

Non-Peptide GnRH Antagonists

The present invention relates to a series of compounds that act as antagonists at the GnRH receptor. The compounds are useful in the treatment of endometriosis and hormone-dependent cancers, and in the control of ovulation during *in vitro* fertilisation protocols.

Background

Gonadotropin Releasing Hormone (GnRH, also known as Luteinizing Hormone Releasing Hormone, LHRH) is a decapeptide hormone produced in the hypothalamus. Upon release it is transported to the pituitary, where it causes the secretion of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH). These two hormones then act at the ovaries (in females) or the testes (in males). They control folliculogenesis and ovulation in females and the release of steroid hormones in both males and females.

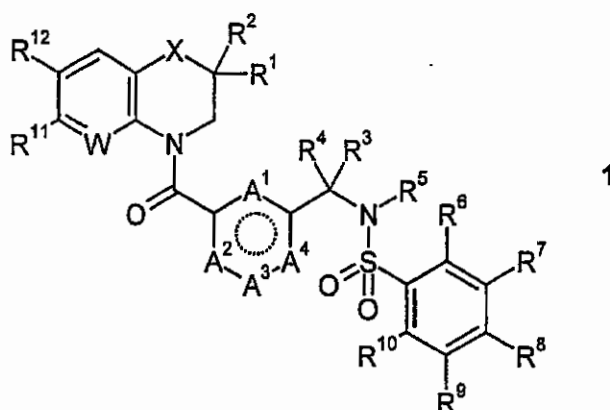
It is widely recognised that over-secretion of steroid hormones can be detrimental to the health. For example, certain neoplasms (such as breast and prostate cancer) and endometriosis are promoted by high steroid levels. Agents that modulate the hypothalamic-pituitary-gonadal axis are therefore of therapeutic interest. The first compounds used clinically were GnRH super-agonists. These are analogues of GnRH that retain all the biological actions of the native hormone, but which are administered in such a way as to cause chronic activation of the GnRH receptors. Within a period of a few days this chronic activation causes down-regulation of the receptor signaling, and FSH and LH levels fall. The disadvantage with these agents is that, in the first few days, they cause an over-production of FSH and LH which can result in a "flare" reaction. Because of this, attention then moved to the development of GnRH antagonists. Modification of the peptide sequence has led to the discovery of a number of peptide antagonists that are now in clinical trials. However, because these compounds are still peptides, they must be given parenterally (usually by subcutaneous or intramuscular injection). They are also relatively expensive to make and purify. Accordingly, there exists a need for therapeutically effective non-peptide GnRH antagonists, and particularly for compounds that can be administered orally and that are inexpensive.

where a is 0-4. The groups R^{16} and R^{17} are each independently selected from H, lower alkyl and $(CH_2)_aR^{18}$ or together are $-(CH_2)_2-Z-(CH_2)_2-$. The group R^{18} is OH, a phenyl group or an aromatic heterocycle selected from pyridyl, pyrimidinyl, pyrazinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl and thiadiazolyl, each of which may optionally have a lower alkyl group or lower alkenyl group substituent. Z is selected from O, CH_2 , S, SO_2 , NH, N-lower alkyl and N-lower alkenyl.

In further aspects, the present invention comprises a pharmaceutical composition wherein one of the active agents is a compound according to general formula 1, the use of a compound according to general formula 1 for the preparation of such a pharmaceutical composition, and methods of treatment of certain medical conditions.

Detailed Description of the Invention

In a first aspect, the present invention comprises compounds which are derivatives according to general formula 1.

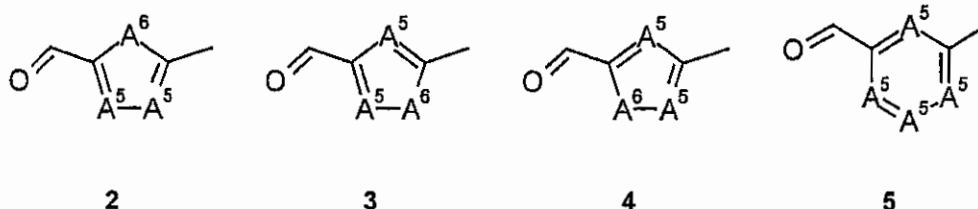


The ring including $A^1 - A^4$ is a five- or six-membered carbocyclic or heterocyclic group. The dotted circle within this group is intended to indicate that the ring incorporates the appropriate number of double and single bonds for an aromatic ring of the corresponding size, namely two double bonds and three single bonds for a five-membered ring, and three double bonds and three single bonds for a six-membered ring. Subject to certain provisions depending on the nature of A^4 , $A^1 - A^3$ each may be selected from A^5 and A^6 , where A^5 may be either $=CR^{13}-$ or $=N-$ and A^6 may be $-NR^{14}-$, $-O-$ or $-S-$. A^4 may be either a covalent bond or A^5 . When A^4 is a covalent bond, such that the ring including $A^1 - A^4$ is

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a five-membered ring, one of $A^1 - A^3$ must be A^6 and the other two must be A^5 . When A^4 is A^5 such that the ring is a six-membered ring, then all of $A^1 - A^3$ must be A^5 . These restrictions allow for the ring to have one of the following four part-structures.



For part structures 2 - 4 the two groups represented by A^5 are independent of each other, so that both may be =N- or =CR¹³-, or one may be =N- and the other =CR¹³-. Similarly, in part-structure 5, the four groups represented by A^5 are independent, so that all may be =N-, all =CR¹³-, or between one and three may be =N- and the rest =CR¹³-. Furthermore, when a compound has more than one occurrence of =CR¹³-, the value of R¹³ for each occurrence is independent of the others. In all cases, the 1,3-relationship between the carbonyl and aminomethyl substituents is preserved.

The group R¹ may be selected from H (a hydrogen atom), NHY¹ and COY². In any of these cases the group R² is H. Alternatively, R¹ and R² may both be methyl or together may represent =O so as to form a carbonyl group.

The groups R³, R⁴ and R⁵ are each independently selected from H, lower alkyl and lower alkenyl groups.

The groups R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹ and R¹² are each independently selected from H, lower alkyl and lower alkenyl groups, NH₂, halogens (F, Cl and Br) O-alkyl, CH₂NMe₂ and CF₃.

The group R¹³ is selected from H, F, Cl, Br, NO₂, NH₂, OH, Me, Et, OMe, NMe₂ and CF₃.

The group R¹⁴ is selected from H, methyl and ethyl.

W is selected from =CH- and =N-.

X is selected from CH₂, O, S, SO₂, NH, N-lower alkyl and N-lower alkenyl.

The group Y¹ is selected from CO-lower alkyl, CO-lower alkenyl, CO(CH₂)_bY³, CO(CH₂)_bCOY³ and CO(CH₂)_bNHCOY³, where b is 1-3.

The group Y^2 is selected from OR^{15} , $NR^{16}R^{17}$ and $NH(CH_2)_cCOY^3$, where c is 1-3.

The group Y^3 is selected from lower alkyl, lower alkenyl, OR^{15} and $NR^{16}R^{17}$.

The group R^{15} is selected from H, lower alkyl, lower alkenyl, and $(CH_2)_aR^{18}$ where a is 0-4.

The groups R^{16} and R^{17} are each independently selected from H, lower alkyl, lower alkenyl and $(CH_2)_aR^{18}$, or together are $-(CH_2)_2-Z-(CH_2)_2-$.

The group R^{18} is OH, a phenyl group or an aromatic heterocycle selected from pyridyl, pyrimidinyl, pyrazinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl and thiadiazolyl, each of which may optionally have a lower alkyl or lower alkenyl group substituent.

Z is selected from O, CH_2 , S, SO_2 , NH, N-lower alkyl and N-lower alkenyl groups.

In the context of the present specification, lower alkyl groups include linear, branched and cyclic alkyl groups of up to six carbon atoms, including, but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pentyl, *tert*-amyl, neopentyl, cyclopropyl, cyclohexyl, cyclopropylmethyl, and the like. Lower alkenyl groups include mono-unsaturated linear, branched and cyclic alkenyl groups of up to six carbons, including, but not limited to, allyl, but-2-enyl, cyclopent-3-enyl and the like. Alkenyl groups wherein the double bond is at the point of attachment, such as vinyl and 1-propenyl, are not considered to be lower alkenyl groups in the context of the present specification.

Certain compounds according to general formula 1 are capable of forming salts with acids or bases. For example, compounds according to general formula 1 which have an acidic functional group may be capable of forming sodium, potassium, calcium, magnesium or tetraalkylammonium salts upon treatment with the corresponding hydroxide, carbonate or bicarbonate, or of forming trialkylammonium salts upon reaction with the corresponding amine. Alternatively, compounds according to general formula 1 which have a basic group may be capable of forming addition salts with inorganic and organic acids such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, benzoic acid, pantoic acid, citric acid, fumaric acid, methanesulphonic acid and the like. To the extent that such salts are pharmaceutically acceptable, they are considered to be included within the scope of the present invention.

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The compounds according to general formula 1 may include one or more stereogenic ("asymmetric") centres. Such compounds exhibit optical isomerism, and so can exist as enantiomers or diastereomers. Such isomers, either alone or as mixtures, including but not limited to racemic mixtures, are also considered to be within the scope of the present invention.

In a preferred embodiment, the present invention comprises a compound according to general formula 1 wherein R^3 and R^4 are both H.

In another preferred embodiment, the present invention comprises a compound according to general formula 1 wherein R^6 is a lower alkyl or lower alkenyl group, and more preferably a methyl group.

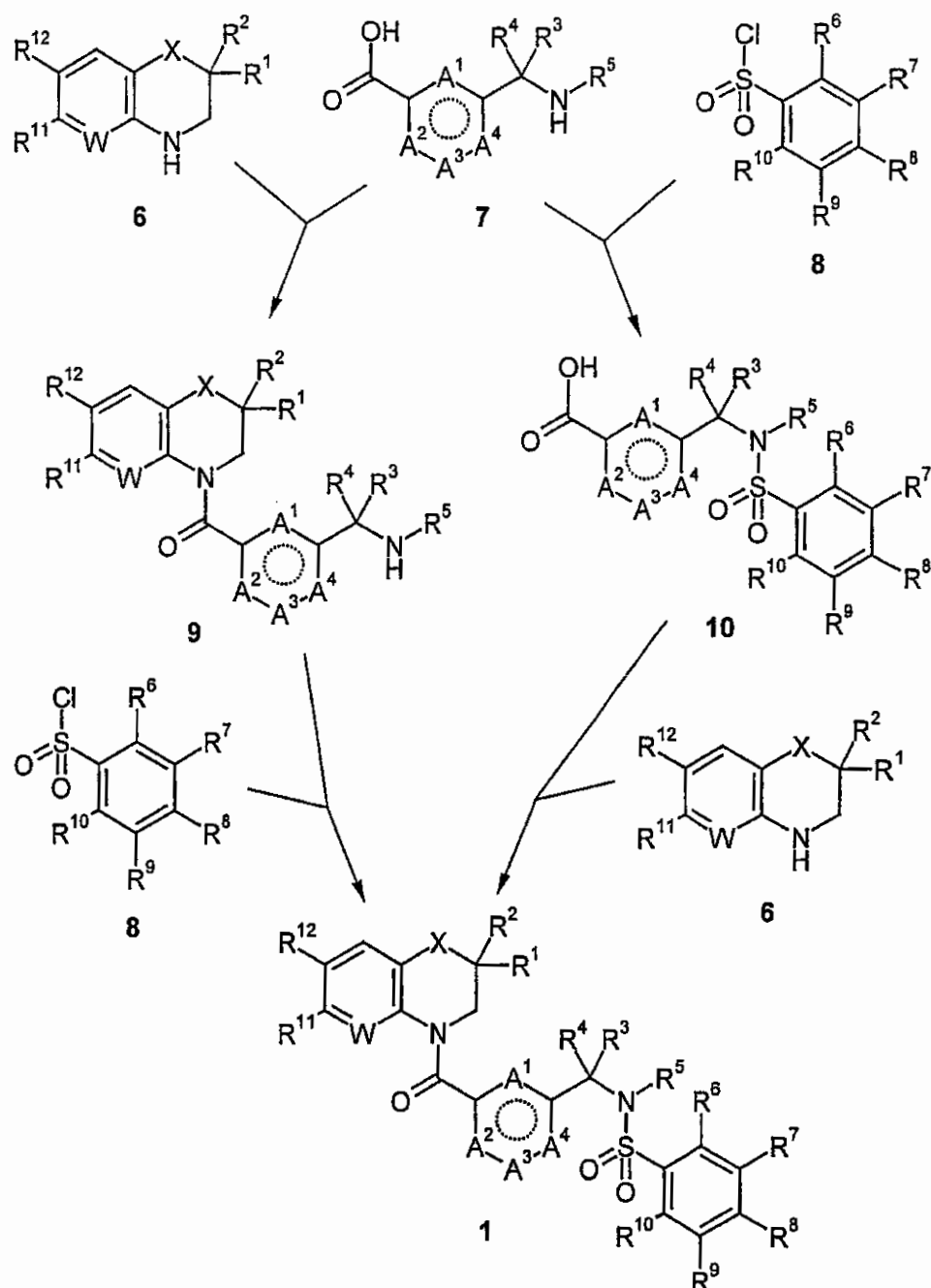
In another preferred embodiment, the present invention comprises a compound according to general formula 1 wherein A^1 , A^2 , A^3 and A^4 are all A^5 . More preferably, they are all $=CR^{13}-$ or three are $=CR^{13}-$ and one is $=N-$. More preferably still, A^1 , A^3 and A^4 are $=CH-$ and A^2 is $=CR^{13}-$. Most preferably, A^1 , A^3 and A^4 are $=CH-$ and A^2 is $=CF-$ or $=CCl-$. In an alternative more preferred embodiment, one of A^1 , A^2 , A^3 and A^4 is $=N-$ and the others are $=CH-$. Most preferably, A^1 is $=N-$ and A^2 , A^3 and A^4 are $=CH-$.

In another preferred embodiment, the present invention comprises a compound according to general formula 1 wherein A^4 is a covalent bond. More preferably, A^1 and one of A^2 and A^3 are A^5 , with the other being A^6 . Most preferably, A^1 is A^5 , one of A^2 and A^3 is $=CH-$ and the other is $-S-$.

In another preferred embodiment, the present invention comprises a compound according to general formula 1 wherein at least three of $R^6 - R^{10}$ are H. More preferably, four of $R^6 - R^{10}$ are H and one is halogen or trifluoromethyl. Most preferably, R^6 , R^7 , R^9 and R^{10} are H and R^8 is halogen or trifluoromethyl.

In another preferred embodiment, the present invention comprises a compound according to general formula 1 wherein R^1 is COY^2 and R^2 is H. More preferably, Y^2 is $NR^{16}R^{17}$ or $NHCH_2COY^3$. Most preferably, Y^2 is $NH-CH_2-R^{18}$ or $NHCH_2CONHCH_3$, where R^{18} is pyridyl or 3-methyl-1,2,4-oxadiazol-5-yl.

The compounds according to general formula 1 can be prepared by two routes, as outlined in the following Scheme.



Three starting materials, corresponding to general formulae 6, 7 and 8 are required. Either 6 and 7 are combined to give an intermediate of general formula 9, or 7 and 8 are combined to give an intermediate of general formula 10. Thereafter, either 8 and 9 or 6 and 10 are combined to give the product of general formula 1. In order to avoid side-

reactions, it will usually be necessary to employ appropriate protecting groups during certain stages of the synthesis. The use of such protecting groups is well known in the art. For example, see Greene, TW; "*Protective Groups in Organic Synthesis*", Wiley, New York 1999. In particular, the amino group of starting material **7** is likely to be incompatible with the conditions required to effect the reaction of **6** with **7** and so will need to be protected. Suitable protecting groups are, for example, *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Z) groups. The carboxylic acid group of **7** may also require protection. If so, it may be protected as an ester such as the methyl, ethyl, *tert*-butyl or benzyl ester.

It will be apparent from the Scheme that the two synthetic strategies require the same chemical transformations and differ only in the order in which these are carried out. The two transformations are:

- i formation of an amide from a carboxylic acid and a cyclic amine ($6 + 7 \rightarrow 9$; $6 + 10 \rightarrow 1$); and
- ii formation of a sulphonamide from a sulphonyl chloride and an amine ($7 + 8 \rightarrow 10$; $8 + 9 \rightarrow 1$).

The formation of an amide is a well known operation. The carboxylic acid and the amine are mixed in an appropriate solvent, which is generally an aprotic solvent such as dichloromethane or dimethylformamide, and a condensing agent is added. A large number of such agents are now available. Suitable agents include carbodiimides such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), and *N*-(dimethylamino-propyl)-*N'*-(ethyl)-carbodiimide (water-soluble carbodiimide, WSC.HCl, phosphorus derivatives such as (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOPtrademark) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), and urea derivatives such as O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU). A tertiary amine may also be included in the reaction mixture. Examples of such tertiary amines include triethylamine, diisopropylethylamine and 4-dimethylaminopyridine. The reaction is generally carried out at room temperature or at a lower temperature such as 0°C or -20°C. In cases where the reaction is slow, it is also possible to warm the mixture to a temperature not greater than the boiling point of the solvent.

The formation of a sulphonamide is also a well known operation. Generally, the sulphonyl chloride and the amine are mixed in an aprotic solvent such as dichloromethane or dimethylformamide in the presence of a tertiary amine (for example triethylamine, diisopropylethylamine and 4-dimethylaminopyridine). There is no need to add a condensing agent. The reaction is generally performed at around room temperature.

The starting materials (6, 7 and 8) are prepared according to published methods, or by modifications to these methods. In some cases it may be necessary or desirable to carry out final modifications to the molecule after the three components have been assembled. Such extensions and modifications will be obvious to those familiar with the art.

The compounds according to general formula 1 are potent and specific antagonists of the GnRH receptor. Therefore they are useful in the treatment of conditions wherein GnRH is implicated in the pathophysiology. For example, the compounds can be used in the treatment of certain hormone-dependent cancers, such as cancer of the breast or of the prostate. They may also be used to treat non-cancerous conditions such as benign prostate hyperplasia and endometriosis. Because of their ability to block the release of LH and FSH, the compounds can be used to regulate fertility. They can be used as contraceptive agents in either male or female subjects. They can also be used in assisted fertilisation programs where it is necessary to control the levels of circulating hormones in order to optimise the chances of obtaining mature ova. They may also be used in the management of criminal anti-social behaviour.

In a second aspect, therefore, the present invention comprises a use for a compound of general formula 1, which use is as a therapeutic agent in human or animal medicine. When employed for this purpose, the compound will be formulated and administered as is generally known in the art, and as further described below.

In a preferred embodiment, the compound is used as in the treatment of a hormone-dependent cancer, benign prostate hyperplasia, or endometriosis, as a contraceptive agent, as an adjunct to an assisted fertilisation program, or as a behaviour-modifying agent. In another preferred embodiment, the compound is used in human medicine.

In a third aspect, the present invention comprises a pharmaceutical composition which is characterised in that it includes at least one compound according to general formula 1 as an active agent. The composition may be a solid, such as a tablet, capsule, powder, suppository or the like, or a liquid, such as a solution, suspension, emulsion or cream. The

composition may include such excipients as are generally known in the art, including bulking agents, binding agents, diluents, dispersants, lubricants, solvents, preservatives and flavouring agents.

In a preferred embodiment, the composition is a tablet or capsule suitable for oral administration.

In another preferred embodiment, the composition is intended for the treatment of a hormone-dependent cancer, benign prostate hyperplasia, or endometriosis, as a contraceptive agent, as an adjunct to an assisted fertilisation program, or as a behaviour-modifying agent

In a fourth aspect, the present invention comprises a use for a compound according to general formula 1, which use is as a component of a pharmaceutical composition.

In a fifth aspect, the present invention comprises a new method of treatment in human or animal medicine, which method is characterised in that a therapeutically effective amount of a compound according to general formula 1 is administered to the subject in order to bring about the desired outcome.

The compound, when formulated as an appropriate pharmaceutical composition, may be administered by any suitable route, including oral, buccal, nasal, pulmonary, rectal, vaginal, transdermal, intramuscular, subcutaneous and intravenous administration. The amount administered, and the frequency with which the administration is repeated, will be determined by the attending physician (or veterinarian), taking in to account the condition and medical history of the subject and the therapeutic outcome desired. A typical human dose will be in the range of 0.1mg to 500mg. The dose may be administered once per day or up to four times per day. The course of treatment may involve a single administration or repeated administration for a period of a few days or weeks up to several years when the condition being treated is chronic.

In a preferred embodiment, the subject is a human male or female.

In another preferred embodiment, the condition being treated is a hormone-dependent cancer. More preferably, it is prostate cancer or breast cancer.

In another preferred embodiment, the condition being treated is endometriosis.

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In another preferred embodiment, the condition being treated is benign prostate hyperplasia.

In another preferred embodiment, the condition being treated is infertility. In particular, the treatment is part of a program of assisted fertilisation.

In another preferred embodiment, the aim of the treatment is to provide contraception.

In another preferred embodiment, the subject is a "sex offender", i.e. the subject has committed sexual attacks on other people.

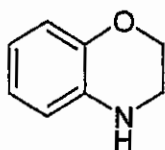
The present invention, as described above, is further described by means of the following Examples, which are intended to be illustrative of the invention rather than limiting in any way the scope of the invention.

Examples

Chromatography refers to "flash" chromatography on silica gel unless otherwise stated.

A. Synthesis of Intermediates

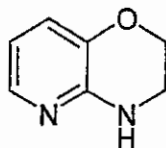
Benzomorpholine



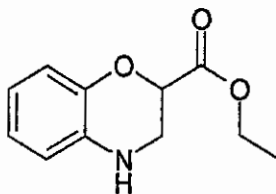
2*H*-1,4-benzoxazin-3(4*H*)-one (4.5g, 30mmol) was added portionwise to a stirred suspension of lithium aluminium hydride (4.7g, 120mmol) in THF (100ml) and heated at reflux for 3h. The mixture was cooled in an ice/water bath and ammonia solution (8ml) and water (40ml) were added while stirring. The mixture was filtered through Celite and reduced. Chromatography (50% EtOAc/50% 60-80 petroleum ether) afforded benzomorpholine (3.7g, 91%) as a pale brown oil.

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Pyrido[3,2-*b*]morpholine

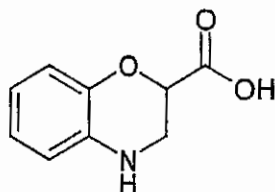
2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (1.9g, 12.6mmol) was added to a suspension of lithium aluminium hydride (2.0g, 53mmol) in dry THF (100ml) while cooling in an ice/water bath. The mixture was warmed to 60°C and stirred for 4h. The mixture was cooled again in an ice/water bath and water (20ml) was added slowly, followed by ethyl acetate (200ml). The mixture was filtered and separated. The organic phase was washed with water and brine, dried and reduced to afford pyrido[3,2-*b*]morpholine (1.5g, 89%) as a white solid.

Ethyl benzomorpholine-2-carboxylate

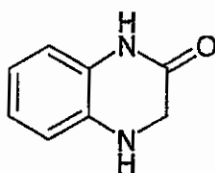
Ethyl 2,3-dibromopropionate (24g, 92mmol) was added dropwise to a refluxing solution of *o*-aminophenol (10g, 92mmol) and potassium carbonate (15g, 110mmol) in acetone (100ml). After 18h the mixture was cooled and reduced. Ethyl acetate and water were added and the mixture separated. The organic phase was washed with brine, filtered and reduced. Chromatography (30% EtOAc/70% 60-80 petroleum ether) afforded ethyl benzomorpholine-2-carboxylate (4.5g, 24%) as a red oil.

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Benzomorpholine-2-carboxylic acid

A solution of lithium hydroxide (290ml, 7.0mmol) in water (10ml) was added to a solution of ethyl benzomorpholine-2-carboxylate (750mg, 3.6mmol) in dioxan (15ml). The mixture was stirred for 18h and reduced to afford benzomorpholine-2-carboxylic acid as its lithium salt, which was used without further purification.

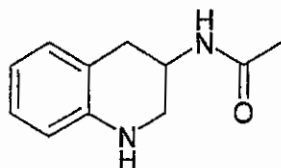
1,2,3,4-Tetrahydroquinoxalin-2-one

a) Glycine methyl ester hydrochloride (2.2g, 18mmol), diisopropylethylamine (2.9g, 29 mmol), 18-crown-6 (370mg, 1.4mmol) and potassium fluoride (1.6g, 28mmol) were added to a solution of 1-fluoro-2-nitrobenzene (2g, 14mmol) in acetonitrile (150ml). The mixture was heated at 80°C for 48h and cooled. 0.3N potassium hydrogen sulphate and ethyl acetate were added and the mixture separated. The organic phase was washed with water and brine, filtered through phase separation paper and reduced. Chromatography (15% EtOAc/85% 60-80 petroleum ether) afforded *N*-(2-nitrophenyl)glycine methyl ester as a yellow solid (2.5g, 85%).

b) A solution of *N*-(2-nitrophenyl)glycine methyl ester (740mg, 3.6mmol) in ethyl acetate (50ml) and methanol (25ml) was hydrogenated at atmospheric pressure over a catalytic amount of 10% palladium on carbon. After 1h the mixture was filtered and reduced to afford 1,2,3,4-tetrahydroquinoxalin-2-one as a yellow solid (530mg, 99%).

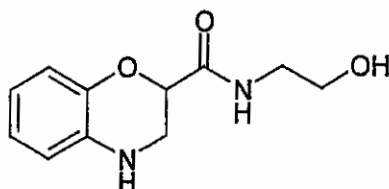
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3-Acetamido-1,2,3,4-tetrahydroquinoline

a) Acetyl chloride (410mg, 5.2mmol) and triethylamine (620mg, 6.2mmol) were added to a solution of 3-aminoquinoline (710mg, 4.9mmol) in dichloromethane (50ml) and the mixture was stirred at room temperature for 18h. Chloroform (100ml) was added, the mixture acidified with 1N hydrochloric acid (50ml) and the phases separated. The aqueous phase was basified with 1N sodium hydroxide solution and extracted with chloroform/IPA (85:15, 175ml). The organic extract was washed with water, brine, dried and reduced to afford 3-acetamidoquinoline (780mg, 84%) as a yellow solid.

b) Borane-pyridine complex (320mg, 3.5mmol) was added to a solution of 3-acetamidoquinoline (320mg, 1.7mmol) in acetic acid (20ml) and the mixture was stirred at room temperature for 18h. Chloroform (150ml) was added and the mixture was washed with 2N sodium hydroxide solution, water and brine. The organic phase was dried and reduced. Chromatography (80% EtOAc/20% 60-80 pet. ether) afforded 3-acetamido-1,2,3,4-tetrahydroquinoline (180mg, 55%) as a pale yellow solid.

N-(2-Hydroxyethyl)benzomorpholine-2-carboxamide

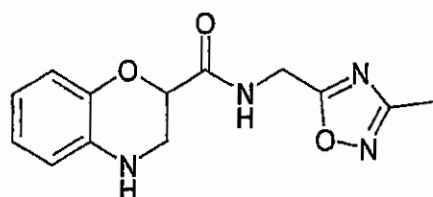
HOBT (3.1g, 20mmol) was added to a solution of lithium benzomorpholine-2-carboxylate (2.6g, 15mmol) in dichloromethane (75ml) and DMF (7.0ml) and cooled in an ice/water bath. WSC.HCl (3.2g, 17mmol) was added, the mixture was allowed to warm to room temperature and stirred for 1h. The mixture was cooled in an ice/water bath again and ethanolamine (1.0g, 17mmol) and triethylamine (2.8ml, 2.0g, 20mmol) were added.

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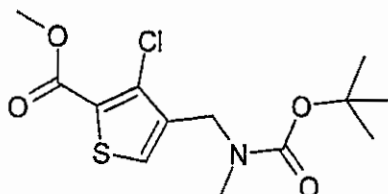
Stirring was continued at room temperature for 3 days. The mixture was reduced and taken up in ethyl acetate and 0.3N potassium hydrogen sulphate solution. The phases were separated. The organic phase was washed with saturated sodium hydrogen carbonate solution and the aqueous phase was back-extracted with ethyl acetate and chloroform. The combined organic phases were dried and reduced. Chromatography (6% methanol/94% chloroform) afforded *N*-(2-hydroxyethyl)benzomorpholine-2-carboxamide (1.1g, 33%) as a brown gum.

***N*-(3-Methyl-1,2,4-oxadiazol-5-ylmethyl)benzomorpholine-2-carboxamide**



HOBT (1.0g, 6.5mmol) and WSC.HCl (1.1g, 5.8mmol) were added to a solution of lithium benzomorpholine-2-carboxylate (900mg, 5.0mmol) in dichloromethane (25ml) and DMF (4.0ml) while cooling in an ice/water bath. The mixture was allowed to warm to room temperature and stirred for 45min. Triethylamine (0.73ml, 530mg, 5.2mmol) and a solution of 3-methyl-1,2,4-oxadiazol-5-ylmethylamine (590mg, 5.2mmol, prepared according to H. Biere *et al.*, *Liebigs Ann. Chem.* 1749 (1986)) in dichloromethane (5.0ml) were added and the mixture was stirred for 18h. The mixture was reduced, taken up in ethyl acetate and washed with 0.3N potassium hydrogen sulphate, saturated sodium hydrogen carbonate and brine. The organic phase was dried and reduced. Chromatography (80% ethyl acetate/20% 60-80 petroleum ether) afforded *N*-(3-methyl-1,2,4-oxadiazol-5-ylmethyl)benzomorpholine-2-carboxamide (900mg, 65%) as a brown gum.

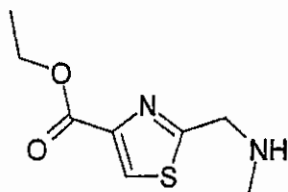
***tert*-Butyl *N*-(3-chloro-2-(methyloxycarbonyl)thiophene-4-methyl)-*N*-methylcarbamate**



a) A solution of methyl 3-chloro-4-methylthiophenecarboxylate (10g, 53mmol), *N*-bromosuccinimide (9.4g, 53mmol) and azo-*bis*-(isobutyronitrile) (860mg, 5.3mmol) in carbon tetrachloride (300ml) was heated at reflux for 18h. The mixture was filtered and reduced. Chromatography (10% EtOAc/ 90% hexanes) afforded methyl 4-bromomethyl-3-chlorothiophene-2-carboxylate (5.5g, 39%) as a white solid.

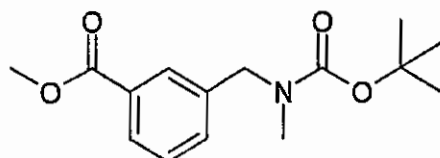
b) A solution of methyl 4-bromomethyl-3-chlorothiophene-2-carboxylate (7.6g, 28mmol) in saturated ammonia/ethanol (200ml) was stirred at room temperature for 18h. The mixture was reduced *in vacuo*, triturated in ether and taken up in dioxan (200ml). Sodium hydroxide (3.4g, 85mmol), di-*tert*-butyl dicarbonate (9.2g, 42mmol) and water (200ml) were added and the mixture stirred for 18h. Excess sodium hydroxide was added and the mixture heated at 70°C for 3h. The mixture was washed with diethyl ether and acidified with solid potassium hydrogen sulphate. The mixture was extracted with ethyl acetate and dichloromethane, dried and reduced to afford *tert*-butyl *N*-(3-chloro-2-carboxythiophene-4-methyl)carbamate (6.0g, 73%) as a brown oil.

c) Sodium hydride (60% dispersion, 820mg, 21mmol) was added to a solution of *tert*-butyl *N*-(3-chloro-2-carboxythiophene-4-methyl)carbamate (2.0g, 6.8mmol) in DMF (30ml) while cooling in an ice/water bath. The mixture was allowed to warm to room temperature over 1h. Iodomethane (4.0ml) was added and the mixture was stirred for 18h. Water was added and the mixture was acidified with dilute potassium hydrogen sulphate solution and extracted with EtOAc. The organic phase was washed with water and brine, dried and reduced. Chromatography (20% EtOAc, 80% hexanes) afforded *tert*-butyl *N*-(3-chloro-2-(methyloxycarbonyl)thiophene-4-methyl)-*N*-methylcarbamate (1.52g, 70%) as a brown oil.

Ethyl 2-(methylaminomethyl)thiazole-4-carboxylate

a) A solution of ethyl 2-methylthiazole-4-carboxylate (5.0g, 29mmol), *N*-bromosuccinimide (6.2g, 35mmol) and azo-*bis*-(isobutyronitrile) (480mg, 2.9mmol) in carbon tetrachloride (150ml) was heated at reflux for 18h. The mixture was filtered and reduced. Chromatography (20% EtOAc/ 80% hexanes and 30% EtOAc/70% hexanes) afforded ethyl 2-bromomethylthiazole-4-carboxylate (3.25g, 44%).

b) A solution of ethyl 2-bromomethylthiazole-4-carboxylate (4.25g, 17mmol) in THF (50ml) was added to a solution of methylamine in THF (2M, 30ml, 60mmol) drop-wise while cooling to -10°C. The mixture was allowed to warm to room temperature and stirred for a further 30min. The mixture was diluted with EtOAc and washed with 0.3N potassium hydrogen sulphate solution and brine. The organic phase was dried and reduced to yield ethyl 2-(methylaminomethyl)thiazole-4-carboxylate (3.06g, 70%) as an orange oil which was used without further purification.

***tert*-Butyl *N*-methyl-*N*-(3-(methyloxycarbonyl)benzyl)carbamate**

a) A mixture of 3-cyanobenzoic acid (5.0g, 34mmol), 10% palladium on carbon (1g) and concentrated hydrochloric acid (3ml) in methanol (150ml) was stirred under hydrogen gas at atmospheric pressure for 6h. The mixture was filtered through Celite®, reduced and azeotroped with toluene. The residue was taken up in 1M potassium hydrogen carbonate solution (105ml) and dioxan (50ml) and cooled in an ice/water bath. A solution of di-*tert*-butyl dicarbonate (7.9g, 36mmol) in dioxan (25ml) was added and the mixture was allowed

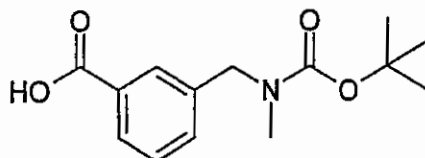
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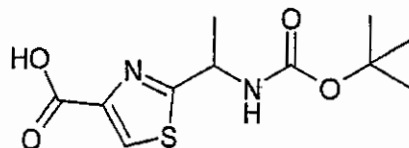
to warm to room temperature. After stirring for 3 days the dioxan was removed *in vacuo*. The aqueous residue was washed with 60-80 pet.ether, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine, dried and reduced to afford *tert*-butyl *N*-(3-carboxybenzyl)carbamate (8.2g, 86%) as a white solid.

b) Sodium hydride (60% dispersion, 700mg, 18mmol) was added to a solution of *tert*-butyl *N*-(3-carboxybenzyl)carbamate (2.0g, 8.0mmol) in DMF (40ml) while cooling in an ice/water bath. After 15min the mixture was allowed to warm to room temperature for 15min. The mixture was cooled again in an ice/water bath and iodomethane (3.7ml, 8.4g, 60mmol) was added. The mixture was stirred at room temperature for 18h. Water was added and the mixture was concentrated *in vacuo*. Ethyl acetate and 0.3N potassium hydrogen sulphate were added and the mixture separated. The organic phase was washed with brine, dried and reduced. Chromatography (20% EtOAc, 80% 60-80 pet.ether) afforded *tert*-butyl *N*-methyl-*N*-(3-(methyloxycarbonyl)benzyl)carbamate (1.6g, 69%) as a colourless oil.

***tert*-Butyl *N*-(3-carboxybenzyl)-*N*-methylcarbamate**



Lithium hydroxide monohydrate (420mg, 10mmol) and water (15ml) were added to a solution of *tert*-butyl *N*-methyl-*N*-(3-(methyloxycarbonyl)benzyl)carbamate (1.6g, 5.6mmol) in dioxan (20ml) and the mixture was stirred for 2h. The dioxan was removed *in vacuo* and the residue was taken up in 0.3N potassium hydrogen sulphate. The mixture was extracted with ethyl acetate and the organic phase was washed with water and brine, dried and reduced to afford *tert*-butyl *N*-(3-carboxybenzyl)-*N*-methylcarbamate (1.4g, 95%).

***tert*-Butyl (1-(4-carboxythiazol-2-yl)ethyl)carbamate**

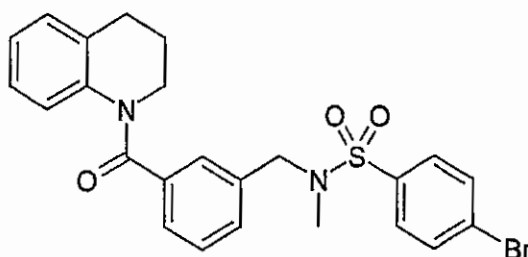
a) Potassium hydrogen carbonate (1.58g, 15.7mmol) and ethyl bromopyruvate (2.1ml, 16.9mmol) were added to a solution of (*R,S*)-2-(*tert*-butoxycarbonylamino)-thiopropionamide (800mg, 3.9mmol) in 1,2-dimethoxyethane (10ml) at -10°C . The mixture was stirred and allowed to warm to 0°C over 2h and to room temperature over 1.5h. The mixture was filtered and the solid washed with diethyl ether. The filtrate was concentrated, taken up in 1,2-dimethoxyethane (10ml) and cooled to -30°C . To this solution was added trifluoroacetic anhydride (1.8ml, 12.8mmol) and 2,6-lutidine (3.2ml, 27.2mmol). After 50min the solution was concentrated and partitioned between chloroform and water. The organic layer was dried and concentrated to afford *tert*-butyl (1-(4-(ethyloxycarbonyl)thiazol-2-yl)ethyl)carbamate (1.4g) as crude material that was used directly in the next step.

b) Lithium hydroxide monohydrate (165mg, 3.9mmol) was added to a solution of *tert*-butyl (1-(4-(ethyloxycarbonyl)thiazol-2-yl)ethyl)carbamate (1.4g crude material) in THF (25ml) and water (20ml) and stirred at room temperature for 18h. A further amount of lithium hydroxide monohydrate was added (165mg) and stirring continued for 4h. The THF was removed *in vacuo*, the aqueous residue acidified with 1N hydrochloric acid and extracted twice with chloroform. The combined organic layers were washed with brine, dried and reduced. Chromatography (50:2:1 chloroform, methanol, acetic acid) and recrystallisation (EtOAc/hexanes) afforded *tert*-butyl (1-(4-carboxythiazol-2-yl)ethyl)carbamate (686mg, 64% over two steps).

B. Synthesis of Compounds of the Invention

EXAMPLE 1

4-Bromo-*N*-methyl-*N*-(3-(1,2,3,4-tetrahydroquinoline-1-carbonyl)benzyl)benzene-sulphonamide



a) 1,2,3,4-tetrahydroquinoline (4.2g, 31mmol) was added dropwise to a solution of 3-cyanobenzoyl chloride (5.2g, 31mmol) and triethylamine (3.1g, 31mmol) in dichloromethane (125ml) while cooling in an ice/water bath. The mixture was allowed to warm to RT and stirred for 18h. It was washed with 0.3M potassium hydrogen sulphate solution, saturated sodium hydrogen carbonate solution and brine. The organic phase was filtered through phase separation paper and reduced to yield 1-(3-cyanobenzoyl)-1,2,3,4-tetrahydroquinoline (7.1g, 86%).

b) A solution of 1-(3-cyanobenzoyl)-1,2,3,4-tetrahydroquinoline (7.1g, 27mmol) and hydrochloric acid (2.2ml) in methanol (100ml) was hydrogenated at atmospheric pressure for 8h over a catalytic amount of 10% palladium on carbon. The mixture was filtered through Celite® and reduced to yield 1-(3-aminomethylbenzoyl)-1,2,3,4-tetrahydroquinoline hydrochloride (8.1g, 99%) as a white solid.

c) Di-*tert*-butyl dicarbonate (7.1g, 32mmol) was added to a solution of 1-(3-aminomethylbenzoyl)-1,2,3,4-tetrahydroquinoline hydrochloride (8.1g, 27mmol) and triethylamine (7.5ml, 54mmol) in dichloromethane (200ml) and stirred for 18h. The mixture was washed with 0.3M potassium hydrogen sulphate solution, water, sodium hydrogen carbonate solution and brine. The organic phase was dried over sodium sulphate, filtered through phase separation paper and reduced. Chromatography (silica gel, 30% EtOAc, 70% 40-60 petroleum ether) afforded *tert*-butyl *N*-(3-(1,2,3,4-tetrahydroquinoline-1-carbonyl)benzyl)carbamate (8.0g, 84%) as a white solid.

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d) Sodium hydride (0.91g, 60% dispersion in oil, 23mmol) was added to a solution of *tert*-butyl *N*-(3-(1,2,3,4-tetrahydroquinoline-1-carbonyl)benzyl)carbamate (8.0g, 22mmol) in DMF under nitrogen, while cooling in an ice/water bath. Allowed to warm to room temperature over 45min. The mixture was cooled in an ice/water bath and iodomethane (9.8g, 68mmol) was added dropwise. Allowed to warm to room temperature and stirred for 5h. 0.3N Potassium hydrogen sulphate was added and the mixture was extracted with EtOAc. The organic phase was washed with water, dried over sodium sulphate and evaporated. Chromatography (30% EtOAc, 70% 60-80 petroleum ether) afforded *tert*-butyl *N*-methyl-*N*-(3-(1,2,3,4-tetrahydroquinoline-1-carbonyl)benzyl)carbamate (7.7g, 93%) as a yellow gum.

e) A solution of *tert*-butyl *N*-methyl-*N*-(3-(1,2,3,4-tetrahydroquinoline-1-carbonyl)benzyl)carbamate (7.7g, 20mmol) in 4N hydrogen chloride/dioxan solution (20ml) was stirred for 30min. The mixture was reduced and azeotroped with toluene and dichloromethane to yield 1-(3-methylaminomethylbenzoyl)-1,2,3,4-tetrahydroquinoline hydrochloride as a glass (6.3g, 99%).

f) 1-(3-Methylaminomethylbenzoyl)-1,2,3,4-tetrahydroquinoline free base was isolated by aqueous work-up of the HCl salt with saturated sodium hydrogen carbonate solution, extraction with dichloromethane and reduction *in vacuo*. 4-Bromobenzenesulphonyl chloride (41mg, 0.16mmol) was added to a solution of the free base (42mg, 0.15mmol) and triethylamine (30 μ l, 0.20mmol) in dichloromethane (10ml) and stirred for 3h. The mixture was evaporated and chromatographed (35% EtOAc/65% 60-80 pet ether) to afford 4-bromo-*N*-methyl-*N*-(3-(1,2,3,4-tetrahydroquinoline-1-carbonyl)benzyl)benzenesulphonamide as a white solid (40mg, 53%).

^1H NMR (CDCl_3), 1.88-2.08 (2H, m), 2.35 (3H, s), 2.65-2.75 (2H, m), 3.70-3.90 (2H, m), 3.95 (2H, s), 6.55-6.62 (1H, m), 6.75 (1H, t, $J=8\text{Hz}$), 6.90 (1H, t, $J=8\text{Hz}$), 7.05-7.15 (2H, m), 7.20-7.35 (3H, m), 7.50-7.65 (4H, m).

ESIMS m/z = 499.4, 501.4 (50:50, MH^+).

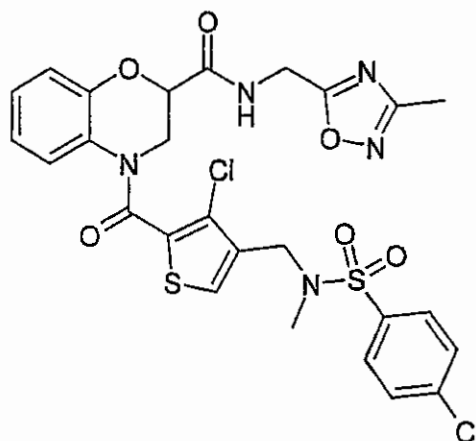
Microanalysis; Found: C 57.79%; H 4.69%; N 5.76%; Calc. for $\text{C}_{24}\text{H}_{23}\text{BrN}_2\text{O}_3\text{S}$: C 57.72%; H 4.64%; N 5.61%.

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EXAMPLE 2

4-(3-Chloro-4-(*N*-(4-chlorobenzenesulphonyl)-*N*-methylaminomethyl)thiophene-2-carbonyl)-*N*-(3-methyl-1,2,4-oxadiazol-5-ylmethyl)benzomorpholine-2-carboxamide



a) 4-Chlorobenzenesulfonyl chloride (10g, 47mmol) was added to a solution of methylamine hydrochloride (3.5g, 52mmol) and triethylamine (16.5ml, 12.0g, 119mmol) in dichloromethane (100ml) while cooling in an ice/water bath. The mixture was allowed to warm to room temperature and stirred for 18h. The mixture was reduced and chromatography (30% EtOAc/70% hexanes) afforded 4-chloro-*N*-methylbenzenesulfonamide (7.9g, 81%) as a colourless oil.

b) Sodium hydride (60% dispersion, 150mg, 3.8mmol) was added to a solution of 4-chloro-*N*-methylbenzenesulfonamide (640mg, 3.1mmol) in DMF (12ml) while cooling in an ice/water bath. After stirring for 15min the mixture was allowed to warm to room temperature and stirred for a further 30min. Methyl 4-bromomethyl-3-chlorothiophene-2-carboxylate (1.08g, 4.0mmol) was added and the mixture was stirred for 18h. 0.3N Potassium hydrogen sulphate solution was added and the mixture evaporated. The mixture was extracted with ethyl acetate and the organic extract was washed with brine, dried and reduced. Chromatography (25% EtOAc/75% 60-80 pet. ether) yielded methyl 3-chloro-4-(*N*-(4-chlorobenzenesulphonyl)-*N*-methylaminomethyl)thiophene-2-carboxylate (1.25g, 79%) as a white solid.

c) Lithium hydroxide (210mg, 5.0mmol) and water (10ml) were added to a solution of methyl 3-chloro-4-(*N*-(4-chlorobenzenesulphonyl)-*N*-methylaminomethyl)thiophene-2-carboxylate (990mg, 2.5mmol) in dioxan (20ml) and the mixture stirred for 18h. The

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mixture was evaporated and 0.3N potassium hydrogen sulphate was added. The mixture was extracted with ethyl acetate and the organic extracts were washed with water and brine, dried and reduced to afford 3-chloro-4-(*N*-(4-chlorobenzenesulphonyl)-*N*-methylaminomethyl)thiophene-2-carboxylic acid (800mg, 84%) as a white solid.

d) A solution of 3-chloro-4-(*N*-(4-chlorobenzenesulphonyl)-*N*-methylaminomethyl)thiophene-2-carboxylic acid (57mg, 0.15mmol) in thionyl chloride (2ml) and dichloromethane (5ml) was heated at reflux for 1h. The mixture was cooled and reduced *in vacuo*. The residue was added to a solution of *N*-(3-methyl-1,2,4-oxadiazol-5-ylmethyl)benzomorpholine-2-carboxamide (40mg, 0.15mmol) and triethylamine (42μl, 0.30mmol) in dichloromethane (10ml) and stirred at room temperature for 3 days. The mixture was reduced and chromatography (30% EtOAc/70% hexanes and 100% EtOAc) afforded 4-(3-chloro-4-(*N*-(4-chlorobenzenesulphonyl)-*N*-methylaminomethyl)thiophene-2-carbonyl)-*N*-(3-methyl-1,2,4-oxadiazol-5-ylmethyl)benzomorpholine-2-carboxamide as a colourless oil (31mg, 33%).

¹H NMR (CDCl₃), 2.37 (3H, s), 2.65 (3H, s), 4.01 (1H, dd, J=6.9Hz, 13.3Hz), 4.09 (2H, s), 4.38 (1H, dd, J=3.0Hz, 13.3Hz), 4.72 (1H, dd, J=5.4Hz, 17.3Hz), 4.82 (1H, dd, J=6.2Hz, 17.3Hz), 4.91 (1H, dd, J=3.0Hz, 6.9Hz), 6.81-6.92 (1H, m), 7.03-7.14 (3H, m), 7.28 (1H, s), 7.51 (1H, s) 7.52 (2H, d, J=8.4Hz), 7.74 (2H, d, J=8.4Hz).

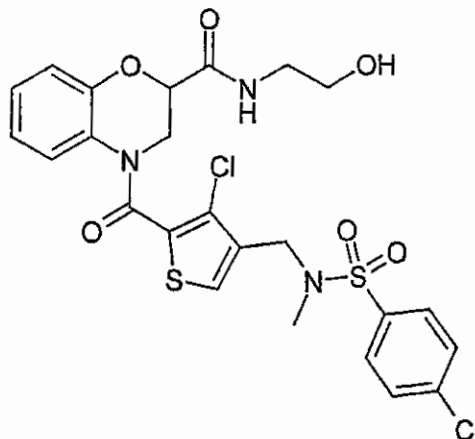
APCI MS *m/z* = 635.9 (MH⁺).

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EXAMPLE 3

4-(3-Chloro-4-(*N*-(4-chlorobenzenesulphonyl)-*N*-methylaminomethyl)thiophene-2-carbonyl)-*N*-(2-hydroxyethyl)benzomorpholine-2-carboxamide



a) *tert*-Butyldimethylsilyl chloride (135mg, 0.9mmol) was added to a solution of *N*-(2-hydroxyethyl)benzomorpholine-2-carboxamide (185mg, 0.83mmol) and imidazole (61mg, 0.90mmol) in DMF (3ml) while cooling in an ice/water bath. The mixture was allowed to warm to room temperature and stirred for 18h. The mixture was reduced, taken up in ethyl acetate, washed with 0.3N potassium hydrogen sulphate and brine, filtered through phase separation paper and reduced. Chromatography (70% EtOAc/30% 60-80 petroleum ether) afforded *N*-(2-(*tert*-butyldimethylsilyloxyethyl)benzomorpholine-2-carboxamide (230mg, 82%) as a brown gum.

b) 3-Chloro-4-(*N*-(4-chlorobenzenesulphonyl)-*N*-methylaminomethyl)thiophene-2-carboxylic acid (69mg, 0.18mmol) was dissolved in thionyl chloride (5ml) and heated to reflux for 90min. The mixture was cooled, reduced and dissolved in dichloromethane (5ml). This solution was added to a solution of *N*-(2-(*tert*-butyldimethylsilyloxyethyl)benzomorpholine-2-carboxamide (61mg, 0.18mmol) and triethylamine (84μl, 0.6mmol) in dichloromethane (5ml). The mixture was stirred for 1h and reduced. Chromatography (40% EtOAc/60% 60-80 petroleum ether) afforded *N*-(2-(*tert*-butyldimethylsilyloxyethyl)-4-(3-chloro-4-(*N*-(4-chlorobenzenesulphonyl)-*N*-methylaminomethyl)thiophene-2-carbonyl)benzomorpholine-2-carboxamide (65mg, 52%) as a white solid.

c) A solution of tetrabutylammonium fluoride in THF (1.0M, 1.0ml, 1.0mmol) was added to a solution of *N*-(2-(*tert*-butyldimethylsilyloxyethyl)-4-(3-chloro-4-(*N*-(4-chlorobenzene-

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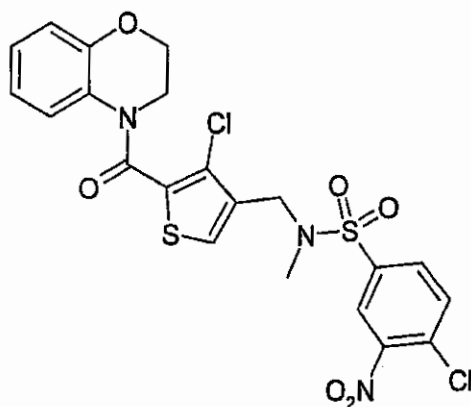
sulphonyl)-*N*-methylaminomethyl)thiophene-2-carbonyl)benzomorpholine-2-carboxamide (65mg, 0.093mmol) in THF (4.0ml) and stirred for 1h. The mixture was reduced, taken up in ethyl acetate, washed with 1N hydrochloric acid and brine, filtered and reduced. Chromatography (95% 60-80 petroleum ether/ 5% EtOAc) afforded 4-(3-chloro-4-(*N*-(4-chlorobenzenesulphonyl)-*N*-methylaminomethyl)thiophene-2-carbonyl)-*N*-(2-hydroxyethyl)-benzomorpholine-2-carboxamide as a white solid (25mg, 46%).

^1H NMR (CDCl_3), 2.67 (3H, s), 3.36-3.46 (2H, m), 3.64-3.70 (2H, m), 4.09-4.16 (4H, m), 4.85 (1H, t, $J=4.2\text{Hz}$), 6.85-6.90 (2H, m), 7.01-7.10 (2H, m), 7.25-7.29 (1H, m), 7.51 (1H, s), 7.53 (2H, d, $J=8.4\text{Hz}$), 7.74 (2H, d, $J=8.4\text{Hz}$).

APCI MS m/z = 584 (MH^+).

EXAMPLE 4

4-(3-Chloro-4-(*N*-(4-chloro-3-nitrobenzenesulphonyl)-*N*-methylaminomethyl)-thiophene-2-carbonyl)benzomorpholine



a) 1N Lithium hydroxide (aq) (7.0ml, 7.0mmol) was added to a solution of *tert*-butyl *N*-(3-chloro-2-(methyloxycarbonyl)thiophene-4-methyl)-*N*-methylcarbamate (1.52g, 4.75mmol) in dioxan (20ml) and the mixture stirred at room temperature for 18h. The mixture was diluted with ethyl acetate, acidified with 1N potassium hydrogen sulphate (aq) and separated. The organic phase was washed with water and brine, dried and reduced to afford *tert*-butyl *N*-(2-carboxy-3-chlorothiophene-4-methyl)-*N*-methylcarbamate as a colourless oil (1.38g, 95%).

b) Benzomorpholine (405mg, 3.0mmol) and triethylamine (0.49ml, 356mg, 3.5mmol) were added to a solution of *tert*-butyl *N*-(3-chloro-2-carboxythiophene-4-methyl)-*N*-methylcarbamate (0.73g, 2.5mmol) in dichloromethane (10ml) and the mixture cooled in an ice/water bath. Pybrop® (1.4g, 3.0mmol) was added and the mixture stirred for 10mins. The mixture was allowed to warm to room temperature and stirred for 3 days. The mixture was washed with water, dried over sodium sulfate and reduced. Chromatography (25% EtOAc/75% 60-80 pet. ether) afforded a mixture of the product and unreacted benzomorpholine. The mixture was taken up in ethyl acetate, washed twice with 1N hydrochloric acid, once with brine, dried over sodium sulphate and reduced to yield *tert*-butyl *N*-(2-(benzomorpholine-4-carbonyl)-3-chlorothiophene-4-methyl)-*N*-methylcarbamate (0.70g, 66%) as pale brown gum.

c) 4N Hydrogen chloride/dioxan solution (5ml) was added to a solution of *tert*-butyl *N*-(2-(benzomorpholine-4-carbonyl)-3-chlorothiophene-4-methyl)-*N*-methylcarbamate (0.70g, 1.7mmol) in dioxan (10ml) while cooling to 12°C. The mixture was allowed to warm to room temperature and stirred for 18h. The mixture was reduced *in vacuo* and azeotroped with toluene and 60-80 pet. ether to yield 4-(3-chloro-4-(methylaminomethyl)thiophene-2-carbonyl)benzomorpholine hydrochloride (0.58g, 95%) as white solid.

d) 4-Chloro-3-nitrobenzenesulfonyl chloride (0.46g, 1.8mmol) was added to a solution of 4-(3-chloro-4-(methylaminomethyl)thiophene-2-carbonyl)benzomorpholine hydrochloride (0.54g, 1.49mmol) and triethylamine (0.50ml, 0.36g, 3.6mmol) in dichloromethane (20ml) while cooling in an ice/water bath. The mixture was allowed to warm to room temperature and stirred for 3 days. The mixture was reduced and chromatographed to afford 4-(3-chloro-4-(*N*-(4-chloro-3-nitrobenzenesulphonyl)-*N*-methylaminomethyl)thiophene-2-carbonyl)benzomorpholine (0.61g, 76%) as a white crystalline solid.

¹H NMR (d₆ DMSO) 2.61 (3H, s), 3.86-3.98 (2H, m), 4.17 (2H, s), 4.30-4.40 (2H, m), 6.75 (1H, dt, J=1.5, 8.4Hz), 6.91 (1H, dd, J=1.5, 8.4Hz), 7.05 (1H, dt, J=1.5, 8.4Hz), 7.20 (1H, d, J=8.4Hz), 7.85 (1H, s), 8.04 (1H, d, J=8.4Hz), 8.10 (1H, dt, J=2.0, 8.4Hz), 8.50 (1H, d, J=2.0Hz).

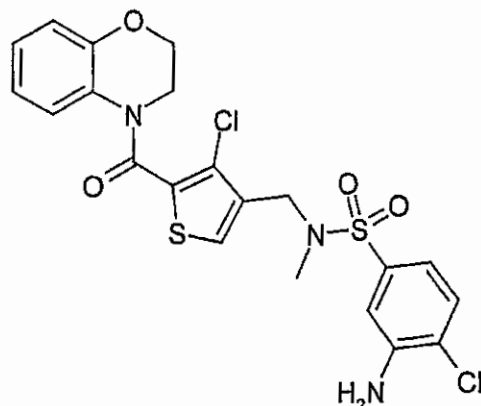
ESIMS *m/z* = 541.6 (MH⁺).

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EXAMPLE 5

4-(4-(*N*-(3-Amino-4-chlorobenzenesulphonyl)-*N*-methylaminomethyl)-3-chlorothiophene-2-carbonyl)benzomorpholine

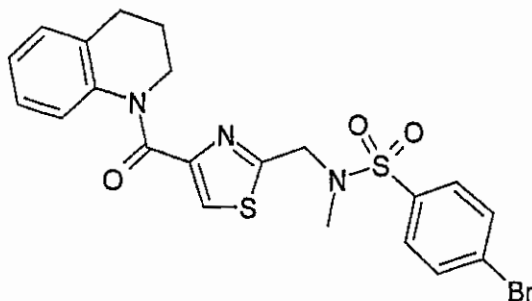


A mixture of 4-(3-chloro-4-(*N*-(4-chloro-3-nitrobenzenesulphonyl)-*N*-methylaminomethyl)-thiophene-2-carbonyl)benzomorpholine (200mg, 0.37mmol) and zinc powder (400mg) in glacial acetic acid (10ml) was heated at 100°C for 5h. The mixture was cooled in an ice/water bath and diluted with water. Sodium hydroxide pellets (5g) were added slowly to give pH = 14. The mixture was extracted with dichloromethane, dried over sodium sulfate and reduced. Flash chromatography (35% EtOAc/65% 60-80 pet. ether) yielded a mixture of product and unreacted starting material. Preparative HPLC of this mixture afforded 4-(4-(*N*-(3-amino-4-chlorobenzenesulphonyl)-*N*-methylaminomethyl)-3-chlorothiophene-2-carbonyl)benzomorpholine (102mg, 54%) as a white solid.

¹H NMR (d₆ DMSO) 2.51 (3H, s), 3.92 (2H, t, J = 4.3Hz), 4.03 (2H, s), 4.34 (2H, J = 4.3Hz), 6.76 (1H, t, J = 6.9Hz), 6.88-6.96 (2H, m), 7.05 (1H, t, J = 6.9Hz), 7.18-7.30 (2H, m), 7.45 (1H, d, J = 8.4Hz), 7.86 (1H, s).

APCI MS *m/z* = 512 (MH⁺).

EXAMPLE 6

1-(2-(*N*-(4-Bromobenzenesulphonyl)-*N*-methylaminomethyl)thiazole-4-carbonyl)-1,2,3,4-tetrahydroquinoline

a) 4-Bromobenzenesulfonyl chloride (2.1g, 8.2mmol) was added to a solution of ethyl 2-(methylaminomethyl)thiazole-4-carboxylate (1.5g, 7.5mmol) and triethylamine (2.1ml, 1.5g, 15mmol) in dichloromethane (30ml) and the mixture was stirred for 18h. The mixture was diluted with ethyl acetate and washed with 1N potassium hydrogen sulphate, water and brine, dried and reduced. Chromatography (35% EtOAc/65% hexanes) afforded ethyl 2-(*N*-(4-bromobenzenesulphonyl)-*N*-methylaminomethyl)thiazole-4-carboxylate (2.1g, 67%) as a white solid.

b) Ethyl 2-(*N*-(4-bromobenzenesulphonyl)-*N*-methylaminomethyl)thiazole-4-carboxylate (2.1g, 5.2mmol) was added to mixture of 1N lithium hydroxide solution (10ml, 10mmol) and dioxan (20ml) and heated to 50°C until a solution was obtained. The mixture was stirred at room temperature for a further 3 days. The mixture was evaporated, taken up in EtOAc and acidified with 1N potassium hydrogen sulphate solution. The phases were separated and the organic phase washed with water and brine, dried and reduced to afford 2-(*N*-(4-bromobenzenesulphonyl)-*N*-methylaminomethyl)thiazole-4-carboxylic acid (1.86g, 95%) as a white solid.

c) Thionyl chloride (2.0ml) was added to a solution of 2-(*N*-(4-bromobenzenesulphonyl)-*N*-methylaminomethyl)thiazole-4-carboxylic acid (460mg, 1.2mmol) in dichloromethane (20ml) and the solution heated at reflux for 2h. The mixture was cooled to room temperature, reduced *in vacuo* and azeotroped with toluene to yield a white solid. This was dissolved in dichloromethane (20ml) and to it were added triethylamine (0.34ml, 250mg, 2.4mmol) and 1,2,3,4-tetrahydroquinoline (0.18ml, 190mg, 1.4mmol). After stirring for 1h the mixture was reduced *in vacuo*. Chromatography (50% EtOAc/50% hexanes) afforded

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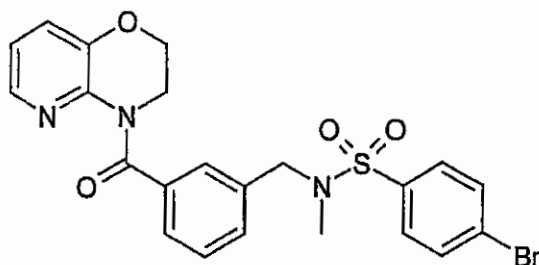
1-(2-(*N*-(4-bromobenzenesulphonyl)-*N*-methylaminomethyl)thiazole-4-carbonyl)-1,2,3,4-tetrahydroquinoline (580mg, 97%) as a white solid.

¹H NMR (CDCl₃), 1.98 (2H, quintet, J=6.6Hz), 2.60 (3H, s), 2.75 (2H, t, J=6.6Hz), 3.87 (2H, t, J=6.6Hz), 4.36 (2H, s), 6.62-6.78 (1H, m), 6.85-6.90 (1H, m), 6.95 (1H, dt, J=1.3, 7.3Hz), 7.08 (1H, d, J=7.3 Hz), 7.59-7.64 (4H, m), 7.65 (1H, s).

ESIMS *m/z* = 506.1, 508.1 (50:50 MH⁺).

EXAMPLE 7

4-Bromo-*N*-methyl-*N*-(3-(pyrido[3,2-*b*]morpholine-1-carbonyl)benzyl)benzene-sulphonamide



a) WSC.HCl (470mg, 2.5mmol) and 4-(dimethylamino)pyridine (290mg, 2.4mmol) were added to a solution of *tert*-butyl *N*-(3-carboxybenzyl)-*N*-methylcarbamate (520mg, 2.0mmol) and pyrido[3,2-*b*]morpholine (290mg, 2.1mmol) in dichloromethane (25ml). The mixture was heated at reflux for 18h. The mixture was concentrated *in vacuo*, taken up in ethyl acetate, washed with water and brine, dried and reduced. Chromatography (40% EtOAc/60% 60-80 pet.ether) afforded *tert*-butyl *N*-methyl-*N*-(3-(pyrido[3,2-*b*]morpholine-1-carbonyl)benzyl)carbamate (700mg, 94%) as a colourless oil.

b) A solution of *tert*-butyl *N*-methyl-*N*-(3-(pyrido[3,2-*b*]morpholine-1-carbonyl)benzyl)-carbamate (610mg, 1.6mmol) in 4N hydrogen chloride/dioxan (30ml) was stirred for 1h. The mixture was reduced *in vacuo* to afford 1-(3-(methylaminomethyl)benzoyl)pyrido[3,2-*b*]morpholine dihydrochloride (512mg, 100%) as a white solid.

c) 4-Bromobenzenesulphonyl chloride (31mg, 0.12mmol) was added to a solution of 1-(3-(methylaminomethyl)benzoyl)pyrido[3,2-*b*]morpholine dihydrochloride (35mg, 0.11mmol) in

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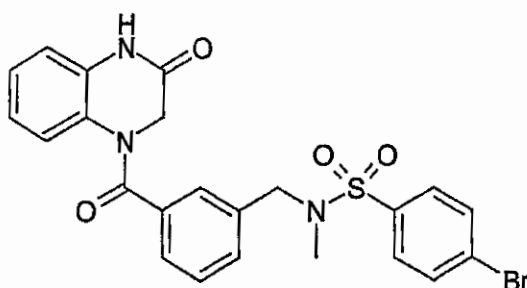
dichloromethane (20ml). The pH was adjusted to pH9 with triethylamine and the mixture stirred for 18h. The mixture was reduced *in vacuo*, taken up in ethyl acetate, washed with water and brine, dried and reduced. Chromatography (80% chloroform/20% cyclohexane) afforded 4-bromo-*N*-methyl-*N*-(3-(pyrido[3,2-*b*]morpholine-1-carbonyl)benzyl)benzenesulphonamide (42mg, 77%) as an off-white solid.

^1H NMR (CDCl_3), 2.49 (3H,s), 4.09 (2H,s), 4.13(2H,t, $J=4.6\text{Hz}$), 4.46(2H,t, $J=4.8\text{Hz}$), 6.87-6.91(1H,m), 7.19-7.51 (5H,m), 7.52 (1H,d, $J=1.6\text{Hz}$), 7.63-7.71 (4H,m).

ESIMS m/z = 502, 504 (50:50, MH^+)

EXAMPLE 8

4-Bromo-*N*-methyl-*N*-(3-(1,2,3,4-tetrahydroquinoxalin-3-one-1-carbonyl)benzyl)benzenesulphonamide



a) WSC.HCl (640mg, 3.4mmol) and 4-(dimethylamino)pyridine (330mg, 2.7mmol) were added to a solution of *tert*-butyl *N*-(3-carboxybenzyl)-*N*-methylcarbamate (700mg, 2.6mmol) and 1,2,3,4-tetrahydroquinoxalin-2-one (440mg, 2.9mmol) in dichloromethane (20ml). The mixture was stirred for 18h, reduced *in vacuo* and taken up in ethyl acetate. This solution was washed with 0.3N potassium hydrogen sulphate and saturated sodium hydrogen carbonate solutions, dried and reduced. Chromatography (50% EtOAc/50% 60-80 pet.ether) afforded *tert*-butyl *N*-(3-(1,2,3,4-tetrahydroquinoxalin-3-on-1-carbonyl)benzyl)-*N*-methylcarbamate (280mg, 27%) as an orange oil.

b) A solution of *tert*-butyl *N*-(3-(1,2,3,4-tetrahydroquinoxalin-3-on-1-carbonyl)benzyl)-*N*-methylcarbamate (280mg, 0.71mmol) in 4N hydrogen chloride/dioxan (30ml) was stirred at room temperature for 1h. The mixture was reduced *in vacuo*, taken up in chloroform,

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washed with saturated sodium hydrogen carbonate solution and brine, dried and reduced. Chromatography (10% methanol/90% chloroform) afforded 1-(3-(methylaminomethyl)benzoyl)-1,2,3,4-tetrahydroquinoxalin-3-one (98mg, 49%) as an orange solid.

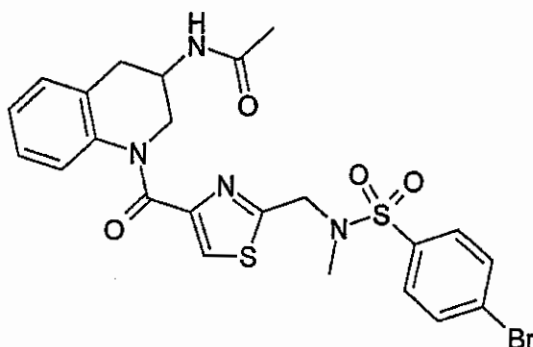
c) 4-Bromobenzenesulphonyl chloride (29mg, 0.11mmol) was added to a solution of 1-(3-(methylaminomethyl)benzoyl)-1,2,3,4-tetrahydroquinoxalin-3-one (30mg, 0.10mmol) in dichloromethane (10ml). The pH was adjusted to pH9 with triethylamine and the mixture stirred for 18h. The mixture was reduced *in vacuo*, taken up in ethyl acetate, washed with water and brine, dried and reduced. Chromatography (50% EtOAc/50% 60-80 pet ether) afforded 4-bromo-*N*-methyl-*N*-(3-(1,2,3,4-tetrahydroquinoxalin-3-one-1-carbonyl)benzyl)-benzenesulphonamide (34mg, 60%) as a white solid.

¹H NMR (CDCl₃), 2.46 (3H,s), 4.06 (2H,s), 4.59 (2H,s), 6.66 (1H,s), 6.76 (1H,t,J=7.6Hz), 6.97 (1H,d, J=6.6Hz), 7.06-7.12 (1H,m), 7.21 (1H,s), 7.31-7.43 (3H,m), 7.63-7.71 (4H,m), 8.97 (1H,s).

ESIMS *m/z* = 514, 516 (50:50, MH⁺).

EXAMPLE 9

3-Acetamido-1-(2-(*N*-(4-bromobenzenesulphonyl)-*N*-methylaminomethyl)thiazole-4-carbonyl)-1,2,3,4-tetrahydroquinoline



Thionyl chloride (5.0ml) was added to a solution of 2-(*N*-(4-bromobenzenesulphonyl)-*N*-methylaminomethyl)thiazole-4-carboxylic acid (250mg, 0.64mmol) in dichloromethane (20ml) and the solution was heated at reflux for 2h. The mixture was cooled and reduced *in vacuo* to afford the acid chloride as a white solid. This acid chloride (130mg, 0.32mmol)

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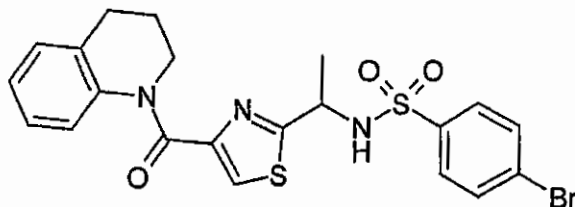
was taken up in dichloromethane (10ml) and to it were added 3-acetamido-1,2,3,4-tetrahydroquinoline (61mg, 0.32mmol) and triethylamine (0.089ml, 65mg, 0.64mmol). The mixture was stirred at room temperature for 18h and reduced *in vacuo*. Chromatography (EtOAc) afforded 3-acetamido-1-(2-(*N*-(4-bromobenzenesulphonyl)-*N*-methylaminomethyl)thiazole-4-carbonyl)-1,2,3,4-tetrahydroquinoline (96mg, 53%) as a white solid.

¹H NMR (CDCl₃), 1.85 (3H,s), 2.61 (3H,s), 2.78 (1H,dd, J=3.6Hz, 16.8Hz), 3.21 (1H,dd, J=5.9Hz, 16.8Hz), 3.69 (1H, dd, J=3.0Hz, 12.9Hz), 4.30-4.35 (3H,m), 4.55-4.60 (1H,m), 6.02 (1H,d, J=7.6Hz), 6.97-7.15 (3H,m), 7.15-7.20 (1H,m), 7.66 and 7.69 (each 2H,each d, J=3.6Hz), 7.88 (1H,s).

ESIMS *m/z* = 563.0, 565.0 (50:50, MH⁺).

EXAMPLE 10

1-(2-(1-(4-Bromobenzenesulphonylamino)ethyl)thiazole-4-carbonyl)-1,2,3,4-tetrahydroquinoline



a) HBTU (306mg, 0.81mmol) was added to a solution of *tert*-butyl (1-(4-carboxythiazol-2-yl)ethyl)carbamate (200mg, 0.73mmol) in DMF (5ml) at room temperature. Diisopropylethylamine (0.26ml, 190mg, 1.5mmol) and 1,2,3,4-tetrahydroquinoline (0.11ml, 117mg, 0.88mmol) were added and the mixture was stirred for 18h. The mixture was partitioned between ethyl acetate and 1N hydrochloric acid and separated. The organic layer was washed with water and brine, dried and reduced. Chromatography (45% EtOAc/55% hexanes) afforded *tert*-butyl (1-(4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)thiazol-2-yl)ethyl)carbamate (180mg, 63%).

b) A solution of *tert*-butyl (1-(4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)thiazol-2-yl)ethyl)carbamate (180mg, 0.47mmol) in 4N hydrogen chloride/dioxan (10ml) was stirred in an ice/water bath and allowed to warm to room temperature. The mixture was concentrated

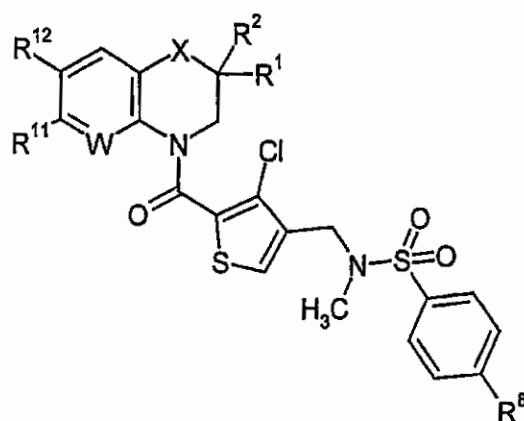
and azeotroped with toluene twice, tetrachloromethane twice and dichloromethane once to afford 1-(2-(1-aminoethyl)thiazole-4-carbonyl)-1,2,3,4-tetrahydroquinoline hydrochloride. The yield was assumed to be quantitative and the material was used directly by taking up in dichloromethane (5ml) and triethylamine (0.16ml, 118mg, 1.2mmol). The resulting solution was cooled in an ice/water bath and to it was added 4-bromobenzenesulphonyl chloride (119mg, 0.47mmol). The mixture was allowed to warm to room temperature and stirred for 18h. Evaporation and chromatography (50% EtOAc/50% hexanes) afforded 1-(2-(1-(4-bromobenzenesulphonylamino)ethyl)thiazole-4-carbonyl)-1,2,3,4-tetrahydroquinoline as a white solid (144mg, 61%).

^1H NMR (CDCl_3), 1.38 (3H, d, $J=6.9$ Hz), 2.05 (2H, dt, $J = 3.3\text{Hz}, 6.6$ Hz), 2.79-2.84 (2H, m), 3.80-4.01 (2H, m), 4.56 (1H, quintet, $J=6.9$ Hz), 5.29 (1H, d, $J = 7.6$ Hz), 6.63-6.79 (1H, br m), 6.94 (1H, t, $J=7.6$ Hz), 7.07 (1H, dt, $J=1.3\text{Hz}, 7.6\text{Hz}$), 7.18 (1H, d, $J=7.6\text{Hz}$), 7.58 (2H, d, $J=8.9\text{Hz}$), 7.59 (1H, s), 7.64 (2H, d, $J=8.9\text{Hz}$).

ESIMS $m/z = 506.0, 507.9$ (50:50, MH^+).

EXAMPLES 11 - 70

The following compounds were prepared using analogous methods.

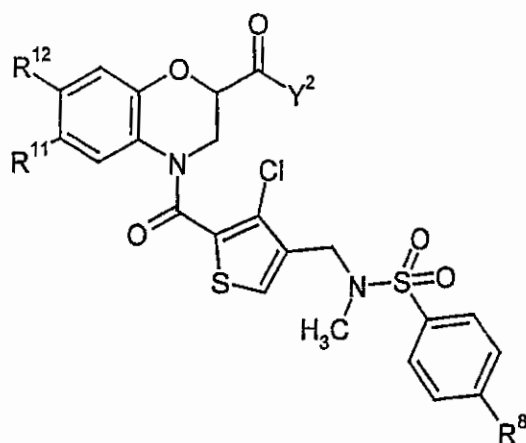


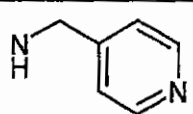
Ex.	R ¹	R ²	R ⁸	R ¹¹	R ¹²	W	X	[M+H] ⁺
12	H	H	Br	H	H	CH	CH ₂	539.0
13	H	H	Br	H	H	N	O	541.9

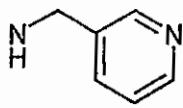
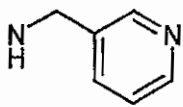
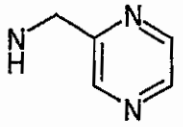
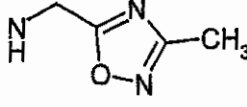
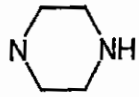
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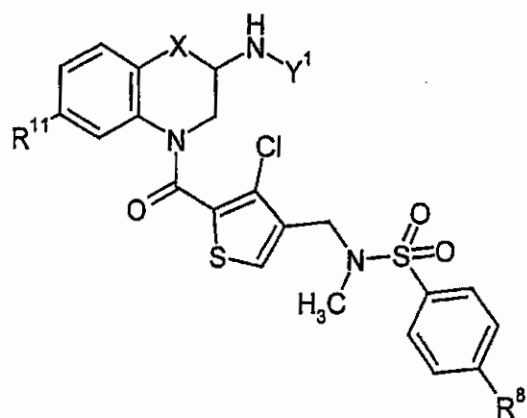
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Ex.	R ¹	R ²	R ⁸	R ¹¹	R ¹²	W	X	[M+H] ⁺
14	H	H	Cl	CH ₂ NMe ₂	H	CH	O	553.9
15	H	H	Cl	H	F	CH	O	514.9
16	Me	Me	Cl	H	H	CH	NH	524.0
17	=O		Br	H	H	CH	NH	554.1



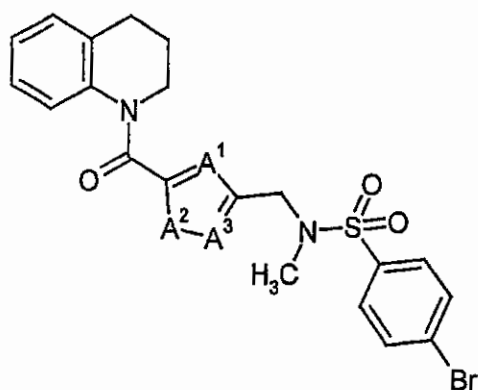
Ex.	Y ²	R ⁸	R ¹¹	R ¹²	[M+H] ⁺
18	OH	Br	H	H	584.9
19	NHMe	Br	H	H	598.0
20	NHCH ₂ CH ₂ OH	Br	H	H	627.9
21	NHCH ₂ CH ₂ OH	Cl	OMe	H	630.9
22	NHCH ₂ CH ₂ OH	Cl	H	F	601.9
23	NHCH ₂ CO ₂ Me	Br	H	H	655.9
24	NHCH ₂ CONHMe	Cl	H	H	611.0
25	NHCH ₂ CONHMe	Cl	OMe	H	641.0
26		Br	H	H	674.9

Ex.	Y ²	R ⁸	R ¹¹	R ¹²	[M+H] ⁺
27		Cl	H	H	631.0
28		Cl	OMe	H	661.0
29		Cl	OMe	H	662.0
30		Cl	OMe	H	666.0
31		Br	H	H	653.0

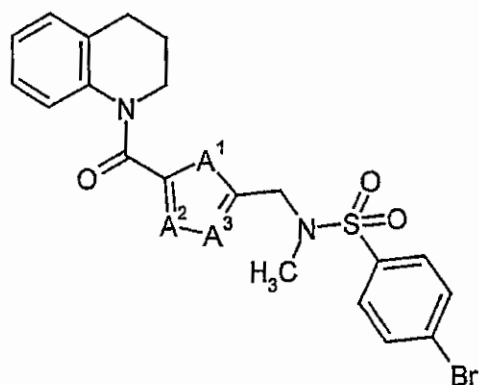


Ex.	Y ¹	R ⁸	R ¹¹	X	[M+H] ⁺
32	C(=O)Me	Br	H	CH ₂	596.1
33	C(=O)CH ₂ NHMe	Br	H	CH ₂	625.0

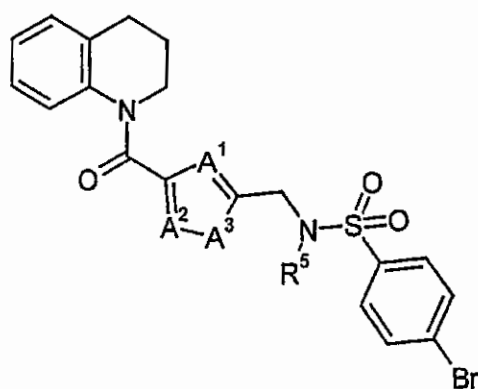
Ex.	Y ¹	R ⁸	R ¹¹	X	[M+H] ⁺
34	C(=O)(CH ₂) ₂ NH ₂	Br	H	CH ₂	625.0
35	C(=O)(CH ₂) ₂ NH ₂	Br	H	O	627.0
36	C(=O)(CH ₂) ₂ NH ₂	Cl	OMe	O	613.0
37	C(=O)(CH ₂) ₃ NH ₂	Br	H	CH ₂	639.0
38	C(=O)(CH ₂) ₃ NH ₂	Br	H	O	641.0
39	C(=O)(CH ₂) ₃ NHMe	Br	H	CH ₂	653.0
40	C(=O)(CH ₂) ₂ NHC(=O)Me	Br	H	CH ₂	668.9
41	C(=O)(CH ₂) ₃ NHC(=O)Me	Br	H	CH ₂	682.9
42	C(=O)(CH ₂) ₃ NHC(=O)NH ₂	Br	H	CH ₂	711.9



Ex.	A ¹	A ²	A ³	[M+H] ⁺
43	CH	S	CH	504.9
44	CH	N(CH ₂ CH ₃)	N	517.1
45	C(NMe ₂)	S	CH	548.1



Ex.	A ¹	A ²	A ³	[M+H] ⁺
46	S	CH	CH	505.1
47	O	CH	CH	489
48	S	CH	N	505.9

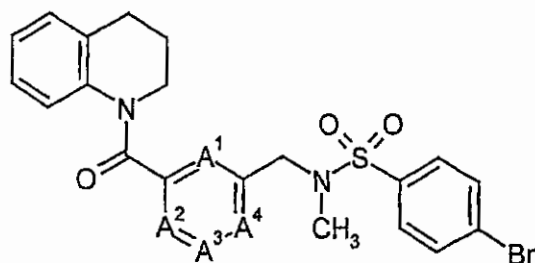


Ex.	R ⁵	A ¹	A ²	A ³	[M+H] ⁺
49	H	N	CH	S	492.0
50	Me	N	CH	O	490.1
51	Me	N	CH	NH	489.0
52	Me	N	CH	NMe	502.9
53	Me	N	C(Et)	S	534.2

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Ex.	R ⁵	A ¹	A ²	A ³	[M+H] ⁺
54	Me	CH	N	O	490.1
55	Me	CH	N	NMe	503.0



Ex.	A ¹	A ²	A ³	A ⁴	[M+H] ⁺
56	CH	CH	CH	C(OMe)	529.1
57	CH	CH	N	CH	500
58	CH	CH	CH	N	500
59	CH	CH	C(Me)	N	514
60	C(NO ₂)	CH	CH	CH	544.2
61	C(NH ₂)	CH	CH	CH	514.3
62	N	CH	CH	CH	499.9
63	CH	C(Cl)	CH	CH	533.1
64	C(Cl)	CH	CH	CH	533
65	CH	C(NH ₂)	CH	CH	514
66	CH	C(OH)	CH	CH	515.0
67	CH	C(F)	CH	CH	517
68	CH	C(NO ₂)	CH	CH	544
69	CH	C(Br)	CH	CH	577
70	CH	CH	CH	C(Cl)	533.1

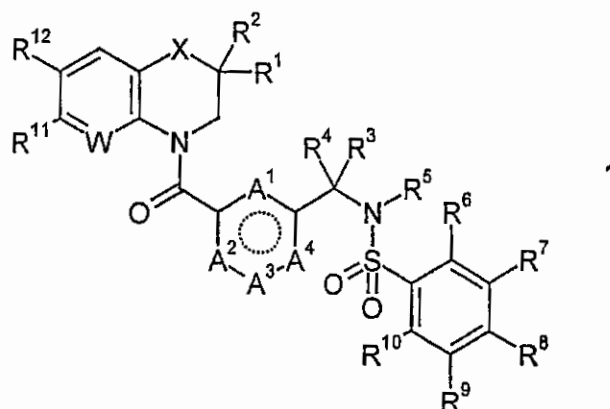
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The compounds described above displace radiolabelled ligand from GnRH receptor-containing membrane preparations at concentrations below 5 μ M.

Claims

- 1 A compound which is a derivative of general formula 1, or a pharmaceutically acceptable salt thereof,



wherein:

A^1 , A^2 and A^3 are each independently selected from A^5 and A^6 ; and

A^4 is either a covalent bond or A^5 ; provided that

when A^4 is a covalent bond then one of A^1 - A^3 is A^6 and the other two are A^5 and that

when A^4 is A^5 then all of A^1 - A^3 are A^5 ;

A^5 is selected from C- R^{13} and N;

A^6 is selected from N- R^{14} , S and O;

R^1 is selected from H, $NH Y^1$ and $CO Y^2$ and R^2 is H; or R^1 and R^2 are both methyl or together are =O;

R^3 , R^4 and R^5 are each independently H, lower alkyl or lower alkenyl;

R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} and R^{12} are each independently selected from H, lower alkyl, lower alkenyl, NH_2 , F, Cl, Br, O-alkyl, O-lower alkenyl, CH_2NMe_2 and CF_3 ;

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R^{13} is selected from H, F, Cl, Br, NO_2 , NH_2 , OH, Me, Et, OMe, NMe_2 and CF_3 ;

R^{14} is selected from H, methyl and ethyl;

W is selected from CH and N;

X is selected from CH_2 , O, S, SO_2 , NH, N-lower alkyl and N-lower alkenyl;

Y^1 is selected from CO-lower alkyl, CO-lower alkenyl, $CO(CH_2)_bY^3$, $CO(CH_2)_bCOY^3$ and $CO(CH_2)_bNHCOY^3$;

Y^2 is selected from OR^{15} , $NR^{16}R^{17}$ and $NH(CH_2)_cCOY^3$;

Y^3 is selected from alkyl, lower alkenyl, OR^{15} and $NR^{16}R^{17}$;

R^{15} is selected from H, lower alkyl, lower alkenyl and $(CH_2)_aR^{18}$

R^{16} and R^{17} are each independently selected from H, lower alkyl, lower alkenyl and $(CH_2)_aR^{18}$, or together are $-(CH_2)_2-Z-(CH_2)_2-$;

R^{18} is selected from OH and phenyl, pyridyl, pyrimidinyl, pyrazinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl and thiadiazolyl, each of which may optionally have a lower alkyl, lower alkenyl group substituent;

Z is selected from O, CH_2 , S, SO_2 , NH, N-lower alkyl and N-lower alkenyl;

a is 0-4; and

b and c are 1-3.

2 A compound according to Claim 1 wherein R^3 and R^4 are both H.

3 A compound according to any preceding Claim wherein R^5 is lower alkyl or lower alkenyl.

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- 4 A compound according to Claim 3 wherein R^5 is methyl.
- 5 A compound according to any preceding Claim wherein A^1 , A^2 , A^3 and A^4 are all A^5 .
- 6 A compound according to Claim 5 wherein at least three of A^1 , A^2 , A^3 and A^4 are $=CR^{13}-$.
- 7 A compound according to Claim 6 wherein A^1 , A^3 and A^4 are $=CH-$ and A^2 is $=CR^{13}-$.
- 8 A compound according to Claim 7 wherein A^2 is $=CF-$ or $=CCl-$.
- 9 A compound according to Claim 6 wherein one of A^1 , A^2 , A^3 and A^4 is $=N-$ and the others are $=CH-$.
- 10 A compound according to Claim 9 wherein A^1 is $=N-$ and A^2 , A^3 and A^4 are $=CH-$.
- 11 A compound according to any of Claims 1 to 4 wherein A^4 is a covalent bond.
- 12 A compound according to Claim 11 wherein A^1 is A^5 .
- 13 A compound according to Claim 12 wherein one of A^2 and A^3 is $=CH-$ and the other is $-S-$.

- 14 A compound according to any preceding Claim wherein at least three of R^6 to R^{10} are H.
- 15 A compound according to Claim 14 wherein four of R^6 to R^{10} are H and the other is F, Cl, Br or CF_3 .
- 16 A compound according to Claim 15 wherein R^6 , R^7 , R^9 and R^{10} are H and R^8 is F, Cl, Br or CF_3 .
- 17 A compound according to any preceding Claim wherein R^1 is COY^2 and R^2 is H.
- 18 A compound according to Claim 17 wherein Y^2 is $NR^{16}R^{17}$ or $NHCH_2COY^3$.
- 19 A compound according to Claim 18 wherein Y^2 is $NHCH_2R^{18}$ or $NHCH_2CONHCH_3$, and R^{18} is pyridyl or 3-methyl-1,2,4-oxadiazol-5-yl.
- 20 A compound according to claim 1 selected from
- 4-(3-Chloro-4-[(4-chloro-benzenesulfonyl)-methyl-amino]-methyl)-thiophene-2-carbonyl-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid (3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-amide
- 4-(3-Chloro-4-[(4-chloro-benzenesulfonyl)-methyl-amino]-methyl)-thiophene-2-carbonyl-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid (2-hydroxy-ethyl)-amide
- 4-Chloro-N-[4-chloro-5-(2,3-dihydro-benzo[1,4]oxazine-4-carbonyl)-thiophen-3-ylmethyl]-N-methyl-3-nitro-benzenesulfonamide

ylmethyl]-N-methyl-3-nitro-benzenesulfonamide

3-Amino-4-chloro-N-[4-chloro-5-(2,3-dihydro-benzo[1,4]oxazine-4-carbonyl)-thiophen-3-ylmethyl]-N-methyl-benzenesulfonamide

4-Bromo-N-[4-(3,4-dihydro-2H-quinoline-1-carbonyl)-thiazol-2-ylmethyl]-N-methyl-benzenesulfonamide

N-[1-(2-[(4-Bromo-benzenesulfonyl)-methyl-amino]-methyl)-thiazole-4-carbonyl)-1,2,3,4-tetrahydro-quinolin-3-yl]-acetamide

4-Bromo-N-[4-chloro-5-(3,4-dihydro-2H-quinoline-1-carbonyl)-thiophen-3-ylmethyl]-N-methyl-benzenesulfonamide

4-Bromo-N-[4-chloro-5-(2,3-dihydro-pyrido[3,2-b][1,4]oxazine-4-carbonyl)-thiophen-3-ylmethyl]-N-methyl-benzenesulfonamide

4-Chloro-N-[4-chloro-5-(7-fluoro-2,3-dihydro-benzo[1,4]oxazine-4-carbonyl)-thiophen-3-ylmethyl]-N-methyl-benzenesulfonamide

4-Chloro-N-[4-chloro-5-(3,3-dimethyl-3,4-dihydro-2H-quinoxaline-1-carbonyl)-thiophen-3-ylmethyl]-N-methyl-benzenesulfonamide

4-Bromo-N-[4-chloro-5-(3-oxo-3,4-dihydro-2H-quinoxaline-1-carbonyl)-thiophen-3-ylmethyl]-N-methyl-benzenesulfonamide

4-(4-[(4-Bromo-benzenesulfonyl)-methyl-amino]-methyl)-3-chloro-thiophene-2-carbonyl)-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid methylamide

4-(5-[(4-Bromo-benzenesulfonyl)-methyl-amino]-methyl)-4-chloro-thiophene-3-carbonyl)-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid (2-hydroxy-ethyl)-amide

4-(3-Chloro-4-[(4-chloro-benzenesulfonyl)-methyl-amino]-methyl)-thiophene-2-carbonyl)-6-methoxy-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid (2-hydroxy-ethyl)-amide

4-(3-Chloro-4-[(4-chloro-benzenesulfonyl)-methyl-amino]-methyl)-thiophene-2-carbonyl)-7-fluoro-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid (2-hydroxy-ethyl)-amide

[[4-(5-[(4-Bromo-benzenesulfonyl)-methyl-amino]-methyl)-4-chloro-thiophene-3-carbonyl)-3,4-dihydro-2H-benzo[1,4]oxazine-2-carbonyl]-amino]-acetic acid methyl

ester

4-(3-Chloro-4-[[4-chloro-benzenesulfonyl]-methyl-amino]-methyl)-thiophene-2-carbonyl)-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid
methylcarbamoylmethyl-amide

4-(3-Chloro-4-[[4-chloro-benzenesulfonyl]-methyl-amino]-methyl)-thiophene-2-carbonyl)-6-methoxy-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid
methylcarbamoylmethyl-amide

4-(5-[[4-Bromo-benzenesulfonyl]-methyl-amino]-methyl)-4-chloro-thiophene-3-carbonyl)-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid (pyridin-4-ylmethyl)-amide

4-(3-Chloro-4-[[4-chloro-benzenesulfonyl]-methyl-amino]-methyl)-thiophene-2-carbonyl)-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid (pyridin-3-ylmethyl)-amide

4-(3-Chloro-4-[[4-chloro-benzenesulfonyl]-methyl-amino]-methyl)-thiophene-2-carbonyl)-6-methoxy-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid (pyridin-3-ylmethyl)-amide

4-(3-Chloro-4-[[4-chloro-benzenesulfonyl]-methyl-amino]-methyl)-thiophene-2-carbonyl)-6-methoxy-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid (pyrazin-2-ylmethyl)-amide

4-(3-Chloro-4-[[4-chloro-benzenesulfonyl]-methyl-amino]-methyl)-thiophene-2-carbonyl)-6-methoxy-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid (3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-amide

N-[1-(4-[[4-Bromo-benzenesulfonyl]-methyl-amino]-methyl)-3-chloro-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-3-yl]-acetamide

3-Amino-N-[1-(4-[[4-bromo-benzenesulfonyl]-methyl-amino]-methyl)-3-chloro-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-3-yl]-propionamide

4-(4-[[4-Bromo-benzenesulfonyl]-methyl-amino]-methyl)-3-chloro-thiophene-2-carbonyl)-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid (2-amino-ethyl)-amide

4-(3-Chloro-4-[[4-chloro-benzenesulfonyl]-methyl-amino]-methyl)-thiophene-2-carbonyl)-6-methoxy-3,4-dihydro-2H-benzo[1,4]oxazine-2-carboxylic acid (2-

amino-ethyl)-amide

3-Acetylamino-N-[1-(4-[(4-bromo-benzenesulfonyl)-methyl-amino]-methyl)-3-chloro-thiophene-2-carbonyl]-1,2,3,4-tetrahydro-quinolin-3-yl]-propionamide

4-Acetylamino-N-[1-(4-[(4-bromo-benzenesulfonyl)-methyl-amino]-methyl)-3-chloro-thiophene-2-carbonyl]-1,2,3,4-tetrahydro-quinolin-3-yl]-butyramide

N-[1-(4-[(4-Bromo-benzenesulfonyl)-methyl-amino]-methyl)-3-chloro-thiophene-2-carbonyl]-1,2,3,4-tetrahydro-quinolin-3-yl]-4-(3-ethyl-ureido)-butyramide

4-Bromo-N-[5-(3,4-dihydro-2H-quinoline-1-carbonyl)-thiophen-3-ylmethyl]-N-methyl-benzenesulfonamide

4-Bromo-N-[5-(3,4-dihydro-2H-quinoline-1-carbonyl)-furan-2-yl]-N-methyl-benzenesulfonamide

4-Bromo-N-[6-(3,4-dihydro-2H-quinoline-1-carbonyl)-pyridin-2-ylmethyl]-N-methyl-benzenesulfonamide

4-Bromo-N-[4-chloro-3-(3,4-dihydro-2H-quinoline-1-carbonyl)-benzyl]-N-methyl-benzenesulfonamide

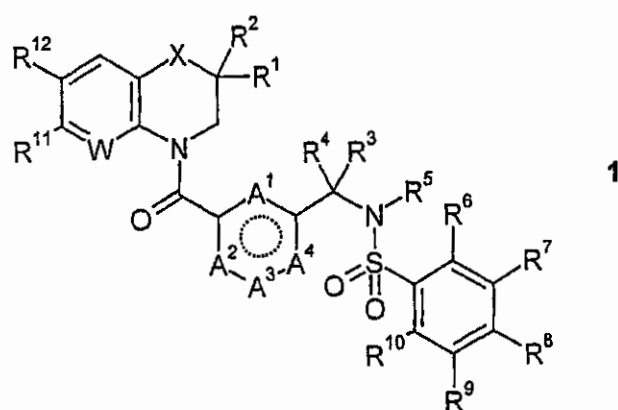
4-Bromo-N-[3-(3,4-dihydro-2H-quinoline-1-carbonyl)-4-fluoro-benzyl]-N-methyl-benzenesulfonamide

4-Bromo-N-[3-(3,4-dihydro-2H-quinoline-1-carbonyl)-4-nitro-benzyl]-N-methyl-benzenesulfonamide

4-Bromo-N-[4-bromo-3-(3,4-dihydro-2H-quinoline-1-carbonyl)-benzyl]-N-methyl-benzenesulfonamide; or pharmaceutically acceptable salts thereof.

21. A compound according to any preceding Claim, for use in therapy.
22. A compound according to Claim 21, for use in the therapy of hormone-dependent cancer.
23. A compound according to Claim 21, for use in the therapy of endometriosis.
24. A compound according to Claim 21, for use in the therapy of benign prostate hyperplasia.
25. A compound according to Claim 21, for use as a contraceptive agent.
26. A compound according to Claim 21, for use as an adjunct to an assisted fertilization program
27. A compound according to Claim 21, for use as a behaviour-modifying agent.
28. A use of compound according to any preceding Claim, for the manufacture of a medicament for the treatment of hormone-dependent cancer.
29. A use of compound according to any preceding Claim, for the manufacture of a medicament for the treatment of endometriosis.
30. A use of compound according to any preceding Claim, for the manufacture of a medicament for the treatment of benign prostate hyperplasia.
31. A use of compound according to any preceding Claim, for the manufacture of a medicament for contraception.
32. A use of compound according to any preceding Claim, for the manufacture of a medicament for assisting fertility.

33. A use of compound according to any preceding Claim, for the manufacture of a medicament for modifying behaviour.
34. A pharmaceutical composition comprising a compound according to any of claims 1 to 20.
35. A composition according to claim 34, which is a tablet or capsule for oral administration.
36. A composition according to any of claims 1 to 20 having one or more stereogenic centres.
37. A process of preparation of a composition which is a derivative according to general formula 1, or a pharmaceutically acceptable salt thereof,



wherein:

A^1 , A^2 and A^3 are each independently selected from A^5 and A^6 ; and

A^4 is either a covalent bond or A^5 ; provided that

when A^4 is a covalent bond then one of A^1 - A^3 is A^6 and the other two are A^5 and that

when A^4 is A^5 then all of A^1 - A^3 are A^5 ;

A^5 is selected from C- R^{13} and N;

A^6 is selected from N- R^{14} , S and O;

R^1 is selected from H, NH^{Y^1} and CO^{Y^2} and R^2 is H; or R^1 and R^2 are both methyl or together are =O;

R^3 , R^4 and R^5 are each independently H, lower alkyl or lower alkenyl;

R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} and R^{12} are each independently selected from H, lower alkyl, lower alkenyl, NH_2 , F, Cl, Br, O-alkyl, O-lower alkenyl, CH_2NMe_2 and CF_3 ;

R^{13} is selected from H, F, Cl, Br, NO_2 , NH_2 , OH, Me, Et, OMe, NMe_2 and CF_3 ;

R^{14} is selected from H, methyl and ethyl;

W is selected from CH and N;

X is selected from CH_2 , O, S, SO_2 , NH, N-lower alkyl and N-lower alkenyl;

Y^1 is selected from CO-lower alkyl, CO-lower alkenyl, $CO(CH_2)_bY^3$, $CO(CH_2)_bCO^{Y^3}$ and $CO(CH_2)_bNHCO^{Y^3}$;

Y^2 is selected from OR^{15} , $NR^{16}R^{17}$ and $NH(CH_2)_cCO^{Y^3}$;

Y^3 is selected from alkyl, lower alkenyl, OR^{18} and $NR^{16}R^{17}$;

R^{15} is selected from H, lower alkyl, lower alkenyl and $(CH_2)_aR^{18}$

R^{16} and R^{17} are each independently selected from H, lower alkyl, lower alkenyl and $(CH_2)_aR^{18}$, or together are $-(CH_2)_2-Z-(CH_2)_2-$;

R^{18} is selected from OH and phenyl, pyridyl, pyrimidinyl, pyrazinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl and thiadiazolyl, each of which may optionally have a lower alkyl, lower alkenyl group substituent;

Z is selected from O, CH_2 , S, SO_2 , NH, N-lower alkyl and N-lower alkenyl;

a is 0-4; and

b and c are 1-3;

which comprises the steps of:

- a) formation of an amide from a carboxylic acid and a cyclic amine; and
- b) formation of a sulphonamide from a sulphonyl chloride and an amine.

38. A process according to claim 37 in which step a) is reaction of a composition of formula 7 and a composition of formula 6 to obtain composition of formula 9; and step b) is reaction of the composition of formula 9 with a composition of formula 8 to form composition of formula 1, wherein formulae 6, 7, 8 and 9 are as defined in the specification.
39. A process according to claim 37 in which step a) is reaction of a composition of formula 10 and a composition of formula 6 to obtain composition of formula 1; and step b) is reaction of the composition of formula 7 with a composition of formula 8 to form the composition of formula 10, wherein formulae 6, 7, 8 and 9 are as defined in the specification.