4 represents hydroxy or the group NR_5R_6 or more preferably NR_5R_6.

A further preferred class of compounds is represented by formula (1a)



(1a)

wherein the groups R_1, R_2, R_3 and R_4 have the meanings defined for formula (I)
Conveniently R_1 is a group selected from 2-phenethyl or 2-indanyl optionally substituted by hydroxyl and more particularly 2-indanyl. Conveniently R_2 is a group selected from isopropyl, 1-methyl propyl, 2-methylpropyl or cyclopentyl and more preferably R_2 is a group selected from 1-methylpropyl, or 2-methylpropyl.

Conveniently R_3 is a group selected from phenyl, halophenyl such as 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2-chloro-4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2 fluoro-4-bromophenyl, 4-chloro-3-fluorophenyl 2,3,4-trifluorophenyl 2,4,5-trifluorophenyl or 2,4,6-trifluorophenyl, 2-fluoro-4,5-dimethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-fluoro-4 methoxyphenyl, 2- fluoro-4 hydroxyphenyl, 2-fluoro-4-dimethylaminomethylphenyl, 2-fluoro-4-hydroxymethylphenyl, 3-fluoro-4-(4-morpholino)phenyl, 3-fluoro-4-carboxymethyloxyphenyl, 3-fluoro-4-t-butyloxycarbonylmethyloxyphenyl, 3-fluoro-4-dimethylaminocarbonyloxyphenyl, 3-chloro-4 trifluoromethoxyphenyl, 2,3-difluoro-4-methyl-phenyl, 4-trifluoromethoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxyphenyl, 4-

methoxyphenyl, 4-methoxycarbonylphenyl, 3-methoxycarbonyphenyl, 4-methylsulphonylphenyl, 4-methylaminocarbonylphenyl, 4- aminocarbonylphenyl, 4-methylaminosulphonylphenyl, 3-(3-pyrazyolyl)phenyl, 4-(3-pyrazolyl)phenyl, 4-(4-pyrazolyl)phenyl, 4-(3-pyridyl)phenyl, 4-(2-pyridylphenyl), 4-(2-imidazolyl)phenyl, 3-(2-imidazolyl)phenyl, 4-(1-t-butyl-tetrazol-5-yl)phenyl, 4-methylaminophenyl, 4-dimethylaminophenyl, 4-diethylaminophenyl, 4-acetylaminophenyl, 3-acetylaminophenyl, 4-hydroxy-3-acetylaminophenyl, 4-methylsulphonylaminophenyl, 4-N-methylpiperazinophenyl, 4-N-pyrrolidinophenyl, 2-fluoro-4-(4-morpholino)phenyl, 4-(4-morpholino)phenyl, 4-(4-hydroxypiperidino)phenyl, 2-fluoro-4-(4-hydroxypiperidino)phenyl, 3-(1-pyrazolyl)phenyl, 4-(1-pyrazolyl)phenyl, , 4-(1-3,5 di-t-butylpyrazolyl)phenyl, 3-(1-imidazolyl)phenyl, 4-(1-imidazolyl)phenyl, 4-(1-1,2,4-triazolyl)phenyl, 4-(1-1,2,3-triazolyl)phenyl, 4-(2-4,-t-butylthiazolyl)phenyl, 4-(5- 2-t-butyltetrazolyl)phenyl, 4-(4 spiro-1,3-dioxolanyl)piperidinophenyl, 4-(4-fluorophenyl)phenyl, 4-(4-ethylaminosulphonylphenyl)phenyl, 4-dimethylaminoethoxyphenyl,3-(dihydroxyboryl)phenyl, 2-furanyl, 3-thienyl, 3-furanyl, 2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-chloro-2-thienyl, 3-fluoro-5-methyl-2-thienyl, 5-methyl-2-thienyl, 5-methyl-2-furanyl, 5-bromo-2-furanyl, 4,5-dimethyl-2-furanyl, 5-trifluoromethyl-2-furanyl, 2-furanyl-4-carboxylic acid methylamide, 2-furanyl-5-carboxylic acid methylamide, 2-pyridyl, 6-methyl-2-pyridyl, 6-methyl-3-pyridyl, 6-methoxy-3-pyridyl, 6-hydroxy-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 3-pyridyl, 4-pyridyl, 3,5-pyrimidinyl, 2-thiazolyl, , 2-methyl-4-oxazolyl, 2-ethyl-4-oxazolyl, 2-cyclopropyl-4-oxazolyl, 2-trifluoromethyl-4-oxazolyl, 2,5-dimethyl-4-oxazolyl, 4-thiazolyl, 2-methyl-4-thiazolyl, 2-trifluoromethyl-4-thiazolyl, 2-trifluoromethyl-5-thiazolyl, 1-methyl-4-pyrazolyl, 1,3-dimethyl-5-pyrazolyl, 5-(2-pyridyl)-2-thienyl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 1H-1,2,3-benzotriazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,3-benzothiazol-6-yl, 1-methyl-1H-1,2,3-benzotriazol-5-yl, 1-methyl-1H-1,2,3-benzotriazol-6-yl, 1,2,3-benzothiadiazol-6-yl, 2-methyl-1,3-benzoxazol-5-yl, 2-methyl-1,3-benzoxazol-6-yl, 1-benzofuran-5-yl, 1-methy-1H-lindol-5-yl, 1-benzothien-5-yl, 1-benzofuran-6-yl, 1H-indol-6-yl, 1-methyl-1H-benzimidazol-6-yl, 1-methyl-1H-benzimidazol-5-yl, 3-methyl-1,2-benzoisoxazol-5-yl, 2-fluoro-1-benzofuran-5-yl, 1H-indol-5-yl, 2-methyl-1H-benzofuran-5-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1-benzofuran-2-yl or 1-methyl-1H-benzimidazol-2-yl.

Conveniently the group R_5 is hydrogen, C_{1-4}alkyl e.g. methyl or C_{1-4}alkoxyC_{2-4}alkyl e.g. 2-methoxyethyl and R_6 is a group selected from hydrogen, C_{1-4}alkoxy e.g. methoxy, C_{1-4}alkyl e.g. methyl, n-propyl, isopropyl or t-butyl, C_{1-4} alkyl substituted by 1 to 3 halogen atoms e.g. 2,2,2-trifluoroethyl or 2-fluoroethyl, C_{1-4}alkyl substituted by alkoxycarbonyl or carboxyl e.g. methoxycarbonylmethyl or carboxymethyl, alkyl substituted by alkoxy e.g methoxyethyl, 2,2-dimethoxyethyl, alkyl substituted by hydroxy e.g. hydroxyethyl or alkyl substituted by dialkylamino e.g. dimethylaminoethyl, 2-benzyloxyphenyl, dimethoxybenzyl, optionally substituted heteroarylmethyl e.g. 2-pyridylmethyl, 3-

pyridylmethyl, 4-pyridylmethyl, 3-methylimidazolylmethyl, heteroaryl such as thiazolyl e.g. 2-1,3-thiazolyl, alkyl substituted by NR_7R_8 [wherein NR_7R_8 form a 6-membered heterocyclic ring (e.g. piperidinoethyl or morpholinoethyl)], cycloalkyl e.g. cyclopropyl or cyclohexyl, or NR_5R_6 represents, azetidino, 3-hydroxyazetidino, 3-methoxyazetidino, pyrrolidino, piperidino, 4-dimethylaminopiperidino, 4-methyl 1,4-diazepan-1-yl, morpholino, an optionally substituted piperazino ring e.g. N-methylpiperazino,N-methanesulphonylpiperazino, N-2-methoxyethylpiperazino, thiomorpholino or the sulphoxide or sulphone thereof.

A preferred class of compounds of the invention are those of formula (1a) wherein $R_1$is 2-indanyl, R_2 is a group selected from 1-methylpropyl or 2-methylpropyl and R_4 is hydroxy and/or more particularly the group NR_5R_6.

A further preferred class of compounds of the invention are those of formula (1a) wherein R_5 is a group selected from hydrogen, C_{1-4}alkyl e.g. methyl or C_{1-4}alkoxyC_{2-4}alkyl e.g. 2-methoxyethyl and R_6 is a group selected from hydrogen, C_{1-4}alkoxy e.g. methoxy, C_{1-4}alkyl e.g. methyl, n-propyl, isopropyl or t-butyl, C_{1-4} alkyl substituted by 1 to 3 halogen atoms e.g. 2,2,2-trifluoroethyl or 2-fluoroethyl, C_{1-4}alkyl substituted by alkoxycarbonyl or carboxyl e.g. methoxycarbonylmethyl or carboxymethyl, alkyl substituted by alkoxy e.g methoxyethyl, 2,2-dimethoxyethyl, alkyl substituted by hydroxy e.g. hydroxyethyl or alkyl substituted by dialkylamino e.g. dimethylaminoethyl, 2-benzyloxyphenyl, dimethoxybenzyl, optionally substituted heteroarylmethyl e.g. 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 3-methylimidazolylmethyl, heteroaryl such as thiazolyl e.g. 2-1,3-thiazolyl, alkyl substituted by NR_7R_8 [wherein NR_7R_8 form a 6-membered heterocyclic ring (e.g. piperidinoethyl or morpholinoethyl)], cycloalkyl e.g. cyclopropyl or cyclohexyl, or NR_5R_6 represents, azetidino, 3-hydroxyazetidino, 3-methoxyazetidino, pyrrolidino, piperidino, 4-dimethylaminopiperidino, 4-methyl 1,4-diazepan-1-yl, morpholino, an optionally substituted piperazino ring e.g. N-methylpiperazino, N-methanesulphonylpiperazino, N-2-methoxyethylpiperazino, thiomorpholino or the sulphoxide or sulphone thereof.

A yet further preferred class of compounds of the invention are those of formula (1a) wherein R_3 is a group selected from phenyl, halophenyl such as 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2-chloro-4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2 fluoro-4-bromophenyl, 4-chloro-3-fluorophenyl 2,3,4-trifluorophenyl 2,4,5-trifluorophenyl or 2,4,6-trifluorophenyl, 2-fluoro-4,5-dimethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-fluoro-4 methoxyphenyl, 2- fluoro-4 hydroxyphenyl, 2-fluoro-4-dimethylaminomethylphenyl, 2-fluoro-4-hydroxymethylphenyl, 3-fluoro-4-(4-morpholino)phenyl, 3-fluoro-4-carboxymethyloxyphenyl, 3-fluoro-4-t-butyloxycarbonylmethyloxyphenyl, 3-fluoro-4-

dimethylaminocarbonyloxyphenyl, 3-chloro-4 trifluoromethoxyphenyl, 2,3-difluoro-4-methyl-phenyl, 4-trifluoromethoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-methoxycarbonylphenyl, 3-methoxycarbonyphenyl, 4-methylsulphonylphenyl, 4-methylaminocarbonylphenyl, 4- aminocarbonylphenyl, 4-methylaminosulphonylphenyl, 3-(3-pyrazyolyl)phenyl, 4-(3-pyrazolyl)phenyl, 4-(4-pyrazolyl)phenyl, 4-(3-pyridyl)phenyl, 4-(2-pyridylphenyl), 4-(2-imidazolyl)phenyl, 3-(2-imidazolyl)phenyl, 4-(1-t-butyl-tetrazol-5-yl)phenyl, 4-methylaminophenyl, 4-dimethylaminophenyl, 4-diethylaminophenyl, 4-acetylaminophenyl, 3-acetylaminophenyl, 4-hydroxy-3-acetylaminophenyl, 4-methylsulphonylaminophenyl, 4-N-methylpiperazinophenyl, 4-N-pyrrolidinophenyl, 2-fluoro-4-(4-morpholino)phenyl, 4-(4-morpholino)phenyl, 4-(4-hydroxypiperidino)phenyl, 2-fluoro-4-(4-hydroxypiperidino)phenyl, 3-(1-pyrazolyl)phenyl, 4-(1-pyrazolyl)phenyl, , 4-(1-3,5 di-t-butylpyrazolyl)phenyl, 3-(1-imidazolyl)phenyl, 4-(1-imidazolyl)phenyl, 4-(1-1,2,4-triazolyl)phenyl, 4-(1-1,2,3-triazolyl)phenyl, 4-(2-4,-t-butylthiazolyl)phenyl, 4-(5- 2-t-butyltetrazolyl)phenyl, 4-(4 spiro-1,3-dioxolanyl)piperidinophenyl, 4-(4-fluorophenyl)phenyl, 4-(4-ethylaminosulphonylphenyl)phenyl, 4-dimethylaminoethoxyphenyl,3-(dihydroxyboryl)phenyl, 2-furanyl, 3-thienyl, 3-furanyl, 2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-chloro-2-thienyl, 3-fluoro-5-methyl-2-thienyl, 5-methyl-2-thienyl, 5-methyl-2-furanyl, 5-bromo-2-furanyl, 4,5-dimethyl-2-furanyl, 5-trifluoromethyl-2-furanyl, 2-furanyl-4-carboxylic acid methylamide, 2-furanyl-5-carboxylic acid methylamide, 2-pyridyl, 6-methyl-2-pyridyl, 6-methyl-3-pyridyl, 6-methoxy-3-pyridyl, 6-hydroxy-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 3-pyridyl, 4-pyridyl, 3,5-pyrimidinyl, 2-thiazolyl, , 2-methyl-4-oxazolyl, 2-ethyl-4-oxazolyl, 2-cyclopropyl-4-oxazolyl, 2-trifluoromethyl-4-oxazolyl, 2,5-dimethyl-4-oxazolyl, 4-thiazolyl, 2-methyl-4-thiazolyl, 2-trifluoromethyl-4-thiazolyl, 2-trifluoromethyl-5-thiazolyl, 1-methyl-4-pyrazolyl, 1,3-dimethyl-5-pyrazolyl, 5-(2-pyridyl)-2-thienyl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 1H-1,2,3-benzotriazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,3-benzothiazol-6-yl, 1-methyl-1H-1,2,3-benzotriazol-5-yl, 1-methyl-1H-1,2,3-benzotriazol-6-yl, 1,2,3-benzothiadiazol-6-yl, 2-methyl-1,3-benzoxazol-5-yl, 2-methyl-1,3-benzoxazol-6-yl, 1-benzofuran-5-yl, 1-methy-1H-lindol-5-yl, 1-benzothien-5-yl, 1-benzofuran-6-yl, 1H-indol-6-yl, 1-methyl-1H-benzimidazol-6-yl, 1-methyl-1H-benzimidazol-5-yl, 3-methyl-1,2-benzoisoxazol-5-yl, 2-fluoro-1-benzofuran-5-yl, 1H-indol-5-yl, 2-methyl-1H-benzofuran-5-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1-benzofuran-2-yl or 1-methyl-1H-benzimidazol-2-yl.

Particular preferred compounds of the invention include:

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
(2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

(2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]- morpholinamide
(2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-hydroxypiperidin-1-yl)phenyl]ethanamide.
(2R)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl}-2-(2-fluoro-4-morpholin-4-ylphenyl)-N-isopropylethanamide.
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide.
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
(2R)-N-cyclopropyl-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
(3R,6R)-1-[(1R)-2-azetidin-1-yl-1-(2,4-difluorophenyl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyethyl)-N-methylethanamide
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-[2-(methylsulfonyl)ethyl]ethanamide
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(2,2,2-trifluoroethyl)ethanamide
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(pyridin-2-ylmethyl)ethanamide
(3R,6R)-1-{(1R)-1-(2,4-difluorophenyl)-2-[4-(methylsulfonyl)piperazin-1-yl]-2-oxoethyl}-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methoxy-N-methylethanamide
(2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid
methyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5 dioxopiperazin-1-yl]ethanoate
propyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate

1-(acetyloxy)ethyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate

(2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl}ethanamide

(2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxopiperazin-1-yl}ethanamide

(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]piperazine-2,5-dione.

(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]piperazine-2,5-dione.

(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione.

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide.

(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-methylthien-2-yl)ethanamide.

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide.

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide.

(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-morpholin-4-yl-2-oxoethyl]piperazine-2,5-dione.

(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(5-methylthien-2-yl)ethanamide

(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-5-methylthien-2-yl)-N,N-dimethylethanamide

(2R)-2-(1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

(2R)-2-(1,2,3-benzothiadiazol-6-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.

(2R)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

(2R)-2-(1,3-benzodioxol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.

(2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide.

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide.

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]- N-isopropyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide.

(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]piperazin-2,5-dione.
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N,N-dimethylethanamide.
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N-isopropylethanamide.
(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-fluoro-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]-6-isobutylpiperazine-2,5-dione.
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N,N-dimethylethanamide.
(2R)-2-(1-benzothien-5-yl) -2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide.

The ability of the compounds of formula (I) to inhibit the actions of oxytocin may be determined using a variety of conventional procedures.

Thus, compounds of formula (I) have a high affinity for the oxytocin receptors on the uterus of rats and humans and this may be determined using conventional procedure. For example the affinity for the oxytocin receptors on the rat uterus may be determined by the procedure of Pettibone et al, Drug Development Research 30. 129-142 (1993). The compounds of the invention also exhibit high affinity at the human recombinant oxytocin receptor in CHO cells and this may be conveniently demonstrated using the procedure described by Wyatt et al. Bioorganic & Medicinal Chemistry Letters, 2001 (11) p1301-1305.

The compounds of the invention are therefore useful in the treatment or prevention of diseases and/or conditions mediated through the action of oxytocin. Examples of such diseases and/or conditions include pre-term labour, dysmenorrhea and endometriosis.

The compounds may also be useful to delay labour prior to elective caesarean section or transfer of the patient to a tertiary care centre. The compounds of the invention may also be useful for improving fertility rates in animals, e.g. farm animals.

The invention therefore provides for the use of a compound of formula (I) and/or physiologically acceptable salts for use in therapy and in particular use as medicine for antagonising the effects of oxytocin upon the oxytocin receptor.

The invention also provides for the use of a compound of formula (I) and/or a physiologically acceptable salt thereof for the manufacture of a medicament for antagonising the effects of oxytocin on the oxytocin receptor.

According to a further aspect, the invention also provides for a method for antagonising the effects of oxytocin upon the oxytocin receptor, comprising administering to a patient in need thereof an antagonistic amount of a compound of formula (I) and/or a physiologically acceptable salt thereof.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylactics as well as the treatment of established diseases or symptoms.

It will further be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated, the route of administration and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician. In general however doses employed for adult human treatment will typically be in the range of 2 to 800mg per day, dependent upon the route of administration.

Thus for parenteral administration a daily dose will typically be in the range 2 to 50mg, preferably 5 to 25mg per day. For oral administration a daily dose will typically be within the range 10 to 800mg, e.g. 20 to 150 mg per day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt or non-toxic metabolically labile esters thereof together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compositions of the invention include those in a form especially formulated for oral, buccal, parenteral, inhalation or insufflation, implant or rectal administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for

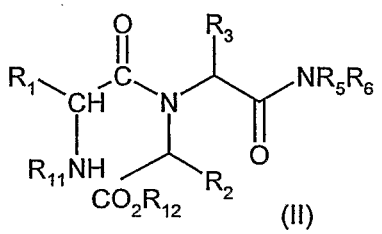
example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; solubilizers such as surfactants for example polysorbates or other agents such as cyclodextrins; and preservatives, for example, methyl or propyl p-hydroxybenzoates or ascorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

The compositions according to the invention may contain between 0.1-99% of the active ingredient, conveniently from 30-95% for tablets and capsules and 3-50% for liquid preparations.

Compounds of formula (I) wherein R_4 is the group NR_5R_6 may be prepared by cyclisation of the compound of formula (II)



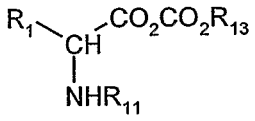
(II)

wherein R_1, R_2 and R_3 have the meanings defined in formula (I) R_{11} is hydrogen and R_{12} is a C_{1-3}alkyl group(e.g. methyl) in a suitable solvent such as an alkanol e.g. methanol and/or 2,2,2-trifluoroethanol, dioxan or a mixture thereof or a halohydrocarbon e.g. dichloromethane.

The compound of formula (II) wherein R_{11} is hydrogen is conveniently prepared in-situ by treating a compound of formula (II) wherein R_{11} is an acid labile nitrogen protecting group and R_{12} is hydrogen or C_{1-3}alkyl, with an acid in a suitable solvent followed by treatment with a hydrohalic acid and methanol if R_{12} in the starting material is hydrogen, and then addition of a suitable base e.g. triethylamine or by treating a compound of formula (II) wherein R_{11} is an hydrogenolysable nitrogen protecting group and R_{12} is C_{1-3}alkyl in a suitable solvent such as methanol or 2,2,2-trifluoroethanol with hydrogen in the presence of a suitable catalyst e.g. palladium on carbon.

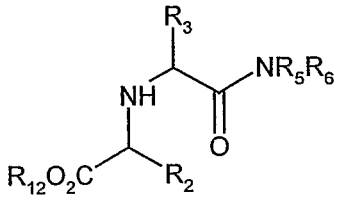
Examples of suitable nitrogen protecting groups R_{11} include alkoxycarbonyl e.g. t-butyloxycarbonyl or an optionally substituted benzyloxycarbonyl group.
When R_{12} is C_{1-3}alkyl this is conveniently ethyl or more particularly methyl.
Examples of a suitable acids include mineral acids such as hydrohalic acids e.g. hydrochloric acid or organic acids such as trifluoroacetic acid. The reaction is conveniently carried out in a solvent such as 1,4-dioxan or an alkanol e.g. methanol or a mixture thereof, or halohydrocarbon e.g. dichloromethane.

The compounds of formula (II) may be prepared by reaction of the mixed anhydride (III)



(III)

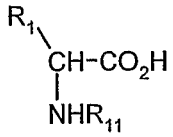
wherein R_1 and R_{11} have the meanings defined above and wherein R_{13} is a C_{1-6} straight or branched chain alkyl, optionally substituted phenyl or benzyl group, with the amine (IV)



(IV)

wherein R_2, R_3, R_5 and R_6 have the meanings defined above, and R_{12} is hydrogen.

The reaction is preferably carried out in an aprotic solvent such as an ether e.g. tetrahydrofuran or a tertiary amide such as N, N-dimethylformamide or a mixture thereof. The compounds of formula (III) may be prepared by treating the N-protected amino acid (V)



(V)

wherein R_1 and R_{11} have the meanings defined above with the corresponding haloformate (VI; $R_{13}CO_2X$ wherein R_{13} has the meaning defined in formula (III) and X is halogen e.g. chlorine, or bromine) in the presence of a suitable tertiary organic amine e.g. N-methylmorpholine and in an aprotic solvent e.g. an ether such as tetrahydrofuran or a hydrocarbon e.g. toluene.

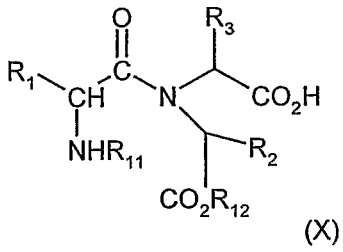
The amine (IV) wherein R_5 is hydrogen may be prepared treating the amino acid (VII)

$$R_{12}O_2CCH(R_2)NH_2$$

(VII)

wherein R_2 has the meanings defined above and R_{12} is hydrogen with the aldehyde (VIII; R_3CHO wherein R_3 has the meaning defined in formula (I)) in a suitable solvent such as an alkanol e.g. methanol followed by reaction with the isonitrile (IX; $R_6N{=}C$ wherein R_6 has the meanings defined in formula I other than hydrogen). Alternatively, the compounds of formula (II) wherein R_1, R_2 and R_3 have the meanings given in formula (I) and R_{11} is a nitrogen protecting group and R_{13} is a carboxyl protecting group may be prepared by reacting the amino acid derivative (VII) wherein R_2 has the meaning given in formula (I) and R_{12} is a carboxyl protecting group with the aldehyde (VIII) wherein R_3 has the meaning given in formula (I) in a solvent such as an alkanol e.g. methanol or 2,2,2-trifluoroethanol followed by the sequential addition of the amino acid (V) wherein R_1 has the meanings given in formula (I) and R_{11} is a carboxyl protecting group and the isonitrile (IX) wherein R_6 has the meanings given in formula (I).

Compounds of formula (II) wherein R_{12} is a C_{1-3}alkyl group may also be prepared by reacting the carboxylic acid (X) or an activated derivative thereof



(X)

wherein R_1, R_2, R_3 and R_{11} have the meanings defined above and R_{12} is a C_{1-3}alkyl group, with the amine NHR_5R_6 wherein R_5 and R_6 have the meanings defined in formula (I). Examples of a suitable activated derivative of the carboxylic acid (X) include those commonly used in peptide synthesis e.g. that derived from reaction of benzotriazol-1-yloxytri-pyrrolidinophosphonium hexafluorophosphate in the presence of a suitable amine such as disopropylethylamine.

The carboxylic acid (X) may be prepared from the corresponding compound of formula (II) wherein R_5 represents hydrogen and R_6 represents the 2-hydroxyphenyl by reaction with carbonyldiimidazole or thiocarbonyldimidazole in a suitable solvent such as dichloromethane and subsequent reaction of the product thus formed with aqueous acetone.

Compounds of formula (II) wherein R_6 represents 2-hydroxyphenyl are conveniently prepared by catalytic hydrogenolysis (e.g. Pd/H_2) of the corresponding compound wherein R_6 is a 2-benyloxyphenyl group.

In a further aspect of the invention compounds of formula (I) as defined above may be converted into other compounds of formula (I). Thus compounds of formula (I) wherein R_4 is hydroxyl maybe prepared from a compound of formula (I) wherein R_4 is the group NR_5R_6 and R_5 is hydrogen R_6 is 2-hydroxyphenyl by reaction with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent such as dichloromethane and subsequent reaction of the product thus formed with aqueous acetone.

Compounds of formula (I) wherein R_5 is hydrogen and R_6 is 2-hydroxphenyl may be from the corresponding compound of formula (I) wherein R_6 is a 2-benyloxyphenyl group by hydrogenolysis using hydrogen and a palladium catalyst.

Compounds of formula (I) wherein R_4 is the group NR_5R_6 may be prepared by reaction of the compound of formula (I) wherein R_4 is hydroxyl or an activated derivative thereof with the amino NHR_5R_6 wherein R_5 and R_6 have the meaning defined in formula (I) under the standard condition for preparing amides from a carboxylic acid and an amine such as NHR_5R_6.

Thus the amides may be prepared by treating the compound of formula (I) wherein R_4 is hydroxyl with an activating agent such as BOP (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate),TBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate), BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride) or oxalyl chloride in an aprotic solvent such as dichloromethane optionally in the presence of a tertiary amine such as triethylamine and subsequent reaction of the product thus formed with the amine NHR_5R_6.

Alternatively compounds of formula (I) wherein R_4 is the group NR_5R_6 may be prepared by reacting a compound of formula (I) wherein R_5 is hydrogen and R_6 is 2-hydroxyphenyl with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent such as dichloromethane and subsequent reaction of the product thus formed with the amine NHR_5R_6.

Compounds of formula (I) wherein R_4 is OC_{1-4} alkyl (optionally substituted with C_{1-4}alkylcarbonyloxy) may be prepared by reacting the corresponding carboxylic acid (R_4 is OH) or an activated derivative thereof with the appropriate alcohol (R_4OH) or alkyl halide (R_4halide) under standard conditions for preparing such esters. Suitable activated derivatives include the acid halides, mixed anhydrides, those formed with coupling reagents commonly used in peptide synthesis e.g. carbonyldiimidazole and base salts of the acid e.g. alkali meatal salts.

Compounds of formula (IV) may be converted into other compounds of formula (IV) using standard procedures. Thus compound of formula (IV) wherein R_5 is hydrogen and R_6 is 2-benzyloxyphenyl may be converted into other compounds of formula (IV) wherein R_5 and R_6 have other meanings as defined in formula (I) using the same procedures as described above for carrying out analogous reactions on compounds of formula (1).

Compounds of formula (I) wherein the stereochemistry of any of the substituents R_1, R_2 and R_3 is as shown in formula (1a) may be prepared starting from the corresponding single isomers of the intermediates (III), (IV) and (VII) and/or the various isomeric mixtures may be separated by conventional procedures.

The intermediates (V), (VI), (VII), (VIII) and (IX) are either known compounds may be prepared by analogous methods to those known for preparing structurally related compounds.

Compounds of formula group (I) wherein R_4 is OH may be prepared by cyclisation of a corresponding compound of formula (II) under the conditions described above for preparing compounds of formula (I).

Physiologically acceptable salts of a compound of formula (I) wherein R_4 is OH or one of the groups R_1, R_2, R_3 or NR_4R_5 has a basic or acidic centre may be prepared by treating the said base or acid with the required physiologically acceptable acid or base and this reaction is conveniently carried out in a solvent for the said compound of formula (I). Physiologically acceptable derivatives of a compound of formula (I) may be prepared from the appropriate intermediate corresponding to formula (II) using the process described above for preparing compounds of formula (I) or directly from the compounds of formula (I) by conventional procedures for preparing such derivatives. Thus metabolically labile esters may be prepared by esterification of the free carboxyl or hydroxyl group using standard esterification techniques.

The following examples are illustrative, but not limiting of the embodiments of the present invention.

General purification and analytical methods

Analytical HPLC was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID), eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO_2H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 minutes 0%B, 0.7-4.2 minutes 0%-100%B, 4.2-5.3 minutes 100%B, 5.3-5.5 minutes 0%B at a flow rate of 3 ml/minute. The mass spectra (MS) were recorded on a Fisons VG Platform spectrometer using electrospray positive [(ES+ve to give MH^+ and $M(NH_4)^+$ molecular ions] or electrospray negative [(ES-ve to give $(M-H)^-$ molecular ion] modes on a Micromass series 2 or a Waters ZQ mass spectrometer. ^1H NMR spectra were recorded using a Bruker DPX 400MHz spectrometer using tetramethylsilane as the external standard. Biotage™ chromatography refers to purification carried out using equipment sold by Dyax Corporation (either the Flash 40i or Flash 150i) and cartridges pre-packed with KPSil. Mass directed autoprep refers to methods where the material was purified by high performance liquid chromatography on a HPLCABZ+ 5μm column (5cmx10mm i.d.) with 0.1% HCO_2H in water and 95% MeCN, 5% water (0.5% HCO_2H) utilising gradient elution at a flow rate of 8ml $minutes^{-1}$. The Gilson 202-fraction collector was triggered by a VG Platform Mass Spectrometer on detecting the mass of interest.

Hydrophobic frits refer to filtration tubes sold by Whatman. SPE (solid phase extraction) refers to the use of cartridges sold by International Sorbent Technology Ltd. TLC (thin layer chromatography) refers to the use of TLC plates sold by Merck coated with silica gel 60 F_{254}. Oasis™ refers to Waters® Oasis™ HLB Extraction Cartridges, sold by Waters Corporation®.

Method 1

Example 1

(2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide

To a solution of (D)-leucine methyl ester hydrochloride (300mg) in methanol (4ml) was added triethylamine (230 µl) and 4-fluorobenzaldehyde (177µl). The mixture was stirred for 2.5 hours before (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (481mg) and isopropylisocyanide (225µl) were sequentially added. After stirring for 16hr, the solvent was removed *in vacuo* and the residue was dissolved in chloroform. This solution was washed with a saturated aqueous sodium carbonate solution (x2), aqueous citric acid (0.5M, x2) and brine (x1), dried over magnesium sulphate and evaporated *in vacuo*. The residue was dissolved in dichloromethane (2ml) and trifluoroacetic acid (5ml) and stirred for 3 hours at ambient temperature. After this time, the solvent was removed *in vacuo* and the residue co-evaporation with toluene (x3) and cyclohexane/ ether (1:1, x2). The residue was treated with a solution of triethylamine in dioxane (2% solution, 10ml) and was left to stir overnight. After this time, the dioxane was removed *in vacuo* and the residue was dissolved in ethyl acetate. The solution was washed with citric acid solution (0.5M, x2), saturated aqueous sodium bicarbonate solution (x1) and brine (x1). The liquors were then dried over magnesium sulphate and *in vacuo* and were then co-evaporated with cyclohexane: ether (1:1, x2). This crude material was purified by Biotage™ (90g, silica) eluting with toluene: ethyl acetate: cyclohexane (5: 3: 2) with 5% triethylamine to give (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide (149mg)

HPLC Rt = 3.42 minutes; m/z $[M+H]^+ = 480$.

^{1}H NMR ($CDCl_3$) δ 7.44 (m, 2H), 7.22 (m, 2H), 7.16 (m, 2H), 7.11 (t, 2H), 6.50 (d, 1H), 5.60 (d, 1H), 5.11 (s, 1H), 4.10 (m, 1H), 3.96 (m, 2H), 3.16 (dd, 1H), 3.07 (d, 1H), 2.91 (m, 1H), 2.77 (m, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 1.42 (m, 1H), 1.13 (d, 3H), 1.12 (d, 3H), 0.84 (d, 3H), 0.79 (d, 3H)

Similarly prepared

Example 2

(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-hydroxypiperidin-1-yl)phenyl]ethanamide.

HPLC Rt = 3.27 minutes; m/z $[M+H]^+ = 575$.

($CDCl_3$) δ 7.3 (d,2H), 7.2 (m, 2H), 7.15 (m, 2H), 6.9 (d, 2H), 6.1 (d, 1H), 5.5 (s, 1H), 5.15 (s, 1H), 3.95 (m, 2H), 3.9 (m, 1H), 3.6 (m, 2H), 3.15 (m, 1H), 3.1 (m, 2H), 3.0 (m, 2H), 2.9 (m, 1H), 2.75 (m, 1H), 2.0 (m, 2H), 1.75 (m, 1H), 1.65 (m, 3H), 1.45 (m, 1H), 1.3 (s, 9H), 0.8 (d, 3H), 0.7 (d, 3H).

Example 3

(2R)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl}-2-(2-fluoro-4-morpholin-4-ylphenyl)-N-isopropylethanamide.

HPLC Rt = 3.34 minutes; m/z $[M+H]^+$ = 565

^{1}H NMR ($CDCl_3$) δ 7.52 (t, 1H), 7.22-7.11 (m, 4H), 7.04 (br s, 1H), 6.66 (dd, 1H), 6.56 (dd, 1H), 5.07 (s, 1H), 4.19-4.08 (m, 2H), 3.98 (dd, 1H), 3.86-3.81 (4H, m), 3.21-2.91 (m, 8H), 2.80-2.73 (m, 1H), 1.96-1.86 (m, 1H), 1.72-1.61 (m, 1H), 1.51-1.40 (m, 1H), 1.19 (d, 3H), 1.16 (d, 3H), 1.06 (d, 3H), 0.92 (t, 3H).

Method 2

Example 4

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide

Methyl (2R)-2-{[(1R,S)-2-{[2-(benzyloxy)phenyl]amino}-1-(4-fluorophenyl)-2-oxoethyl][(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]amino}-4-methylpentanoate

A mixture of 4-fluorobenzaldehyde (1.2g), (D)-leucine methyl ester hydrochloride (1.7g), triethylamine and methanol (56ml) was stirred at room temperature for 3 hours. 2-Benzyloxyphenylisocynanide (2.0g) and N-*tert*-butoxycarbonyl-(D)-indanyl glycine (2.77g) were then added sequentially. After 40 hours the reaction mixture was partitioned between 2M hydrochloric acid and ethyl acetate. The separated organic layer was washed with a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated *in vacuo*. The resultant crude material was purified by column chromatography (eluting with 0.5% and 0.2% methanol/ dichloromethane) to afford methyl (2R)-2-{[(1R,S)-2-{[2-(benzyloxy)phenyl]amino}-1-(4-fluorophenyl)-2-oxoethyl][(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]amino}-4-methylpentanoate (4.3g)

HPLC Rt = 4.34 minutes, m/z $[M+H]^+$ = 752

Methyl N-[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]-N-{(1R,S)-1-(4-fluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-D-leucinate

A mixture of methyl (2R)-2-{[(1R,S)-2-{[2-(benzyloxy)phenyl]amino}-1-(4-fluorophenyl)-2-oxoethyl][(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]amino}-4-methylpentanoate (560mg), palladium on carbon (70mg) and ethanol (15ml) was stirred under an atmosphere of hydrogen for 5 hours. The mixture was filtered through Celite and the filtrate was evaporated *in vacuo*. The crude product was purified by column chromatography (silica) eluting with ethyl acetate: cyclohexane

(10% to 15%) to give methyl N-[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]-N-{(1R,S)-1-(4-fluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-D-leucinate.

HPLC Rt = 4.06 minutes, m/z $[M+H]^+$ = 662

(2R)-{[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl][(1R)-1-(methoxycarbonyl)-3-methylbutyl]amino}(4-fluorophenyl)ethanoic acid.

Carbonyldiimidazole (558mg) was added to a solution of methyl N-[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]-N-{(1R,S)-1-(4-fluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-D-leucinate (2.0g) in dichloromethane (20ml) and the resultant mixture was stirred at room temperature for 24 hours. The reaction was then concentrated to dryness, dissolved in a mixture of acetone: water (60ml: 40ml) and stirred for 17 hours at room temperature. The solution was then partitioned between 2M aqueous hydrochloric acid and ethyl acetate. The separated organic layer was washed with saturated aqueous sodium bicarbonate solution and brine before being dried over magnesium sulphate and evaporated *in vacuo*. Half of the material was taken to be used crude in further experiments. The second half was purified by Biotage™ (silica, 90g) eluting with methanol: dichloromethane: ammonia (1: 98.5: 0.5 to 2.5: 86.5: 1). Evaporation of the appropriate fractions gave (2R)-{[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl][(1R)-1-(methoxycarbonyl)-3-methylbutyl]amino}(4-fluorophenyl)ethanoic acid. (173mg).
HPLC Rt = 3.91 minutes, m/z $[M+H]^+$ = 571

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide

A solution of (2R)-{[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl][(1R)-1-(methoxycarbonyl)-3-methylbutyl]amino}(4-fluorophenyl)ethanoic acid (73mg) in N,N-dimethylformamide (2ml) was sequentially treated with diisopropylethylamine (51µl), phosphorus^I (1-hydroxy-1H-benzotriazolato-O)tri-1-pyrrolidinyl-(T-4)-hexafluorophosphate (80mg) and then after 2 minutes, 2,2,2-trifluoroethylamine (25µl). This reaction mixture was stirred for 2 hours before being partitioned between 2M aqueous hydrochloric acid and ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine before being dried over magnesium sulphate and evaporated *in vacuo*. The residue was dissolved in 4M hydrogen chloride in dioxane and stirred for 7 hours at room temperature. The reagent was removed *in vacuo* and the residue partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The separated organic fraction was washed with brine before being dried over magnesium sulphate and evaporated *in vacuo*. The crude material was purified by column chromatography (silica) eluting with

methanol: dichloromethane (1% to 3%) to furnish ((2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide (10mg)
HPLC Rt = 3.4 minutes, m/z $[M+H]^+ = 520$
^1H NMR ($CDCl_3$) δ 7.42 (m, 2H), 7.34 (d, 1H), 7.20-7.10 (m, 6H), 6.61 (t, 1H), 5.28 (s, 1H), 4.08-3.96 (m, 3H), 3.88 (m, 1H), 3.14 (dd, 1H), 3.02 (m, 2H), 2.95-2.77 (m, 2H), 1.88-1.70 (m, 2H), 1.40 (ddd, 1H), 0.85 (d, 3H), 0.79 (d, 3H).

The following compounds were prepared in a similar manner

Example 5
(2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
HPLC Rt = 3.37minutes, m/z $[M+H]^+ = 466$
1H NMR (CDCl3); δ 7.47-7.40 (m, 2H), 7.25-7.12 (m, 6H), 6.50 (d, 1H), 6.47 (s, 1H), 4.15 (dd, 1H), 3.98 (dd, 1H), 3.21-3.01 (m, 3H), 2.99 (s, 3H), 2.92-2.73 (m, 2H), 2.83 (m, 3H), 1.59-1.49 (m, 1H), 1.42 (dt, 1H), 0.66-0.57 (m, 1H), 0.62 (d, 3H), 0.40 (d, 3H).

Example 6
(2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]- morpholinamide
HPLC Rt = 3.32 minutes, m/z $[M+H]^+ = 508$
1H NMR (CDCl3); δ 7.44-7.39 (m, 2H), 7.26-7.12 (m, 6H), 6.87 (d, 1H), 6.51 (s, 1H), 4.12 (dd, 1H), 4.00 (dd, 1H), 3.73-3.62 (m, 3H), 3.60-3.54 (m, 2H), 3.37 (m, 1H), 3.23 (m, 1H), 3.20-3.02 (m, 4H), 2.91-2.75 (m, 2H), 1.60-1.50 (m, 1H), 1.45 (dt, 1H), 0.63 (d, 3H), 0.62-0.55 (m, 1H), 0.42 (d, 3H).

The 2-fluoro-4-(morpholino)-benzaldehyde used in this synthesis was prepared by the following procedure.

2-Fluoro-4-(morpholino)-benzonitrile
A solution of 2,4-difluorobenzonitrile (6.03g, 43.35mmol) and morpholine (8.3ml, 95.17mmol) in tetrahydrofuran (27ml) was stirred at room temperature for 24hr. The mixture was evaporated and the white solid purified by Biotage™ column (90g, silica) eluting with cyclohexane: ethyl acetate: (4: 1) to give 2-fluoro-4-(morpholino)-benzonitrile as a white solid (5.81g, 65%).
HPLC Rt = 2.83 minutes; m/z $[M+H]^+ = 207$.

2-Fluoro-4-(morpholino)-benzaldehyde
To a solution of 2-fluoro-4-(morpholino)-benzonitrile (2.82g, 13.7mmol) in tetrahydrofuran (27ml) under a nitrogen atmosphere was added dropwise a 1.5 M solution of DIBAL-H in toluene (18.3ml, 27.3mmol) during 13minutes and the resulting mixture

stirred for 23.5hr at room temperature. The mixture was cooled to -50 °C and the excess DIBAL-H deastoyed by careful addition of methanol (27ml). The mixture was then stirred at room temperature for 10 mins, saturated ammonium chloride (27ml) added and the resulting mixture stirred at room temperature for 40 mins., and then evaporated under reduced pressure to a yellow solid. This solid was partitioned between dichloromethane (120ml) and water (120ml) and solid potassium carbonate added until the aqueous phase was pH10. The phases were separate via a hyrophobic frit and the oraganic phase evaporated and the residue purified by a Biotage™ column (40g, silica) eluting with cyclohexane: ethyl acetate: (7:3) to give 2-fluoro-4-(morpholino)-benzaldehyde (1.96g, 68%) as a white solid.
HPLC Rt = 2.63 minutes; m/z $[M+H]^+ = 210$.

Method 3

Example 7
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide

Methyl N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucinate

To a stirred suspension of (L)-Leucine (1.3g) in methanol (100ml) under a nitrogen atmosphere was added 2,4-difluorobenzaldehyde (1.42g). After stirring at ambient temperature for 3 days, the suspension was cooled to –30°C and a solution of isopropylisocyanide (0.691g) in methanol (5ml) was added. After 3 hours at –30°C the reaction was allowed to warm to room temperature and was stirred for a further 20 hours. The solvent was removed *in vacuo*, the residue purified using a Biotage™ column (40g, silica) eluting with cyclohexane: ethyl acetate (gradient from 8:1 to 1:1). The required fractions were combined and concentrated *in vacuo* to furnish methyl N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucinate (1.326g). ^{1}H NMR ($CDCl_3$) d 7.32 (m, 1H), 6.88 (m, 1H), 6.82 (m, 1H), 6.78 (m, 1H), 4.42 (s, 1H), 4.07 (m, 1H), 3.69 (s, 3H), 3.18 (t, 1H), 1.66 (m, 1H), 1.49 (t, 2H), 1.18 (d, 3H), 1.15 (d, 3H), 0.88 (d, 3H), 0.77 (d, 3H)

N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucine

To a solution of methyl N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucinate (1.32g) in methanol (15ml) was added a solution of lithium hydroxide (294mg) in water (15ml). The reaction was rapidly stirred for 1.5 hours and then evaporated *in vacuo.* The residue was dissolved in water and neutralised using 2N hydrochloric acid. The resulting solid was collected by filtration and dried *in vacuo*. The filtrate was applied to 4 Oasis cartridges (6g), which were eluted with water (x2) and methanol (x2). The required fractions were combined and concentrated *in vacuo* to afford

N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucine (1.01g).
HPLC Rt = 2.51 minutes; m/z $[M+H]^+$ = 343.

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

To a solution of (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (291mg) in dry tetrahydrofuran (5ml) under a nitrogen atmosphere at –20°C was added N-methylmorpholine (101mg) and a solution of isopropylchloroformate in toluene (1.0M, 1ml). After 10 minutes, a solution of N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucine (342mg) in N,N-dimethylformamide/ tetrahydrofuran (5ml/ 10ml) was added and the resultant mixture was stirred at room temperature for 4 hours. The solvent was then removed *in vacuo* and the residue was treated with 4N hydrochloric acid in dioxane (2ml). After 4 hours, methanol (5ml) was added to the reaction mixture and this was left to stand for 18 hours. The solvent was then removed *in vacuo* and the residue was purified on an SPE cartridge (50g, silica) eluting with cyclohexane/ ethyl acetate (gradient from 4:1 to neat ethyl acetate), which furnished the two diastereomers as white solids (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide; (0.137g)

HPLC Rt = 3.47 minutes, m/z $[M+H]^+$ = 498

^{1}H NMR ($CDCl_3$) δ 7.68 (m, 1H), 7.21 (m, 2H), 7.17 (m, 2H), 6.95 (m, 1H), 6.89 (m, 1H), 6.79 (d, 1H), 5.91 (d, 1H), 5.33 (s, 1H), 4.12 (m, 1H), 4.02 (m, 1H), 3.92 (dd, 1H), 3.16 (m, 1H), 3.05 (m, 2H), 2.90 (m, 1H), 2.78 (m, 1H), 1.85 (m, 1H), 1.79 (m, 1H), 1.49 (m, 1H), 1.17 (m, 6H), 0.88 (d, 3H), 0.82 (d, 3H)

Method 4

Example 8

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

Methyl N-[(1R)-2-{[2-(benzyloxy)phenyl]amino}-1-(2,4-difluorophenyl)-2-oxoethyl]-L-leucinate

To a suspension of L-leucine (2.33g) in methanol (200ml) at –30°C under nitrogen was added a solution of 2,4-difluorobenzaldehyde (2.52g) in methanol (10ml) and a suspension of 2-benzyloxyphenylisonitrile (3.7g) in methanol (40ml). The reaction was stirred at –30°C for 2.5 hours and then allowed to warm to room temperature and stirred for a further 6 days. The solvent was removed *in vacuo* and the residue was passed through a Biotage™ column (90g) eluting with cyclohexane: ethyl acetate (8:1 and 7:1) to afford after evaporation of the appropriate fractions methyl N-[(1R)-2-{[2-

(benzyloxy)phenyl]amino}-1-(2,4-difluorophenyl)-2-oxoethyl]-L-leucinate (5.06g).
HPLC Rt=4.0 minutes, m/z $[M-H]^-$ = 495

Methyl N-{(1R)-1-(2,4-difluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-L-leucinate

A mixture of palladium on carbon (10%, 300mg), methyl N-[(1R)-2-{[2-(benzyloxy)phenyl]amino}-1-(2,4-difluorophenyl)-2-oxoethyl]-L-leucinate (2.88g) and ethyl acetate (30ml) was stirred under a hydrogen atmosphere for 3 hours. The reaction was then filtered through Celite and the filter pad was washed with further portions of ethyl acetate. The combined organic fractions were evaporated to give methyl N-{(1R)-1-(2,4-difluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-L-leucinate (2.179g).
HPLC Rt=3.52 min, m/z $[M-H]^-$ = 405

Methyl N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate

A solution of methyl N-{(1R)-1-(2,4-difluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-L-leucinate (203mg) and 1,1'-thiocarbonyldiimidazole (100mg) in dichloromethane (5ml) was left to stand for 18 hours. Water (10□l) was added to the reaction mixture and this was then stirred rapidly for 30 minutes. After this, 1H-Benzotriazolium, 1-[bis(dimethylamino)methylene]-, tetrafluoroborate(1-), 3-oxide (TBTU, 321mg) and a solution of dimethylamine in tetrahydrofuran (0.5ml of 2M solution) were added. The reaction mixture was stirred for a further 18 hours and was then passed down an SPE (5g, silica) eluting with a gradient (8:1 to 1:2 cyclohexane: ethyl acetate). The required fractions were combined and evaporated to furnish methyl N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate (100mg).
HPLC Rt = 3.16 minutes m/z $[M+H]^+$ = 343

N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucine

To a solution of methyl N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate (100mg) in methanol (3ml) was added a solution of lithium hydroxide (15.4mg) in water (1ml). After stirring vigorously for 4 hours the solvent was removed *in vacuo*. The residue was diluted with water (10ml) then neutralised with 2N hydrochloric acid. This solution was applied to an Oasis™ cartridge (6g) and eluted with water (x2) and methanol (x2). The required fractions were combined and evaporated to afford N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucine (95mg).
HPLC Rt = 2.23 minutes m/z $[M+H]^+$ = 329

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

To a solution of (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (84mg) in dry tetrahydrofuran (6ml) at –20°C under a nitrogen atmosphere was added N-methylmorpholine (32□l) and a solution of isopropylchloroformate in toluene (1.0M, 290□l). After 10 minutes, a solution of N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucine (95mg) in tetrahydrofuran (10ml) was added and the reaction was allowed to warm to room temperature. After 20 hours, the solvent was removed *in vacuo* and the residue was dissolved in 4N hydrochloric acid in dioxan (4ml). After 4 hours methanol (5ml) was added and the reaction was left to stand for a further18 hours. The solvent was then removed *in vacuo* and the residue was dissolved in dioxan (5ml) and to this was added triethylamine (0.5ml). After 1 hour, the solvent was removed and the residue was applied to an SPE (10g, silica). The product was eluted using methanol. A second SPE was used to further purify the material (2g, silica) using an ethyl acetate: methanol gradient (20:1 to 1:1) to afford (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide (38mg).

HPLC Rt=3.5 minutes, m/z $[M+H]^+ = 484$

^1H NMR ($CDCl_3$) δ 7.42 (m, 1H), 7.22 (m, 2H), 7.17 (m, 2H), 7.02-6.90 (m, 2H), 6.62 (s, 1H), 6.37 (m, 1H), 4.09 (m, 1H), 3.98 (dd, 1H), 3.20-3.02 (m, 3H), 2.99 (s, 3H), 2.87 (m, 1H), 2.85 (s, 3H), 2.74 (m, 1H), 1.55 (m, 2H), 0.70 (m, 1H), 0.67 (d, 3H), 0.41 (d, 3H)

Similarly prepared

Example 9

(2R)-N-cyclopropyl-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.

HPLC Rt=3.41 minutes, m/z $[M+H]^+ = 496$.

^1H NMR ($CDCl_3$) δ 7.67 (dt, 1H), 7.59 (1H, d), 7.21-7.11 (m, 4H), 6.99-6.92 (m, 1H), 6.92-6.84 (m, 1H), 6.35 (d, 1H), 5.43 (s, 1H), 3.99 (dd, 1H), 3.93 (dd, 1H), 3.17-2.71 (m, 6H), 1.88-1.70 (m, 2H), 1.48-1.38 (m, 1H), 0.86 (s, 3H), 0.81-0.74 (m, 5H), 0.51-0.45 (m, 2H).

Example 10

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide:

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide

A mixture of 2,4-difluorobenzaldehyde (1.421g), (D)-leucine methyl ester hydrochloride (1.817g), triethylamine (1.391ml) and methanol (20ml) was stirred at room temperature for 16 hours. N-*tert*-butoxycarbonyl-(D)-indanylglycine (2.914g) and 2-benzyloxy-phenylisocyanide (2.090g) were then added sequentially. After 24 hours the solvent was

removed under reduced pressure and the reaction mixture was taken up in dichloromethane (ca. 20ml) and purified by Biotage™ flash column chromatography (2x90g silica cartridges on a Biotage Quad 3 system eluted with 1:9 ethyl acetate:cyclohexane) to afford methyl (2R)-2-{[(1R,S)-2-{[2-(benzyloxy)phenyl]amino}-1-(2,4-difluorophenyl)-2-oxoethyl][(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]amino}-4-methylpentanoate (5.100g) (HPLC Rt = 4.40 minutes m/z $[M+H]^+$ = 770). This was taken up in 4M hydrogen chloride in 1,4-dioxane (20ml) and the mixture was left at room temperature for 3 hours. The solvent and hydrogen chloride were blown off using a stream of nitrogen overnight. The crude material was taken up in methanol (90ml) containing triethylamine (10ml). After 30 minutes, the methanol and excess of triethylamine were removed under reduced pressure. The crude product was purified by Biotage™ flash column chromatography (2x90g silica cartridges on a Biotage Quad 3 system eluted with 1:2 ethyl acetate:cyclohexane) to yield (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide (3.381g).
HPLC Rt = 3.99 minutes, m/z $[M+H]^+$ = 638

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide (3.381g) was dissolved in ethyl acetate (200ml) and hydrogenated at atmospheric pressure over 10% palladium on carbon catalyst (0.980g of 10% Pd/C:water 1:1w/w) at room temperaure for five hours. The reaction mixture was filtered through Celite and the sovent was removed under reduced pressure to give the (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide as a cream-coloured foam (2.650g).

HPLC Rt = 3.61 minutes, m/z $[M-H^+]^-$ = 546 (no $[M+H\}^+$ visible)

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-ethanoic acid.

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (2.650g) was stirred in dichloromethane (20ml) and carbonyldiimidazole (1.178g) was added. the mixture was left at room temperature for 16 hours then the solvent was removed under reduced pressure. The residue was then taken up in 1:1 acetone:water (v/v) (80ml) and left at room temperature for 30 minutes. The bulk of the acetone was then removed under reduced pressure and the residue was partitioned between dichloromethane and 0.5M hydrochloric acid. The organic phase was separated (hydrophobic frit) and evaporated

under reduced pressure. The crude product was purified (Biotage™ flash chromatography column, 90g silica cartridge eluted with (i) 1:1 ethyl acetate:cyclohexane (ii) ethyl acetate (iii) ethyl acetate:methanol 9:1) to afford (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-ethanoic acid.as a colourless solid 1.524g as a mixture of epimers.
HPLC Rt = 3.44 and 3.58 minutes, both m/z $[M+H^+] = 457$

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

The acid (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-ethanoic acid (0.747g) prepared as described above was dried over P_4O_{10} in vacuo for five hours to give 0.724g drier material; this was dissolved in anhydrous dichloromethane:acetonitrile (1:1 v/v, 6ml) and treated with triethylamine (0.223ml) and BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride, dissolved in anhydrous dichloromethane:acetonitrile (1:1 v/v, 6ml) and treated with triethylamine (0.223ml) and BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride, 0.450g) and the mixture was sonicated for ca. 1 min to give a gelatinous mass. After 10 minutes at room temperature a solution of dimethylamine in tetrahydrofuran (10ml of 2M solution) was added to give a clear solution; this was left for 16 hours at room temperature. The solvents were removed under reduced pressure and the mixture was partitioned beween dichloromethane and 0.1M hydrochloric acid. The organic phase was separated (hydrophobic frit) and evaporated under reduced pressure. The crude product was purified by flash column chromatography (12g Biotage™ silica cartridge eluted with (i) 1:1 ethyl acetate:cyclohexane (ii) ethyl acetate (iii) ethyl acetate:methanol 9:1) to give the (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide as a colourless solid 0.285g.
HPLC Rt = 3.43 minutes, m/z $[M+H]^+ = 484$
^1H NMR ($CDCl_3$) δ 7.47 –7.40 (m, 1H), 7.24-7.11 (m, 4H), 7.01-6.91 (m, 3H), 6.62 (s, 1H), 4.09 (dd, 1H), 3.98 (dd, 1H), 3.19-3.01(m, 3H), 2.99 (3, 3H), 2.92-2.75 (m, 5H), 1.64-1.51 (m, 2H), 0.76-0.66 (m, 4H), 0.43 (d, 3H).

Method 5

Example 11
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

(2R)-[(benzyloxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid

R-Indanylglycine (1.91g) was suspended in dioxane (10ml) and water (10ml). To this was added triethylamine (1.7ml) and N-(benzyloxycarbonyloxy)succinimide (2.54g) and the reaction mixture was stirred rapidly at room temperature for 2 days. The reaction mixture was poured into water (50ml) and extracted with chloroform (100ml). The organic phase was washed with 1N hydrochloric acid (50ml) and water (50ml). This was dried over magnesium sulphate and the solvent removed *in vacuo* to give (2R)-[(benzyloxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (3.06g).
HPLC Rt = 3.35 minutes; m/z $[M+H]^+ = 326$.
^1H NMR ($CDCl_3$) δ 7.40-7.29 (m, 5H), 7.21-7.11 (m, 4H), 5.28 (d, 1H), 5.11 (s, 2H), 4.57 (m, 1H), 3.14-2.79 (m, 5H).

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide

To a solution of (D)-leucine methyl ester hydrochloride (1.45g) in methanol (10ml) was added triethylamine (1.12ml) and 2,4-difluorobenzaldehyde (0.875ml). The mixture was stirred for 3 days before (2R)-[(benzyloxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (2.6g) and 2-benzyloxyphenylisocyanide (1.76g) were sequentially added. The reaction mixture was left to stand for 24 hours. The solvent was removed *in vacuo* and the residue was separated between ethyl acetate (200ml) and water (200ml). The organic phase was washed with brine. To this solution was added palladium on carbon (2.0g) and acetic acid (10ml) and the reaction mixture was stirred under an atmosphere of hydrogen for 2 hours. The mixture was filtered through Celite and washed with water (3x100ml), saturated sodium bicarbonate solution, brine and dried over magnesium sulphate. The solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica) eluting with ethyl acetate: cyclohexane (50% to 66%) to give (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (2.0g).
HPLC Rt = 3.59 minutes; m/z $[M+H]^+ = 548$.

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

Carbonyldiimidazole (4.80g, 1.54 equiv.) was suspended in anhydrous dichloromethane (40mL) and the suspension was left at room temperature for 15 minutes. (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (10.50g, pre-dried in vacuo over P_4O_{10} for 24 hours) was then added with stirring and the resultant solution was stirred at room temperature for 6 hours. The resulting yellow solution was then treated with a 2.0M solution of dimethylamine in tetrahydrofuran (54mL, 5.6 equiv.)and the resulting mixture was stirred at room temperature for 16 hours. The solvents plus residual dimethylamine were removed under reduced pressure and the reaction mixture was taken up in

dichloromethane (200mL) and washed with 1M hydrochloric acid (200mL). The organic phase was separated using a hydrophobic frit and was evaporated under reduced pressure to ca. 50mL. The crude product was applied to 4x90g silica Biotage™ columns on a Quad 3 system; each column being eluted with (i) 2:1v/v ethyl acetate:cyclohexane (12x50mL fractions), (ii) ethyl acetate (12x50mL fractions), (iii) 9:1v/v ethyl acetate:methanol to give (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide (5.753g, 62%) as a colourless solid.

HPLC Rt = 3.41 minutes, m/z $[M+H]^+ = 484$

^1H NMR ($CDCl_3$) δ 7.48 –7.38 (m, 2H), 7.24-7.11 (m, 4H), 7.01-6.90 (m, 2H), 6.62 (s, 1H), 4.09 (dd, 1H), 3.98 (dd, 1H), 3.19-3.01(m, 3H), 2.99 (3, 3H), 2.92-2.75 (m, 5H), 1.64-1.51 (m, 2H), 0.76-0.66 (m, 4H), 0.43 (d, 3H).

Similarly prepared:

Example 12

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide colourless solid, 41%

HPLC Rt = 3.4 minutes, m/z $[M+H]^+ = 470$

Example 13

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide colourless solid, 36%

HPLC Rt = 3.3 minutes, m/z $[M+H]^+ = 456$

Example 14

(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione colourless solid, 61%

HPLC Rt = 3.4 minutes, m/z $[M+H]^+ = 526$

Example 15

(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione colourless solid, 45%

HPLC Rt = 3.2 minutes, m/z $[M+H]^+ = 512$

(azetidin-3-ol prepared by the method of S S Chatterjee and D J Triggle; J Chem. Soc. Chem. Comm. (2) 93 (1968)

Example 16

(3R,6R)-1-[(1R)-2-azetidin-1-yl-1-(2,4-difluorophenyl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione colourless solid, 46%

HPLC Rt = 3.4 minutes, m/z $[M+H]^+ = 496$

Example 17
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyethyl)-N-methylethanamide colourless solid, 59%
HPLC Rt = 3.3 minutes, m/z $[M+H]^+$ = 514

Example 18
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-[2-(methylsulfonyl)ethyl]ethanamide colourless solid, 22%
HPLC Rt = 3.2 minutes, m/z $[M+H]^+$ = 576

Example 19
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(2,2,2-trifluoroethyl)ethanamide colourless solid, 11%
HPLC Rt = 3.5 minutes, m/z $[M+H]^+$ = 552
(2,2,2-trifluoroethylmethylamine hydrochloride was prepared by the method of E R Bissell and M Finger; J. Org. Chem. 24 1256-1259 (1959))

Example 20
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(pyridin-2-ylmethyl)ethanamide tan foam, 19%
HPLC Rt = 3.5 minutes, m/z $[M+H]^+$ = 561

Example 21
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methoxy-N-methylethanamide
HPLC Rt = 3.4 minutes, m/z $[M+H]^+$ = 500

Example 22
(2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid
Carbonyldiimidazole (1.42g, 1.6 equiv.) was suspended in anhydrous dichloromethane (10mL)and the suspension was left at room temperature for 15 minutes. (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (3.00g) was then added and the resultant solution was stirred at room temperature for 16 hours. The resulting yellow solution was was then evaporated under reduced pressure and the residue was treated with a 1:1(v/v) mixture of water and acetone (10 mL). The mixture was stirred for 2 hours, then the acetone was removed under reduced pressure and the residue was partitioned between dichloromethane and 0.1M HCl aq. The organic phase was separated using a hydrophobic frit then evaporated to low volume and purified by chromatography

on a Biotage Quad 3 system (90g silica column) eluted with 1:1(v/v) ethyl acetate:cyclohexane, then ethyl acetate, then 1:1 (v/v) ethyl acetate:methanol to give a mixture of diastereomers (2.61g). These were separated on a chiral reverse-phase column (Chiralcel OD, eluted with 15% propan-2-ol/heptane containing 0.1%TFA) to give: (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid (1.60g)
HPLC Rt = 3.4 minutes, m/z $[M+H]^+$ = 457

Example 23

methyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
Carbonyldiimidazole (0.324g, 1.6 equiv.) was suspended in anhydrous dichloromethane (4mL)and the suspension was left at room temperature for 15 minutes. (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (0.800g) was then added with stirring and the resultant solution was left at room temperature for 16 hours. The mixture was then treated with methanol (10mL) and left at room temperature overnight. The solvents were removed under reduced pressure and the residue was purified by preparative plate chromatography on silica (20x20cm plates x4 eluted with 1:3 ethyl acetate:cyclohexane x5) to give:methyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate (0.453g, 66%)
HPLC Rt = 3.42 minutes, m/z $[M+H]^+$ = 471

Similarly prepared:

Example 24

propyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
HPLC Rt = 3.71 minutes, m/z $[M+H]^+$ = 499

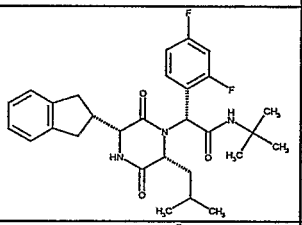
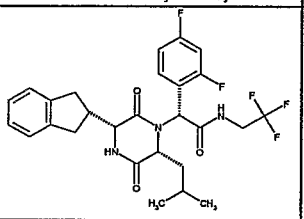
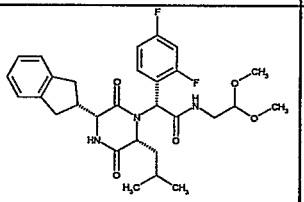
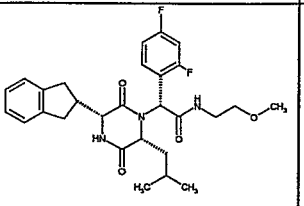
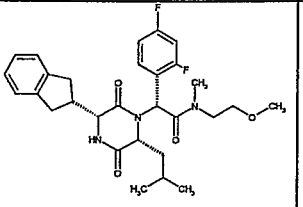
Example 25

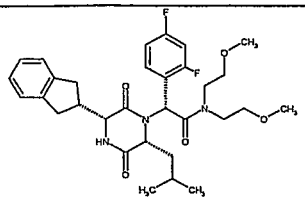
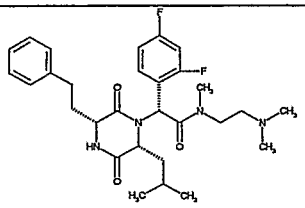
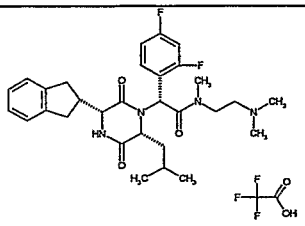
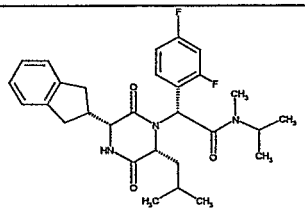
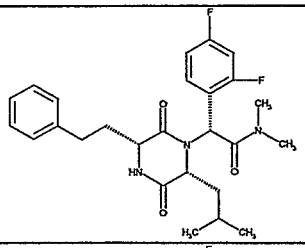
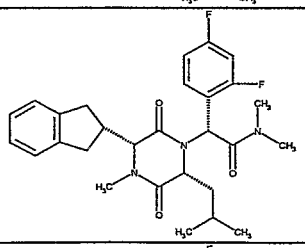
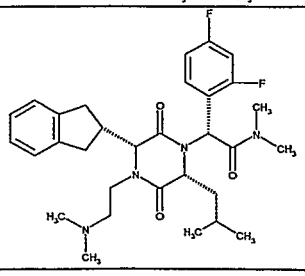
1-(acetyloxy)ethyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
(2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid (example 22) (0.130g) was stirred in anhydrous DMF (1mL) and anhydrous potassium carbonate (0.020g, 0.5 eq.) was added. The mixture was stirred at room temperature for 1 hour then cooled to –10°C (ice-salt bath). The heterogeneous mixture was treated with 1-bromoethyl acetate (0.120mL, excess) and stirred for 3.5 hours keeping the bath temperature between –10 and –5°C. It was then partitioned between DCM and 1M HCl aq. (20 mL each). The organic phase was separated (hydrophobic frit) and evaporated under reduced pressure to give a purple gum; this was purified by SPE cartridge (5g, silica eluted with (i) cyclohexane x2, (ii) DCM x2,

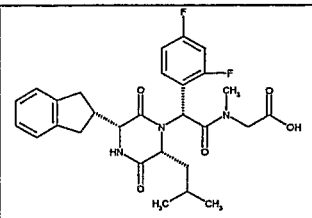
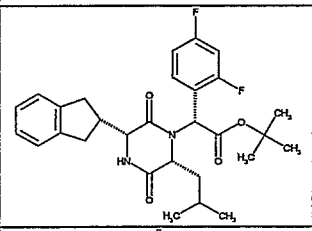
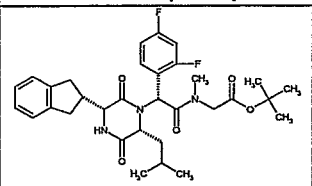
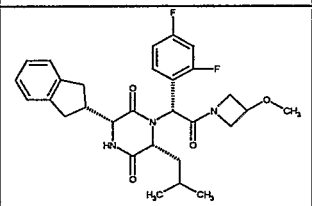
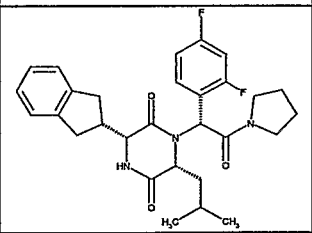
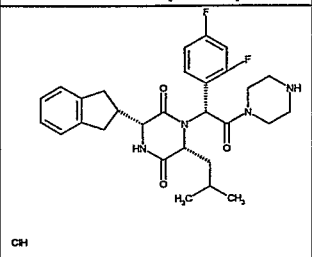
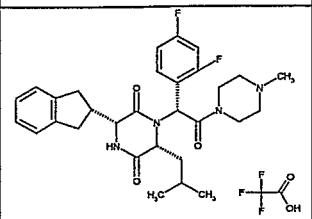
(iii) diethl ether x2, (iv) ethyl acetate x2, (v) methanol x2 to give 1-(acetyloxy)ethyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate (0.081g) as a yellow foam.
HPLC Rt = 3.5 minutes, m/z $[M+H]^+$ = 543

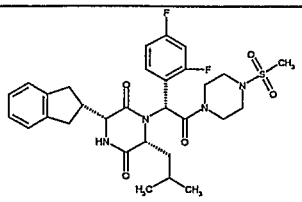
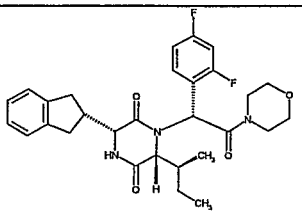
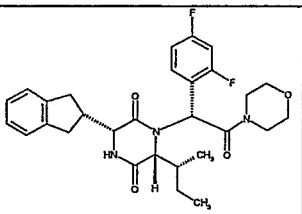
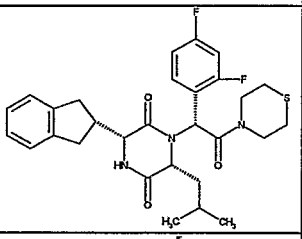
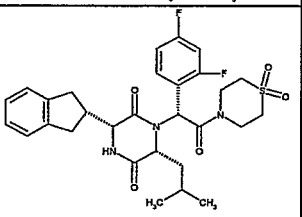
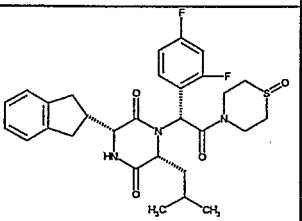
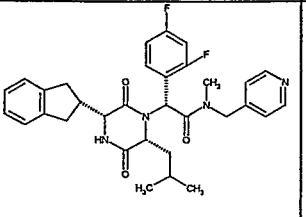
Similarly prepared:

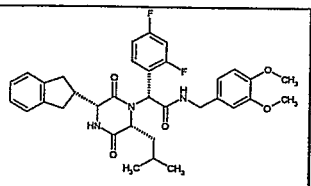
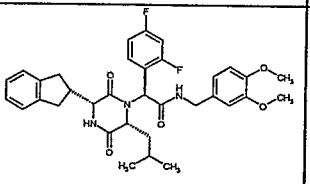
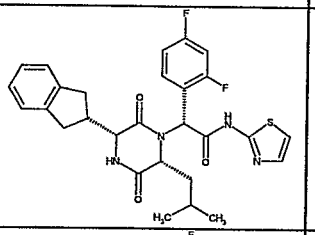
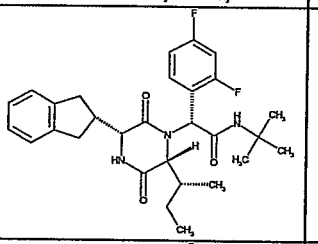
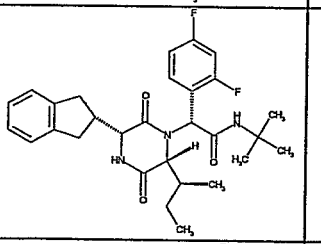
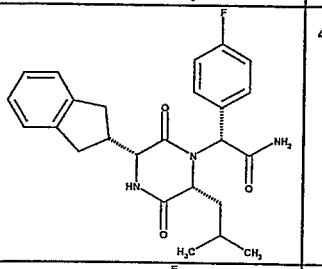
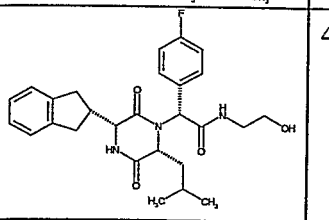
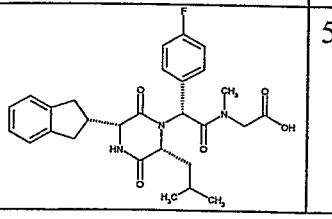
In the table below, Examples 26, 54-55, 66-104, 107-117, 124-131 were prepared via method 1. The t-butyl ester Example 39 was prepared via perchloric acid-catalysed transesterification of the corresponding acid (Example 22) with t-butyl acetate by the procedure of T Kolasa and M J Miller; Journal of Organic Chemistry (1990), 55(6), 1711-21. Other Examples in the table below were prepared via method 5.

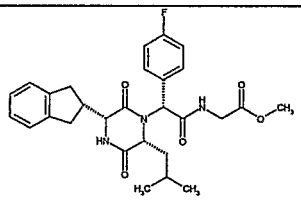
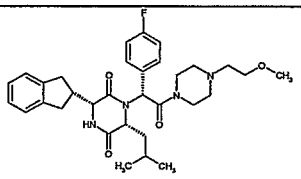
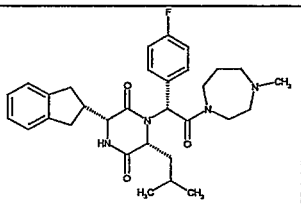
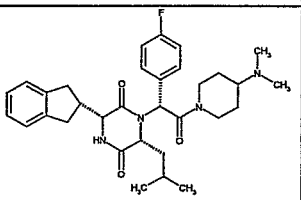
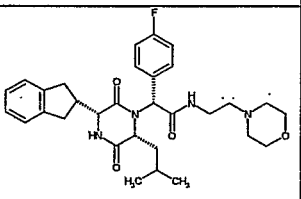
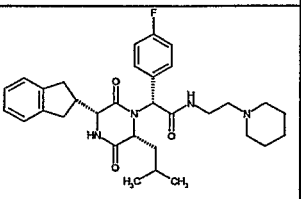
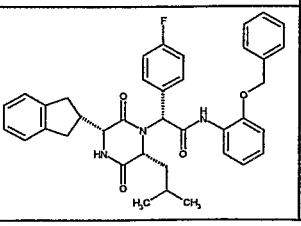
Eg No.	Regno	Mwt	Rt /min	+ve ion	-ve ion	name
26		511.6	3.6	512	510	(2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
27		537.5	3.4	538	536	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2,2,2-trifluoroethyl)ethanamide
28		543.6	3.2	544	542	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2,2-dimethoxyethyl)ethanamide
29		513.6	3.3	513	511	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-methoxyethyl)ethanamide
30		527.6	3.4	528	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-methoxyethyl)-N-methylethanamide

31		571.7	3.3	572	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-bis(2-methoxyethyl)ethanamide
32		528.6	2.7	529	none	(2R)-2-(2,4-difluorophenyl)-N-[2-(dimethylamino)ethyl]-2-[(2R,5R)-2-isobutyl-3,6-dioxo-5-(2-phenylethyl)piperazin-1-yl]-N-methylethanamide
33		654.7	2.7	541	539	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-[2-(dimethylamino)ethyl]-N-methylethanamide trifluoroacetate
34		511.6	3.6	512	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-N-methylethanamide
35		471.6	3.2	472	470	(2R)-2-(2,4-difluorophenyl)-2-[(2R,5R)-2-isobutyl-3,6-dioxo-5-(2-phenylethyl)piperazin-1-yl]-N,N-dimethylethanamide
36		497.6	3.5	498	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-4-methyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
37		554.7	2.7	555	none	(2R)-2-(2,4-difluorophenyl)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-4-[2-(dimethylamino)ethyl]-6-isobutyl-2,5-dioxopiperazin-1-yl}-N,N-dimethylethanamide

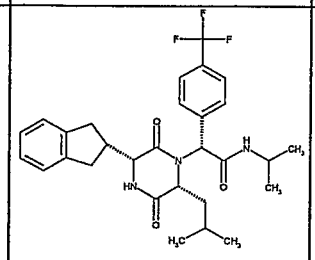
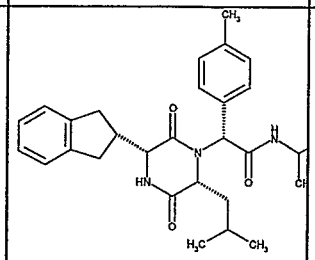
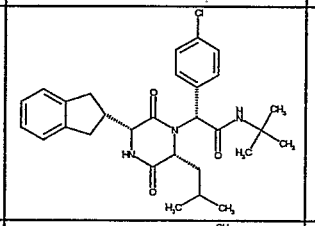
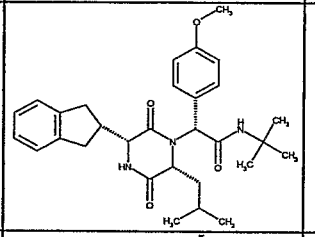
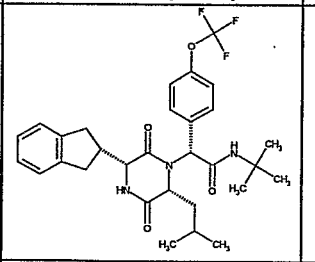
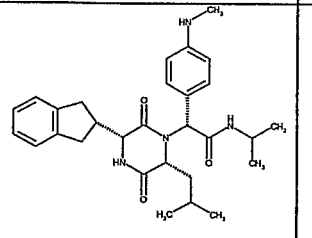
38		527.6	3.3	528	526	[{(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoyl}(methyl)amino]acetic acid
39		512.6	3.7	513	511	tert-butyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
40		583.7	3.6	584	none	tert-butyl [{(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoyl}(methyl)amino]acetate
41		525.6	3.3	526	524	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-methoxyazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
42		509.6	3.5	510	none	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-oxo-2-pyrrolidin-1-ylethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
43		561.1	2.7	525	none	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-oxo-2-piperazin-1-ylethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione hydrochloride
43a		652.7	2.7	539	583(M+45)	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione trifluoroacetate

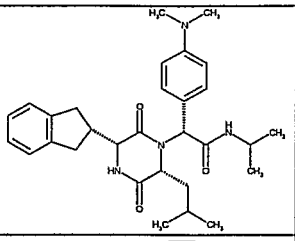
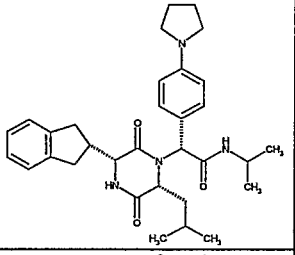
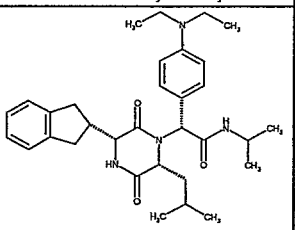
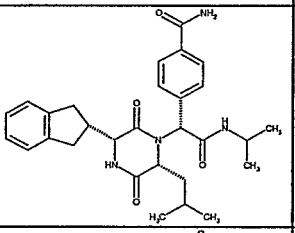
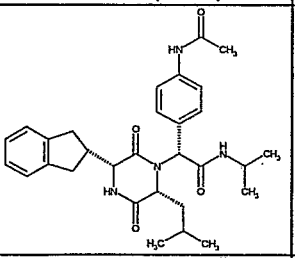
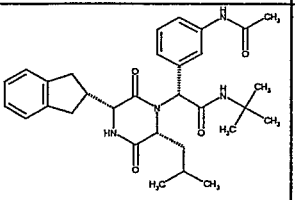
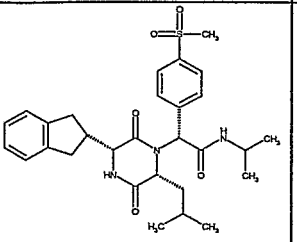
44		602.7	3.3	603	601	(3R,6R)-1-{(1R)-1-(2,4-difluorophenyl)-2-[4-(methylsulfonyl)piperazin-1-yl]-2-oxoethyl}-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
45		525.6	3.2	526	524	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]piperazine-2,5-dione
46		525.6	3.2	526	524	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]piperazine-2,5-dione
47		541.7	3.6	542	540	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-oxo-2-thiomorpholin-4-ylethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
48		573.7	3.3	574	572	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(1,1-dioxidothiomorpholin-4-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
49		557.7	3.1	558	556	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(1-oxidothiomorpholin-4-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
50		560.6	3	561	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(pyridin-4-ylmethyl)ethanamide

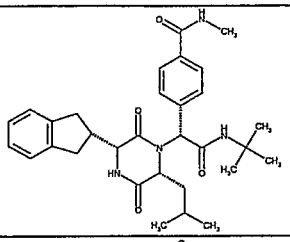
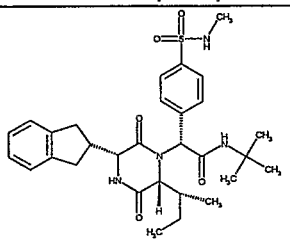
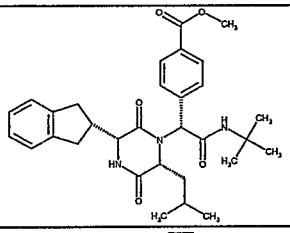
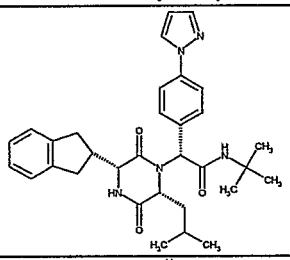
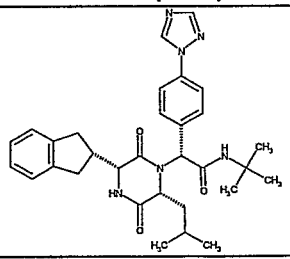
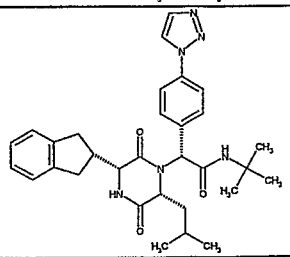
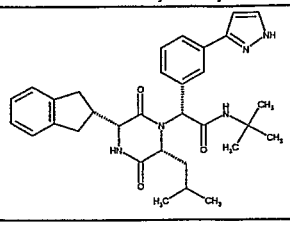
51		605.7	3.5	606	604	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(3,4-dimethoxybenzyl)ethanamide
52		605.7	3.5	606	604	(2S)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(3,4-dimethoxybenzyl)ethanamide
53		538.6	3.4	539	537	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(1,3-thiazol-2-yl)ethanamide
54		511.6	3.6	512	510	(2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl}ethanamide
55		511.6	3.6	512	510	(2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxopiperazin-1-yl}ethanamide
56		437.5	3.3	438	436	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)ethanamide
57		481.6	3	482	480	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2-hydroxyethyl)ethanamide
58		509.6	3.4	510	508	[[(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-

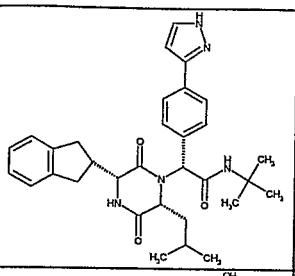
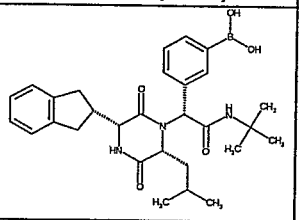
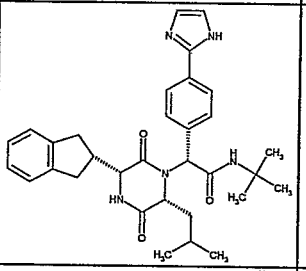
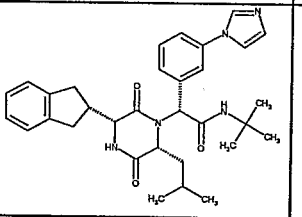
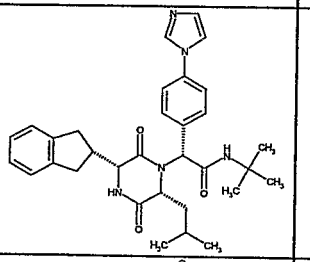
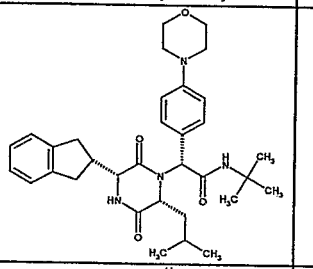
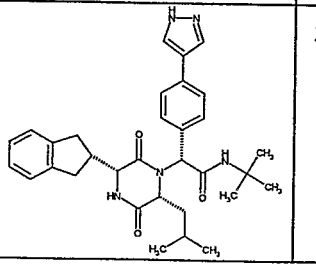
						fluorophenyl)ethanoyl](methyl)amino]acetic acid
59		509.6	3.4	510	508	methyl {[(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)ethanoyl]amino}acetate
60		564.7	2.6	565	563	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-{(1R)-1-(4-fluorophenyl)-2-[4-(2-methoxyethyl)piperazin-1-yl]-2-oxoethyl}-6-isobutylpiperazine-2,5-dione
61		534.7	2.6	535	533	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(4-fluorophenyl)-2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl]-6-isobutylpiperazine-2,5-dione
62		548.7	2.6	549	547	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-2-[4-(dimethylamino)piperidin-1-yl]-1-(4-fluorophenyl)-2-oxoethyl]-6-isobutylpiperazine-2,5-dione
63		550.7	2.7	551	549	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2-morpholin-4-ylethyl)ethanamide
64		548.7	2.8	549	547	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2-piperidin-1-ylethyl)ethanamide
65		619.7	3.9	620	618	(2R)-N-[2-(benzyloxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)ethanamide

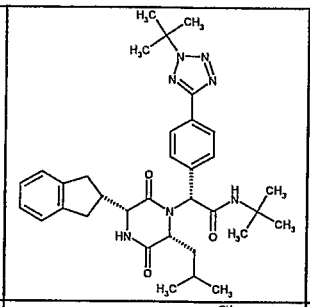
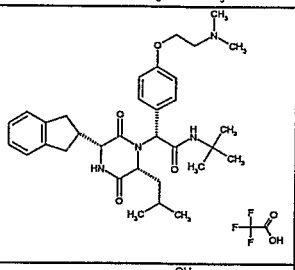
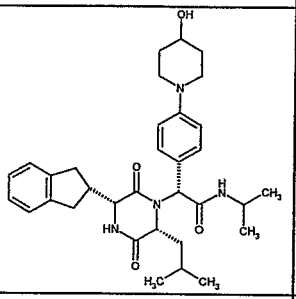
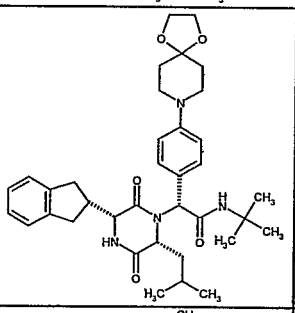
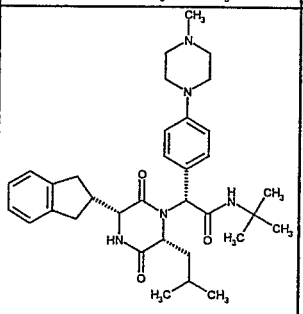
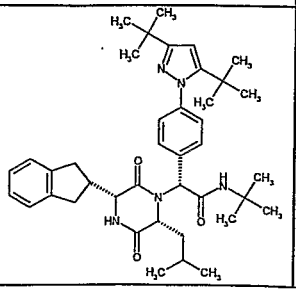
Similarly prepared:

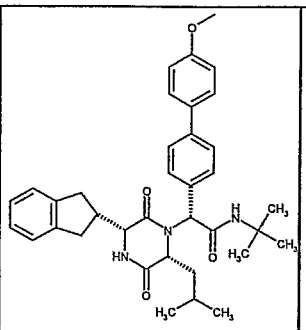
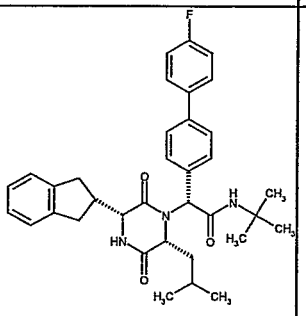
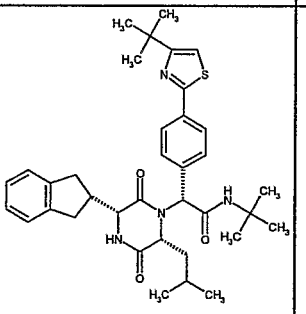
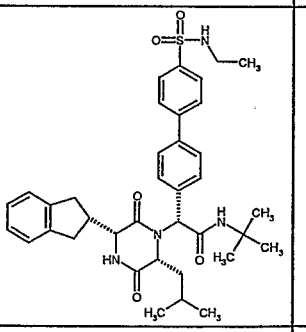
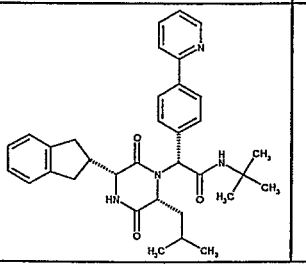
Eg No.	Regno	Mwt	Rt /min	+ve ion	-ve ion	name
66		529.6	3.8	530	528	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[4-(trifluoromethyl)phenyl]ethanamide
67		475.6	3.6	476	474	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(4-methylphenyl)ethanamide
68		510.1	3.8	510	508	(2R)-N-(tert-butyl)-2-(4-chlorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
69		505.7	3.5	506	504	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-methoxyphenyl)ethanamide
70		559.7	3.8	560	558	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(trifluoromethoxy)phenyl]ethanamide
71		490.6	3.4	491	489	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[4-(methylamino)phenyl]ethanamide

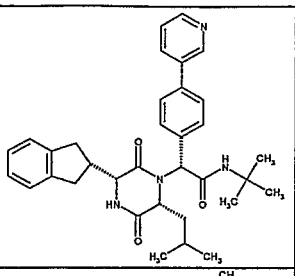
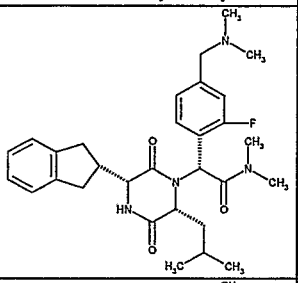
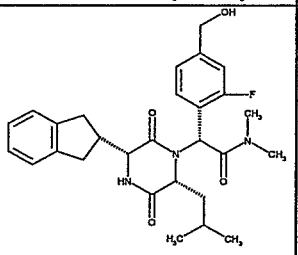
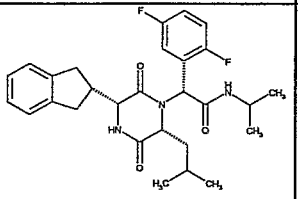
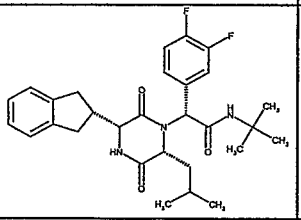
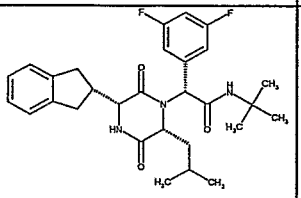
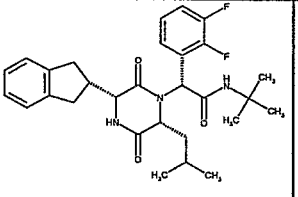
72		504.7	3.6	505	503	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(dimethylamino)phenyl]-N-isopropylethanamide
73		530.7	3.7	553(M+Na)	529	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(4-pyrrolidin-1-ylphenyl)ethanamide
74		532.7	3.7	533	531	(2R)-2-[4-(diethylamino)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
75		504.6	3.1	505	503	4-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(isopropylamino)-2-oxoethyl]benzamide
76		518.6	3.0	519	517	(2R)-2-[4-(acetylamino)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
77		532.7	3.2	533	531	(2R)-2-[3-(acetylamino)phenyl]-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
78		539.7	3.3	540	538	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[4-(methylsulfonyl)phenyl]ethanamide

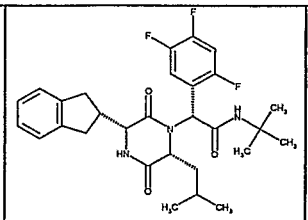
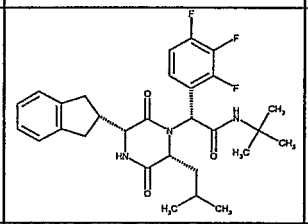
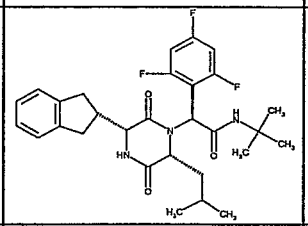
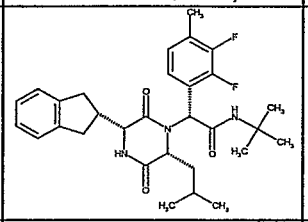
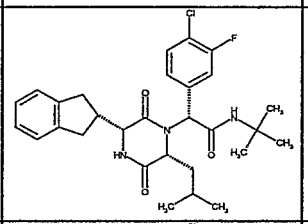
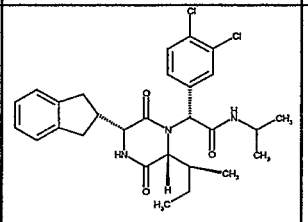
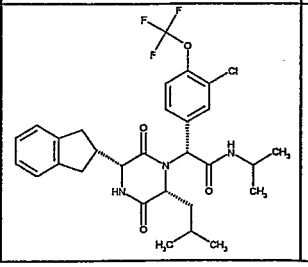
79		532.7	3.3	533	531	4-{(1R)-2-(tert-butylamino)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-oxoethyl}-N-methylbenzamide
80		568.7	3.4	569	567	(2R)-N-(tert-butyl)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl}-2-{4-[(methylamino)sulfonyl]phenyl}ethanamide
81		533.7	3.6	532	534	methyl 4-{(1R)-2-(tert-butylamino)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-oxoethyl}benzoate
82		541.8	3.3	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-pyrazol-1-yl)phenyl]ethanamide
83		542.8	3.3	543	541	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-1,2,4-triazol-1-yl)phenyl]ethanamide
84		542.8	3.2	543	541	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-1,2,3-triazol-1-yl)phenyl]ethanamide
85		541.7	3.5	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[3-(1H-pyrazol-3-yl)phenyl]ethanamide

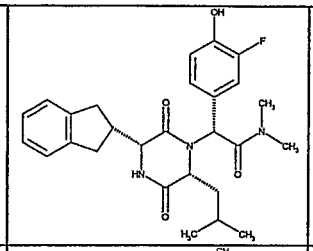
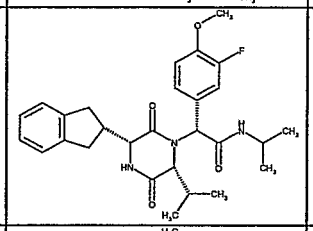
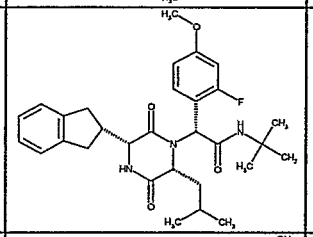
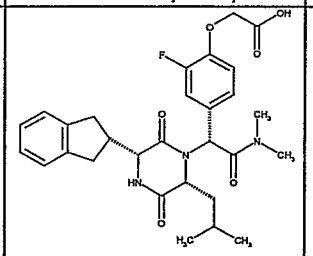
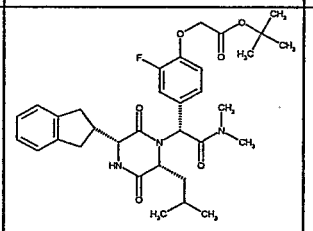
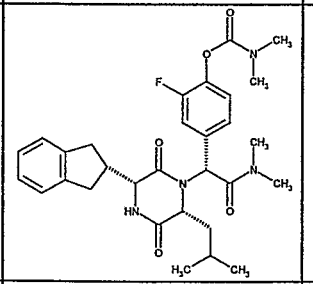
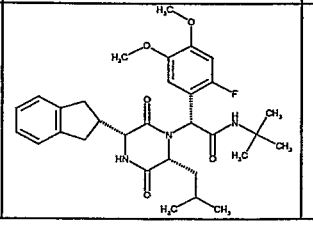
86		541.8	3.3	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-pyrazol-3-yl)phenyl]ethanamide
87		519.4	3.4	520	518	3-{(1R)-2-(tert-butylamino)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-oxoethyl}phenylboronic acid
88		541.7	3.0	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-imidazol-2-yl)phenyl]ethanamide
89		541.7	3.1	542.0	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[3-(1H-imidazol-1-yl)phenyl]ethanamide
90		541.7	3.0	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-imidazol-1-yl)phenyl]ethanamide
91		560.8	3.4	561	559	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-morpholin-4-ylphenyl)ethanamide
92		541.7	3.3	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-pyrazol-4-yl)phenyl]ethanamide

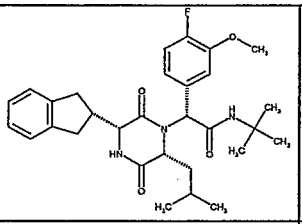
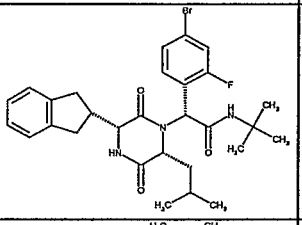
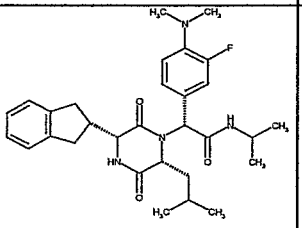
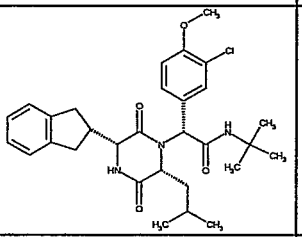
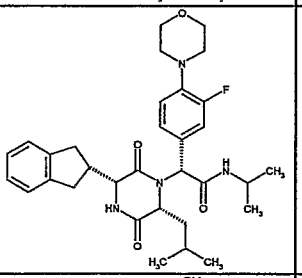
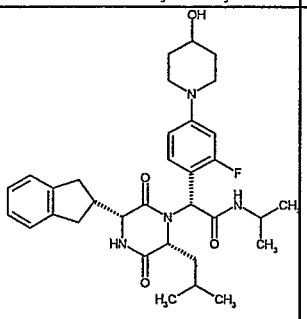
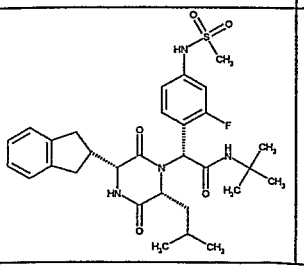
93		599.8	3.9	600	598	(2R)-N-(tert-butyl)-2-[4-(2-tert-butyl-2H-tetraazol-5-yl)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
94		562.7	2.9	563	none	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-{4-[2-(dimethylamino)ethoxy]phenyl}ethanamide trifluoroacetate
95		560.8	3.0	561	559	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-hydroxypiperidin-1-yl)phenyl]-N-isopropylethanamide
96		616.9	3.5	617	none	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)phenyl]ethanamide
97		573.8	2.9	574	none	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-methylpiperazin-1-yl)phenyl]ethanamide
98		654.0	4.1	654	652	(2R)-N-(tert-butyl)-2-[4-(3,5-ditert-butyl-1H-pyrazol-1-yl)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide

99		581.7	4.0	582	580	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4'-methoxy-1,1'-biphenyl-4-yl)ethanamide
100		569.8	3.9	none	568	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4'-fluoro-1,1'-biphenyl-4-yl)ethanamide
101		614.8	4.3	615	613	(2R)-N-(tert-butyl)-2-[4-(4-tert-butyl-1,3-thiazol-2-yl)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
102		658.9	3.6	659	657	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-{4'-[(ethylamino)sulfonyl]-1,1'-biphenyl-4-yl}ethanamide
103		552.8	3.6	553	551	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-pyridin-2-ylphenyl)ethanamide

104		552.8	3.3	553	551	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-pyridin-3-ylphenyl)ethanamide
105		522.7	2.4	523	none	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-{4-[(dimethylamino)methyl]-2-fluorophenyl}-N,N-dimethylethanamide
106		495.6	2.9	496	none	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[2-fluoro-4-(hydroxymethyl)phenyl]-N,N-dimethylethanamide
107			3.4	498	496	(2R)-2-(2,5-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
108			3.6	512	510	(2R)-N-(tert-butyl)-2-(3,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
109			3.6	512	510	(2R)-N-(tert-butyl)-2-(3,5-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
110			3.6	512	510	(2R)-N-(tert-butyl)-2-(2,3-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide

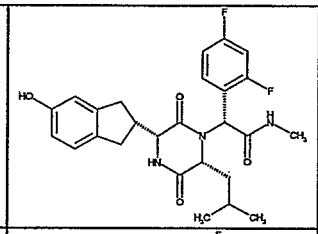
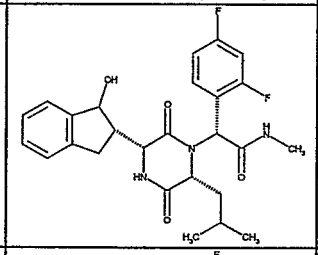
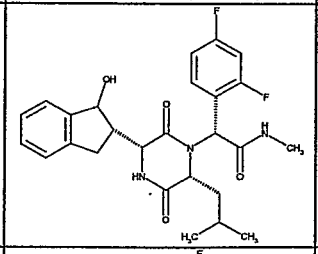
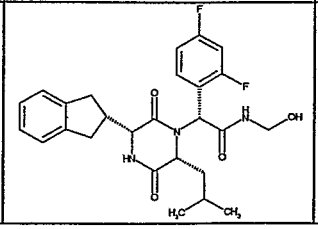
111			3.7	530	528	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2,4,5-trifluorophenyl)ethanamide
112			3.7	530	528	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2,3,4-trifluorophenyl)ethanamide
113			3.6	530	528	(2S)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2,4,6-trifluorophenyl)ethanamide
114			3.8	526	524	(2R)-N-(tert-butyl)-2-(2,3-difluoro-4-methylphenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
115			3.8	528	526	(2R)-N-(tert-butyl)-2-(4-chloro-3-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
116			3.7	530	528	(2R)-2-(3,4-dichlorophenyl)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxopiperazin-1-yl}-N-isopropylethanamide
117			3.7	580	578	(2R)-2-[3-chloro-4-(trifluoromethoxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide

118			3.0	482	480	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-4-hydroxyphenyl)-N,N-dimethylethanamide
119			3.3	496	494	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isopropyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-4-methoxyphenyl)-N-isopropylethanamide
120			3.6	524	522	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-4-methoxyphenyl)ethanamide
121			3.1	540	538	{4-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(dimethylamino)-2-oxoethyl]-2-fluorophenoxy}acetic acid
122			3.6	596	594	tert-butyl {4-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(dimethylamino)-2-oxoethyl]-2-fluorophenoxy}acetate
123			3.3	553	none	4-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(dimethylamino)-2-oxoethyl]-2-fluorophenyl dimethylcarbamate
124			3.5	none	552	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-4,5-dimethoxyphenyl)ethanamide

125			3.7	524	522	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluoro-3-methoxyphenyl)ethanamide
126			3.8	none	570/572	(2R)-2-(4-bromo-2-fluorophenyl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
127			3.5	523	521	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(dimethylamino)-3-fluorophenyl]-N-isopropylethanamide
128			3.7	540	538	(2R)-N-(tert-butyl)-2-(3-chloro-4-methoxyphenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
129			3.3	565	563	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-4-morpholin-4-ylphenyl)-N-isopropylethanamide
130			3.2	579	577	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[2-fluoro-4-(4-hydroxypiperidin-1-yl)phenyl]-N-isopropylethanamide
131			3.3	587	585	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-{2-fluoro-4-[(methylsulfonyl)amino]phenyl}ethanamide

Hydroxylated metabolites of (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide were prepared as follows:

2 litres of growing cell cultures of *Streptomyces rimosus* BS33 was used to biotransform GW796679x. 500mg of GW796679X was added after 3 days growth and the broth harvested after another 5 days incubation. At harvest, 2 litres of methanol was added, then the cells removed by centrifugation. Methanol was removed from the supernatant by evaporation. The compounds were then extracted with ethyl acetate, evaporated to dryness, and purified by preparative HPLC to give examples 132,133,134 and 135.

132		485.5	2.9	486	484	(2R)-2-(2,4-difluorophenyl)-2-{(3R,6R)-3-[(2S)-5-hydroxy-2,3-dihydro-1H-inden-2-yl]-6-isobutyl-2,5-dioxopiperazin-1-yl}-N-methylethanamide
133		485.5	2.9	486	484	(2R)-2-(2,4-difluorophenyl)-2-{(3R,6R)-3-[(2R)-1-hydroxy-2,3-dihydro-1H-inden-2-yl]-6-isobutyl-2,5-dioxopiperazin-1-yl}-N-methylethanamide
134		485.5	2.9	486	484	(2R)-2-(2,4-difluorophenyl)-2-{(3R,6R)-3-[(2R)-1-hydroxy-2,3-dihydro-1H-inden-2-yl]-6-isobutyl-2,5-dioxopiperazin-1-yl}-N-methylethanamide
135		485.5	3.1	486	530(M+45)	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(hydroxymethyl)ethanamide

Example 136

(2R)-2-(1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

Benzofuran-5-carboxaldehyde (215 mg, 1.47 mmol) and D-leucine t-butyl ester hydrochloride (329 mg, 1.47 mmol) were dissolved in methanol (1.5ml) and triethylamine (0.205 ml, 1.47 mmol) added. The mixture, a pale yellow solution, was left to stand at room temperature overnight (23.5 hours). Then Boc-D-indanylglycine (429 mg, 1.47 mmol) was added followed by isopropylisonitrile (0.138 ml, 1.51 mmol). The mixture, a yellow solution, was left to stand at room temperature overnight (23.5 hours) before the solvent was evaporated under reduced pressure to leave a yellow gum. The gum was dissolved in 4M hydrogen chloride in dioxan (3 ml, 12 mmol) and left to stand at room temperature for 7.5 hours before it was evaporated under reduced pressure to leave an orange / brown gum. The gum was dissolved in methanol (2 ml) and 4M hydrogen chloride in dioxan (1 ml, 4 mmol) added. The mixture was left to stand at room temperature for 5.5 hours before the solvent was removed by evaporation under reduced pressure. The residue was dissolved in dichloromethane (4ml) and triethylamine (0.5 ml, excess) added. The mixture was stirred at room temperature overnight (18.3 hours) before the solvent was removed by evaporation under reduced pressure. The residue was loaded in dichloromethane onto a SPE column (10g silica, Mega Bond Elut cartridge, pre-eluted with cyclohexane). The column was eluted stepwise (40 – 45 ml each step) with 100% chloroform, 3 : 1 cyclohexane : diethyl ether, 1 : 1 cyclohexane : diethyl ether, 1 : 3 cyclohexane : diethyl ether, 100% diethyl ether, 1 : 1 cyclohexane : ethyl acetate, 1 : 2 cyclohexane : ethyl acetate and 100% ethyl acetate. The 1 : 3 cyclohexane : diethyl ether to 1 : 2 cyclohexane : ethyl acetate fractions inclusive were combined to give a pale yellow solid (336 mg). The solid was loaded in dichloromethane onto 6 preparative chromatography plates (silica gel 60 plates, 20 × 20 cm^2). The plates were eluted four times with 30 : 1 dichloromethane : isopropanol. The required band was extracted with 9 : 1 ethyl acetate : methanol to give (2R)-2-(1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide as a white solid (141mg, 0.28 mmol)

HPLC Rt = 3.46 minutes; m/z $[M+H]^+$ = 502.

^{1}H NMR δ 7.95 (d, 1H), 7.73 (d, 1H), 7.68 (d, 1H), 7.53 (d, 1H), 7.37 (dd, 1H), 7.16 (m, 4H), 6.79 (d, 1H), 5.79 (d, 1H), 5.37 (s, 1H), 4.11 (m, 1H), 4.03 (br dd, 1H), 3.99 (dd, 1H), 3.16-2.97 (m, 3H), 2.95-2.78 (m, 2H), 1.79(m, 1H), 1.69 (m, 1H), 1.33 (m, 1H), 1.09 (t, 6H), 0.78 (d, 3H), 0.67 (d, 3H).

Similarly prepared

Example 137

(2R)-2-(1,2,3-benzothiadiazol-6-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.

HPLC Rt = 3.50 minutes; m/z $[M+H]^+$ = 534.

^{1}H NMR δ 8.66 (d, 1H), 7.82 (d, 1H), 7.67 (dd, 1H), 7.20 (m, 4H), 6.72 (br d, 1H), 6.13 (s, 1H), 5.19 (s, 1H), 4.06 (br dd, 1H), 4.00 (dd, 1H), 3.18 (m, 1H), 3.07 (m, 2H), 2.92

(m, 1H), 2.81 (m, 1H), 1.86(m, 1H), 1.80 (m, 1H), 1.54 (m, 1H), 1.36 (s, 9H), 0.85 (d, 3H), 0.78 (d, 3H).

Example 138

(2R)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

HPLC Rt = 3.34 minutes; m/z $[M+H]^+$ = 504.

^{1}H NMR δ 7.81 (br s, 1H), 7.18 (m, 5H), 6.79 (d, 1H), 6.44 (br d, 1H), 5.50 (d, 1H), 5.06 (s, 1H), 4.61 (t, 2H), 4.08 (m, 1H), 3.96 (m, 2H), 3.22 (t, 2H), 3.15 (m, 1H), 3.07 (d, 2H), 2.90 (m, 1H), 2.79 (dd, 1H), 1.82(m, 1H), 1.71 (m, 1H), 1.42 (m, 1H), 1.12 (dd, 6H), 0.83 (d, 3H), 0.77 (d, 3H).

Example 139

(2R)-2-(1,3-benzodioxol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.

HPLC Rt = 3.48; m/z $[M+H]^+$ = 520

^{1}H NMR ($CDCl_3$) δ 7.21 (m, 2H), 7.16 (m, 2H), 6.97 (d, 1H), 6.88 (dd, 1H), 6.82 (d, 1H), 6.58 (m, 1H), 6.06 (m, 2H), 5.64 (s, 1H), 5.02 (m, 1H), 3.95 (m, 2H), 3.16 (m, 1H), 3.07 (m, 2H), 2.89 (m, 1H), 2.77 (m, 1H), 1.82 (m, 1H), 1.71 (m, 1H), 1.41 (m, 1H), 1.32 (s, 9H), 0.83 (d, 3H), 0.79 (d, 3H)

Example 140

(2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

Methyl N-[(1R)-2-{[2-(benzyloxy)phenyl]amino}-1-(benzofuran-5-yl)-2-oxoethyl]-L-leucinate

To a suspension of L-leucine (2.62g) in methanol (250ml) at –30°C under nitrogen was added a solution of benzofuran-5-carbaldehyde (2.92g) in methanol (15ml) and a suspension of 2-benzyloxyphenylisonitrile (4.19g) in methanol (15ml). The reaction was stirred at –30°C for 2 hours and then allowed to warm to room temperature and stirred for a further 3 days. The solvent was removed *in vacuo* and the residue was passed through a Biotage™ column (3x90g) eluting with cyclohexane: ethyl acetate (5:1) to afford after evaporation of the appropriate fractions methyl N-[(1R)-2-{[2(benzyloxy)phenyl]amino}-1-(benzofuran-5-yl)-2-oxoethyl]-L-leucinate (5.11g).

HPLC Rt=3.97 minutes, m/z $[M+H]^+$ = 499

Methyl N-{(1R)-1-(benzofuran-5-yl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-L-leucinate

A mixture of palladium on carbon (10%, 500mg), methyl N-[(1R)-2-{[2-(benzyloxy)phenyl]amino}-1-(benzofuran-5-yl)-2-oxoethyl]-L-leucinate (5.1g) and ethyl acetate (60ml) was stirred under a hydrogen atmosphere for 5 hours. The reaction was then filtered through Celite and the filter pad was washed with further portions of ethyl acetate. The combined organic fractions were evaporated to give methyl N-{(1R)-1-(benzofuran-5-yl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-L-leucinate (3.429g).
HPLC Rt=3.49 min, m/z $[M+H]^+ = 411$

Methyl N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate

A solution of methyl N-{(1R)-1-(benzofuran-5-yl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl}-L-leucinate (410mg) and 1,1'-thiocarbonyldiimidazole (196mg) in dichloromethane (5ml) was left to stand for 18 hours. Water (20□l) was added to the reaction mixture and this was then stirred rapidly for 30 minutes. After this, 1H-Benzotriazolium, 1-[bis(dimethylamino)methylene]-, tetrafluoroborate(1-), 3-oxide (TBTU, 710mg) and a solution of dimethylamine in tetrahydrofuran (3ml of 2M solution) were added. The reaction mixture was stirred for a further 18 hours and was then passed down an SPE (5g, silica) eluting with a gradient (3:1 to 1:2 cyclohexane: ethyl acetate). The required fractions were combined and evaporated to furnish methyl N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate (140mg).
HPLC Rt = 2.70 minutes m/z $[M+H]^+ = 347$

N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucine

To a solution of methyl N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate (520mg) in methanol (5ml) was added a solution of lithium hydroxide (91mg) in water (3ml). After stirring vigorously for 24 hours the solvent was removed *in vacuo*. The residue was diluted with water (10ml) then neutralised with 2N hydrochloric acid. This solution was applied to an Oasis™ cartridge (2x6g) and eluted with water (x2) and methanol (x2). The required fractions were combined and evaporated to afford N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucine (478mg).
HPLC Rt = 2.27 minutes m/z $[M+H]^+ = 333$

(2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

To a solution of (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (419mg) in dry tetrahydrofuran (5ml) at –20°C under a nitrogen atmosphere was

added N-methylmorpholine (158μl) and a solution of isopropylchloroformate in toluene (1.0M, 1.44ml). After 10 minutes, a solution of N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucine (478mg) in dimethylformamide (5ml) was added and the reaction was allowed to warm to room temperature. After 20 hours, the solvent was removed *in vacuo* and the residue was dissolved in 4N hydrochloric acid in dioxan (4ml). After 4 hours methanol (13ml) was added and the reaction was left to stand for a further 18 hours. The solvent was then removed *in vacuo* and the residue was separated between dichloromethane and saturated sodium bicarbonate solution. The organic phase was evaporated *in vacuo* and the residue was applied to an SPE (10g, silica). The product was eluted using an ethyl acetate: methanol gradient (3:1 to 1:3) to afford (2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide (51mg).

HPLC Rt=3.36 minutes, m/z $[M+H]^+ = 488$

^1H NMR (D_6-DMSO) δ 8.47 (d, 1H), 8.07 (d, 1H), 7.71 (m, 1H), 7.69 (d, 1H), 7.38 (dd, 1H), 7.21 (m, 2H), 7.12 (m, 2H), 7.03 (m, 1H), 6.47 (s, 1H), 3.88 (m, 1H), 3.69 (dd, 1H), 3.07-2.67 (m, 5H), 2.87 (s, 3H), 2.77 (s, 3H), 1.40-1.70 (m, 2H), 0.46 (m, 1H), 0.42 (d, 3H), 0.02 (d, 3H)

Example 141

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide

(2RS)-2-(2-methyl-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide

A mixture of 2-methyl-5-formylbenzofuran (1.26g), (D)-leucine methyl ester hydrochloride (1.57g), triethylamine (1.2ml) and methanol (20ml) was stirred at room temperature for 6 hours and then left to stand for 19 hours. N-benzylcarbonyl-(D)-indanylglycine (2.80g) and 2-benzyloxy-phenylisocyanide (1.89g) were then added sequentially and the mixture stirred for 2 days. The reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate. This was washed with 1N hydrochloric acid, saturated sodium bicarbonate solution and brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was diluted with ethyl acetate (100ml) and acetic acid (10ml) and hydrogenated at atmospheric pressure over 10% palladium on activated carbon (1.5g). After 4 hours the catalyst was removed by filtration through a pad of celite and washed with dichloromethane/methanol (500ml of 1:1 v/v). The filtrate and washings were combined, evaporated under reduced pressure. The residue was separated between ethyl acetate and water. The organic phase was washed with water, saturated sodium bicarbonate solution and brine. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was applied to a silica cartridge (100g) and eluted with cyclohexane/ethyl acetate (500ml of 3:1, 2:1, 1:1 v/v) and ethyl acetate (500ml). The required fractions were combined and evaporated

in vacuo to give (2RS)-2-(2-methylbenzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (1.58g).
HPLC Rt = 3.60 minutes; m/z $[M+H]^+$ = 566.

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide

Carbonyldiimidazole (92mg, 1.6 equiv.) was suspended in anhydrous dichloromethane (5mL) and the suspension was left at room temperature for 15 minutes. (2RS)-2-(2-mrthylbenzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (200mg) was then added and the mixture was stirred at room temperature for 5 hours. The resulting brown solution was then treated with a 2.0M solution of dimethylamine in tetrahydrofuran (1.06mL, 6 equiv.) and the resulting mixture was stirred for 30 minutes and then left to stand at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane (2mL) and washed with 1M hydrochloric acid (2mL). The organic phase was separated using a hydrophobic frit and was evaporated under reduced pressure to leave a brown gum. The crude product was applied to a silica cartridge (10g). This was eluted with cyclohexane (100ml), cyclohexane/ethyl acetate (100ml of 2:1, 3:2, 1:1, 2:3 and 1:2 v/v), ethyl acetate (200ml) and ethyl acetate/methanol (100ml of 19:1 v/v). The required fractions were combined and evaporated *in vacuo* to give (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]- N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide as an off-white solid (88mg).
HPLC Rt = 3.40 minutes; m/z $[M+H]^+$ = 502.
^{1}H NMR ($CDCl_3$) δ 7.52 (d, 1H), 7.43 (d, 1H), 7.27-7.13 (m, 5H), 6.54 (s, 1H), 6.38 (m, 1H), 6.31 (d, 1H), 4.24 (m, 1H), 3.99 (dd, 1H), 3.22-3.05 (m, 3H), 2.99 (s, 3H), 2.86 (m, 1H), 2.82 (s, 3H), 2.75 (m, 1H), 2.48 (m, 3H), 1.45 (m, 1H), 1.36 (m, 1H), 0.57 (m, 1H), 0.51 (d, 3H), 0.19 (d, 3H).

Similarly prepared: -

Example 142
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]- N-isopropyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide
HPLC Rt = 3.40 minutes; m/z $[M+H]^+$ = 516.
^{1}H NMR ($CDCl_3$) δ 7.57 (m, 1H), 7.41 (d, 1H), 7.28-7.11 (m, 5H), 6.61 (m, 1H), 6.37 (m, 1H), 5.49 (d, 1H), 5.23 (s, 1H), 4.11 (m, 1H), 4.02-3.93 (m, 2H), 3.19-3.05 (m, 3H), 2.92 (m, 1H), 2.77 (m, 1H), 2.48 (m, 3H), 1.79 (m, 1H), 1.70 (m, 1H), 1.38 (m, 1H), 1.10 (m, 6H), 0.78 (d, 3H), 0.69 (d, 3H).

Example 143

(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]piperazin-2,5-dione

HPLC Rt = 3.38 minutes; m/z $[M+H]^+$ = 544.

^{1}H NMR ($CDCl_3$) δ 7.51 (d, 1H), 7.45 (d, 1H), 7.26-7.14 (m, 5H), 6.57 (s, 1H), 6.39 (m, 1H), 6.34 (m, 1H), 4.20 (m, 1H), 3.99 (m, 1H), 3.73-3.33 (6H), 3.22-3.03 (m, 5H), 2.88 (m, 1H), 2.75 (m, 1H), 2.49 (m, 3H), 1.45 (m, 1H), 1.37 (m, 1H), 0.54 (m, 1H), 0.51 (d, 3H), 0.20 (d, 3H).

Example 144

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N,N-dimethylethanamide

HPLC Rt = 3.39 minutes; m/z $[M+H]^+$ = 505.

^{1}H NMR ($CDCl_3$) δ 7.56 (d, 1H), 7.45 (d, 1H), 7.32 (dd, 1H), 7.23 (m, 2H), 7.16 (m, 2H), 6.55 (s, 1H), 6.23 (d, 1H), 5.89 (d, 1H), 4.22 (m, 1H), 3.99 (dd, 1H), 3.21-3.04 (m, 3H), 3.00 (s, 3H), 2.87 (m, 1H), 2.84 (s, 3H), 2.75 (m, 1H), 1.47 (m, 1H), 1.38 (m, 1H), 0.58-0.49 (m, 4H), 0.22 (d, 3H).

5-Bromo-2-fluoro-1-benzofuran

5-Bromobenzofuran-2-carboxylic acid (4.68g) was suspended in carbon tetrachloride (150ml) and water (50ml). To this was added sodium bicarbonate (3.36g), followed by Selectflor (7.1g) and the reaction mixture was stirred rapidly for 20 hours. The reaction mixture was diluted with dichloromethane and 2N sodium hydroxide solution. The organic phase was separated, washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure at room temperature. The residue was applied to a silica cartridge (20g) and eluted with diethyl ether. This gave 5-bromo-2-fluoro-1-benzofuran (1.4g).

^{1}H NMR ($CDCl_3$) δ 7.61 (d, 1H), 7.36 (dd, 1H), 7.26 (d, 1H), 5.84 (dd, 1H).

2-Fluoro-5-formyl-1-benzofuran

A slurry of magnesium powder (219mg) and iodine (cat) in dry tetrahydrofuran (3ml) was heated at 50°C under nitrogen for 20 minutes. 5-Bromo-2-fluoro-1-benzofuran (1.4g) was dissolved in dry tetrahydrofuran (6ml). A 1ml portion of the solution was added to the slurry at 50°C without stirring. After 30 minutes the rest of the solution was added slowly and the reaction was heated at reflux for 3 hours. The reaction was cooled in an ice/water bath and dimethylformamide (1ml) was added dropwise maintaining the temperature below 10°C. After 1 hour a mixture of 2N hydrochloric acid (12.5ml) and brine (12.5ml) was added. The reaction mixture was extracted using ethyl acetate (3x25ml). The combined organics were washed with brine and dried over anhydrous magnesium sulphate. The solvent was removed in vacuo and the residue applied to a silica cartridge (50g). This was eluted with cyclohexane, cyclohexane/ethyl acetate (6:1, 5:1 v/v). This gave 2-fluoro-5-formyl-1-benzofuran (376mg).

^{1}H NMR ($CDCl_3$) δ 10.05 (s, 1H), 8.04 (m, 1H), 7.83 (dd, 1H), 7.54 (d, 1H), 6.01 (dd, 1H).

Example 145

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N-isopropylethanamide

HPLC Rt = 3.42 minutes; m/z $[M+H]^+$ = 520.

^{1}H NMR ($CDCl_3$) δ 7.61 (d, 1H), 7.42 (d, 1H), 7.31 (dd, 1H), 7.21 (m, 2H), 7.16 (m, 2H), 6.70 (d, 1H), 5.89 (d, 1H), 5.57 (d, 1H), 5.18 (s, 1H), 4.11 (m, 1H), 3.98 (m, 2H), 3.16 (m, 1H), 3.08 (m, 2H), 2.91 (m, 1H), 2.78 (m, 1H), 1.82 (m, 1H), 1.73 (m, 1H), 1.41 (m, 1H), 1.12 (d, 3H), 1.10 (d, 3H), 0.81 (d, 3H), 0.72 (d, 3H).

Example 146

(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-fluoro-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]-6-isobutylpiperazine-2,5-dione

HPLC Rt = 3.35 minutes; m/z $[M+H]^+$ = 548.

^{1}H NMR ($CDCl_3$) δ 7.55 (d, 1H), 7.47 (d, 1H), 7.31 (dd, 1H), 7.27-7.14 (m, 4H), 6.58 (s, 1H), 6.38 (d, 1H), 5.91 (d, 1H), 4.19 (m, 1H), 4.00 (dd, 1H), 3.73-3.50 (m, 5H), 3.39 (m, 1H), 3.23-3.04 (m, 5H), 2.87 (m, 1H), 2.76 (m, 1H), 1.47 (m, 1H), 1.40 (m, 1H), 0.53 (d, 3H), 0.51 (m, 1H), 0.24 (d, 3H).

Example 147

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N,N-dimethylethanamide

HPLC Rt = 3.38 minutes; m/z $[M+H]^+$ = 487.

^{1}H NMR ($CDCl_3$) δ 9.03 (s, 1H), 7.66 (d, 1H), 7.49 (d, 1H), 7.30 (m, 1H), 7.21 (m, 1H), 7.18-7.10 (m, 4H), 7.02 (m, 1H), 6.57 (s, 1H), 6.55 (m, 1H), 4.29 (m, 1H), 4.00 (dd, 1H), 3.22-3.03 (m, 3H), 3.00 (s, 3H), 2.92-2.73 (m, 5H), 1.40 (m, 1H), 1.33 (m, 1H), 0.57 (m, 1H), 0.45 (d, 3H), 0.06 (d, 3H).

Example 148

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N-methyl-N-[2-(methylsulphonyl)ethyl]ethanamide

HPLC Rt = 3.20 minutes; m/z $[M+H]^+$ = 579.

^{1}H NMR ($CDCl_3$) δ 9.62 (s, 1H), 7.64 (d, 1H), 7.41 (d, 1H), 7.30 (m, 1H), 7.26-7.10 (m, 6H), 6.51 (m, 1H), 6.48 (s, 1H), 4.18 (m, 1H), 4.05-3.90 (m, 2H), 3.68-3.50 (m, 2H), 3.28-3.01 (m, 4H), 2.96-2.69 (m, 8H), 1.41 (m, 2H), 0.65 (m, 1H), 0.47 (d, 3H), -0.10 (d, 3H).

Example 149

(2R)-2-(1-benzothien-5-yl) -2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

(2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide

A mixture of 5-formylbenzothiophene (2.0g), (D)-leucine methyl ester hydrochloride (2.24g), triethylamine (1.72ml) and methanol (20ml) was stirred at room temperature for 24 hours. N-*tert*-butoxycarbonyl-(D)-indanylglycine (3.59g) and 2-benzyloxy-phenylisocyanide (2.58g) were then added sequentially and the mixture stirred for 4 days. Then the solvent was removed under reduced pressure. The residue was taken up in dichloromethane (20ml) and 4M hydrogen chloride in 1,4-dioxane (20ml) and the mixture was stirred at room temperature for 2 hours. The solvent and hydrogen chloride were evaporated under reduced pressure. The crude material was dissolved in dichloromethane (30ml) and triethylamine (10ml) added. The mixture was stirred for 18 hours before the dichloromethane and excess of triethylamine were removed under reduced pressure. The crude product was dissolved in dichloromethane (100ml) and washed with 1N hydrochloric acid (2x100ml) and brine. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo* to yield (2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide as a brown foam (7.5g).
HPLC Rt = 3.88 minutes, m/z $[M+H]^+$ = 658.

(2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide

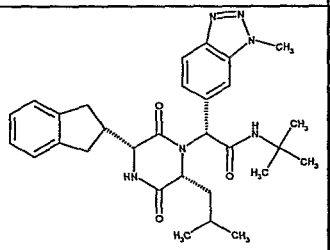
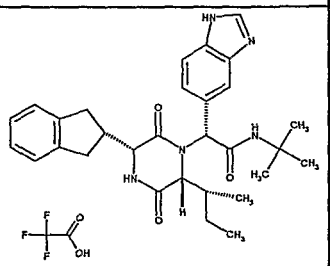
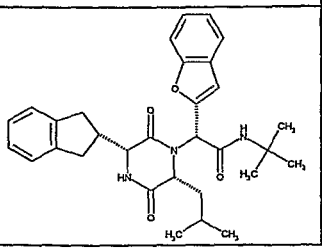
(2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide (1.0g) was dissolved in dichloromethane (5ml) and to this was added dropwise a 1.0M solution of BBr_3 in dichloromethane (2.0ml). The reaction mixture was stirred at room temperature for 2 hours. To the reaction mixture was added 1N hydrochloric acid (30ml) and dichloromethane (20ml). The phases were separated and the organic phase was washed with 1N hydrochloric acid (30ml) and brine (30ml). The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by Biotage™ flash column chromatography, eluting with 3:2 ethyl acetate:cyclohexane. The required fractions were combined and evaporated *in vacuo* to give (2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (210mg).

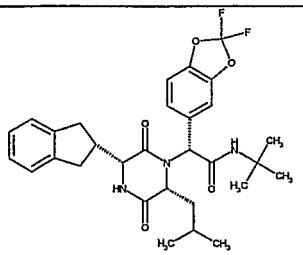
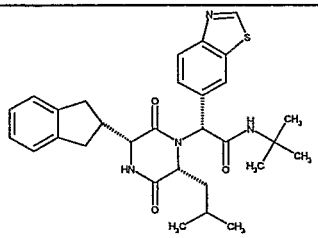
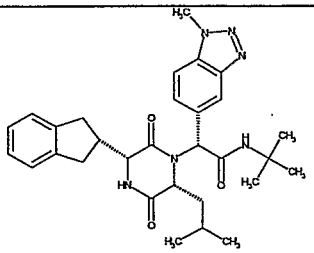
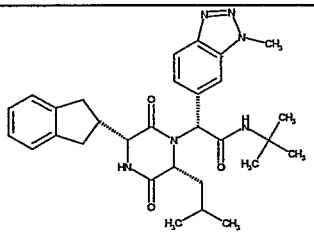
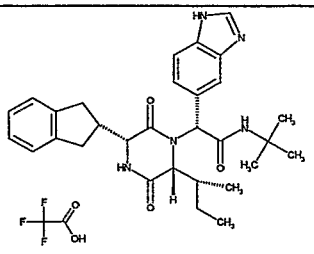
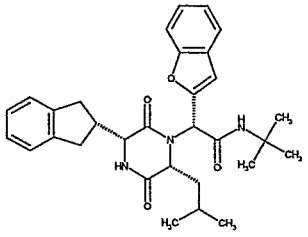
HPLC Rt = 3.55 minutes, m/z $[M+H]^+$ = 568.

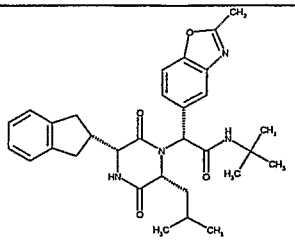
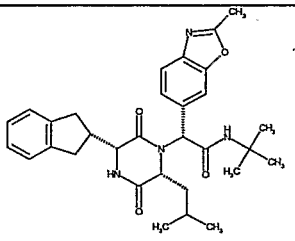
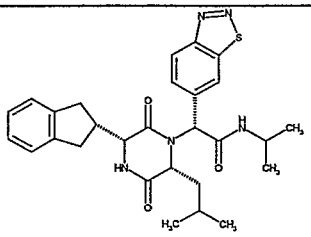
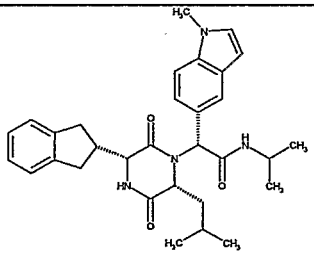
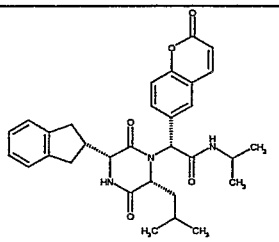
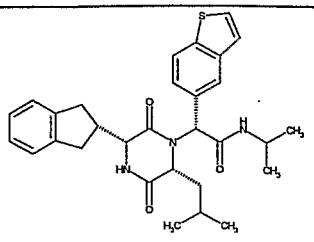
(2R)-2-(1-benzothien-5-yl) -2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

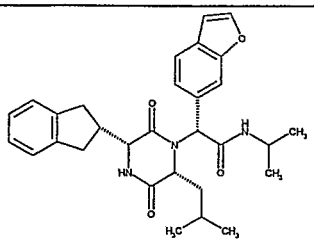
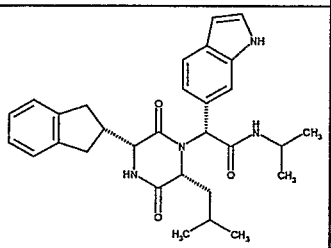
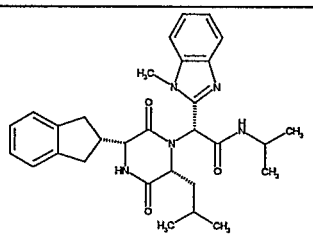
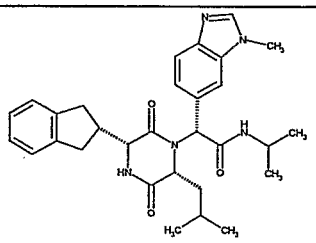
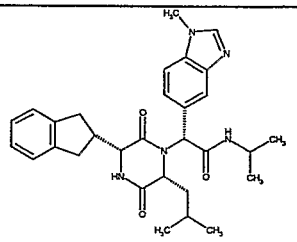
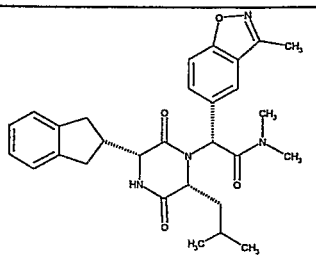
Carbonyldiimidazole (100mg) was suspended in anhydrous dichloromethane (1mL) and the suspension was left at room temperature for 15 minutes. 2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (200mg) was then added and the mixture was stirred at room temperature for 5 hours 20 minutes. The resulting brown solution was then treated with a 2.0M solution of dimethylamine in tetrahydrofuran (1.0mL, 6 equiv.) and the resulting mixture was stirred for 30 minutes and then left to stand at room temperature for 18 hours 15 minutes. The reaction mixture was evaporated under reduced pressure. The crude product was purified by silica column chromatography eluting with 1:1v/v ethyl acetate:cyclohexane. The required fractions were combined and evaporated *in vacuo* to give (2R)-2-(benzothien-5-yl) -2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide as a white solid (90mg).
HPLC Rt = 3.35 minutes, m/z $[M+H]^+ = 504$.
^1H NMR ($CDCl_3$) δ 7.94 (d, 1H), 7.89 (m, 1H), 7.70 (d, 1H), 7.54 (d, 1H), 7.41 (m, 1H), 7.35 (d, 1H), 7.23 (m, 1H), 7.13 (m, 3H), 6.63 (s, 1H), 4.25 (m, 1H), 4.02 (dd, 1H), 3.23-3.04 (m, 3H), 3.01 (s, 3H), 2.93-2.77 (m, 5H), 1.50-1.32 (m, 2H), 0.52 (m, 1H), 0.49 (d, 3H), 0.12 (d, 3H).

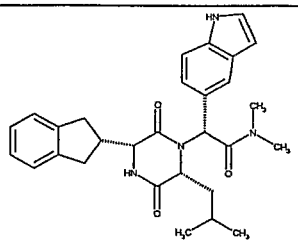
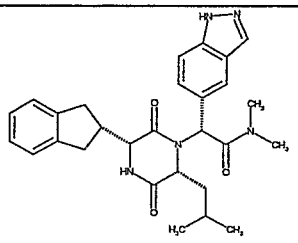
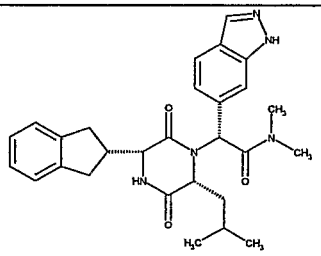
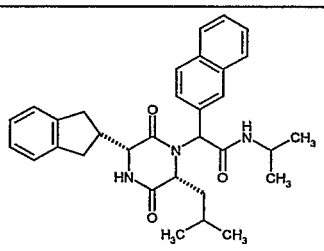
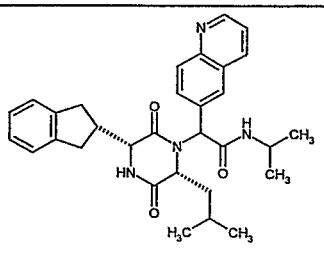
Compounds 150-169 and 174-175 were prepared via method 1. Compound 170 was prepared via method 2. Compounds 171, 172 and 173 were prepared via method 5.

No.	Regno	MWt	Rt/min	MH+	MH-	Name
150		517.7	3.62	518	516	(2R)-N-(tert-butyl)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
151		516.6	3.12	517	515	2-(1H-1,2,3-benzotriazol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]acetamide
152		533.7	3.42	534		(2R)-N-(tert-butyl)-2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide

153		555.6	3.71	556	554	(2R)-N-(tert-butyl)-2-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
154		532.7	3.32	533	531	(2R)-2-(1,3-benzothiazol-6-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
155		530.7	3.18	531	529	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1-methyl-1H-1,2,3-benzotriazol-5-yl)ethanamide
156		530.7	3.22	531	529	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1-methyl-1H-1,2,3-benzotriazol-6-yl)ethanamide
157		629.7	3.06		514	(2R)-2-(1H-benzimidazol-5-yl)-N-(tert-butyl)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl}ethanamide trifluoroacetate
158		515.7	3.72	516	514	(2R)-2-(1-benzofuran-2-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide

159		530.7	3.3	531	529	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-methyl-1,3-benzoxazol-5-yl)ethanamide
160		530.7	3.35	531	529	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-methyl-1,3-benzoxazol-6-yl)ethanamide
161		519.7	3.37	520	518	(2R)-2-(1,2,3-benzothiadiazol-6-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
162		514.7	3.41	515		(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-indol-5-yl)ethanamide
163		529.6				(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(2-oxo-2H-chromen-6-yl)ethanamide
164		517.7	3.53	518	516	(2R)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide

165		501.6	3.42	502	500	(2R)-2-(1-benzofuran-6-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
166		500.6	3.35	501	499	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N-isopropylethanamide
167		515.7	4.88	516	514	2R-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-benzimidazol-2-yl)acetamide
168		515.7	4.32	516	514	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-benzimidazol-6-yl)ethanamide
169		515.7	2.65	516	514	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-benzimidazol-5-yl)ethanamide
170		502.6	3.35	503	501	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(3-methyl-1,2-benzisoxazol-5-yl)ethanamide

171		486.6	3.07	487	485	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-5-yl)-N,N-dimethylethanamide
172		487.6	2.94	488		(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indazol-5-yl)-N,N-dimethylethanamide
173		487.6	2.99	488	486	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indazol-6-yl)-N,N-dimethylethanamide
174		511.7	3.56	512		(2R,S)-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(2-naphthyl)acetamide
175		512.7	3.19	513		(2R,S)-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-quinolin-6-ylacetamide

Example 176

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide

To a solution of 5-trifluoromethyl-furan-2-carbaldehyde (140mg)[prepared as in ref. Chem. Heterocycl. Compd. 13, *1977,* 1280-1282 by R.V.Grigorash, V.V.Lyalin, L.A.Alekseeva and L.M.Yagupol'skii: 5-Trifluoromethylfuran Derivatives] in methanol

(1.1ml) was added triethylamine (118 μl) and (D)-leucine t-butyl ester hydrochloride (190mg). The mixture was left to stand for 16.33 hours before (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (246mg) and isopropylisocyanide (77.4μl) were sequentially added. The mixture, a yellow solution, was left to stand for 24 hours before the solvent was removed *in vacuo*. The residue was dissolved in 4M hydrogen chloride in dioxane (3ml) and left to stand for 6.75 hours at ambient temperature. After this time, the solvent was removed *in vacuo*. The residue was dissolved in methanol (4ml) and treated with a solution of 4M hydrogen chloride in dioxane (0.2ml) and was left to stand overnight. After this time, the solvent was removed *in vacuo*. The residue was stirred in dioxane (9.5ml) containing triethylamine (0.5ml) and dichloromethane (5ml) for 4.75 hours. Then the mixture was evaporated *in vacuo* to leave a light brown solid. This crude material was purified by SPE column (10g, silica Mega Bond Elut™) eluting stepwise with 100% chloroform, 4:1 cyclohexane : diethyl ether, 3:1 cyclohexane : diethyl ether, 2:1 cyclohexane : diethyl ether, 1:1 cyclohexane : diethyl ether, 1:2 cyclohexane : diethyl ether, 1:3 cyclohexane : diethyl ether, 100% diethyl ether, 1:1 ethyl acetate : cyclohexane, 2:1 ethyl acetate : cyclohexane, 3:1 ethyl acetate : cyclohexane, 100% ethyl acetate. The 1:2 cyclohexane : diethyl ether to 2:1 ethyl acetate : cyclohexane fractions inclusive were combined to give an orange gum (215mg). The gum was purified further, to separate the isomers, by preparative plate chromatography. Whatman PK6F silicagel 60 plates 20 × 20 cm^2, eluted in 1:1 ethyl acetate : cyclohexane six times and extracted with 9:1 ethyl acetate : methanol to give (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide (64mg),
HPLC Rt = 3.59 minutes; m/z $[M+H]^+$ = 520.
^1H NMR ($CDCl_3$) δ 7.88 (d, 1H), 7.16 (m, 4H), 6.85 (d, 1H), 6.74 (d,1H), 6.30 (d,1H), 5.73 (s, H), 4.19 (dd, 1H), 4.08 (m, 1H), 3.97 (dd, 1H), 3.14 (m, 2H), 3.01 (m, 1H), 2.84 (m, 2H), 1.81 (m, 1H), 1.68 (m, 1H), 1.15 (d, 6H), 1.11 (m, 1H), 0.82 (dd, 6H).

Similarly prepared

Example 177

(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-methylthien-2-yl)ethanamide

By the procedure of Example 176 but using 5-methyl-thiophene-2-carbaldehyde
HPLC Rt = 3.46 minutes; m/z $[M+H]^+$ = 482.
^1H NMR ($CDCl_3$) δ 7.21 (m, 2H), 7.16 (m, 2H), 6.94 (d, 1H), 6.67 (d, 1H), 6.63 (d, 1H), 5.73 (d, 1H), 4.94 (s, 1H), 4.07 (m, 1H), 3.93 (m, 2H), 3.16 (dd, 1H), 3.05 (m, 2H), 2.93 (m, 1H), 2.77 (m, 1H), 2.47 (s, 3H), 1.96 (m, 1H), 1.86 (m, 1H), 1.72 (m, 1H), 1.17 (d, 3H), 1.12 (d, 3H), 0.94 (d, 3H), 0.92 (d, 3H)

Example 178

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide

N-[2-(benzyloxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[5-(trifluoromethyl)-2-furyl]acetamide

A mixture of 5-trifluoromethyl-furan-2-carbaldehyde (351mg), (D)-leucine methyl ester hydrochloride (389mg), triethylamine (0.298ml) and methanol (2.2ml) was stirred at room temperature for 4 hours and then left to stand for 19 hours. N-*tert*-butoxycarbonyl-(D)-indanylglycine (623mg) and 2-benzyloxy-phenylisocyanide (448mg) were then added sequentially and the mixture stirred for 7 hours before being left to stand at room temperature for 41 hours. Then the solvent was removed under reduced pressure to leave an orange / brown syrup. This was taken up in 4M hydrogen chloride in 1,4-dioxane (2.8ml) and the mixture was stirred at room temperature for 2 hours. The solvent and hydrogen chloride were evaporated under reduced pressure. The crude material was dissolved in methanol (5ml) and triethylamine (0.54ml) added. The mixture was stirred for 18 hours before the methanol and excess of triethylamine were removed under reduced pressure. The crude product was purified by Biotage™ flash column chromatography (40g silica cartridge eluted with 1:5 ethyl acetate:cyclohexane (600ml), 1:3 ethyl acetate:cyclohexane (400ml) and 1:2 ethyl acetate:cyclohexane (450ml)) to yield N-[2-(benzyloxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[5-(trifluoromethyl)-2-furyl]acetamide as an orange solid (472mg).

HPLC Rt = 4.04 minutes, m/z $[M+H]^+$ = 660.

2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-[5-(trifluoromethyl)-2-furyl]acetamide

N-[2-(benzyloxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[5-(trifluoromethyl)-2-furyl]acetamide (469mg) was dissolved in ethyl acetate (10ml) and hydrogenated at atmospheric pressure over 10% palladium on activated carbon (100mg). After 4 hours the catalyst was removed by filtration through glass fibre filters and washed with ethyl acetate. The filtrate and washings were combined, evaporated under reduced pressure and dried *in vacuo* at room temperature to leave a yellow / brown solid (400mg). The solid was dried over P_2O_5 overnight to give 2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-[5-(trifluoromethyl)-2-furyl]acetamide (365mg).
HPLC Rt = 3.64 minutes, m/z $[M+H]^+$ = 570.

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide

Carbonyldiimidazole (78mg, 1.6 equiv.) was suspended in anhydrous dichloromethane (1mL) and the suspension was left at room temperature for 15 minutes. (R)-N-(2-Hydroxy-phenyl)-2-((3R,6R)-3-indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-2-(5-trifluoromethyl-furan-2-yl)-acetamide (172mg) was then added and the mixture was stirred at room temperature for 5 hours 20 minutes. The resulting brown solution was then treated with a 2.0M solution of dimethylamine in tetrahydrofuran (0.9mL, 6 equiv.)and the resulting mixture was stirred for 30 minutes and then left to stand at room temperature for 18 hours 15 minutes. The reaction mixture was diluted with dichloromethane (2mL) and washed with 1M hydrochloric acid (2mL). The organic phase was separated using a hydrophobic frit and was evaporated under reduced pressure to leave a brown gum. The crude product was applied to 3 preparative chromatography plates, which were eluted with 1:1v/v ethyl acetate:cyclohexane. The required band was extracted with ethyl acetate to give the (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide as a pale yellow solid (87mg).

HPLC Rt = 3.51 minutes, m/z $[M+H]^+$ = 506.

^{1}H NMR ($CDCl_3$) δ 7.19 (m, 5H), 6.86 (dd, 1H), 6.64 (d, 1H), 6.61 (s, 1H), 4.25 (m, 1H), 3.97 (dd, 1H), 3.20-3.02 (m, 3H), 3.01 (s, 3H), 2.96 (s, 3H), 2.88 (m, 1H), 2.80 (m, 1H), 1.70 (m, 1H), 1.67 (m, 1H), 0.74 (d, 3H), 0.70 (m, 1H), 0.63 (d, 3H).

Example 179

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide

By the procedure of Example 178, using (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-(2-methyl-1,3-oxazol-4-yl)ethanamide

HPLC: Rt = 2.88 minutes ; m/z $(M+H)^+$ = 453

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-(2-methyl-1,3-oxazol-4-yl)ethanamide

A mixture of 2-methyl-oxazole-4-carbaldehyde[(1)] (340mg), (D)-leucine methyl ester hydrochloride (568mg), triethylamine (0.435ml) and anhydrous methanol (20ml) was stirred at room temperature for 18 hours. N-benzyloxycarbonyl-(D)-indanylglycine (1.015g) and 2-benzyloxy-phenylisocyanide (648mg) were then added sequentially and the mixture stirred for 12 days before being left to stand at room temperature for 10 days. The solvent was removed under reduced pressure to leave a dark orange gum which was dissolved in ethyl acetate (150mL) and washed with 2M hydrochloric acid (100mL), saturated sodium bicarbonate solution (100mL) and saturated sodium chloride solution (50mL) then dried over anhydrous magnesium sulphate and concentrated under reduced pressure to a volume of 5mL. This crude solution was diluted with ethanol (80mL)

containing acetic acid (1.6mL) and added under vacuum to 10% palladium on carbon (50% water, 425mg). The resulting suspension was stirred under an atmosphere of hydrogen for 20 hours, filtered (celite filteraid) washed with ethanol (50mL) and the filtrate added under vacuum to a second quantity of 10% palladium on carbon (50% water, 670mg). The suspension was stirred under an atmosphere of hydrogen for 2 hours, the hydrogenation apparatus was then evacuated and refilled with hydrogen and the suspension stirred for a further 20 hours. The suspension was filtered (celite filteraid) washed with ethanol (200mL) and the combined filtrates concentrated under reduced pressure. The residue was partitioned between saturated sodium bicarbonate solution (100mL) and dichloromethane (60mL), then the organic layer dried (hydrophobic frit) and the solvent removed under reduced pressure. Purification by Biotage flash chromatography (40g silica) eluting with ethyl acetate : cyclohexane (3:1, 300mL) ethyl acetate (300mL) then ethyl acetate : methanol (20:1, 600mL) gave (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-(2-methyl-1,3-oxazol-4-yl)ethanamide as a brown foam (197mg).
HPLC : Rt = 3.28 minutes ; m/z $(M+H)^+$ = 517
Ref (1) CAS 113732-84-6

Example 180

(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-morpholin-4-yl-2-oxoethyl]piperazine-2,5-dione
By the procedure of Example 179, using morpholine
HPLC: Rt = 2.89 minutes ; m/z $(M+H)^+$ = 495

Example 181

(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(5-methylthien-2-yl)ethanamide
By the procedure of Example 180, using 5-methyl-thiophene -2-carbaldehyde
HPLC Rt = 3.25 minutes; m/z M^+ = 468.

Example 182

(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-5-methylthien-2-yl)-N,N-dimethylethanamide
By the procedure of Example 178, using 3-fluoro-5-methyl-thiophene-2-carbaldehyde
HPLC: Rt = 3.20 minutes ; m/z M^+ = 486

2-(3-Bromo-5-methyl-thiophen-2-yl)-[1,3]dioxane
3-Bromo-5-methyl-2-thiophenecarbaldehyde (1.00g) was dissolved in dry 1,4-dioxane (8ml). Molecular sieves (4 Angstrom, 2g), 1,3-propandiol (9ml), p-toluene sulphonic acid (362mg) were added and the mixture was stirred under a nitrogen atmosphere, at room temperature, over night. Molecular sieves were removed by filtration and the filtrate evaporated. The residue was taken up with ethyl acetate and washed with

saturated solution of sodium carbonate. The aqueous was extracted with more ethyl acetate and the combined layers washed with brine, dried over magnesium sulphate, filtrated and concentrated to a yellow oil (1g).

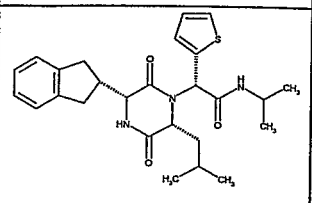
Purification was performed by filtration on a SPE cartridge (Silica-10g) using dichloromethane as eluent. The solution was eventually concentrated to yield 2-(3-bromo-5-methyl-thiophen-2-yl)-[1,3]dioxane as a yellow solid (1.18g).
^{1}H-NMR ($CDCl_3$, 400MHz): 6.60ppm (s, 1H); 5.72ppm (s, 1H); 4.23ppm (m, 2H); 3.98ppm (m, 2H); 2.44ppm (d, 3H); 2.22ppm (m, 1H); 1.42ppm (m, 1H).

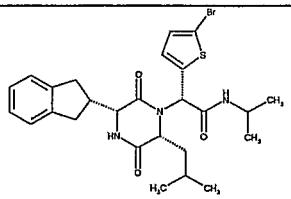
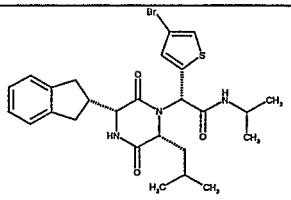
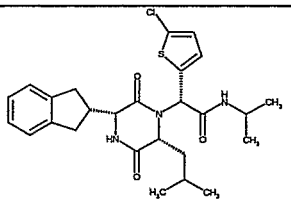
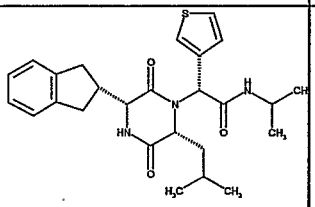
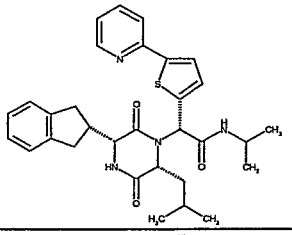
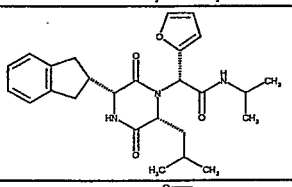
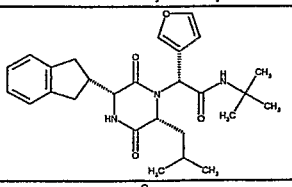
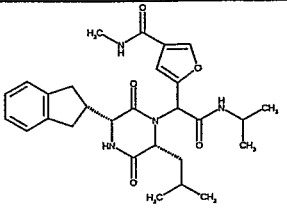
3-Fluoro-5-methyl-thiophene-2-carbaldehyde

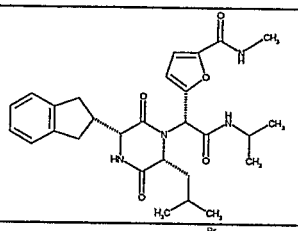
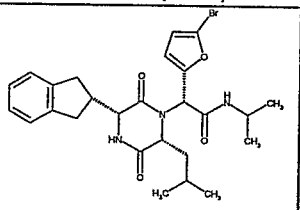
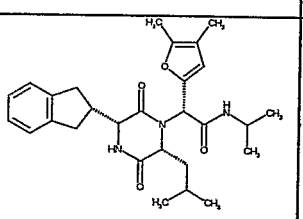
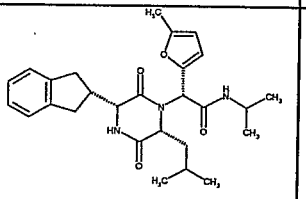
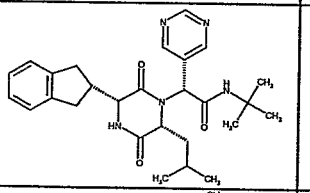
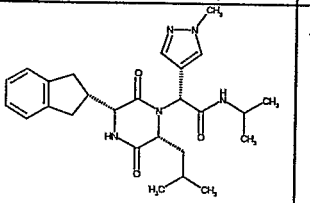
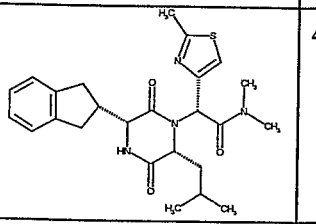
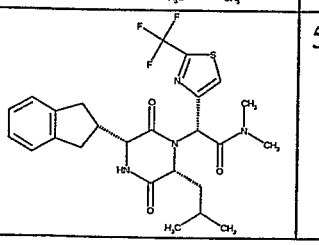
To a solution of 2-(3-bromo-5-methyl-thiophen-2-yl)-[1,3]dioxane (1.16g) in dry tetrahydrofuran (10ml), under a nitrogen atmosphere, at –78 °C, 1.6M *n*-butyl lithium in hexane (3.30ml) was added dropwise. After 15 minutes stirring, N-fluoro-benzene-sulfonyl-imide (1.66g) was added portionwise. The solution was stirred at –78 °C for further 10 minutes, allowed to warm to room temperature and then stirred for a further 60 minutes. The reaction was quenched with water (5ml), diluted with diethyl ether (20ml) and washed with 1N sodium hydroxide (30ml). The aqueous was extracted with diethyl ether again (2x10ml), the combined organic layers were dried over magnesium sulphate, filtrated and evaporated. The residue was redissolved in 1,4-dioxane (15ml) and water (10), p-toluene sulphonic acid (837mg) was added and the solution was stirrer at room temperature, over night. Neutralised with a saturated solution of sodium bicarbonate (10ml), then extracted with ether twice. The organic was dried over magnesium sulphate and evaporated at reduced pressure (200mbar). The residual dioxane was removed by distillation at reduced pressure, the residue further purified by flash chromatography (petroleum ether / dichloromethane 55/45), giving 3-fluoro-5-methyl-thiophene-2-carbaldehyde as a colourless oil (366mg), approximately 70% pure.
^{1}H-NMR ($CDCl_3$, 400MHz): δ 9.93ppm (s, 1H); 6.62ppm (s, 1H); 2.52ppm (m, 3H).

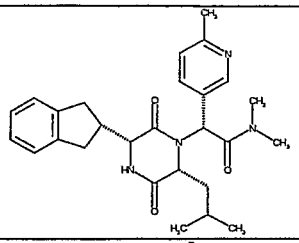
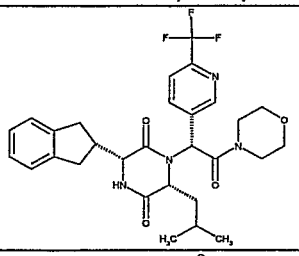
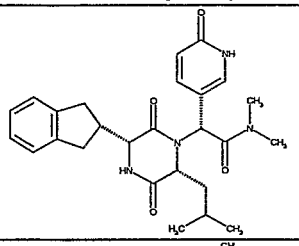
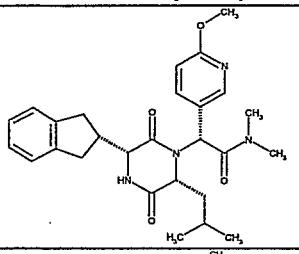
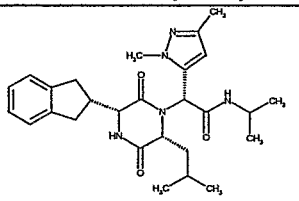
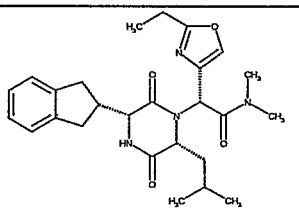
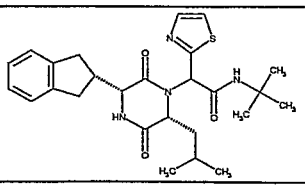
Similarly prepared:

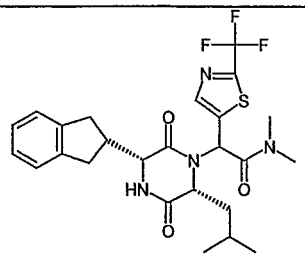
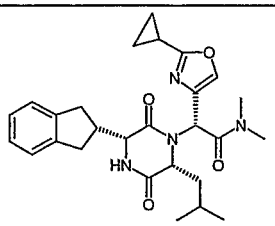
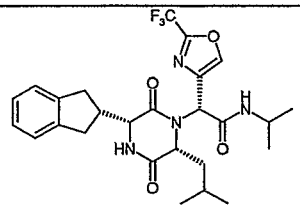
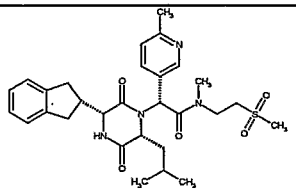
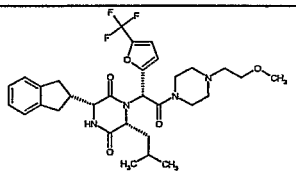
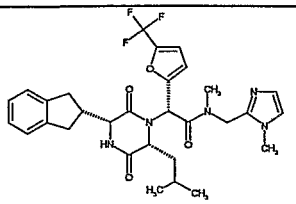
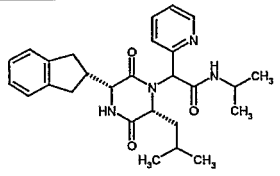
Compounds 183 -206,213,215,218,222-225 were prepared via method 1. Compounds 207,208,216, were prepared via method 2. Compounds 209-212, 214,217,219-221 and 226 were prepared via method 5.

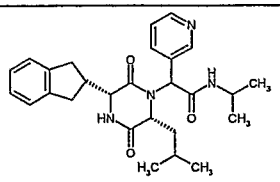
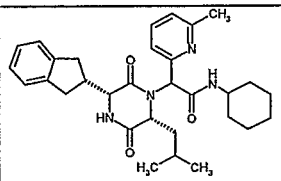
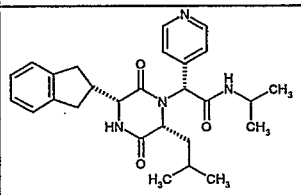
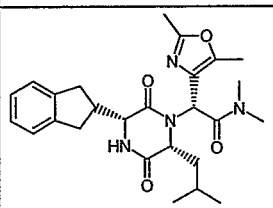
Eg No.	Structure	MWt	Rt /min	+ve ion	-ve ion	name
183		467.7	3.4	468	466	(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-thien-2-ylethanamide

184		546.6	3.6	546/548	546/544	(2S)-2-(5-bromothien-2-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
185		546.6	3.6	546/548	544/546	(2S)-2-(4-bromothien-2-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
186		502.1	3.6	501-3	499-501	(2S)-2-(5-chlorothien-2-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
187		467.7	3.3	468	466	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-thien-3-ylethanamide
188		544.8	3.4	545	543	(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-pyridin-2-ylthien-2-yl)ethanamide
189		451.6	3.3	452	450	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-furyl)-N-isopropylethanamide
190		465.7	3.4	466	464	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-furyl)ethanamide
200		508.7	2.9	509	507	5-[1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(isopropylamino)-2-oxoethyl]-N-methyl-3-furamide

201		508.7	3	509	507	5-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(isopropylamino)-2-oxoethyl]-N-methyl-2-furamide
202		530.5	3.5	529/531	527/529	(2R)-2-(5-bromo-2-furyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
203		479.7	3.5	480	478	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4,5-dimethyl-2-furyl)-N-isopropylethanamide
204		465.7	3.4	466	464	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-methyl-2-furyl)ethanamide
205		477.6	3.3	478	476	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-pyrimidin-5-ylethanamide
206		465.7	2.9	466	464	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-pyrazol-4-yl)ethanamide
207		468.7	3	469	none	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1,3-thiazol-4-yl)ethanamide
208		522.6	3.4	523	521	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[2-(trifluoromethyl)-1,3-thiazol-4-yl]ethanamide

209		462.7	3.1	463	none	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(6-methylpyridin-3-yl)ethanamide
210		558.7	3.3	559	557	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-{(1R)-2-morpholin-4-yl-2-oxo-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}piperazine-2,5-dione
211		464.6	2.7	465	463	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(6-oxo-1,6-dihydropyridin-3-yl)ethanamide
212		478.6	3.04	479.23	477.26	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(6-methoxypyridin-3-yl)-N,N-dimethylethanamide
213		479.6	3.03	480	478	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1,3-dimethyl-1H-pyrazol-5-yl)-N-isopropylethanamide
214		466.56	3.1	467	-	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-ethyl-1,3-oxazol-4-yl)-N,N-dimethylethanamide
215		482.6	3.58	483	481	N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1,3-thiazol-2-yl)acetamide

216		522.6	3.46	523	521	2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[2-(trifluoromethyl)-1,3-thiazol-5-yl]acetamide
217		478.6	3.07	479	477	(2R)-2-(2-cyclopropyl-1,3-oxazol-4-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
218		520.5	3.47	521	519	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[2-(trifluoromethyl)-1,3-oxazol-4-yl]ethanamide
219		554.7	2.8	555	553	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-2-(6-methylpyridin-3-yl)-N-[2-(methylsulfonyl)ethyl]ethanamide
220		604.7	2.7	605	603	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-{(1R)-2-[4-(2-methoxyethyl)piperazin-1-yl]-2-oxo-1-[5-(trifluoromethyl)-2-furyl]ethyl}piperazine-2,5-dione
221		585.6	2.8	586	584	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-[(1-methyl-1H-imidazol-2-yl)methyl]-2-[5-(trifluoromethyl)-2-furyl]ethanamide
222		462.6	3.29	463	461	2-((3R,6R)-3-Indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-N-isopropyl-2-pyridin-2-yl-acetamide

223		462.6	3.09	463	461	2-((3R,6R)-3-Indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-N-isopropyl-2-pyridin-3-yl-acetamide
224		516.7	3.41	517	515	N-Cyclohexyl-2-((3R,6R)-3-indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-2-(6-methyl-pyridin-2-yl)-acetamide
225		462.6	2.93	463	461	2-((3R,6R)-3-Indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-N-isopropyl-2-pyridin-4-yl-acetamide
226		466.6	3.06	467	-	(R)-2-(2,5-Dimethyl-oxazol-4-yl)-2-((3R,6R)-3-indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-N,N-dimethylacetamide

Example 227

(3R,6R)-1-[(1R)-1-(2,4-Difluorophenyl)-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione

The azetidinol (Example 15) (57 mg) in anhydrous dichloromethane (2 mL) was stirred at –5°C and diethylaminosulfur trifluoride (50 μL, excess) was added in one portion. The mixture was left at room temperature overnight and saturated aqueous sodium hydrogen carbonate (3 mL) was added. The mixture was diluted with dichloromethane (10 mL) and the organic phase was separated using a hydrophobic frit and blown down with nitrogen. The crude reaction mixture was purified using the mass-directed autoprep system to give (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione (26 mg) as a white solid.

HPLC Rt = 3.34 minutes, m/z $[M+H]^+$ = 514

PharmcyExamples

Tablets

a)	Compound of the invention	50.0mg
	Lactose	70.0mg
	Microcrystalline Cellulose	70.0mg
	Cross-linked polyvinylpyrrolidone	8.0mg
	Magnesium Stearate	2.0mg
	Compression weight	200.0mg

The compound of the invention, microcrystalline cellulose, lactose and cross-linked polyvinylpyrrolidone are sieved through a 500 micron sieve and blended in a suitable mixer. The magnesium stearate is sieved through a 250 micron sieve and blended with the active blend. The blend is compressed into tablets using suitable punches.

b)	Compound of the invention	50.0mg
	Lactose	120.0mg
	Pregelatinised Starch	20.0mg
	Cross-linked polyvinylpyrrolidone	8.0mg
	Magnesium Stearate	2.0mg
	Compression weight	200.0mg

The compound of the invention, lactose and pregelatinised starch are blended together and granulated with water. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granule. The resultant blend is compressed using suitable tablet punches.

Capsules

a)	Compound of the invention	50.0mg
	Lactose	148.0mg
	Magnesium Stearate	2.0mg
	Fill weight	200.0mg

The compound of the invention and pregelatinised starch are screened through a 500 micron mesh sieve, blended together and lubricated with magnesium stearate, (meshed through a 250 micron sieve). The blend is filled into hard gelatine capsules of a suitable size.

b)	Compound of the invention	50.0mg
	Lactose	132.0mg
	Polyvinylpyrrolidone	8.0mg
	Cross-linked polyvinylpyrrolidone	8.0mg

Magnesium Stearate	2.0mg
Fill weight	200.0mg

The compound of the invention and lactose are blended together and granulated with a solution of polyvinylpyrrolidone. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granules. The resultant blend is filled into hard gelatine capsules of a suitable size.

Injection Formulation

	% w/v
Compound of the invention	0.10
Water for injections B.P. to	100.00

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability and/or to facilitate solution of the compound of the invention using dilute acid or alkali or by the addition of suitable buffer salts. Solubilisers, such as cosolvents, may also be added to facilitate solution of the compound of the invention. Antioxidants and metal chelating salts may also be included. The solution is clarified, made up to final volume with water and the pH remeasured and adjusted if necessary, to provide 1mg/ml of the compound of formula (I).

The solution may be packaged for injection, for example by filling and sealing in ampoules, vials or syringes. The ampoules, vials or syringes may be aseptically filled (e.g. the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions) and/or terminally sterilised (e.g. by heating in an autoclave using one of the acceptable cycles). The solution may be packed under an inert atmosphere of nitrogen.

Preferably the solution is filled into ampoules, sealed by fusion of the glass and terminally sterilised.

Further sterile formulations are prepared in a similar manner containing 0.05, 0.20 and 0.5% w/v of the compound of the invention, so as to provide respectively 0.5, 2 and 5mg/ml of the compound of the invention.

Measurement of Oxytocin Antagonist Activity

Assay Buffer used throughout the assay: 50mM HEPES, 10mM MgCl2, 0.125mg/ml BSA, pH adjusted to 7.4 with KOH.

hOT-CHO membranes were prepared at a concentration of 0.3mg protein/ml in assay buffer. Test compounds were initially dissolved in DMSO (to 10mM) and diluted in DMSO (Beckman Biomek FX). 1μl of compound was transferred to black 384 assay plates (NUNC) using a Biomek FX. 20μl of 1nM Bodipy TMR Oxytocin (Perkin Elmer) in assay buffer was added to all wells (Labsystems Multidrop) then 20μl membrane added to all wells (Multidrop). Plates were incubated at room temp for 60 min.

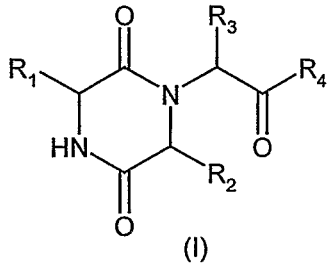
Polarisation was read on LJL Analyst (λEx=535nm, λEm=580nM, λDichroic=555nm). Data were fitted to a 4 parameter logistic equation. An estimated Ki was calculated as IC50/5.

In the above test compounds of the invention in general have a pKi value within the range of 7 to 11 . Thus the compounds of examples 1 to 227 have a pKi within the range 8.5 to 10.8.

The compounds of the invention are essentially non toxic at therapuetically active doses. Thus compound of the example 10 has been administered to rats at doses of up to 300mg/kg p.o for 4 days. and no adverse toxicological effects were observed.

Claims

1. A method of treating or preventing diseases or conditions mediated through the action of oxytocin which comprises administering to a mammal in need thereof of an effective amount of a compound of the formula (I)



(I)

and/or a physiologically acceptable derivative thereof, wherein:

R_1 represents aryl (C_{1-4}) alkyl or a 5-7 membered cycloalkyl group optionally substituted with one or more hydroxyl groups which is fused to an optionally substituted benzene ring;

R_2 represents C_{1-6}alkyl (optionally substituted by a C_{1-2}alkoxy, C_{1-2}alklthio, di(C_{1-2}alkyl) amino or a C_{3-6} cycloalkyl group) or C_{3-6}cycloalkyl, or 5-6 membered heterocyclic group containing a single hetero atom selected from O, S or N, which nitrogen atom carries a hydrogen atom or a methyl or ethyl group;

R_3 represents optionally substituted phenyl, a 5 or 6 membered hetero aryl group or a fused bicyclic ring system containing 9-10 ring members which may be a carbocyclic group or it may contain up to 3 heteroatoms selected from O, S or N and one of the fused rings is benzene;

R_4 represents OH or OC_{1-4} alkyl (optionally substituted with C_{1-4}alkylcarbonyloxy) or NR_5R_6;

R_5 represents hydrogen, C_{1-6}alkyl (optionally substituted with C_{1-4}alkoxy) or C_{3-7}cycloalkyl;

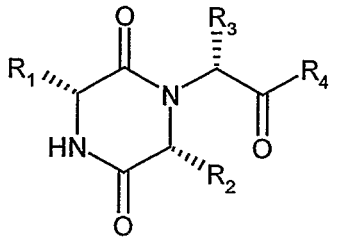
R_6 represents hydrogen, methyl, C_{1-4}alkoxy, C_{3-7}cycloalkyl, C_{2-4}alkyl [optionally substituted with one or more groups selected from: carboxyl, C_{1-4}alkylsulphonyl, or C_{1-4}alkoxycarbonyl], C_{2-4}alkyl [optionally substituted with one or more groups selected from halogen, hydroxy, C_{1-4}alkoxy or NR_7R_8 wherein R_7 and R_8 independently represent hydrogen or C_{1-4}alkyl or together with the nitrogen atom to which they are attached to form a 3-7 membered saturated heterocyclic ring which may contain an additional heteroatom selected from O, S or N (and which heterocyclic group may be substituted by 1 to 3 groups selected from C_{1-3}alkyl, hydroxy, C_{1-3} alkoxy (optionally substituted by C_{3-6} cycloalkyl or optionally subtituted phenyl), C_{3-6}cycloalkyl or NR_cR_d wherein R_c and R_d each independently represent a group selected from C_{1-3}alkyl (optionally substituted by C_{3-6} cycloalkyl or optionally substituted phenyl) or C_{3-6} cycloalkyl)] or R_6 represents a phenyl or benzyl group (optionally substituted by one or more methoxy or benzyloxy groups) or an optionally substituted heteroarylmethyl group or a heteroaryl group or C_{3-7}

cycloalkyl or the group $CH_2CONR_9R_{10}$ wherein R_9 represents hydrogen or C_{1-4}alkyl, R_{10} represents hydrogen, C_{1-4}alkyl optionally substituted by a 5 or 6 membered heteroaryl group or R_9, R_{10} and the nitrogen atom to which they are attached together form a 5 or 6 membered saturated heterocyclic ring and wherein the 6 membered heterocyclic group may contain an additional heteroatom selected from oxygen, sulphur or nitrogen and the additional nitrogen atom either carries a hydrogen atom or a C_{1-4}alkyl or C_{1-4}alkanoyl group; or R_5 and R_6 together with the nitrogen atom to which they are attached form a 3 to 7 membered saturated heterocyclic ring which heterocycle may contain an additional heteroatom selected from oxygen, sulphur and nitrogen and wherein the sulphur atom may be in an oxidised form e.g. SO_2 and the additional nitrogen atom either carries a hydrogen atom or a C_{1-4}alkyl or a C_{1-4}alkanoyl group or a C_{1-4}alkylsulphonyl group or a C_{1-3} alkoxyC_{2-4} alkyl [and which heterocyclic groups may be substituted by one or more halogen atoms or a group selected from C_{1-3}alkyl, hydroxy, oxo, C_{3-6}cycloalkyl or NR_eR_f wherein R_e and R_f each independently represent a group selected from C_{1-3}alkyl (optionally substituted by C_{3-6} cycloalkyl or optionally substituted phenyl) or C_{3-6} cycloalkyl.].

2. A compound of formula (1) as defined in claim 1 wherein R_1 is a 2-indanyl group and R_2, R_3 and R_4 have the meanings defined in claim 1.

3. A compound of formula (1) as defined in claim 1 or claim 2 wherein R_4 is hydroxy or the group NR_5R_6.

4. A compound of formula (1) as defined in claim in any of claims 1 to 3 wherein the compounds have the stereochemistry as defined in formula (1a).



(1a)

wherein the groups R_1, R_2, R_3 and R_4 have the meanings defined for formula (I).

5. A compound of formula (1) as defined in claim in any of claims 1 to 4 wherein R_2 is a group selected from 1-methylpropy lor 2-methylpropyl .

6. A compound of formula (1) as defined in claim in any of claims 1 to 5 wherein R_3 is an optionally substituted phenyl group.

7. A compound of formula (1) as defined in claim in any of claims 1 to 6 wherein R_3 is a 5 or 6 membered hetero aryl group.

8. A compound of formula (1) as defined in claim in any of claims 1 to 7 wherein R_3 is a fused bicyclic ring system containing 9-10 ring members which may be a carbocyclic group or it may contain up to 3 heteroatoms selected from O, S or N and one of the fused rings is benzene.

9. A compound of formula (1) as defined in claim in any of claims 1 to 8 wherein R_3 is a group selected from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2-chloro-4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2 fluoro-4-bromophenyl, 4-chloro-3-fluorophenyl 2,3,4-trifluorophenyl 2,4,5-trifluorophenyl or 2,4,6-trifluorophenyl, 2-fluoro-4,5-dimethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-fluoro-4 methoxyphenyl, 2- fluoro-4 hydroxyphenyl, 2-fluoro-4-dimethylaminomethylphenyl, 2-fluoro-4-hydroxymethylphenyl, 3-fluoro-4-(4-morpholino)phenyl, 3-fluoro-4-carboxymethyloxyphenyl, 3-fluoro-4-t-butyloxycarbonylmethyloxyphenyl, 3-fluoro-4-dimethylaminocarbonyloxyphenyl, 3-chloro-4 trifluoromethoxyphenyl, 2,3-difluoro-4-methyl-phenyl, 4-trifluoromethoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-methoxycarbonylphenyl, 3-methoxycarbonyphenyl, 4-methylsulphonylphenyl, 4-methylaminocarbonylphenyl, 4- aminocarbonylphenyl, 4-methylaminosulphonylphenyl, 3-(3-pyrazyolyl)phenyl, 4-(3-pyrazolyl)phenyl, 4-(4-pyrazolyl)phenyl, 4-(3-pyridyl)phenyl, 4-(2-pyridylphenyl), 4-(2-imidazolyl)phenyl, 3-(2-imidazolyl)phenyl, 4-(1-t-butyl-tetrazol-5-yl)phenyl, 4-methylaminophenyl, 4-dimethylaminophenyl, 4-diethylaminophenyl, 4-acetylaminophenyl, 3-acetylaminophenyl, 4-hydroxy-3-acetylaminophenyl, 4-methylsulphonylaminophenyl, 4-N-methylpiperazinophenyl, 4-N-pyrrolidinophenyl, 2-fluoro-4-(4-morpholino)phenyl, 4-(4-morpholino)phenyl, 4-(4-hydroxypiperidino)phenyl, 2-fluoro-4-(4-hydroxypiperidino)phenyl, 3-(1-pyrazolyl)phenyl, 4-(1-pyrazolyl)phenyl, , 4-(1-3,5 di-t-butylpyrazolyl)phenyl, 3-(1-imidazolyl)phenyl, 4-(1-imidazolyl)phenyl, 4-(1-1,2,4-triazolyl)phenyl, 4-(1-1,2,3-triazolyl)phenyl, 4-(2-4,-t-butylthiazolyl)phenyl, 4-(5- 2-t-butyltetrazolyl)phenyl, 4-(4 spiro-1,3-dioxolanyl)piperidinophenyl, 4-(4-fluorophenyl)phenyl, 4-(4-ethylaminosulphonylphenyl)phenyl, 4-dimethylaminoethoxyphenyl,3-(dihydroxyboryl)phenyl, 2-furanyl, 3-thienyl, 3-furanyl, 2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-chloro-2-thienyl, 3-fluoro-5-methyl-2-thienyl, 5-methyl-2-thienyl, 5-methyl-2-furanyl, 5-bromo-2-furanyl, 4,5-dimethyl-2-furanyl, 5-trifluoromethyl-2-furanyl, 2-furanyl-4-carboxylic acid methylamide, 2-furanyl-5-carboxylic acid methylamide, 2-pyridyl, 6-methyl-2-pyridyl, 6-methyl-3-pyridyl, 6-methoxy-3-pyridyl, 6-hydroxy-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 3-pyridyl, 4-pyridyl, 3,5-pyrimidinyl, 2-thiazolyl, , 2-methyl-4-oxazolyl, 2-ethyl-4-oxazolyl, 2-cyclopropyl-4-oxazolyl, 2-

trifluoromethyl-4-oxazolyl, 2,5-dimethyl-4-oxazolyl, 4-thiazolyl, 2-methyl-4-thiazolyl, 2-trifluoromethyl-4-thiazolyl, 2-trifluoromethyl-5-thiazolyl, 1-methyl-4-pyrazolyl, 1,3-dimethyl-5-pyrazolyl, 5-(2-pyridyl)-2-thienyl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 1H-1,2,3-benzotriazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,3-benzothiazol-6-yl, 1-methyl-1H-1,2,3-benzotriazol-5-yl, 1-methyl-1H-1,2,3-benzotriazol-6-yl, 1,2,3-benzothiadiazol-6-yl, 2-methyl-1,3-benzoxazol-5-yl, 2-methyl-1,3-benzoxazol-6-yl, 1-benzofuran-5-yl, 1-methy-1H-lindol-5-yl, 1-benzothien-5-yl, 1-benzofuran-6-yl, 1H-indol-6-yl, 1-methyl-1H-benzimidazol-6-yl, 1-methyl-1H-benzimidazol-5-yl, 3-methyl-1,2-benzoisoxazol-5-yl, 2-fluoro-1-benzofuran-5-yl, 1H-indol-5-yl, 2-methyl-1H-benzofuran-5-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1-benzofuran-2-yl or 1-methyl-1H-benzimidazol-2-yl.

10. A compound of formula (1) as defined in claim in any of claims 1 to 9 wherein R_5 is a group selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxyC_{2-4}alkyl and R_6 is a group selected from hydrogen, C_{1-4}alkoxy, C_{1-4}alkyl, C_{1-4} alkyl substituted by 1 to 3 halogen atoms, C_{1-4}alkyl substituted by alkoxycarbonyl or carboxyl, alkyl substituted by alkoxy, alkyl substituted by hydroxy, alkyl substituted by dialkylamino, 2-benzyloxyphenyl, dimethoxybenzyl, optionally substituted heteroarylmethyl, heteroaryl, alkyl substituted by NR_7R_8 wherein NR_7R_8 form a 6-membered heterocyclic ring, cycloalkyl,or NR_5R_6 represents, azetidino, 3-hydroxyazetidino, 3-methoxyazetidino, pyrrolidino, piperidino, 4-dimethylaminopiperidino, 4-methyl 1,4-diazepan-1-yl, morpholino, an optionally substituted piperazino ring, thiomorpholino or the sulphoxide or sulphone thereof.

11. A compound selected from:-

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
(2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
(2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]- morpholinamide
(2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-hydroxypiperidin-1-yl)phenyl]ethanamide.
(2R)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl}-2-(2-fluoro-4-morpholin-4-ylphenyl)-N-isopropylethanamide.
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide.
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

(2R)-N-cyclopropyl-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
(3R,6R)-1-[(1R)-2-azetidin-1-yl-1-(2,4-difluorophenyl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyethyl)-N-methylethanamide
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-[2-(methylsulfonyl)ethyl]ethanamide
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(2,2,2-trifluoroethyl)ethanamide
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(pyridin-2-ylmethyl)ethanamide
(3R,6R)-1-{(1R)-1-(2,4-difluorophenyl)-2-[4-(methylsulfonyl)piperazin-1-yl]-2-oxoethyl}-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methoxy-N-methylethanamide
(2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid
methyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
propyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
1-(acetyloxy)ethyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
(2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl}ethanamide
(2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-{(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxopiperazin-1-yl}ethanamide
(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]piperazine-2,5-dione
(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]piperazine-2,5-dione
(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione

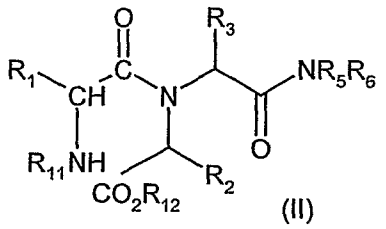
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide
(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-methylthien-2-yl)ethanamide
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide
(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-morpholin-4-yl-2-oxoethyl]piperazine-2,5-dione
(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(5-methylthien-2-yl)ethanamide
(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-5-methylthien-2-yl)-N,N-dimethylethanamide
(2R)-2-(1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
(2R)-2-(1,2,3-benzothiadiazol-6-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
(2R)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
(2R)-2-(1,3-benzodioxol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
(2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide.
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]- N-isopropyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide
(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]piperazin-2,5-dione
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N,N-dimethylethanamide
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N-isopropylethanamide
(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-fluoro-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]-6-isobutylpiperazine-2,5-dione
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N,N-dimethylethanamide
(2R)-2-(1-benzothien-5-yl) -2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

12. A pharmaceutical composition comprising a compound of formula (1) as defined in claim 1 or claim 2 together with one or more pharmaceutically acceptable carriers.

13. The use of compound of formula (1) as defined in claim 1 for the manufacture of a medicament for antagonising the effects of oxytocin on the oxytocin receptor.

14. A process for the preparation of compounds of formula (I) wherein R_4 is the group NR_5R_6 which comprises:

(a) cyclisation of the compound of formula (II)



(II)

wherein R_1, R_2 and R_3 have the meanings defined in formula (I) R_{11} is hydrogen and R_{12} is a C_{1-3}alkyl group in a suitable solvent or

(b) reacting a compound of formula (I) wherein R_4 is hydroxyl or an activated derivative thereof with the amine NHR_5R_6 wherein R_5 and R_6 have the meaning defined in formula (I) under the standard condition for preparing amides from a carboxylic acid and an amine.

(c) reacting a compound of formula (I) wherein R_4 is the group NR_5R_6 and R_5 is hydrogen and R_6 is 2-hydroxyphenyl with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent and subsequent reaction of the product thus formed with amine NHR_5R_6.

15. A process for preparing compounds of formula (I) wherein R_4 is hydroxyl by reacting a compound of formula (I) wherein R_4 is the group NR_5R_6 and R_5 is hydrogen and R_6 is 2-hydroxyphenyl with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent and subsequent reaction of the product thus formed with aqueous acetone.