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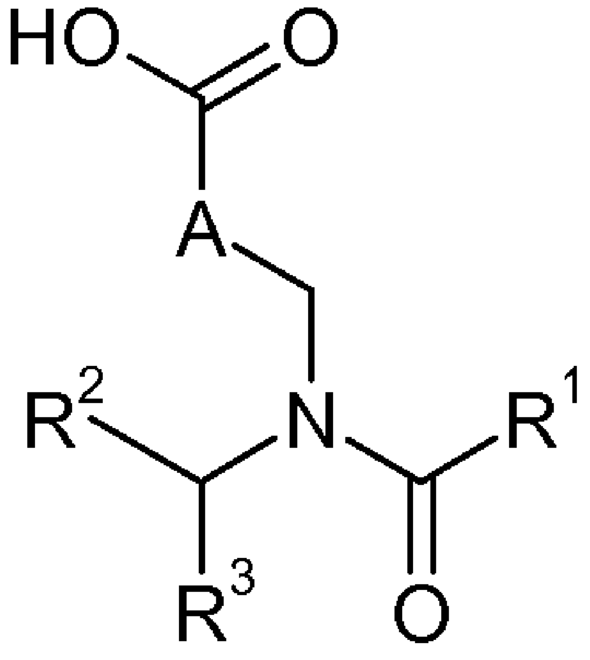

(I)

(57) Abstract: The invention provides a compound of the formula (I): wherein A, R^1, R^2 and R^3 are as defined herein, or a pharmaceutically acceptable salt thereof. Such compounds are small molecule TRPM8 blockers and therefore useful in the propylaxis or treatment of a wide range of diseases, conditions or syndromes, including cold allodynia and Raynaulds syndrome.

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ARYL SUBSTITUTED CARBOXAMIDE DERIVATIVES AS TRPM8 MODULATORS

This invention relates to amide derivatives. More particularly, this invention relates to aryl substituted amide derivatives and to compositions containing and the uses of such derivatives.

The amide derivatives of the present invention are TRPM8 blockers and have a number of therapeutic applications in the propylaxis or treatment of a wide range of diseases, conditions or syndromes affected by the blocking of TRPM8, including urological diseases, conditions or syndromes including over active bladder or interstitial cystitis and pain diseases, conditions or syndromes, including cold allodynia regardless of cause, trigeminal neuralgia, glossopharyngeal neuralgia, Raynauld’s syndrome, and schlerodema. A preferred use is in the treatment of cold allodynia or Raynauld’s syndrome.

Transient receptor potential (TRP) channels are one of the largest groups of ion channels. The super family is known to consist of at least 28 non-selective cation channels divided into 6 sub families including TRPM (melastatin). The TRP channels are cation selective and are activated by a variety of physical (eg temperature, osmolarity, mechanical) and chemical stimuli. The great majority of functionally characterised TRP channels are permeable to Ca^{2+}, are known to be widely distributed and also to participate in various cellular functions. The best characterised example of the TRP family is the capasicin – and heat – sensitive TRPV1 receptor (Caterina et al, Science 288, 306-313, 2000), but much less is known about cool-sensitive TRP’s.

TRPM8 (or Cold-Menthol receptor 1; CMR1), is a member of the TRP channel family and the 8th member of the TRPM family which was first cloned in 2002 (McKemy et al, Nature 2002, 416(6876), 52-58). It is activated by innocuous cool temperatures (with 50% activation around 18-19°C), noxious cold (<15°C) and by menthol and icilin, two substances which produce a cold sensation. It is located on primary nociceptive neurons (A-delta and C-fibres) and expressed by a subpopulation of sensory neurons in dorsal root ganglia and trigeminal ganglia where response to cooling correlate well with mRNA expression and menthol sensitivity.

Cold intolerance and pain induced by chemical or thermal cooling closely parallel symptoms seen in a wide range of clinical disorders and thus provides a rationale for the development of TRPM8 modulators as novel antihyperalgesic or antiallodynic agents. TRPM8 is also known to be expressed in brain, lungs, bladder, gastrointestinal tract, blood vessels, prostatic and immune cells, thereby providing the possibility for therapeutic modulation of a wide range of maladies.

Small molecule approaches to modulating TRPM8 receptors, including for example TRPM8 agonists and TRPM8 antagonists, are known in the art. Examples of such disclosures include those in international patent application WO-A-2006/040136 (publication date 26th April 2006); international patent application WO-A-2007/017093 (publication date 15th February 2007); international patent application WO-A-2007/134107 (publication date 22nd November 2007); international patent application WO-A-2009/012430 (publication date 22nd January 2009); international patent application WO-A-2009/038812 (publication date 26th March 2009); international patent application WO-A-2009/073203 (publication date 11th June 2009); and international patent application WO-A-2010/125831 (publication date 4th November 2010). Also disclosed are the uses of these compounds as medicaments for the prophylaxis or treatment of diseases associated with TRPM8 activity, including urological disorders, pain disorders, inflammatory conditions and certain cancers.

However, there remains a need for further small molecule approaches to the modulation of TRPM8 receptor activity, and in particular for new small molecule TRPM8 blockers.

The compounds of the present invention described herein are small molecule TRPM8 blockers.

The compounds of the present invention, being TRPM8 blockers, are therefore potentially useful in the propylaxis or treatment of a wide range of diseases, conditions or syndromes. Such diseases, conditions or syndromes include urological diseases, conditions or syndromes including, for example, over active bladder (detrusor overactivity), urinary incontinence, neurogenic detrusor overactivity (detrusor hyperflexia), idiopathic detrusor overactivity (detrusor instability), benign prostatic hyperplasia, painful bladder syndrome, interstitial cystitis and lower urinary tract symptoms.

Such diseases, conditions or syndromes which TRPM8 blockers of the present invention may also be useful in the propylaxis or treatment of also include pain diseases, conditions or syndromes including, for example, cold allodynia regardless of cause, thermal hyperalgesia, headaches, migraine, post operative pain, osteoarthritis, acute pain, chronic pain, cutaneous pain, somatic pain, visceral pain, referred pain including myocardial ischaemia, phantom pain, neuropathic pain (neuralgia), neuralgias such as trigeminal neuralgia, glossopharyngeal neuralgia, postherpatic neuralgia and causalgia, pain arising from injuries, cancer pain, pain arising from use of chemotherapeutic agents, pain arising from neurological diseases such as Parkinson’s disease, pain arising from spine and peripheral nerve surgery, brain tumors, traumatic brain injury, spinal cord trauma, chronic pain syndromes, chronic fatigue syndrome, pain arising from lupus, sarcoidosis, arachnoiditis, arthritis, rheumatic disease, period pain, back pain, lower back pain, joint pain, abdominal pain, chest pain, labour pain, musculoskeletal and skin diseases, diabetes, head trauma, fibromyalgia, Raynauld’s syndrome, and schlerodema. A preferred use is in the treatment of cold allodynia or Raynauld’s syndrome.

Other diseases, conditions or syndromes which TRPM8 blockers of the present invention may also be useful in the propylaxis or treatment of include inflammation diseases, conditions or syndromes including, for example, inflammatory bowel disease, rheumatoid arthritis; neurological diseases, conditions or syndromes including, for example, those diseases, conditions or syndromes associated with the modulation of the senstation of saiety perception including obesity, anorexia, weight maintenance, metabolic energy levels inflammatory conditions; and respiratory diseases, conditions or syndromes including, for example, including rhinitis, allergic rhinitis, asthma for example allergen induced asthma, exercise induced asthma, pollution induced asthma, viral induced asthma or cold induced asthma; chronic obstructive pulmonary disease (COPD) including chronic bronchitis; ailments that involve inflammation of one or more components of the respiratory system including emphysema, asthmatic bronchitis, bullous disease, and other pulmonary diseases involving inflammation which include cystic fibrosis, pigeon fancier’s disease, farmer’s lung, acute respiratory distress syndrome, pneumonia, aspiration or inhalation injury, fat embolism in the lung, acidosis inflammation of the lung, acute pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reaction, sepsis, status asthmaticus and hypoxia.

Yet further diseases, conditions or syndromes where acute blockade of TRPM8 may have utility include those such as stroke, traumatic brain injury, neonatal trauma including neonatal encephalopathy and neonatal asphyxia.

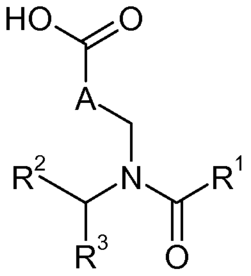
It is an objective of the invention to provide new small molecule TRPM8 blockers suitable for further development as drug candidates. It is a further object of the present invention that the compounds are useful for the treatment of a wide range of diseases, conditions or syndromes, which disease, condition or syndrome is affected by the at least partial blocking of TRPM8, and in particular urological diseases, conditions or syndromes, including over active bladder, painful bladder syndrome, and interstitial cystitis; and pain diseases, conditions or syndromes, including cold allodynia regardless of cause, trigeminal neuralgia, glossopharyngeal neuralgia, Raynauld's syndrome, and schlerodema.

It is preferred that the compounds of the present invention described herein selectively bind at the TRPM8 channels as opposed to other ion channels, in particular other TRP channels. Compounds of formula (I) also preferably have a kinetic interaction with the TRPM8 target such that they are effective for use for the propylaxis or treatment of a wide range of diseases, conditions or syndromes, which disease, condition or syndrome is affected by the at least partial blocking of TRPM8, whilst at the same time demonstrating a reduced side effect profile.

The compounds of the present invention should also preferably be well absorbed from the GI tract, be metabolically stable and possess favourable pharmacokinetic properties. They should preferably be non-toxic to mammals, more preferably be non-toxic to humans. In addition they should preferably not form metabolites which have a toxic or allergic profile. Furthermore, the most preferred compounds will exist in a physical form which is stable, non-hygroscopic, and easily formulated.

Summary of the Invention

The invention provides as Embodiment (1), a compound of the formula (I):



(I)

wherein

A is (i) phenyl substituted at the 1 position by the carboxylic acid and the 3 position by the alkyl amido group and having either no further substituents or a halo group at the 4 position, or
(ii) pyridyl substituted at the 6 position by the carboxylic acid and the 2 position by the alkyl amido group;

R^1 is an 8 to 12 membered unsaturated or partially unsaturated fused bicyclic carbocycle or an 8 to 12 membered unsaturated or partially unsaturated fused bicyclic heterocycle containing 1, 2 or 3 heteroatoms each independently selected from nitrogen, oxygen and sulphur, said R^1 being optionally substituted with one or more substituents each independently selected from the group consisting of halo, $(C_1\text{-}C_3)$alkyl, halo$(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, and halo$(C_1\text{-}C_3)$alkoxy;

R^2 is methyl or ethyl; and

R^3 is: (i) phenyl optionally substituted by one or more halo atoms, or
(ii) furanyl optionally substituted with $(C_1\text{-}C_3)$alkyl;

or a pharmaceutically acceptable salt thereof.

As used herein the term alkyl means an alicyclic, saturated hydrocarbon chain of the formula C_nH_{2n+1} containing the requisite number of carbon atoms, which may be linear or branched. Examples of such groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl.

As used herein the term halo means fluoro, chloro, bromo or iodo.

As used herein the term alkoxy means an alicyclic, saturated hydrocarbon chain of the formula OC_nH_{2n+1} containing the requisite number of carbon atoms, which may be linear or branched. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy.

Haloalkyl and haloalkoxy mean an alkyl or alkoxy group, according to the definitions provided above, containing the requisite number of carbon atoms, substituted with one or more halo atoms as hereinbefore defined.

Specific examples of 5- or 6- membered aromatic heterocycles include oxiranyl, aziridinyl, oxetanyl, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl, each of which may be optionally substituted as specified.

Specific examples of 8 to 12 membered unsaturated or partially unsaturated fused bicyclic carbocycles include indenyl and naphthalenyl, each of which may be optionally substituted as specified.

Specific examples of 8 to 12 membered unsaturated or partially unsaturated fused bicyclic heterocycles containing 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulphur include, but are not limited to, benzodihydrofuranyl, benzodioxolanyl, benzofuranyl, benzimidazolyl, benzoxadiazolyl, benzopyrazolyl, benzothiazolyl, benzothiophenyl, benzotriazolyl, chromanyl, cinnolinyl, dihydroindanolyl, imidazopyridinyl, imidazopyridyl, indazolyl, indolizinyl, indolyl, isoquinolinyl, 1,8-naphthyridinyl, pyridopyridyl, pyrrolopyridinyl, quinolinyl, quinoxalinyl, tetrahydobenzopyrazinyl, tetrahydrobenzopyridyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, 1H-pyrrolo[2,3-c]pyridinyl, 4,5,6,7-tetrahydro-1H-indazolyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridinyl and 1H-pyrrolo[2,3-b]pyridinyl, each of which may be optionally substituted as specified.

In the following embodiments of the invention, any group not specifically defined has the same meaning as given for formula (I) above.

In Embodiment (2), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to Embodiment (1), wherein the

A ring is phenyl. When A is phenyl it is preferred that it has no further substituents or is substituted at the 4 position by fluoro.

In another Embodiment (3), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to Embodiment (1), wherein A is pyridyl. When A is pyridyl, it is preferred that it has no further substituents.

In another Embodiment (4), the invention provies compound of formula (I), or a pharmaceutically acceptable salt thereof, according to Embodiment (1), wherein A is phenyl and has no further substituents.

In another Embodiment (5), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (4), wherein R^1 is an 8 to 10 membered unsaturated or partially unsaturated fused bicyclic carbocycle or an 8 to 10 membered unsaturated or partially unsaturated fused bicyclic heterocycle containing 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulphur, said R^1 being optionally substituted with one or more substituents independently selected from the group consisting of halo, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, (C_1-C_3)alkoxy, and halo(C_1-C_3)alkoxy.

In another embodiment (6), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (4), wherein R^1 an 8 to 12 membered unsaturated or partially unsaturated fused bicyclic carbocycle or an 8 to 12 membered unsaturated or partially unsaturated fused bicyclic heterocycle containing 1, 2 or 3 heteroatoms each independently selected from nitrogen, oxygen and sulphur, providing that said carbocycle or heterocycle is not 1-methyl-1H-benzotriazol-5-yl, quinolin-2-yl, 2-methyl-1H-benzimidazol-5-yl, imidazo[1,2-a]pyrimidin-2-yl, indolizin-2-yl, 2,3-dihydro-1,4-benzodioxin-2-yl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-yl, 1H-indazol-6-yl, 1H-benzimidazol-5-yl or 1H-benzotriazol-5-yl, said R^1 being optionally substituted with one or more substituents each independently selected from the group consisting of halo, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, (C_1-C_3)alkoxy, and halo(C_1-C_3)alkoxy;

In another Embodiment (7), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (4), wherein R^1 is selected from benzodioxolanyl, benzofuranyl, benzimidazolyl, benzopyrazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, imidazopyridinyl, indolyl, isoquinolinyl, naphthalenyl, pyrrolopyridinyl, quinolinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, 1H-pyrrolo[2,3-c]pyridinyl, 4,5,6,7-tetrahydro-1H-indazolyl, benzdihydrofuranyl, benzoxadiazolyl, benztriazolyl, chromanyl, dihydroindanolyl, imidazopyridyl, indazolyl, indolizinyl, 1,8-naphthyridinyl, pyridopyridyl, quinoxalinyl, tetrahydobenzopyrazinyl, tetrahydrobenzopyridyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridinyl, and 1H-pyrrolo[2,3-b]pyridinyl, said R^1 being optionally substituted with one or more substituents independently selected from the group consisting of halo, $(C_1\text{-}C_3)$alkyl, halo$(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, and halo$(C_1\text{-}C_3)$alkoxy.

In another Embodiment (8), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (4), wherein R^1 is selected from benzodioxolanyl, which is unsubstituted; benzofuranyl which is unsubstituted; benzimidazolyl which is unsubstituted, or substituted with halo, for example fluoro; or $(C_1\text{-}C_3)$alkyl, for example methyl; benzopyrazolyl which is unsubstituted or substituted with $(C_1\text{-}C_3)$alkyl, for example methyl; benzothiazolyl which is unsubstituted; benzothiophenyl which is unsubstituted or substituted with $(C_1\text{-}C_3)$alkyl, for example methyl; cinnolinyl which is unsubstituted; imidazopyridinyl which is unsubstituted; indolyl which is unsubstituted, or it is substituted by one or more substituents selected from halo, for example chloro; or $(C_1\text{-}C_3)$alkyl, for example methyl; isoquinolinyl, which is unsubstituted; naphthalenyl which is unsubstituted; pyrrolopyridinyl, which is unsubstituted; quinolinyl, which is unsubstituted or is substituted by one or more substituents selected from $(C_1\text{-}C_3)$alkyl, for example methyl; 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl which is unsubstituted; 1H-pyrrolo[2,3-c]pyridinyl which is unsubstituted; and 4,5,6,7-tetrahydro-1H-indazolyl which is unsubstituted.

In another Embodiment (9), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (4), wherein R^1 is selected from benzodioxolanyl, which is unsubstituted; benzofuranyl which is unsubstituted; benzimidazol-2-yl which is unsubstituted, or substituted with halo, for example fluoro; or $(C_1\text{-}C_3)$alkyl, for example methyl; benzopyrazolyl which is unsubstituted or substituted with $(C_1\text{-}C_3)$alkyl, for example methyl; benzothiazolyl which is unsubstituted; benzothiophenyl which is unsubstituted or substituted with $(C_1\text{-}C_3)$alkyl, for example methyl; cinnolinyl which is unsubstituted; imidazopyridinyl which is unsubstituted; indolyl which is unsubstituted, or it is substituted by one or more substituents selected from halo, for example chloro; or $(C_1\text{-}C_3)$alkyl, for example methyl; isoquinolinyl, which is unsubstituted;

naphthalenyl which is unsubstituted; pyrrolopyridinyl, which is unsubstituted; quinolin-3-yl, which is unsubstituted or is substituted by one or more substituents selected from (C_1-C_3)alkyl, for example methyl; 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl which is unsubstituted; 1H-pyrrolo[2,3-c]pyridinyl which is unsubstituted; and 4,5,6,7-tetrahydro-1H-indazolyl which is unsubstituted.

In another Embodiment (10), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (4), wherein R^1 is quinolinyl, which is unsubstituted or is substituted by one or more substituents selected from (C_1-C_3)alkyl, for example methyl.

In another Embodiment (11), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (4), wherein R^1 is quinolin-3-yl, which is unsubstituted or is substituted by one or more substituents selected from (C_1-C_3)alkyl, for example methyl.

In another Embodiment (12), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (4), wherein R^1 is quinolin-3-yl.

In another Embodiment (13), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (12), wherein R^3 is phenyl which is unsubstituted, or optionally substituted by one or more halo atoms, for example fluoro, chloro or bromo (preferably fluoro), to form, for example, fluorophenyl, difluorophenyl, chlorophenyl, or dibromo, fluorophenyl.

In another Embodiment (14), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (12), wherein R^3 is furanyl, optionally substituted with (C_1-C_3)alkyl, for example methyl to form methylfuranyl.

In another Embodiment (15), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (12), wherein R^3 is 4-fluorophenyl.

In another Embodiment (16), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (15), wherein R^2 is methyl.

In another Embodiment (17), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (15), wherein R^2 is ethyl.

In another Embodiment (18), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to Embodiment (1), wherein A is phenyl; R^1 is selected from benzodioxolanyl, benzofuranyl, benzimidazolyl, benzopyrazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, imidazopyridinyl, indolyl, isoquinolinyl, naphthalenyl, pyrrolopyridinyl, quinolinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, 1H-pyrrolo[2,3-c]pyridinyl, and 4,5,6,7-tetrahydro-1H-indazolyl; R^2 is methyl or ethyl; and R^3 is phenyl or furanyl.

In another Embodiment (19), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to Embodiment (1), wherein A is pyridyl; R^1 is selected from benzodioxolanyl, benzofuranyl, benzimidazolyl, benzopyrazolyl, benzothiazolyl, benzothiophenyl, cinnolinyl, imidazopyridinyl, indolyl, isoquinolinyl, naphthalenyl, pyrrolopyridinyl, quinolinyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, 1H-pyrrolo[2,3-c]pyridinyl, and 4,5,6,7-tetrahydro-1H-indazolyl; R^2 is methyl or ethyl; and R^3 is phenyl or furanyl.

In another Embodiment (20), the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of Embodiments (1) to (19), which has the absolute (R) stereochemistry at the chiral carbon atom bearing the R^2 and R^3 substituents.

Specific preferred compounds according to the invention are those listed in the Examples section below and the pharmaceutically acceptable salts thereof.

Particularly preferred compounds of formula (I) include:
3-({[(1R)-1-(4-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid,
3-({[1-(4-fluorophenyl)ethyl](isoquinolin-3-ylcarbonyl)amino}methyl)benzoic acid,
3-({[1-(2,4-difluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid,
3-({[(1R)-1-(4-fluorophenyl)propyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid,

3-({[(1R)-1-(4-fluorophenyl)propyl](imidazo[1,2-a]pyridin-2-ylcarbonyl)amino}methyl)benzoic acid,
3-({[(1R)-1-(4-fluorophenyl)propyl](isoquinolin-3-ylcarbonyl)amino}methyl)benzoic acid,
3-({[(1R)-1-(5-methyl-2-furyl)propyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid,
3-({[(1R)-1-(4-fluorophenyl)propyl][(7-methylquinolin-3-yl)carbonyl]amino}methyl)benzoic acid,
3-({[(1R)-1-(4-fluorophenyl)propyl][(6-fluoroquinolin-3-yl)carbonyl]amino}methyl)benzoic acid,
3-({[(1R)-1-(4-fluorophenyl)ethyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)benzoic acid,
3-({[(1R)-1-(4-fluorophenyl)ethyl](isoquinolin-3-ylcarbonyl)amino}methyl)benzoic acid,
3-({[(1R)-1-(4-fluorophenyl)ethyl][(6-fluoroquinolin-3-yl)carbonyl]amino}methyl)benzoic acid,
3-({[(1R)-1-(2,4-difluorophenyl)ethyl](isoquinolin-3-ylcarbonyl)amino}methyl)benzoic acid,
3-({[(1R)-1-(2,4-difluorophenyl)propyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)benzoic acid,
3-({[(1R)-1-(2,4-difluorophenyl)propyl](isoquinolin-3-ylcarbonyl)amino}methyl)benzoic acid,
3-({[(1R)-1-(2,4-difluorophenyl)propyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid,
6-({[(1R)-1-(2,4-difluorophenyl)propyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)pyridine-2-carboxylic acid,
6-({[(1R)-1-(2,4-difluorophenyl)propyl](isoquinolin-3-ylcarbonyl)amino}methyl)pyridine-2-carboxylic acid,
3-({[(1R)-1-(2,4-difluorophenyl)ethyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)benzoic acid,
6-({[(1R)-1-(4-fluorophenyl)propyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)pyridine-2-carboxylic acid,
3-({(1-benzothien-2-ylcarbonyl)[(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid,
3-({[(1R)-1-(4-fluorophenyl)ethyl][(3-methyl-1-benzothien-2-yl)carbonyl]amino}methyl)benzoic acid,
3-({[(5-fluoro-1H-benzimidazol-2-yl)carbonyl][(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid,

3-({[(1R)-1-(3-chlorophenyl)ethyl](isoquinolin-3-ylcarbonyl)amino}methyl)benzoic acid,
3-({[(1R)-1-(3-chlorophenyl)ethyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)benzoic acid,
3-({[(1R)-1-(3-chlorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid, and
3-({(cinnolin-3-ylcarbonyl)[(1R)-1-(2,4-difluorophenyl)propyl]amino}methyl)benzoic acid,
or a pharmaceutically acceptable salt of any of these compounds.

A more particularly preferred compound of formula (I) is 3-({[(1R)-1-(4-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid, or a pharmaceutically acceptable salt thereof.

Detailed Description

Figure 1 provides in vivo data demonstrating the effects of Example 71 at 16.3, 46.67 and 153.33ug/kg/min on Menthol Induced Reduction in Bladder Capacity in the Anaesthetised Guinea Pig.

References to compounds of the formula (I) below are to be construed to include a reference to any one of the Embodiments described above, any of the preferred compounds or groups of compounds alluded to above and any of the Examples specifically disclosed below.

Some compounds of the formula (I) may exist in several different tautomeric forms. Tautomerism, or tautomeric isomerism, occurs where structural isomers are interconvertible via a low energy barrier. It can take the form of proton tautomerism, so called valence tautomerism in compounds which contain an aromatic moiety. In some compounds different tautomeric isomers may exist with respect to the position of certain protecting groups or prodrug moieties. All references to compounds of formula (I) should be taken to include tautomers thereof, whether illustrated or not. Furthermore, one of ordinary skill would understand that certain intermediates used in the preparation of compounds capable of tautomerising are themselves capable of existing in different tautomeric forms.

Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isothionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

For a review on suitable salts, see “Handbook of Pharmaceutical Salts: Properties, Selection, and Use” by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

A pharmaceutically acceptable salt of a compound of formula (I) may be readily prepared by mixing together solutions of the compound of formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the salt may vary from completely ionised to almost non-ionised.

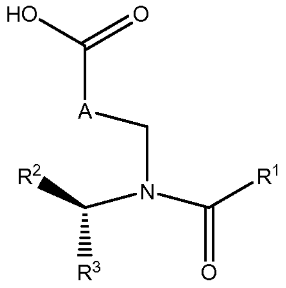
The compounds of formula (I) and their pharmaceutically acceptable salts may exist in both unsolvated and solvated forms. The term ‘solvate’ is used herein to describe a molecular complex comprising the compound of formula (I) and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term ‘hydrate’ is employed when said solvent is water.

The compounds of formula (I) and their pharmaceutically acceptable salts may also exist as complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Such complexes also include complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

Hereinafter all references to compounds of formula (I) include references to pharmaceutically acceptable salts, solvates and complexes thereof and to solvates and complexes of said salts.

The invention covers compounds of formula (I), as hereinbefore defined, as well as polymorphs, prodrugs (including tautomeric forms of such prodrugs), and isomers thereof (including optical, geometric and tautomeric isomers).

Compounds of formula (I) have a chiral centre. For the avoidance of doubt, compounds of Formula (I) include the R-isomers of compounds of Formula (I); the S-isomers of compounds of formula (I); and mixtures thereof, including the racemate, usually defined as a 50:50 mixture of the R-isomer and the S-isomer. Preferred compounds of the present invention are those of Formula (IA) which can be depicted to have the following stereochemical orientation indicated below:



IA

As stated, the invention includes all polymorphs of the compounds of formula (I) as hereinbefore defined.

Also within the scope of the invention are so-called ‘prodrugs’ of the compounds of formula (I). Thus certain derivatives of compounds of formula (I), which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as ‘prodrugs’.

Further information on the use of prodrugs may be found in ‘Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and ‘Bioreversible Carriers in Drug Design’, Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as ‘pro-moieties’ as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

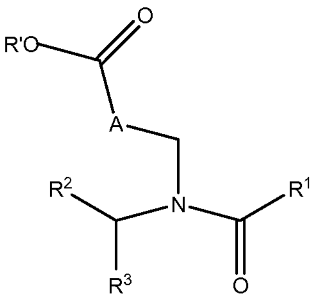
One skilled in the art would recognise that many different pro-drug forms of compounds of the present invention are possible. However, some illustrative examples of prodrugs in accordance with the invention include:

(i) where the compound of formula (I) contains a carboxylic acid functionality (-COOH), an ester thereof, for example, replacement of the hydrogen with (C_1-C_8)alkyl;

(ii) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with (C_1-C_6)alkanoyloxymethyl; and

(iii) where the compound of formula (I) contains a primary or secondary amino functionality ($-NH_2$ or -NHR where $R \neq H$), an amide thereof, for example, replacement of one or both hydrogens with (C_1-C_{10})alkanoyl.

A particularly useful prodrug of compounds of Formula (I), is formed by esterification of the acid group bonded to ring A with R’ wherein R’ is (C_1-C_4) alkyl. Such compounds are prepared by reaction of the COOH group of compounds of Formula (I), with a suitable alcohol, or pharmaceutically acceptable salts thereof. Such prodrug compounds can generally be schematically represented as shown below by Formula (IB):



IB

or pharmaceutically acceptable salts thereof, wherein A, R^1, R^2, and R^3 are as defined in Formula (I) and R' is (C_1-C_4) alkyl.

As such the invention specifically provides for such preferred prodrugs as set out in Formula (IB) above, and pharmaceutically acceptable salts, thereof. Such prodrugs are particularly useful because of their potential for improved bioavailability when compared to the parent compound, i.e. that with the unsubstituted acid group moiety.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Finally, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I).

Compounds of formula (I) may contain one or more asymmetric carbon atoms in addition to the chiral centre discussed above and exist in a number of stereoisomeric forms. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric *cis*/*trans* (or Z/E) isomers are possible. Where the compound contains, for example, a keto or oxime group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof.

Also included are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Cis/*trans* isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC)

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of formula (I) (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, “Stereochemistry of Organic Compounds” by E L Eliel (Wiley, New York, 1994).

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of formula (I) include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, and ^{125}I are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent~~s~~ in place of the non-labeled reagent previously employed.

In one embodiment, the compounds of formula (I) are comprised of atoms such that the average atomic mass or mass number for each atom of each element prsent corresponds to the average atomic mass or mass number for that element as it occurs in nature.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

The compounds of formula (I), being TRPM8 blockers, are potentially useful in the treatment of a range of disorders.

As used herein the term TRPM8 blocker is taken to mean a compound that causes a decrease in the activation of TRPM8 by agonist (menthol or WS-12), cold or voltage stimulation. For example, such a blocker may be identified though measuring the inhibition of Ca^{2+} signal in cells containing TRPM8 ion channels using a method such as the in vitro assay described herein. Alternatively, a TRPM8 blocker can be identified by electrophysiological approaches, for example using those methods disclosed in McKemy et al, Nature 2002, 416(6876), 52-58.

Urological diseases, conditions or syndromes which may be usefully treated or prevented with the compounds of formula (I) include, but are not limited to, over active bladder (detrusor overactivity), urinary incontinence, neurogenic detrusor overactivity (detrusor hyperflexia), idiopathic detrusor overactivity (detrusor instability), benign prostatic hyperplasia, painful bladder syndrome, interstitial cystitis and lower urinary tract symptoms.

Over Active Bladder (**OAB**) is defined as urgency, with or without urge incontinence, usually with frequency and nocturia [Abrams et al., Neurourology and Urodynamics 21:167-178 (2002)]. Prevalence of OAB in men and women is similar, with approximately 16% of the population of the USA suffering from the condition [Stewart et al, Prevalence of Over active Bladder in the United States: Results from the NOBLE Program; Abstract Presented at the 2nd International Consultation on Incontinence, July 2001, Paris, France].

The terms OAB Wet and OAB Dry describe OAB patients with or without urinary incontinence respectively. Until recently, the cardinal symptom of OAB was believed to be urinary incontinence. However, with the advent of the new terms this is clearly not meaningful for the large number of sufferers who are not incontinent (i.e. OAB Dry patients). Thus, a recent study from Liberman et al ['Health Related Quality of Life Among Adults with Symptoms of Over active Bladder:Results From A US Community-Based Survey'; Urology 57(6), 1044-1050, 2001] examined the impact of all OAB symptoms on the quality of life of a community-based sample of the US population. This study demonstrated that individuals suffering from OAB without any demonstrable loss of urine have an impaired quality of life when compared with controls.

Urinary incontinence (any condition in which there is an involuntary leakage of urine), including stress urinary incontinence, urge urinary incontinence and mixed urinary incontinence, over active bladder with associated urinary incontinence, enuresis, nocturnal enuresis, continuous urinary incontinence, and situational urinary incontinence such as incontinence during sexual intercourse.

Interstitial cystitis (IC) is a chronic bladder disease, of unknown origin, characterized by symptoms of pain, such as pelvic pain, and lower urinary tract symptoms (LUTS) such as increased urinary frequency or urgency. More recently terminology has evolved to include painful bladder syndrome (PBS) (MacDiarmid SA et al, Rev Urol, 9(1), 9-16 (2007)) or bladder pain syndrome (BPS) (van der Merve et al, European Urology, 53, 60-67 (2008)), along with IC, that is IC/PBS/BPS to collectively describe this symptom complex.

Prevalence rates of IC/PBS/BPS vary from 67 to 230 per 100,000 women having clinically confirmed disease, although the number is likely higher than this due to under- or mis-diagnosis, commonly as endometriosis, recurrent urinary tract infection, over active bladder or vulvodynia (Forrest J B et al, Clinical Courier 24(3), 1-8 (2006)).
IC has a significant impact on quality of life, affecting travel, family relationships, and employment (Slade et al, Urol., 49 (5A Suppl), 10-3(1997)), as well as being associated with depressive symptoms (Rothrock et al, J. Urol., 167: 1763-1767(2002)).

There are few well-performed, placebo-controlled, randomized trials of therapies aimed at IC and treatment often consists of a multimodal trial-and-error approach, as evidenced by one review of patients in the Interstitial Cystitis Data Base study which reported 183 different types of treatment (Rovner et al, J. Urol., 56, 940-5(2000)).

No single etiology has been identified, and it is most likely a multifactorial process with several urologic insults causing a self-perpetuating process of epithelial cell dysfunction, C-nerve fibre activation and proliferation of mast cells, leading to worsening tissue damage, scarring and fibrosis. The repetitive stimulation of C fibres from inflammation, and upregulation of sensory nerves in the bladder, ultimately leads to permanent alterations (centralization) resulting in hyperalgesia, chronic bladder pain and voiding dysfunction (Forrest et al, Clinical Courier, 24(3):1-8 (2006)).

Although no consensus has been reached on the fundamental causes of IC, existing data have led to speculation that three pathophysiologic mechanisms may be implicated: epithelial dysfunction, mast cell activation and neurogenic inflammation (Nazif et al, Urol., 69 (Suppl 4A), 24-33(2007)).

LUTS comprise three groups of urinary symptoms, which may be defined as storage (irritative), voiding (obstructive) and post-micturition symptoms. Storage symptoms comprise urgency, frequency, nocturia, urgency incontinence and stress incontinence, which can be associated with over active bladder (OAB) and benign prostatic hyperplasia (BPH). Voiding symptoms comprise hesitancy, poor flow, intermittency, straining and dysuria. Post-micturition symptoms comprise terminal dribbling, post-void dribbling and a sense of incomplete emptying.

BPH is a chronically progressive disease that can lead to complications such as acute urinary retention, recurrent urinary tract infections, bladder stones and renal dysfunction. The prevalence and average severity of LUTS associated with BPH in men increases with age.

BPH leads to an increase in prostate volume, creating urethral and bladder outflow obstruction as well as secondary changes in bladder function. The effects of this are manifested by both storage (irritative) and voiding (obstructive) symptoms.

Pain diseases, conditions or syndromes which may be usefully treated or prevented with the compounds of formula (I) include, but are not limited to, cold allodynia regardless of cause, thermal hyperalgesia, headaches, migraine, post operative pain, osteoarthritis, acute pain, chronic pain, cutaneous pain, somatic pain, visceral pain, referred pain including myocardial ischaemia, phantom pain, neuropathic pain (neuralgia), neuralgias such as trigeminal neuralgia, glossopharyngeal neuralgia, postherpatic neuralgia and causalgia, pain arising from injuries, cancer pain, pain arising from use of chemotherapeutic agents, pain arising from neurological diseases such as Parkinson’s disease, pain arising from spine and peripheral nerve surgery, brain tumors, traumatic brain injury, spinal cord trauma, chronic pain syndromes, chronic fatigue syndrome, pain arising from lupus, sarcoidosis, arachnoiditis, arthritis, rheumatic disease, period pain, back pain, lower back pain, joint pain, abdominal pain, chest pain, labour pain, musculoskeletal and skin diseases, diabetes, head trauma, fibromyalgia, Raynauld’s syndrome, and schlerodema.

The treatment of pain using a compound of formula (I) is a preferred embodiment of the invention. The treatment of cold allodynia is a particularly preferred embodiment. The treatment of Raynauld’s syndrome is another particularly preferred embodiment.

Physiological pain is an important protective mechanism designed to warn of danger from potentially injurious stimuli from the external environment. The system operates through a specific set of primary sensory neurones and is activated by noxious stimuli *via* peripheral transducing mechanisms (see Millan, 1999, Prog. Neurobiol., 57, 1-164 for a review). These sensory fibres are known as nociceptors and are characteristically small diameter axons with slow conduction velocities. Nociceptors encode the intensity, duration and quality of noxious stimulus and by virtue of their topographically organised projection to the spinal cord, the location of the stimulus. The nociceptors are found on nociceptive nerve fibres of which there are two main types, A-delta fibres (myelinated) and C fibres (non-myelinated). The activity generated by nociceptor input is transferred, after complex processing in the dorsal horn, either directly, or via brain stem relay nuclei, to the ventrobasal thalamus and then on to the cortex, where the sensation of pain is generated.

Pain may generally be classified as acute or chronic. Acute pain begins suddenly and is short-lived (usually twelve weeks or less). It is usually associated with a specific cause such as a specific injury and is often sharp and severe. It is the kind of pain that can occur after specific injuries resulting from surgery, dental work, a strain or a sprain. Acute pain does not generally result in any persistent psychological response. In contrast, chronic pain is long-term pain, typically persisting for more than three months and leading to significant psychological and emotional problems. Common examples of chronic pain are neuropathic pain (e.g. painful diabetic neuropathy, postherpetic neuralgia), carpal tunnel syndrome, back pain, headache, cancer pain, arthritic pain and chronic post-surgical pain.

When a substantial injury occurs to body tissue, *via* disease or trauma, the characteristics of nociceptor activation are altered and there is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. These effects lead to a hightened sensation of pain. In acute pain these mechanisms can be useful, in promoting protective behaviours which may better enable repair processes to take place. The normal expectation would be that sensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is often due to nervous system injury. This injury often leads to abnormalities in sensory nerve fibres associated with maladaptation and aberrant activity (Woolf & Salter, 2000, Science, 288, 1765-1768).

Clinical pain is present when discomfort and abnormal sensitivity feature among the patient’s symptoms. Patients tend to be quite heterogeneous and may present with various pain symptoms. Such symptoms include: 1) spontaneous pain which may be dull, burning, or stabbing; 2) exaggerated pain responses to noxious stimuli (hyperalgesia); and 3) pain produced by normally innocuous stimuli (allodynia -

Meyer et al., 1994, Textbook of Pain, 13-44). Although patients suffering from various forms of acute and chronic pain may have similar symptoms, the underlying mechanisms may be different and may, therefore, require different treatment strategies. Pain can also therefore be divided into a number of different subtypes according to differing pathophysiology, including nociceptive, inflammatory and neuropathic pain.

Nociceptive pain is induced by tissue injury or by intense stimuli with the potential to cause injury. Pain afferents are activated by transduction of stimuli by nociceptors at the site of injury and activate neurons in the spinal cord at the level of their termination. This is then relayed up the spinal tracts to the brain where pain is perceived (Meyer et al., 1994, Textbook of Pain, 13-44). The activation of nociceptors activates two types of afferent nerve fibres. Myelinated A-delta fibres transmit rapidly and are responsible for sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey a dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of pain from central nervous system trauma, strains/sprains, burns, myocardial infarction and acute pancreatitis, post-operative pain (pain following any type of surgical procedure), posttraumatic pain, renal colic, cancer pain and back pain. Cancer pain may be chronic pain such as tumour related pain (e.g. bone pain, headache, facial pain or visceral pain) or pain associated with cancer therapy (e.g. postchemotherapy syndrome, chronic postsurgical pain syndrome or post radiation syndrome). Cancer pain may also occur in response to chemotherapy, immunotherapy, hormonal therapy or radiotherapy. Back pain may be due to herniated or ruptured intervertabral discs or abnormalities of the lumber facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament. Back pain may resolve naturally but in some patients, where it lasts over 12 weeks, it becomes a chronic condition which can be particularly debilitating.

Neuropathic pain is currently defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system. Nerve damage can be caused by trauma and disease and thus the term ‘neuropathic pain’ encompasses many disorders with diverse aetiologies. These include, but are not limited to, peripheral neuropathy, diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, back pain, cancer neuropathy, HIV neuropathy, phantom limb pain, carpal tunnel syndrome, central post-stroke pain and pain associated with chronic alcoholism, hypothyroidism, uremia, multiple sclerosis, spinal cord injury, Parkinson’s disease, epilepsy and vitamin deficiency. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patient's quality of life (Woolf and Mannion, 1999, Lancet, 353, 1959-1964). The symptoms of neuropathic pain are difficult to treat, as they are often heterogeneous even between patients with the same disease (Woolf & Decosterd, 1999, Pain Supp., 6, S141-S147; Woolf and Mannion, 1999, Lancet, 353, 1959-1964). They include spontaneous pain, which can be continuous, and paroxysmal or abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

The inflammatory process is a complex series of biochemical and cellular events, activated in response to tissue injury or the presence of foreign substances, which results in swelling and pain (Levine and Taiwo, 1994, Textbook of Pain, 45-56). Arthritic pain is the most common inflammatory pain. Rheumatoid disease is one of the commonest chronic inflammatory conditions in developed countries and rheumatoid arthritis is a common cause of disability. The exact aetiology of rheumatoid arthritis is unknown, but current hypotheses suggest that both genetic and microbiological factors may be important (Grennan & Jayson, 1994, Textbook of Pain, 397-407). It has been estimated that almost 16 million Americans have symptomatic osteoarthritis (OA) or degenerative joint disease, most of whom are over 60 years of age, and this is expected to increase to 40 million as the age of the population increases, making this a public health problem of enormous magnitude (Houge & Mersfelder, 2002, Ann Pharmacother., 36, 679-686; McCarthy et al., 1994, Textbook of Pain, 387-395). Most patients with osteoarthritis seek medical attention because of the associated pain. Arthritis has a significant impact on psychosocial and physical function and is known to be the leading cause of disability in later life. Ankylosing spondylitis is also a rheumatic disease that causes arthritis of the spine and sacroiliac joints. It varies from intermittent episodes of back pain that occur throughout life to a severe chronic disease that attacks the spine, peripheral joints and other body organs.

Another type of inflammatory pain is visceral pain which includes pain associated with inflammatory bowel disease (IBD). Visceral pain is pain associated with the viscera, which encompass the organs of the abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain associated with the viscera can be divided into digestive visceral pain and non-digestive visceral pain. Commonly encountered gastrointestinal (GI) disorders that cause pain include functional bowel disorder (FBD) and inflammatory bowel disease (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including, in respect of FBD, gastro-esophageal reflux, dyspepsia, irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and, in respect of IBD, Crohn's disease, ileitis and ulcerative colitis, all of which regularly produce visceral pain. Other types of visceral pain include the pain associated with dysmenorrhea, cystitis and pancreatitis and pelvic pain.

It should be noted that some types of pain have multiple aetiologies and thus can be classified in more than one area, e.g. back pain and cancer pain have both nociceptive and neuropathic components.

Other types of pain include:

- pain resulting from musculo-skeletal disorders, including myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, glycogenolysis, polymyositis and pyomyositis;
- heart and vascular pain, including pain caused by angina, myocardical infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleredoma and skeletal muscle ischemia;
- head pain, such as migraine (including migraine with aura and migraine without aura), cluster headache, tension-type headache mixed headache and headache associated with vascular disorders;
- erythermalgia; and
- orofacial pain, including dental pain, otic pain, burning mouth syndrome and temporomandibular myofascial pain.

Repiratory diseases, conditions or syndromes which may be usefully treated or prevented with the compounds of formula (I) include, but are not limited to, diseases, conditions or syndromes including, for example, including rhinitis, allergic rhinitis, asthma for example allergen induced asthma, exercise induced asthma, pollution induced asthma, viral induced asthma or cold induced asthma; chronic obstructive pulmonary disease (COPD) including chronic bronchitis; aliments that involve inflammation of one or more components of the respiratory system including emphysema, asthmatic bronchitis, bullous disease, and other pulmonary diseases involving inflammation which include cystic fibrosis, pigeon fancier's disease, farmer's lung, acute respiratory distress syndrome, pneumonia, aspiration or inhalation injury, fat embolism in the lung, acidosis inflammation of the lung, acute pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reaction, sepsis, status asthmaticus and hypoxia.

Types of asthma include atopic asthma, non-atopic asthma, allergic asthma, atopic bronchial IgE-mediated asthma, bronchial asthma, essential asthma, true asthma, intrinsic asthma caused by pathophysiologic disturbances, extrinsic asthma caused by environmental factors, essential asthma of unknown or inapparent cause, bronchitic asthma, emphysematous asthma, exercise-induced asthma, allergen induced asthma, cold air induced asthma, occupational asthma, infective asthma caused by bacterial, fungal, protozoal, or viral infection, non-allergic asthma, incipient asthma, wheezy infant syndrome and bronchiolytis.

The treatment of asthma includes palliative treatment for the symptoms and conditions of asthma such as wheezing, coughing, shortness of breath, tightness in the chest, shallow or fast breathing, nasal flaring (nostril size increases with breathing), retractions (neck area and between or below the ribs moves inward with breathing), cyanosis (gray or bluish tint to skin, beginning around the mouth), runny or stuffy nose, and headache.

Inflammation diseases, conditions or syndromes which may be usefully treated or prevented with the compounds of formula (I) include, but are not limited to, inflammatory bowel disease, rheumatoid arthritis.

Neurological diseases, conditions or syndromes which may be usefully treated or prevented with the compounds of formula (I) include, but are not limited to, those diseases, conditions or syndromes associated with the modulation of the senstation of saiety perception including obesity, anorexia, weight maintenance, metabolic energy levels inflammatory conditions.

Yet further diseases where acute blockade of TRPM8 may have utility include those such as treatment of stroke, traumatic brain injury, neonatal trauma including neonatal encephalopathy and neonatal asphyxia.

The term “treatment,” as used herein to describe the present invention and unless otherwise qualified, means administration of the compound, pharmaceutical composition or combination to effect preventative, palliative, supportive, restorative or curative treatment. The term treatment encompasses any objective or subjective improvement in a subject with respect to a relevant condition or disease.

The term “preventative treatment,” as used herein to describe the present invention, means that the compound, pharmaceutical composition or combination is administered to a subject to inhibit or stop the relevant condition from occurring in a subject, particularly in a subject or member of a population that is significantly predisposed to the relevant condition.

The term “palliative treatment,” as used herein to describe the present invention, means that the compound, pharmaceutical composition or combination is administered to a subject to remedy signs and/or symptoms of a condition, without necessarily modifying the progression of, or underlying etiology of, the relevant condition.

The term “supportive treatment,” as used herein to describe the present invention, means that the compound, pharmaceutical composition or combination is administered to a subject as a part of a regimen of therapy, but that such therapy is not limited to administration of the compound, pharmaceutical composition or combination. Unless otherwise expressly stated, supportive treatment may embrace preventive, palliative, restorative or curative treatment, particularly when the compounds or pharmaceutical compositions are combined with another component of supportive therapy.

The term “restorative treatment,” as used herein to describe the present invention, means that the compound, pharmaceutical composition or combination is administered to a subject to modify the underlying progression or etiology of a condition. Non-limiting examples include an increase in forced expiratory volume in one second (FEV 1) for lung disorders, decreased rate of a decline in lung function over time, inhibition of progressive nerve destruction, reduction of biomarkers associated and correlated with diseases or disorders, a reduction in relapses, improvement in quality of life, reduced time spent in hospital during an acute exacerbation event and the like.

The term “curative treatment,” as used herein to describe the present invention, means that compound, pharmaceutical composition or combination is administered to a subject for the purpose of bringing the disease or disorder into complete remission, or that the disease or disorder is undetectable after such treatment.

Compounds of formula (I) intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of formula (I) or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term “excipient” is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in ‘Remington’s Pharmaceutical Sciences’, 19th Edition (Mack Publishing Company, 1995).

ORAL ADMINISTRATION

The compounds of formula (I) may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of formula (I) may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 wt% to 5 wt% of the tablet, and glidants may comprise from 0.2 wt% to 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in “Pharmaceutical Dosage Forms: Tablets, Vol. 1”, by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

PARENTERAL ADMINISTRATION

The compounds of formula (I) may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of formula (I) may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

TOPICAL ADMINISTRATION

The compounds of formula (I) may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Topical administration of the compounds of formula (I) is particularly preferred, especially in the treatment of cold allodynia and/or Reynauld's syndrome.

INHALED/INTRANASAL ADMINISTRATION

The compounds of formula (I) can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of formula (I), a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter.

Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of formula (I) per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or “puff” containing the compound of formula (I). The overall daily dose may be administered in a single dose or, more usually, as divided doses throughout the day.

RECTAL/INTRAVAGINAL ADMINISTRATION

The compounds of formula (I) may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

OCULAR/AURAL ADMINISTRATION

The compounds of formula (I) may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

OTHER TECHNOLOGIES

The compounds of formula (I) may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

KIT-OF-PARTS

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

DOSAGE

For administration to human patients, the total daily dose of the compounds of formula (I) depends, of course, on the mode of administration. For example, oral administration may require a higher total daily dose, than an intravenous dose. The total daily dose may be administered in single or divided doses.

For the avoidance of doubt, references herein to “treatment” include references to curative, palliative and prophylactic treatment.

A TRPM8 blocker may be usefully combined with another pharmacologically active compound, or with two or more other pharmacologically active compounds, particularly in the treatment of urological diseases, conditions or syndromes, more specifically over active bladder, painful bladder syndrome, and interstitial cystitis; and pain diseases, conditions or syndromes, more specifically cold allodynia regardless of cause, trigeminal neuralgia, glossopharyngeal neuralgia, Raynauld’s syndrome, and schlerodema.

For example, TRPM8 blockers, particularly a compound of formula (I), or a pharmaceutically acceptable salt, thereof, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents selected from:

- a muscarinic antagonist, eg oxybutynin, tolterodine, propiverine, tropsium chloride, darifenacin, solifenacin, temiverine, and ipratropium;
- beta 3 adrenergic receptor agonist,such as mirabegron or solabegron
- amitriptyline
- a local anaesthetic such as lidocaine or mexiletine;
- a sodium channel modulator, such as a Nav1.3 modulator, for example those disclosed in WO 2008/118758; A Nav1.7 modulator, for example those disclosed in WO 2009/012242 or WO 2010/079443; or a Nav1.8 modulator, for example those disclosed in WO 2008/135826, more particularly N-[6-Amino-5-(2-chloro-5-methoxyphenyl)pyridin-2-yl]-1-methyl-1H-pyrazole-5-carboxamide;
- a compound which is an inhibitor of mPGEs-1;
- an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;
- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;
- an H_1 antagonist, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- an histamine type 2 receptor antagonist, e.g. loratidine, fexofenadine, desloratidine, levocetirizine, methapyrilene or cetirizine;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphrenadine;
- an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;

- an anticonvulsant, e.g. carbamazepine, lamotrigine, topiratmate or valproate;
- a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;
- a prostaglandin E_2 subtype 4 (EP4) antagonist such as *N*-[({2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl}amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[(1*S*)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
- a coal-tar analgesic, in particular paracetamol;
- a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonepiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclinertant, Miraxion® or sarizotan;
- a vanilloid receptor agonist (e.g. resinferatoxin) or antagonist (e.g. capsazepine);
- a corticosteroid such as dexamethasone;
- a 5-HT receptor agonist or antagonist, for example a 5-$HT_{1B/1D}$ agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan; a 5-HT2c receptor agonist, or a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);
- a cholinergic (nicotinic) analgesic, such as ispronicline ($TC_{-17}34$), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594) or nicotine;
- Tramadol®;
- a PDE inhibitor, such as a PDE3 inhibitor, a PDE4 inhibitor, a PDE5 inhibitor, or a PDE9a inhibitor, such as theophylline, sildenafil, vardenafil, tadalafil, ibudilast, cilomilast or roflumilast;
- an alpha-2-delta ligand such as gabapentin, pregabalin, 3-methylgabapentin, (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-

cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid;

- a cannabinoid;
- metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;
- a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone;
- a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, buproprion, buproprion metabolite hydroxybuproprion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;
- a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and imipramine;
- an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[(1R,3S)-3-amino-4- hydroxy-1-(5-thiazolyl)-butyl]thio]-5-chloro-3-pyridinecarbonitrile; 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3 pyridinecarbonitrile, 2-[[(1R,3S)-3- amino-4-hydroxy- 1 -(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine, or guanidinoethyldisulfide;
- an acetylcholinesterase inhibitor such as donepezil;

- a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl),1,4-benzoquinone (CV-6504);
- a 5-HT3 antagonist, such as ondansetron;
- a 5-lipoxygenase activating protein (FLAP) antagonist;
- a leukotriene antagonist (LTRA) such as an antagonist of LTB_4, LTC_4, LTD_4, LTE_4, $CysLT_1$ or $CysLT_2$, e.g. montelukast or zafirlukast; 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid; 5-[2-(2-carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870;
- an β1-adrenoceptor or β2-adrenoceptor agonist, such as phenylephrine, methoxamine, oxymetazoline or methylnorephrine;
- sodium cromoglycate or sodium nedocromil;
- an anti-inflammatory monoclonal antibody, such as infliximab, adalimumab, tanezumab, ranibizumab, bevacizumab or mepolizumab;
- a β2 agonist, e.g. salmeterol, albuterol, salbutamol, fenoterol or formoterol, particularly a long-acting β2 agonist;
- an intigrin antagonist, such as natalizumab;
- an adhesion molecule inhibitor, such as a VLA-4 antagonist;
- an immunosuppressive agent, such as an inhibitor of the IgE pathway (e.g. omalizumab) or cyclosporine;
- a matrix metalloprotease (MMP) inhibitor, such as an inhibitor of MMP-9 or MMP-12;
- an adenosine A_{2a} receptor agonist;
- an adenosine A_{2b} receptor antagonist;
- a urokinase inhibitor;
- a dopamine receptor agonist (e.g. ropinirole), particularly a dopamine D2 receptor agonist (e.g. bromocriptine);
- a modulator of the NFκB pathway, such as an IKK inhibitor;
- a modulator of a cytokine signalling pathway such as an inhibitor of syk kinase, JAK kinase, p38 kinase, SPHK-1 kinase, Rho kinase, EGF-R or MK-2;
- an epithelial sodium channel (ENaC) blocker or Epithelial sodium channel (ENaC) inhibitor;
- a nucleotide receptor agonist, such as a P2Y2 agonist;
- a thromboxane inhibitor;

- niacin;
- a CRTH2 receptor (DP_2) antagonist;
- a prostaglandin D_2 receptor (DP_1) antagonist;
- a haematopoietic prostaglandin D2 synthase (HPGDS) inhibitor;
- interferon-β;
- a soluble human TNF receptor, e.g. Etanercept;
- a HDAC inhibitor;
- a phosphoinositotide 3-kinase gamma (PI3Kγ) inhibitor;
- a phosphoinositide 3-kinase delta (PI3Kγ) inhibitor; and
- a CXCR-1 or a CXCR-2 receptor antagonist;

including the pharmaceutically acceptable salts of the specifically named compounds and the pharmaceutically acceptable solvates of said specifically named compounds and salts.

Such combinations may offer significant advantages, including synergistic activity, in therapy.

As used herein, the terms “co-administration”, “co-administered” and “in combination with”, referring to a combination of a compound of formula (I) and one or more other therapeutic agents, includes the following:

- simultaneous administration of such a combination of a compound of formula (I) and a further therapeutic agent to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components at substantially the same time to said patient;

- substantially simultaneous administration of such a combination of a compound of formula(I) and a further therapeutic agent to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at substantially the same time by said patient, whereupon said components are released at substantially the same time to said patient;

- sequential administration of such a combination of a compound of formula (I) and a further therapeutic agent to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at consecutive times by said patient with a significant time interval between each administration, whereupon said components are released at substantially different times to said patient; and

- sequential administration of such a combination of a compound of formula (I) and a further therapeutic agent to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components in a controlled manner.

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

All of the compounds of the formula (I) can be prepared by the procedures described in the general methods presented below or by the specific methods described in the Examples section and the Preparations section, or by routine modifications thereof which can be made by employing the common general knowledge of one skilled in the art (see, for example, Comprehensive Organic Chemistry, Ed Barton and Ollis, Elsevier; Comprehensive Organic Transformations: A guide to Functional Group preparations, Larock, John Wiley & Sons). The present invention also encompasses any one or more of these processes for preparing the compounds of formula (I), in addition to any novel intermediates used therein.

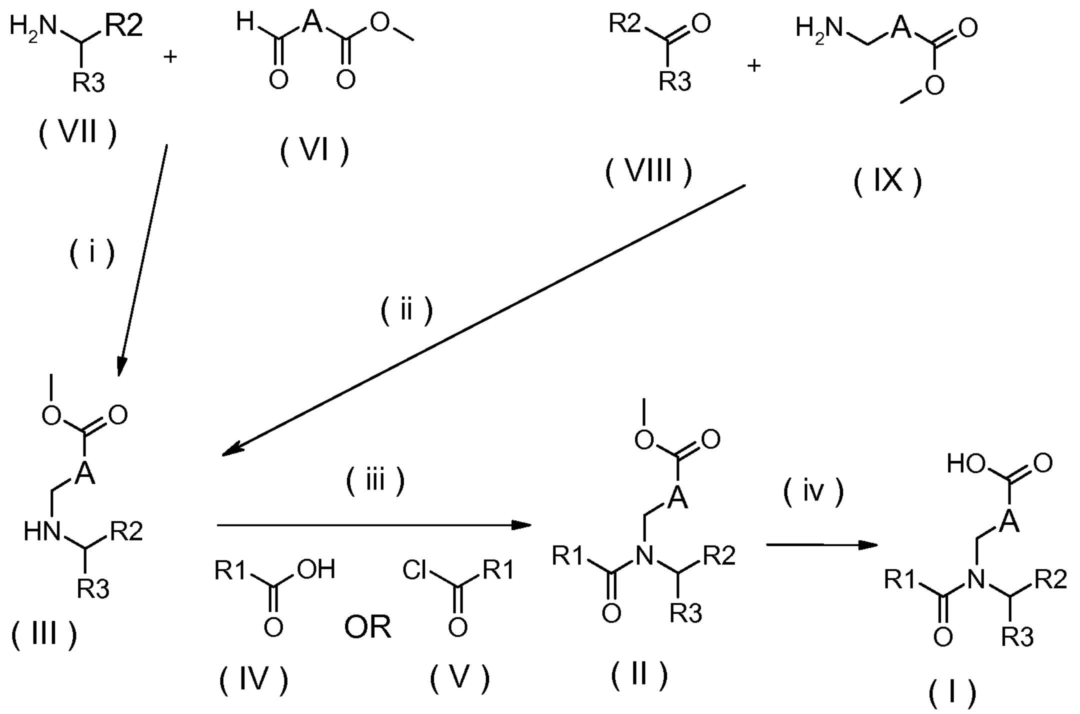
In the following general methods, A, R^1, R^2, and R^3 are as previously defined for a compound of the formula (I) unless otherwise stated.

Compounds of the present invention can be prepared using readily available starting materials or known intermediates. The synthetic schemes set forth below provide exemplary synthetic pathways for the preparation of compounds of formula (I).

When preparing derivatives of formula (I) in accordance with the invention, it is open to a person skilled in the art to routinely select the best order of steps with which to synthesise the intermediates, and to choose the form of the intermediate compounds which provides the best combination of features for this purpose. Such features include the melting point, solubility, processability and yield of the intermediate form and the resulting ease with which the product may be purified on isolation.

The skilled person may undertake the synthetic steps described below in any suitable order in order to arrive at the compounds of formula (I).

According to a first process, compounds of formula (I) may be prepared from compounds of formula (III) by the process illustrated in Scheme 1.



SCHEME 1

Compounds of formula (III) can be prepared in reaction step (i) by reductive amination of compounds of formula (VI) with compounds of formula (VII) using a suitable reducing agent, such as sodium borohydride or sodium triacetoxyborohydride, in a suitable solvent, such as methanol, toluene or diclhloromehtane, from 0°C to ambient temperature. The reaction may optionally be buffered with a suitable base such as triethylamine, or dehydrate with molecular sieves and para-toluene sulphonic acid monohydrate.

Compounds of formula (VI) or (VII) are either commercially available, or can be readily prepared by methods described in the literature.

Alternatively compounds of formula (III) can be prepared in reaction step (ii) by an alternative reductive amination of compounds (VIII) or (IX) using a suitable reducing agent, such as sodium borohydride or sodium triacetoxyborohydride, in a suitable solvent, such as methanol, toluene or dichloromethane, from 0°C to ambient temperature. The reaction may optionally be buffered with a suitable base such as triethylamine, or dehydrate with molecular sieves and para-toluene sulphonic acid monohydrate.

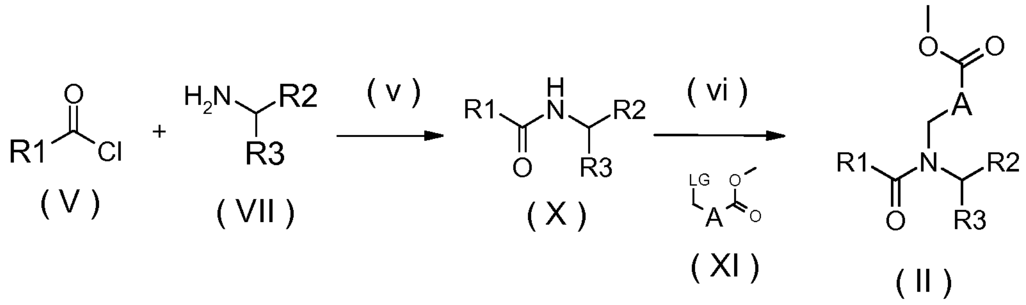
Compounds of formula (VIII) or (IX) are either commercially available, or can be readily prepared by methods described in the literature.

Compounds of formula (II) can then be prepared from compounds of formula (III) in reaction step (iii) by formation of the amide via amide coupling with compounds of formula (IV), using a suitable activating agent, such as hydrosybenzotriazoly urea (HBTU), water soluble carbodiamide (WSCDI), propyl phosphonic anhydride (T3P), chloro-N, N, N', N' – tetramethylformaamidinium hexafluorophosphate (Gohsez reagent), or 2-chloro-1,3-dimethylimidazolinium chloride with a suitable base, such as triethylamine or Hunig's base, in a suitable solvent such as dichlormethane, THF or diethylacetamide from ambient temperature to 65°C.

Alternatively, the compounds of formula (II) can be prepared from compounds of formula (III), again in reaction step (iii), by reaction with an acid chloride, compounds of formula (V), in a suitable solvent, such as dichloromethane, in the presence of a suitable base, such as triethylamine or Hunig's base, at ambient temperatures. The acid chloride can be prepared from the parent acid by standard literature methods, well known to one skilled in the art.

Compounds of formula (I) are then be prepared from compounds of formula (II) in reaction step (iv) by hydrolysis of compound (II) using suitable base, for example aqueous sodium or lithium hydroxide, in a suitable solvent, for example methanol or THF.

According to a second process, compounds of formula (I) may be prepared from compounds of formula (V) and compounds of formula (VII) by the process illustrated in Scheme 2.



SCHEME 2

wherein LG is a suitable leaving group, preferably halo for example chloro, bromo; tosyl; or mesylate.

Compounds of formula (V) are either commercially available or can be prepared by methods described in the literature. Alternatively, they can be prepared from the parent acid by standard literature methods, well known to one skilled in the art.

Compounds of formula (VII) are either commercially available, or can be readily prepared by methods described in the literature.

Compounds of formula (X) can be prepared from compounds of formula (VII) in reaction step (v) by reaction with compounds of formula (V) in a suitable solvent, such as dichloromethane, in the presence of a suitable base, such as triethylamine or Hunig's base, at ambient temperatures.

Compounds of formula (II) may then be prepared from compounds of formula (X) in reaction step (vi) by deprotonation with a suitable base, for example sodium hydride, lithium hydride or lithium hexamethyldisilazide in a suitable solvent such as THF N-methylpyrolidinone, followed by amide alkylation with compounds of formula (XI), wherein LG is a suitable leaving group such as halo for example chloro, bromo; tosyl; or mesylate. Suitable reaction conditions are at a temperature of from -20°C to 50°C.

Compounds of formula (II) can then be converted to compounds of formula (I) as described in reaction step (iv) in Scheme I above.

Referring to the general methods above, it will be readily understood to the skilled person that where protecting groups are present, these will be generally interchangeable with other protecting groups of a similar nature, e.g. where a sulfonamide is described as being protected with a *tert*-butyl or dimethoxybenzyl group, this may be readily interchanged with any suitable sulfonamide protecting group. Suitable protecting groups are described in 'Protective Groups in Organic Synthesis' by T. Greene and P. Wuts (3rd edition, 1999, John Wiley and Sons).

The present invention also relates to novel intermediate compounds as defined above, all salts, solvates and complexes thereof and all solvates and complexes of salts thereof as defined hereinbefore for compounds of formula (I). The invention includes all polymorphs of the aforementioned species and crystal habits thereof.

EXAMPLES & PREPARATIONS

The following experimental details illustrate specifically how certain compounds of formula (I) may be prepared. All examples, unless indicated as a reference example, are compounds of formula (I). Preparations are intermediates useful in the synthesis of compounds of formula (I). All starting materials are available commercially or described in the literature.

^{1}H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. NMR was carried out using a Varian-Unity Inova 400MHz NMR spectrometer or a Varian Mercury 400MHz NMR spectrometer.

Mass spectroscopy was carried out using a Finnigan Navigator single quadrupole electrospray mass spectrometer or a Finnigan aQa APCI mass spectrometer.

All temperatures are in ^{0}C.

The following abbreviations have been used for common solvents: $CDCl_3$, deuterochloroform; d_6-DMSO, deuterodimethylsulphoxide; CD_3OD, deuteromethanol; THF, tetrahydrofuran. 'Ammonia' refers to a concentrated solution of ammonia in water possessing a specific gravity of 0.88.

Flash column chromatography was carried out using Merck silica gel 60 (9385). Thin layer chromatography (TLC) was carried out on Merck silica gel 60 plates (5729). "R_f" represents the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate.

Where compounds were analysed by LCMS the methods used are shown below.

	Analysis System 1	**Analysis System 2**	**Analysis System 3**
Solvent A	0.1 % NH_4OH in H_2O	0.1 % Formic acid in H_2O	0.0375% Trifluroacetic acid in

			H_2O
Solvent B	0.1 % NH_4OH in acetonitrile	0.1 % Formic acid in acetonitrile	0.01875% Trifluroacetic acid in acetonitrile
Column	C18 phase XTerra 50 x 4.6mm with 5 µm	C18 phase Waters Sunfire 50 x 4.6 mm with 5 µm	Xbridge C18 2.1 × 50mm with 5 µm
Gradient	95-5% A over 3min, 1min hold, 1min re-equilibration, 1.5mL/min flow rate	95-5% A over 3min, 1min hold, 1min re-equilibration, 1.5mL/min flow rate	25-100% B over 3.50min, 0.10min re-equilibration, 0.70min hold, 0.8mL/min flow rate
Detection	UV: 225nm – ELSD - MS	UV: 225nm – ELSD - MS	SEDEX 75 ELSD
Temperature	Ambient	Ambient	50°C

	Analysis System 4	**Analysis System 5**	**Analysis System 6**
Solvent A	0.1 % Formic acid in H_2O	0.0375% Trifluroacetic acid in H_2O	0.05% NH_4OH in H_2O
Solvent B	0.1 % Formic acid in acetonitrile	0.01875% Trifluroacetic acid in acetonitrile	100% Acetonitrile
Column	C18 phase Phenomenex 20 x 4.0mm with 3μm	Xbridge C18 2.1 × 50mm with 5μm	Xbridge C18 2.1 × 50mm with 5μm
Gradient	90-5% A over 1.5min, 0.3min hold, 0.2min re-equilibration, 1.8mL/min flow rate	10% B 0.5min hold, 10-100% B over 3.50min, 0.30min re-equilibration, 0.40min hold, 0.8mL/min flow rate	5% B 0.5min hold, 5-100% B over 2.90min, 0.80min hold, 0.01min re-equilibration, 0.49min hold, 0.8mL/min flow rate
Detection	210nm - 450nm DAD	SEDEX 75 ELSD	SEDEX 75 ELSD
Temperature	50°C	50°C	50°C

	Analysis System 7	**Analysis System 8**	**Analysis System 9**
Solvent A	Acetonitrile	0.0375% Trifluroacetic acid in H_2O	10 mM Ammonium acetate in H_2O
Solvent B	10mM Ammonium acetate in H_2O	0.01875% Trifluroacetic acid in acetonitrile	10 mM Ammonium acetate in methanol
Column	Waters XBridge C18 2.1 x 30mm with 5µm	Xbridge C18 2.1×50mm with 5µm	Phenomenex Phenyl Hexyl 150 x 4.6mm with 5µm
Gradient	0-95% A over 3.1min	1-5% B over 0.6min, 5-100% over 3.4min, 0.30min re-equilibration to 1%, 0.40min hold, 0.8mL/min flow rate	98-2% A over 18min, 2min hold, 1mL/min flow rate
Detection		SEDEX 75 ELSD	UV: 210nm - 450nm DAD
Temperature		50°C	50°C

	Analysis System 10	**Analysis System 11**	**Analysis System 12**
Solvent A	0.1 % Formic acid in H_2O	0.1 % Formic acid in H_2O	0.1 % Formic acid in H_2O
Solvent B	0.1 % Formic acid in acetonitrile	0.1 % Formic acid in acetonitrile	0.1 % Formic acid in acetonitrile
Column	C18 phase Phenomenex Gemini 50 x 4.6mm with 5µm	C18 phase Phenomenex 20 x 4.0mm with 3µm	C18 phase Waters Sunfire 50 x 4.6mm with 5µm
Gradient	95% A hold 0.8min, 95-5% A over 3.2min, 5% A hold 0.50min, 5-95% A over 0.1min, 1.4min re-equilibration 1mL/min flow rate	98-10% A over 1.5min, 0.3min hold, 0.2 re-equilibration 2mL/min flow rate	95% A hold 0.8min, 95-5% A over 3.2min, 5% A hold 0.50min, 5-95% A over 0.1min, 1.4min re-equilibration, 1mL/min flow rate
Detection	UV: 210nm - 450nm DAD	UV: 210nm - 450nm DAD	UV:210nm - 450nm DAD
Temperature	50°C	75°C	50°C

	Analysis System 13	**Analysis System 14**
Solvent A	0.1 % Formic acid in H_2O	0.1 % Formic acid in H_2O
Solvent B	0.1 % Formic acid in acetonitrile	0.1 % Formic acid in acetonitrile
Column	C18 phase Waters Sunfire 50 x 4.6mm with 5µm	C18 phase Phenomenex 20 x 4.0mm with 3µm
Gradient	95-5% A over 3min, 1min hold, 2min re-equilibration, 1.5mL/min flow rate	98-2% A over 1.5min, 0.3min hold, 0.2min re-equilbration, 1.8mL/min flow rate
Detection	210nm - 450nm DAD	210nm - 450nm DAD
Temperature	50°C	75°C

Where compounds were analysed by UPLC the method used is shown below.

UPLC Analysis System

A: Acetonitrile

B: 0.1 % Formic acid in H_2O

Column: Xbridge C18 2.1 x 50mm

Gradient: 2-98% A over 0.8min, 98% A hold 0.4min, 98-5% A over 0.05min, 0.8mL/min flow rate

UV: 215 - 350nm

Temperature: 30°C

Where compounds are purified by HPLC, the methods used are shown below.

Preparative System 1

A: 0.1% Formic acid in H_2O

B: 0.1% Formic acid in acetonitrile

Column: C18 phase Sunfire 100 x 19.0mm

Gradient: 95-2% A over 7min, 2min hold, 1min re-equilibration, 18mL/min flow rate

Temperature: Ambient

Preparative System 2

A: 0.1% Diethylamine in H_2O
B: 0.1% Diethylamine in acetonitrile
Column: C18 phase Xterra 100 x 19.0mm
Gradient: 95-2% A over 7min, 2min hold, 1min re-equilibration, 18mL/min flow rate
Temperature: Ambient

Preparative System 3

A: 0.1% Trifluroacetic acid in H_2O
B: Acetonitrile
Column: Phenomenex Luna C18 100 x 21.2mm with 5μm

Preparative System 4

A: Methanol
B: 0.1 % Formic acid in acetonitrile
Column: Xbridge C18 30 x 150mm
Gradient: 60%-75% A over 10min, 50mL/min flow rate
UV: 233nm
Temperature: Ambient

Preparative System 5

A: 0.1% Trifluroacetic acid in H_2O
B: Acetonitrile
Column: Grace Vydac C18 250 x 20mm with 5 μm

Where it is stated that compounds were prepared in the manner described for an earlier Preparation or Example, the skilled person will appreciate that reaction times, number of equivalents of reagents and reaction temperatures may be modified for each specific reaction, and that it may nevertheless be necessary or desirable to employ different work-up or purification conditions.

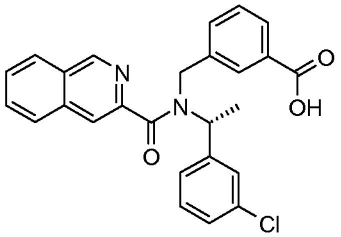
The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

APCI	atmospheric pressure chemical ionisation mass spectrum
br	broad

δ	chemical shift
d	doublet
DMSO	dimethyl sulfoxide
ESI	electrospray ionisation
HPLC	high pressure liquid chromatography
LCMS	liquid chromatography mass spectrum
LRMS	low resolution mass spectrum
m	multiplet
m/z	mass spectrum peak
NMR	nuclear magnetic resonance
ppm	parts per million
psi	pounds per square inch
q	quartet
Rt	retention time
s	singlet
t	triplet
UV	ultraviolet

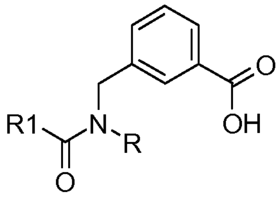
Example 1

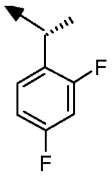
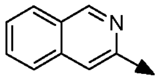
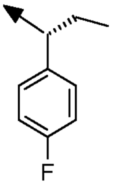
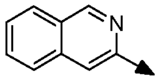
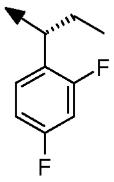
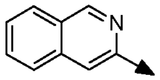
3-({[(1R)-1-(3-chlorophenyl)ethyl](isoquinolin-3-ylcarbonyl)amino}methyl) benzoic acid

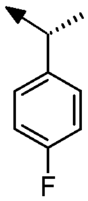
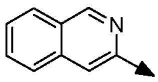
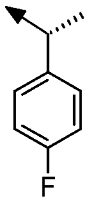
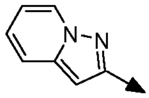
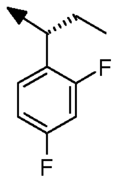
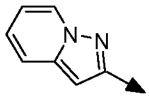
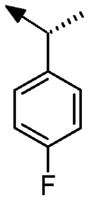
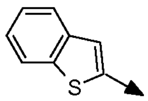
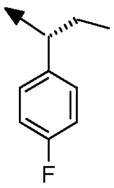
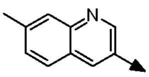
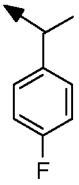
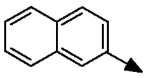


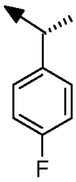
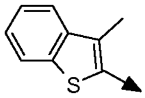
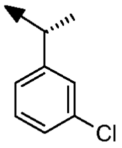
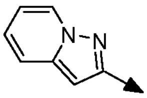
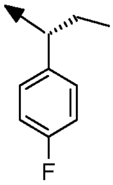
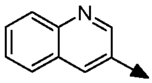
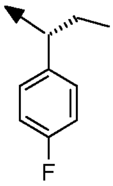
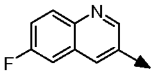
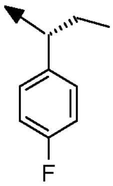
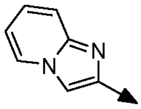
The ester from Preparation 27 (1.692g, 3.687mmol) was dissolved in methanol (50mL). 1M aqueous sodium hydroxide (20mL) was added and the mixture stirred at 50°C for 2 hours. The reaction was concentrated in vacuo and the residue was dissolved in water (50mL) and washed with methyl t-butyl ether (25mL). The aqueous layer was acidified with 2M aqueous hydrochloric acid and extracted with ethyl acetate (50mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was dissolved in 1M aqueous sodium hydroxide (40mL) and stirred rapidly while acidifying with 2M aqueous hydrochloric acid to pH3. The white solid was filtered off and washed with water. The solid was stirred with water and filtered and washed again with water and dried under high vacuum at 50°C to give the title compound as a white solid (1.260g, 76%). ^{1}H NMR (400 MHz, DMSO–d6, 90°C) δ ppm: 1.57 (d, 3H), 4.64 (dd, 2H), 5.50-5.61 (m, 1H), 7.21-7.43 (m, 6H), 7.67-7.85 (m, 4H), 8.03 (d, 1H), 8.09 (s, 1H), 8.16 (d, 1H), 9.33 (bs, 1H).

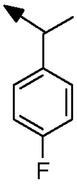
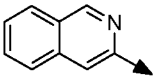
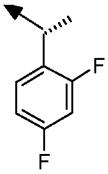
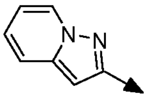
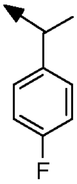
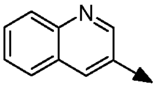
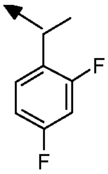
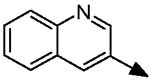
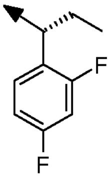
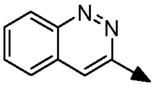
Examples 2-60 were similarly prepared according to the method described above for example 1, starting from the appropriate ester.

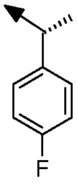
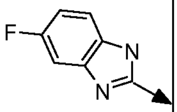
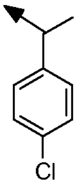
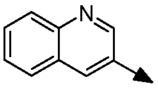
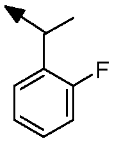
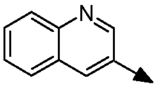
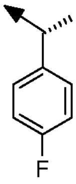
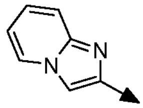
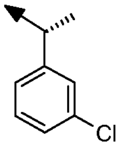
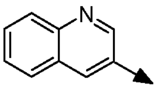
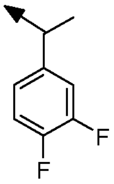
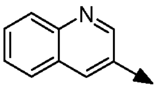


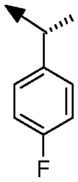
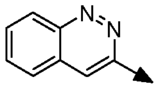
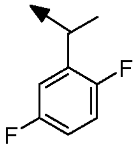
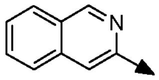
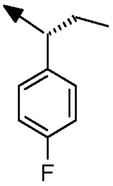
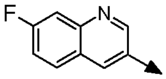
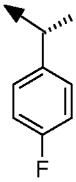
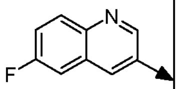
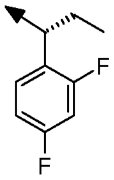
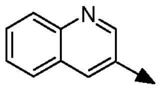
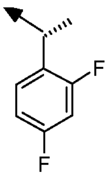
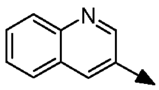
Example	Name	R	R1	Precursor	Data
2	3-({[(1R)-1-(2,4-difluorophenyl)ethyl](isoquinolin-3-ylcarbonyl)amino}methyl) benzoic acid			Preparation 28	^{1}H NMR (400 MHz, DMSO–d6, 90°C) δ ppm: 1.62-1.67 (d, 3H), 2.94-3.05 (m, 2H), 4.62-4.67 (s, 2H), 6.80-6.89 (m, 1H), 6.89-6.96 (m, 1H), 7.24-7.31 (m, 1H), 7.34-7.41 (m, 1H), 7.48-7.56 (m, 1H), 7.65-7.76 (m, 3H), 7.78-7.84 (m, 1H), 8.00-8.08 (m, 2H), 8.12-8.17 (m, 1H), 9.28-9.33 (bs,1H)
3	3-({[(1R)-1-(4-fluorophenyl)propyl](isoquinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 29	^{1}H NMR (400 MHz, DMSO–d6, 100°C) δ ppm: 0.70-0.90 (m, 3H), 2.03-2.14 (m, 2H), 4.61 (q, 2H), 5.38 (bs, 1H), 7.02-7.06 (m, 2H), 7.22-7.27 (m, 2H), 7.48-7.51 (m, 2H), 7.67-7.84 (m, 4H), 8.02-8.17 (m, 3H), 9.34 (s, 1H). LRMS m/z 443 [MH]$^+$
4	3-({[(1R)-1-(2,4-difluorophenyl)propyl](isoquinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 69	LCMS Rt 2.15mins, (ESI) m/z 461 [MH]$^+$ (Analysis System 1, Preparative System 1)

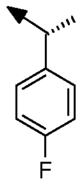
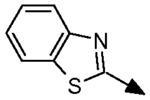
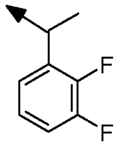
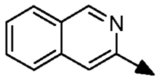
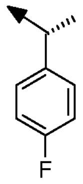
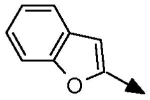
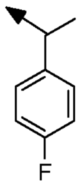
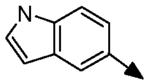
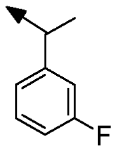
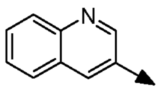
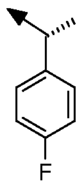
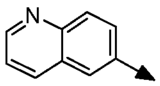
5	3-({[(1R)-1-(4-fluorophenyl)ethyl](isoquinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 70	LCMS Rt 3.43mins, (ESI) m/z 429.154 $[MH]^+$ (Analysis System 2, Preparative System 2)
6	3-({[(1R)-1-(4-fluorophenyl)ethyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)benzoic acid			Preparation 71	LCMS Rt 2.36mins, (ESI) m/z 418.149 $[MH]^+$ (Analysis System 1, Preparative System 2)
7	3-({[(1R)-1-(2,4-difluorophenyl)propyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)benzoic acid			Preparation 72	LCMS Rt 2.18mins, (ESI) m/z 450 $[MH]^+$ (Analysis System 1, Preparative System 1)
8	3-({(1-benzothien-2-ylcarbonyl)[(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid			Preparation 30	LCMS Rt 3.66mins, (ESI) m/z 434 $[MH]^+$ 432 $[M]^-$ (Analysis System 2, Preparative System 1)
9	3-({[(1R)-1-(4-fluorophenyl)propyl][(7-methylquinolin-3-yl)carbonyl]amino}methyl)benzoic acid			Preparation 31	LCMS Rt 3.43mins, (ESI) m/z 457.185 $[MH]^+$ (Analysis System 2, Preparative System 2)
10	3-({[1-(4-fluorophenyl)ethyl](2-naphthoyl)amino}methyl)benzoic			Preparation 82	LCMS Rt 2.838 mins, (APCI&ESI) m/z 428 $[MH]^+$ (Analysis System 3, Preparative System 3)

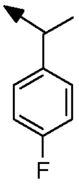
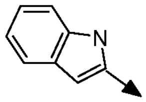
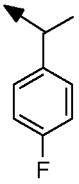
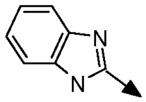
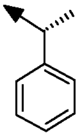
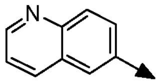
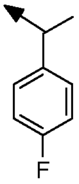
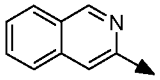
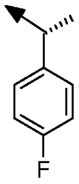
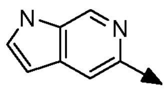
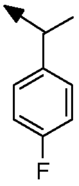
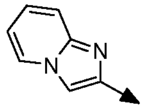
	acid				
11	3-({[(1R)-1-(4-fluorophenyl)ethyl][(3-methyl-1-benzothien-2-yl)carbonyl]amino}methyl)benzoic acid			Preparation 32	LCMS Rt 3.79mins, (ESI) m/z 448 [MH]$^+$ 446 [M]$^-$ (Analysis System 2, Preparative System 1)
12	3-({[(1R)-1-(3-chlorophenyl)ethyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)benzoic acid			Preparation 33	LCMS Rt 2.18 minutes, (ESI) m/z 434 [MH]$^+$ (^{35} Cl) (Analysis System 1, Preparative System 2)
13	3-({[(1R)-1-(4-fluorophenyl)propyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 34	LCMS Rt 3.42mins, (ESI) m/z 443.169 [MH]$^+$ (Analysis System 2, Preparative System 2)
14	3-({[(1R)-1-(4-fluorophenyl)propyl][(6-fluoroquinolin-3-yl)carbonyl]amino}methyl)benzoic acid			Preparation 35	LCMS Rt 1.56 mins, (ES) m/z 461 [MH]$^+$ (Analysis System 4)
15	3-({[(1R)-1-(4-fluorophenyl)propyl](imidazo[1,2-a]pyridin-2-ylcarbonyl)amino}methyl)benzoic			Preparation 73	LCMS Rt 2.30mins, (ESI) m/z 432.165 [MH]$^+$ (Analysis System 1, Preparative System 2)

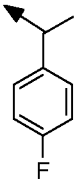
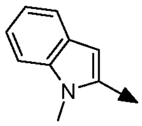
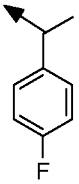
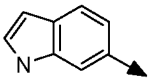
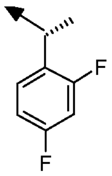
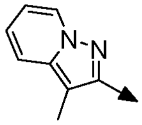
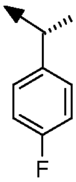
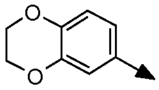
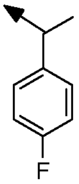
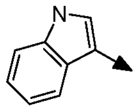
	acid				
16	3-({[1-(4-fluorophenyl)ethyl](isoquinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 83	LCMS Rt 3.139 mins, (API-ES) m/z 429 $[MH]^+$ (Analysis System 5, Preparative System 3)
17	3-({[(1R)-1-(2,4-difluorophenyl)ethyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)benzoic acid			Preparation 36	LCMS Rt 3.31 minutes (ESI) m/z 436 $[MH]^+$ (Analysis System 2, Preparative System 2)
18	3-({[1-(4-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 84	LCMS Rt 2.187 mins, (API-ES) m/z 429 $[MH]^+$ (Analysis System 6, Preparative System 3)
19	3-({[1-(2,4-difluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 37	LCMS Rt 1.08 mins, (ESI) m/z 447 $[MH]^+$ (UPLC Analysis System, Preparative System 4)
20	3-({(cinnolin-3-ylcarbonyl)[(1R)-1-(2,4-difluorophenyl)propyl]amino}methyl)benzoic acid			Preparation 38	LCMS Rt 3.34mins, (ESI) m/z 462 $[MH]^+$ 460 $[M]^-$ (Analysis System 2, Preparative System 1)

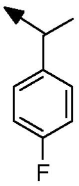
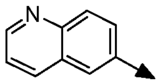
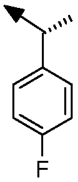
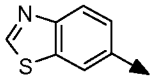
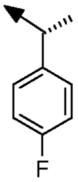
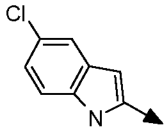
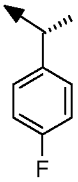
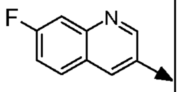
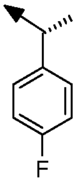
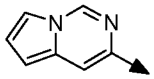
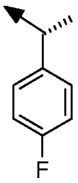
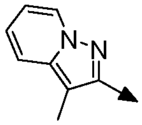
21	3-({[(5-fluoro-1H-benzimidazol-2-yl)carbonyl][(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid			Preparation 74	LCMS Rt 2.41mins, (ESI) m/z 436 [MH]$^+$ 434 [M]$^-$ (Analysis System 1, Preparative System 2)
22	3-({[1-(4-chlorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 39	LCMS Rt 0.83 mins, (ESI) m/z 445/447 [MH]$^+$ (UPLC Analysis System, Preparative System 4)
23	3-({[1-(2-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 40	LCMS Rt 0.77 mins, (ESI) m/z 429 [MH]$^+$ (UPLC Analysis System, Preparative System 4)
24	3-({[(1R)-1-(4-fluorophenyl)ethyl](imidazo[1,2-a]pyridin-2-ylcarbonyl)amino}methyl)benzoic acid			Preparation 75	LCMS Rt 2.16mins, (ESI) m/z 418.149 [MH]$^+$ (Analysis System 1, Preparative System 2)
25	3-({[(1R)-1-(3-chlorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 41	LCMS Rt 3.37 minutes, (ESI) m/z 445 [MH]$^+$ (^{35}Cl) (Analysis System 2, Preparative System 2)
26	3-({[1-(3,4-difluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 42	LCMS Rt 2.55 minutes, (ESI) m/z 447 [MH]$^+$ (Analysis System 7)

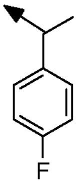
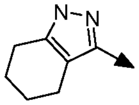
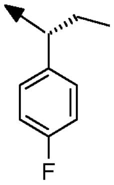
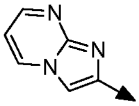
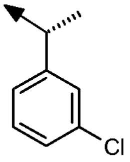
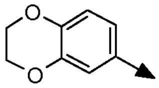
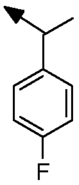
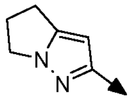
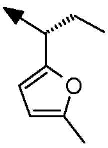
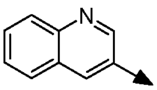
27	3-({(cinnolin-3-ylcarbonyl)[(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid			Preparation 43	LCMS Rt 2.04mins, (ESI) m/z 430 $[MH]^+$ 428 $[M]^-$ (Analysis System 1, Preparative System 1)
28	3-({[1-(2,5-difluorophenyl)ethyl](isoquinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 44	LCMS Rt 3.29 minutes (ESI) m/z 447 $[MH]^+$ (Analysis System 2, Preparative System 2)
29	3-({[(1R)-1-(4-fluorophenyl)propyl][(7-fluoroquinolin-3-yl)carbonyl]amino}methyl)benzoic acid			Preparation 45	LCMS Rt 1.56 mins, (ES) m/z 461 $[MH]^+$ (Analysis System 4)
30	3-({[(1R)-1-(4-fluorophenyl)ethyl][(6-fluoroquinolin-3-yl)carbonyl]amino}methyl)benzoic acid			Preparation 46	LCMS Rt 1.52 mins, (ES) m/z 447 $[MH]^+$ (Analysis System 4)
31	3-({[(1R)-1-(2,4-difluorophenyl)propyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 47	LCMS Rt 2.18mins, (ESI) m/z 461 $[MH]^+$ (Analysis System 1, Preparative System 1)
32	3-({[(1R)-1-(2,4-difluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic			Preparation 48	LCMS Rt 3.27 mins, (ESI) m/z 447 $[MH]^+$ (Analysis System 2, Preparative System 2)

	acid				
33	3-({(1,3-benzothiazol-2-ylcarbonyl)[(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid			Preparation 76	LCMS Rt 3.72mins, (ESI) m/z 435 [MH]$^+$ 433 [M]$^-$ (Analysis System 2, Preparative System 2)
34	3-({[1-(2,3-difluorophenyl)ethyl](isoquinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 49	LCMS Rt 3.31 mins, (ESI) m/z 447 [MH]$^+$ (Analysis System 2, Preparative System 2)
35	3-({(1-benzofuran-2-ylcarbonyl)[(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid			Preparation 50	LCMS Rt 3.63mins, (ESI) m/z 416 [M]$^-$ (Analysis System 2, Preparative System 1)
36	3-({[1-(4-fluorophenyl)ethyl](1H-indol-5-ylcarbonyl)amino}methyl)benzoic acid			Preparation 85	LCMS Rt 3.017 mins, (APCI & ESI) m/z 417 [MH]$^+$ (Analysis System 5, Preparative System 5)
37	3-({[1-(3-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 51	LCMS Rt 1.07 mins, (ESI) m/z 429 [MH]$^+$ (UPLC Analysis System, Preparative System 4)
38	3-({[(1R)-1-(4-fluorophenyl)ethyl](quinolin-6-ylcarbonyl)amino}methyl			Preparation 52	LCMS Rt 2.24mins, (ESI) m/z 429 [MH]$^+$ (Analysis System 1, Preparative System 2)

	)benzoic acid				
39	3-({[1-(4-fluorophenyl)ethyl](1H-indol-2-ylcarbonyl)amino}methyl)benzoic acid			Preparation 86	LCMS Rt 3.304 mins, (APCI & ESI) m/z 417 $[MH]^+$ (Analysis System 5, Preparative System 3)
40	3-({(1H-benzimidazol-2-ylcarbonyl)[1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid			Preparation 87	LCMS Rt 3.141 mins, (APCI & ESI) m/z 418 $[MH]^+$ (Analysis System 5, Preparative System 3)
41	3-({[(1R)-1-phenylethyl](quinolin-6-ylcarbonyl)amino}methyl)benzoic acid			Preparation 88	LCMS Rt 2.473 mins, (APCI & ESI) m/z 411 $[MH]^+$ (Analysis System 5, Preparative System 5)
42	3-({[1-(4-fluorophenyl)ethyl](quinolin-2-ylcarbonyl)amino}methyl)benzoic acid			Preparation 89	LCMS Rt 3.255 mins, (APCI & ESI) m/z 429 $[MH]^+$ (Analysis System 5, Preparative System 3)
43	3-({[(1R)-1-(4-fluorophenyl)ethyl](1H-pyrrolo[2,3-c]pyridin-5-ylcarbonyl)amino}methyl)benzoic acid			Preparation 77	LCMS Rt 2.16mins, (ESI) m/z 418 $[MH]^+$ 416 $[M]^-$ (Analysis System 1, Preparative System 1)
44	3-({[1-(4-fluorophenyl)ethyl](imidazo[1,2-a]pyridin-2-ylcarbonyl)amino}methyl			Preparation 90	LCMS Rt 2.455 mins, (APCI & ESI) m/z 418 $[MH]^+$ (Analysis System 5, Preparative System 5)

	)benzoic acid				
45	3-({[1-(4-fluorophenyl)ethyl][(1-methyl-1H-indol-2-yl)carbonyl]amino}methyl)benzoic acid			Preparation 91	LCMS Rt 3.412 mins, (APCI & ESI) m/z 431 $[MH]^+$ (Analysis System 5, Preparative System 5)
46	3-({[1-(4-fluorophenyl)ethyl](1H-indol-6-ylcarbonyl)amino}methyl)benzoic acid			Preparation 92	LCMS Rt 3.107 mins, (APCI & ESI) m/z 417 $[MH]^+$ (Analysis System 5, Preparative System 3)
47	3-({[(1R)-1-(2,4-difluorophenyl)ethyl][(3-methylpyrazolo[1,5-a]pyridin-2-yl)carbonyl]amino}methyl)benzoic acid			Preparation 78	LCMS Rt 2.18mins, (ESI) m/z 461 $[MH]^+$ (Analysis System 2, Preparative System 2)
48	3-({(2,3-dihydro-1,4-benzodioxin-6-ylcarbonyl)[(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid			Preparation 53	LCMS Rt 2.27mins, (ESI) m/z 436 $[MH]^+$ (Analysis System 1, Preparative System 2)
49	3-({[1-(4-fluorophenyl)ethyl](1H-indol-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 93	LCMS Rt 3.025 mins, (APCI & ESI) m/z 417 $[MH]^+$ (Analysis System 5, Preparative System 5)

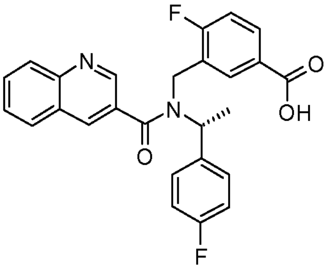
50	3-({[1-(4-fluorophenyl)ethyl](quinolin-6-ylcarbonyl)amino}methyl)benzoic acid			Preparation 94	LCMS Rt 2.529 mins, (APCI & ESI) m/z 429 [MH]$^+$ (Analysis System 5, Preparative System 3)
51	3-({(1,3-benzothiazol-6-ylcarbonyl)[(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid			Preparation 54	LCMS Rt 1.47 mins, (ES) m/z 433 [M-H] (Analysis System 4)
52	3-({[(5-chloro-1H-indol-2-yl)carbonyl][(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid			Preparation 56	LCMS Rt 3.68mins, (ESI) m/z 449 [MH]$^+$ (Analysis System 2, Preparative System 2)
53	3-({[(1R)-1-(4-fluorophenyl)ethyl][(7-fluoroquinolin-3-yl)carbonyl]amino}methyl)benzoic acid			Preparation 57	LCMS Rt 1.52 mins, (ES) m/z 447 [MH]$^+$ (Analysis System 4)
54	3-({[(1R)-1-(4-fluorophenyl)ethyl](pyrrolo[1,2-c]pyrimidin-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 79	LCMS Rt 1.51 mins, (ESI & APCI) m/z 416 [M]$^-$ (Analysis System 4)
55	3-({[(1R)-1-(4-fluorophenyl)ethyl][(3-methylpyrazolo[1,5-a]pyridin-2-			Preparation 80	LCMS Rt 2.21 mins, (ESI) m/z 432 [MH]$^+$ (Analysis System 1, Preparative System 2)

	yl)carbonyl]amino}methyl)benzoic acid				
56	3-({[1-(4-fluorophenyl)ethyl](4,5,6,7-tetrahydro-1H-indazol-3-ylcarbonyl)amino}methyl)benzoic acid			Preparation 95	LCMS Rt 2.94 mins, (APCI & ESI) m/z 422 [MH]$^+$ (Analysis System 5, Preparative System 5)
57	3-({[(1R)-1-(4-fluorophenyl)propyl](imidazo[1,2-a]pyrimidin-2-ylcarbonyl)amino}methyl)benzoic acid			Preparation 58	LCMS Rt 2.15 mins, (ESI) m/z 433.16 [MH]$^+$ (Analysis System 1, Preparative System 1)
58	3-({[(1R)-1-(3-chlorophenyl)ethyl](2,3-dihydro-1,4-benzodioxin-6-ylcarbonyl)amino}methyl)benzoic acid			Preparation 59	^{1}H NMR (400 MHz, CD$_3$OD) δ ppm: 1.60 (d, 3H), 4.25-4.30 (m, 5H), 4.54 (dd, 2H), 6.87-7.08 (m, 3H), 7.20-7.52 (m, 6H), 7.78-7.85 (m, 2H). LRMS (ESI & APCI) m/z 452 [MH]$^+$
59	3-({(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-ylcarbonyl)[1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid			Preparation 96	LCMS Rt 3.148 mins, (API & ESI) m/z 408 [MH]$^+$ (Analysis System 8, Preparative System 5)
60	3-({[(1R)-1-(5-methyl-2-furyl)propyl](quinolin-3-ylcarbonyl)amino}methyl			Preparation 60	LCMS Rt 3.36 mins, (ESI) m/z 429.174 [MH]$^+$ (Analysis System 2, Preparative System 1)

	)benzoic acid				

Example 61

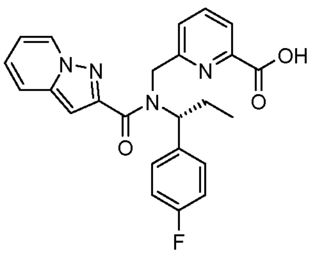
4-fluoro-3-({[(1R)-1-(4-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl) benzoic acid



The crude ester from Preparation 97 (0.20mmol) was dissolved in methanol (500µL). 2.5M aqueous lithium hydroxide (245µL) was added and the mixture stirred at room temperature overnight. Water (3mL) was added and the mixture was washed with diethyl ether (5mL), the aqueous layer was acidified to pH2 with 2M hydrochloric acid. The aqueous was then extracted with dichloromethane (5mL) and the organic layer was dried by passing through a phase separating cartridge. The solvent was removed in vacuo and the residue was dissolved in DMSO (1mL) and purified by HPLC to give the title compound (27.9mg, 30%). LCMS Rt 3.31 mins, (ESI) m/z 447 $[MH]^+$ (Analysis System 2, Preparative System 2)

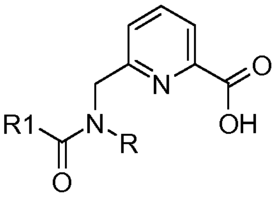
Example 62

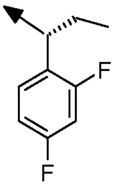
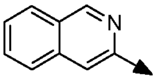
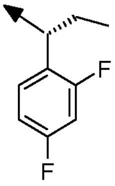
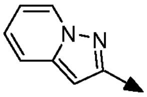
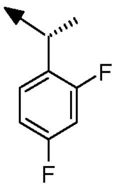
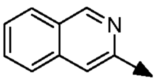
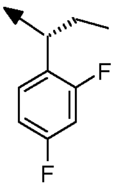
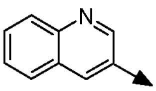
6-({[(1R)-1-(4-fluorophenyl)propyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino} methyl)pyridine-2-carboxylic acid

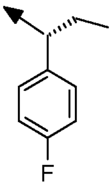
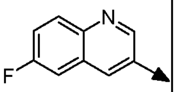
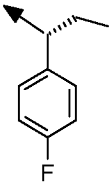
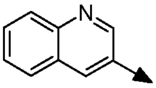
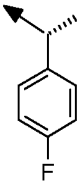
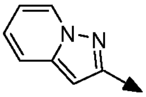
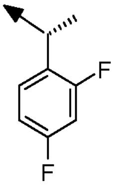
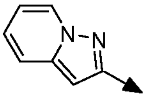


The title compound was prepared according to the method of example 1 from Preparation 98 (10mg, 0.022mmol) to give 5.5mg, 57%. LCMS Rt 2.20mins, (ESI) m/z 433 $[MH]^+$ (Analysis System 1, Preparative System 2).

Examples 63-70 were similarly prepared according to the method described above for example 62, starting from the appropriate ester.

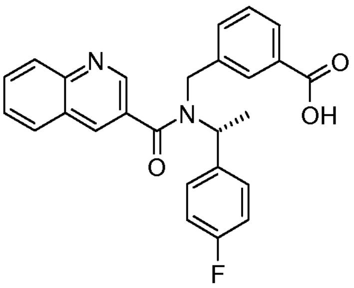


Example	Name	R	R1	Precursor	Data
63	6-({[(1R)-1-(2,4-difluorophenyl)propyl](isoquinolin-3-ylcarbonyl)amino}methyl)pyridine-2-carboxylic acid			Preparation 61	^{1}H NMR (400 MHz, DMSO–d6) Rotamers δ ppm: 0.77 (t, 3H), 1.99-2.15 (m, 1H), 2.22-2.36 (m, 1H), 4.62-4.69 (m, 2H), 5.30-5.33 (m, 1H), 6.90-7.03 (m, 2H), 7.31 (dd, 1H), 7.57-7,95 (m, 6H), 8.16 (d, 1H), 8.24-8.25 (m, 1H), 9.44 (s, 1H). LRMS (ESI & APCI) m/z 462 [MH]$^+$, 460 [M]$^-$
64	6-({[(1R)-1-(2,4-difluorophenyl)propyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)pyridine-2-carboxylic acid			Preparation 81	LCMS Rt 2.14 mins, (ESI) m/z 451 [MH]$^+$ (Analysis System 1, Preparative System 1)
65	6-({[(1R)-1-(2,4-difluorophenyl)ethyl](isoquinolin-3-ylcarbonyl)amino}methyl)pyridine-2-carboxylic acid			Preparation 62	LCMS Rt 17.53 mins, (APCI) m/z 448 [MH]$^+$ 470 [M+Na]$^+$ (Analysis System 9)
66	6-({[(1R)-1-(2,4-difluorophenyl)propyl](quinolin-3-ylcarbonyl)amino}methyl			Preparation 63	LCMS Rt 2.11 mins, (ESI) m/z 462 [MH]$^+$ (Analysis System 1, Preparative System 1)

	)pyridine-2-carboxylic acid				
67	6-({[(1R)-1-(4-fluorophenyl)propyl][(6-fluoroquinolin-3-yl)carbonyl]amino}methyl)pyridine-2-carboxylic acid			Preparation 64	LCMS Rt 3.00 mins, (ES) m/z 460 [M-H] (Analysis System 10)
68	6-({[(1R)-1-(4-fluorophenyl)propyl](quinolin-3-ylcarbonyl)amino}methyl)pyridine-2-carboxylic acid			Preparation 65	LCMS Rt 1.43 mins, (ESI) m/z 444 [MH]$^+$ (Analysis System 4)
69	6-({[(1R)-1-(4-fluorophenyl)ethyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)pyridine-2-carboxylic acid			Preparation 99	LCMS Rt 2.97mins, (ESI) m/z 419 [MH]$^+$ (Analysis System 2, Preparative System 2)
70	6-({[(1R)-1-(2,4-difluorophenyl)ethyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)pyridine-2-carboxylic acid			Preparation 66	LCMS Rt 3.22mins, (ESI) m/z 437 [MH]$^+$ (Analysis System 2, Preparative System 1)

Example 71

3-({[(1R)-1-(4-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid



The ester from Preparation 101 (14.89g, 33.65mmol) was dissolved in methanol (75mL). 5M aqueous sodium hydroxide (17mL, 85mmol) was added and the mixture stirred at room temperature overnight. The reaction was concentrated in vacuo to give an off white solid. Water (75mL) was added followed by ethyl acetate (75mL) resulting in a tri-phasic system that was stirred at room temperature for 10mins. 36.5% hydrochloric acid (0.5mL) was added to pH6 giving a bi-phasic system. 5M aqueous sodium hydroxide was added to pH 9-10 giving a tri-phasic system. The lower layer was removed and water (75mL) was added to the other layers giving a bi-phasic system which was washed with ethyl acetate (60mL). The aqueous layer was acidified to pH 5-6 by addition of a 36.5% hydrochloric acid (1mL) prior to being extracted with ethyl acetate (75mL). The aqueous layer was re-acidified to pH 4 by addition of a 36.5% hydrochloric acid (2mL) before being extracted with ethyl acetate (75mL). The 2 organic layers from the acid extractions were combined and dried ($MgSO_4$) and concentrated in vacuo to give the title compound as an off-white foam (11.34g, 79% yield). ^1H NMR (400 MHz, DMSO–d6, 90°C) δ ppm: 1.58-1.60 (d, 3H), 4.42-4.46 (d, 1H), 4.71-4.75 (d, 1H), 5.40-5.45 (bs, 1H), 7.05-7.11 (m, 2H), 7.28-7.39 (m, 4H), 7.62-7.67 (m, 1H), 7.70-7.75 (m, 2H), 7.78-7.82 (m, 1H), 7.99-8.04 (m, 2H), 8.42 (s, 1H), 8.91 (s, 1H). LRMS (APCI) m/z 429 $[MH]^+$

The following Examples were prepared analogously.

Example number	Name
72	3-({[(1R)-1-(3-chlorophenyl)ethyl](isoquinolin-3-ylcarbonyl)amino}methyl)benzoic acid
73	6-({[(1R)-1-(4-fluorophenyl)propyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)pyridine-2-carboxylic acid
74	3-({[(1R)-1-(4-fluorophenyl)propyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid
75	3-({[(1R)-1-(4-fluorophenyl)ethyl][(7-methylpyrazolo[1,5-a]pyridin-2-yl)carbonyl]amino}methyl)benzoic acid

76	6-({[(1R)-1-(4-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)pyridine-2-carboxylic acid
77	6-({[(1R)-1-(2,4-difluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)pyridine-2-carboxylic acid
78	6-({[(1R)-1-(2,4-difluorophenyl)propyl][(3-methylpyrazolo[1,5-a]pyridin-2-yl)carbonyl]amino}methyl)pyridine-2-carboxylic acid
79	3-({[1-(4-fluorophenyl)ethyl](7H-pyrrolo[2,3-b]pyridin-2-ylcarbonyl)amino}methyl)benzoic acid
80	3-({[1-(4-fluorophenyl)ethyl](isoquinolin-4-ylcarbonyl)amino}methyl)benzoic acid
81	3-({(3,4-dihydro-2H-chromen-3-ylcarbonyl)[(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid
82	3-({[1-(2-chlorophenyl)ethyl](quinolin-6-ylcarbonyl)amino}methyl)benzoic acid
83	3-({[1-(4-fluorophenyl)ethyl](1-naphthoyl)amino}methyl)benzoic acid
84	3-({[1-(4-fluorophenyl)ethyl](pyrazolo[1,5-a]pyridin-3-ylcarbonyl)amino}methyl)benzoic acid
85	3-({[1-(2,5-difluorophenyl)ethyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)benzoic acid
86	3-({(1,3-benzodioxol-5-ylcarbonyl)[1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid
87	3-({[1-(2,3-difluorophenyl)ethyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)benzoic acid
88	2-fluoro-5-({[(1R)-1-(4-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid
89	3-({(2,3-dihydro-1-benzofuran-5-ylcarbonyl)[1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid
90	3-({[(1S)-1-(4-fluorophenyl)ethyl](2-naphthoyl)amino}methyl)benzoic acid
91	3-({[(1S)-1-(4-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid
92	3-({[1-(4-fluorophenyl)ethyl](isoquinolin-1-ylcarbonyl)amino}methyl)benzoic acid
93	3-({[1-(4-fluorophenyl)ethyl](quinoxalin-2-ylcarbonyl)amino}methyl)benzoic acid

94	3-({[1-(4-fluorophenyl)ethyl](5,6,7,8-tetrahydroquinolin-2-ylcarbonyl)amino}methyl)benzoic acid
95	3-({[(1S)-1-(3-chlorophenyl)ethyl](2,3-dihydro-1,4-benzodioxin-6-ylcarbonyl)amino}methyl)benzoic acid
96	3-({(2,3-dihydro-1H-inden-2-ylcarbonyl)[1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid
97	3-({(2,3-dihydro-1-benzofuran-7-ylcarbonyl)[1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid
98	3-({[1-(4-fluorophenyl)ethyl](1,8-naphthyridin-2-ylcarbonyl)amino}methyl)benzoic acid
99	3-({[1-(4-fluorophenyl)ethyl](quinoxalin-6-ylcarbonyl)amino}methyl)benzoic acid
100	3-({[1-(4-fluorophenyl)ethyl](1H-pyrrolo[2,3-b]pyridin-3-ylcarbonyl)amino}methyl)benzoic acid
101	2-chloro-5-({[(1R)-1-(4-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid
102	3-({(2,1,3-benzoxadiazol-5-ylcarbonyl)[1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid
103	3-({(2,3-dihydro-1,4-benzodioxin-6-ylcarbonyl)[(1S)-1-phenylpropyl]amino}methyl)benzoic acid
104	3-({[1-(4-fluorophenyl)ethyl](1,6-naphthyridin-2-ylcarbonyl)amino}methyl)benzoic acid
105	3-({[1-(4-fluorophenyl)ethyl][(1-methyl-1H-benzotriazol-5-yl)carbonyl]amino}methyl)benzoic acid
106	3-({[(1R)-1-(4-fluorophenyl)propyl](quinolin-2-ylcarbonyl)amino}methyl)benzoic acid
107	3-({[1-(4-fluorophenyl)ethyl][(2-methyl-1H-benzimidazol-5-yl)carbonyl]amino}methyl)benzoic acid
108	3-({[(1R)-1-(4-fluorophenyl)ethyl](imidazo[1,2-a]pyrimidin-2-ylcarbonyl)amino}methyl)benzoic acid
109	3-({[(1R)-1-(4-fluorophenyl)ethyl](indolizin-2-ylcarbonyl)amino}methyl)benzoic acid
110	3-({(2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl)[(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid
111	3-({[1-(4-fluorophenyl)ethyl](4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-ylcarbonyl)amino}methyl)benzoic acid

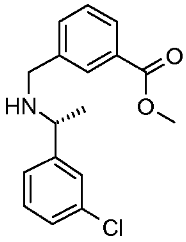
112	3-({[1-(4-fluorophenyl)ethyl](1H-indazol-6-ylcarbonyl)amino}methyl)benzoic acid
113	3-({(1H-benzimidazol-5-ylcarbonyl)[1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid
114	3-({(1H-benzotriazol-5-ylcarbonyl)[1-(4-fluorophenyl)ethyl]amino}methyl)benzoic acid

PREPARATIONS

The following Preparations illustrate the preparation of certain intermediates used to prepare the Examples above.

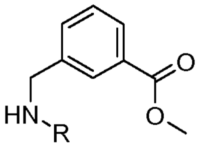
Preparation 1

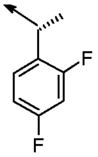
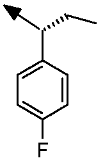
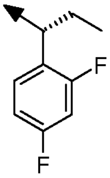
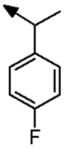
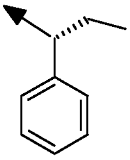
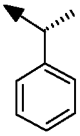
Methyl 3-({[(1R)-1-(3-chlorophenyl)ethyl]amino}methyl)benzoate



Methyl 3-formylbenzoate (1.27g, 7.71mmol) and (1R)-1-(3-chlorophenyl)ethanamine (1g, 6.426mmol) were dissolved in methanol (20mL) and stirred at room temperature over the weekend. The reaction mixture was cooled in an ice/water bath and sodium borohydride (292mg, 7.71mmol) was added in portions as gas was evolved with each addition. After stirring for 1 hour the reaction mixture was quenched with water (5mL) and concentrated in vacuo. The residue was partitioned between dichloromethane (25mL) and water (20mL), the organic layer dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was dissolved in methanol and passed through an ISOLUTE SCX-2 column; washing with methanol and then eluting with 2M ammonia in methanol. The appropriate fractions were combined and concentrated in vacuo. The residue was dissolved in methyl t-butyl ether and filtered and the filtrate was concentrated in vacuo to give the title compound as a colourless oil (1.90g, 97%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.36 (d, 3H), 3.63-3.72 (m, 2H), 3.78-3.81 (m, 1H), 3.93 (s, 3H), 7.22-7.30 (m, 3H), 7.37-7.42 (m, 2H), 7.48-7.50 (m, 1H), 7.92-7.96 (m, 2H).

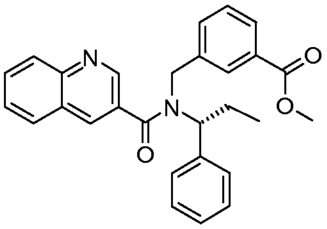
Preparations 2-6 were similarly prepared according to the method described above for Preparation 1, starting from methyl 3-formylbenzoate and the appropriate amine.



Preparation	R	Data
2		LCMS Rt 0.68mins, (ESI & APCI) m/z 306 $[MH]^+$ (Analysis System 11)
3		^{1}H NMR (400 MHz $CDCl_3$) δ ppm: 0.78 (t, 3H), 1.55-1.66 (m, 1H), 1.68-1.78 (m, 1H), 3.50(t, 1H), 3.60 (dd, 2H), 3.90 (s, 3H), 7.00-7.04 (m, 2H), 7.26-7.29 (m, 2H), 7.41-7.46 (m, 2H), 7.89-7.93 (m, 2H). LRMS (ESI & APCI) m/z 302 $[MH]^+$
4		^{1}H NMR (400 MHz $CDCl_3$) δ ppm: 0.85 (t, 3H), 1.62-1.73 (m, 1H), 1.74-1.85 (m, 1H), 3.65 (dd, 2H), 3.89 (t, 1H), 3.93 (s, 3H), 6.76 (m, 1H), 6.87-6.92 (m, 1H), 7.36-7.49 (m, 3H), 7.91-7.95 (m, 2H). LRMS (ESI & APCI) m/z 320 $[MH]^+$
5		No data obtained as compound used straight away
6		^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.82 (t, 3H), 1.50 - 1.82 (m, 2H), 3.52 (dd, 1H), 3.65 (dd, 2H), 3.92 (s, 3H), 7.25 - 7.40 (m, 6H), 7.45 - 7.60 (m, 1H), 7.90 - 7.97 (m, 2H). LRMS (ESI) m/z 284 $[MH]^+$.
7		No data obtained as compound used straight away

<u>Preparation 8</u>

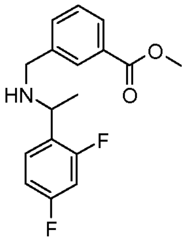
<u>Methyl 3-({[(1R)-1-phenylpropyl](quinolin-3-ylcarbonyl)amino}methyl)benzoate</u>



Quinoline-3-carbonyl chloride (77mg, 0.402mmol) was added in one portion as a solid to a stirred ice cold solution of the amine from preparation 6 (120mg, 0.423mmol) in the dichloromethane. The resulting mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was washed with water, 10% citric acid (2x), $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated in vacuo to give the title compound as a pale yellow gum (125mg, 71%). ^1H NMR (400 MHz, DMSO-d6, 90°C) δ ppm: 0.87 (t, 3H), 2.09-2.17 (m, 2H), 3.90 (s, 3H), 4.62 (dd, 2H), 5.15-5.30 (br m, 1H), 7.15-7.40 (m, 6H), 7.50-7.60 (m, 1H), 7.62-7.70 (m, 2H), 7.80 (dt, 1H), 8.02 (t, 2H), 8.37 (s, 1H), 8.82 (s, 1H). LRMS (APCI) m/z 439 $[MH]^+$.

Preparation 9

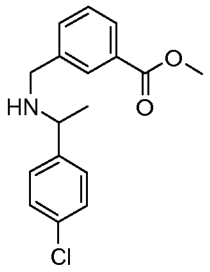
Methyl 3-({[1-(2,4-difluorophenyl)ethyl]amino}methyl)benzoate



Methyl 3-(aminomethyl)benzoate (245mg, 1.48mmol) was dissolved in toluene (8mL) and 1-(2,4-difluorophenyl)ethanone (0.19mL, 1.48mmol), p-toluenesulfonic acid (10mg, catalytic) and 4Å sieve was added. The reaction mixture was heated at reflux over night. The reaction mixture was concentrated in vacuo to give a brown oil which was dissolved in methanol (4mL) and sodium borohydride (56mg, 1.48mmol) was added. The reaction mixture was stirred at room temperature under argon for 1hour. Water was added and the methanol was removed in vacuo. Ethyl acetate was added and the phases separated. The aqueous phase was extracted with ethyl acetate and the combined organic layers were then extracted with diluted aqueous HCl. The acidic extract was basified with NaOH solution and then extracted with dichloromethane (x3). The combined dichloromethane layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (silica, 1:3 ethyl acetate:heptane increasing to 1:1 as eluent) to give the title compound as a pale yellow oil (161mg, 36%). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 1.37 (d, 3H), 3.62-3.71 (m, 2H), 3.91 (s, 3H), 4.11 (q, 1H), 6.74-6.81 (m, 1H), 6.84-6.91 (m, 1H), 7.34-7.50 (m, 3H), 7.88-7.97 (m, 2H). LRMS (ESI) m/z 306 [MH]$^+$.

Preparation 10

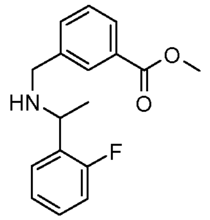
Methyl 3-({[1-(4-chlorophenyl)ethyl]amino}methyl)benzoate



The title compound was prepared according to the method of preparation 9 from methyl 3-(aminomethyl)benzoate (150mg, 0.91mmol) and 1-(4-chlorophenyl)ethanone (0.12mL, 0.91mmol) to give the title compound as a yellow oil (120mg, 44%). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 1.40 (d, 3H), 3.63 (d, 1H), 3.69 (d, 1H), 3.81 (q, 1H), 7.31-7.33 (m, 4H), 7.36-7.42 (m, 1H), 7.49-7.55 (m, 1H), 7.90-7.94 (m, 2H). LRMS (ESI) m/z 304/306 [MH]$^+$.

Preparation 11

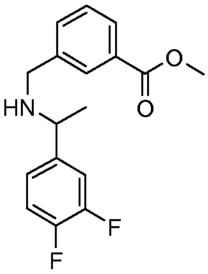
Methyl 3-({[1-(2-fluorophenyl)ethyl]amino}methyl)benzoate



The title compound was prepared according to the method of preparation 9 from methyl 3-(aminomethyl)benzoate (0.26g, 1.57mmol) and 1-(2-fluorophenyl)ethanone (217mg, 1.57mmol) to give the title compound as a yellow oil (230mg, 51%). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 1.40 (d, 3H), 3.66 (d, 1H), 3.70 (d, 1H), 3.91 (s, 3H), 4.14 (q, 1H), 6.99-7.06 (m, 1H), 7.11-7.17 (m, 1H), 7.19-7.26 (m, 1H), 7.37 (t, 1H), 7.41-7.52 (m, 2H), 7.88-7.98 (m, 2H). LRMS (ESI) m/z 288 [MH]$^+$.

Preparation 12

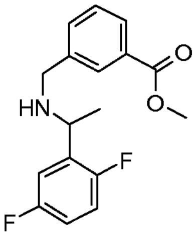
Methyl 3-({[1-(3,4-difluorophenyl)ethyl]amino}methyl)benzoate



The title compound was prepared according to the method of preparation 9 from methyl 3-(aminomethyl)benzoate (0.3g, 1.81mmol) and 1-(3,4-difluorophenyl)ethanone (0.28g, 1.81mmol) to give (264mg, 47%). LCMS Rt 3.10 mins, (ESI) m/z 306 $[MH]^+$ (Analysis System 7).

Preparation 13

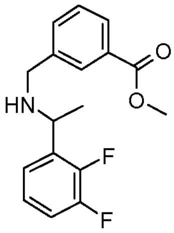
Methyl 3-({[1-(2,5-difluorophenyl)ethyl]amino}methyl)benzoate



To a solution of methyl 3-(aminomethyl)benzoate hydrochloride (200mg, 0.992mmol) in dichloromethane (1mL) was added triethylamine (152uL, 1.09mmol) followed by a solution of 1-(2,5-difluorophenyl)ethanone (1.19mmol) in dichloromethane (1mL) and finally sodium triacetoxyborohydride (252mg, 1.19mmol). The reaction mixture was stirred at room temperature overnight. More sodium triacetoxyborohydride 210mg, 0.992mmol) was added and stirring at room temperature was continued overnight. Dichloromethane (5mL) was added to the reaction mixture and then it was quenched and washed with 1M sodium hydroxide solution. The layers were separated using a phase separating cartridge and the solvent removed in vacuo. The residue was dissolved in methanol and passed through an ISOLUTE SCX-2 column; washing with methanol (25mL) and then eluting with 2M ammonia in methanol (25mL). The appropriate fractions were combined and concentrated in vacuo to afford the title compound as a yellow oil (196mg, 64%). Compound used straight away.

Preparation 14

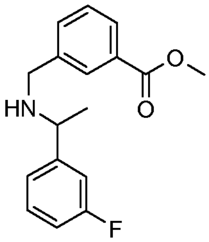
Methyl 3-({[1-(2,3-difluorophenyl)ethyl]amino}methyl)benzoate



The title compound was prepared according to the method of preparation 13 from 1-(2,3-difluorophenyl)ethanone (186mg, 1.19mmol) and methyl 3-(aminomethyl)benzoate hydrochloride (200 mg, 0.992mmol) to give the title compound as a yellow oil (195mg, 64%). Compound used straight away.

Preparation 15

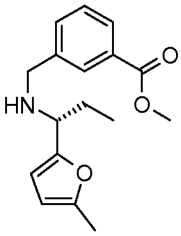
Methyl 3-({[1-(3-fluorophenyl)ethyl]amino}methyl)benzoate



The title compound was prepared according to the method of preparation 9 from methyl 3-(aminomethyl)benzoate (245mg, 1.48mmol) and 1-(3-fluorophenyl)ethanone (0.18mL, 1.48mmol) to give the title compound as a pale yellow oil (147mg, 34%). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 1.35 (d, 3H), 3.61-3.72 (m, 2H), 3.80 (q, 1H), 3.91 (s, 3H), 6.90-6.97 (m, 1H), 7.06-7.13 (m, 2H), 7.25-7.51 (m, 3H), 7.89-7.97 (m, 2H). LRMS (ESI) m/z 288 [MH]$^+$.

Preparation 16

Methyl 3-({[(1R)-1-(5-methyl-2-furyl)propyl]amino}methyl)benzoate

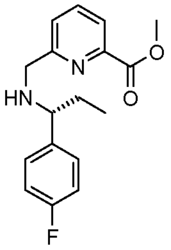


The title compound was prepared according to the method of Preparation 13 from methyl 3-formylbenzoate (58.9mg, 0.359mmol) and (1R)-1-(5-methyl-2-furyl)propan-1-amine (50mg, 0.36mmol) to give the title compound (78mg, 76%). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 0.78 (t, 3H), 1.65-1.72 (m, 2H), 2.20(s, 3H), 3.42 (t, 1H), 3.63

(dd, 2H), 3.83 (s, 3H), 5.80 (d, 1H), 5.93 (d,1H), 7.27 (m, 1H), 7.39-7.44 (m, 1H), 7.81-7.88 (m, 2H).

Preparation 17

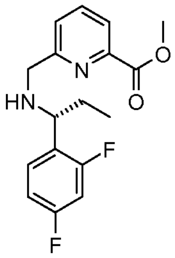
Methyl 6-({[(1R)-1-(4-fluorophenyl)propyl]amino}methyl)pyridine-2-carboxylate



The title compound was prepared according to the method of Preparation 13 from (1R)-1-(4-fluorophenyl)propan-1-amine (404mg, 2.64mmol) and methyl 6-formylpyridine-2-carboxylate (436mg, 2.64mmol) to give the title compound as a viscous oil (442mg, 55%). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 0.82 (t, 3H), 1.59-1.83 (m, 2H), 3.53 (dd, 1H), 3.80 (s, 2H), 4.00 (s, 3H), 6.97-7.03 (m, 2H), 7.27-7.30 (m, 2H), 7.45 (d, 1H), 7.76 (t, 1H), 7.99 (d, 1H).

Preparation 18

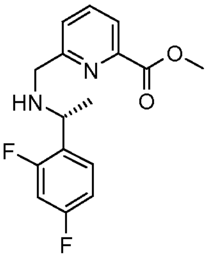
Methyl 6-({[(1R)-1-(2,4-difluorophenyl)propyl]amino}methyl)pyridine-2-carboxylate



The title compound was prepared according to the method of preparation 13 from (1R)-1-(2,4-difluorophenyl)propan-1-amine (299mg, 1.44mmol) and methyl 6-formylpyridine-2-carboxylate (250mg, 1.51mmol) with the addition of acetic acid (1mL) to give the title compound as a colourless gum (310mg, 67%). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 0.87 (t, 3H), 1.76-1.83 (m, 1H), 1.91-1.99 (m, 1H), 3.91 (s, 2H), 3.99-4.04 (m, 4H), 6.76-6.81 (m, 1H), 6.87-6.92 (m, 1H), 7.50-7.56 (m, 2H), 7.80 (t, 1H), 8.01 (d, 1H). LRMS (ESI & APCI) m/z 321[MH]$^+$

Preparation 19

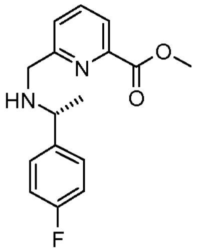
Methyl 6-({[(1R)-1-(2,4-difluorophenyl)ethyl]amino}methyl)pyridine-2-carboxylate



The title compound was prepared according to the method of preparation 1 from (1R)-1-(2,4-difluorophenyl)ethanamine (500mg, 2.58mmol) and methyl 6-formylpyridine-2-carboxylate (512mg, 3.10mmol) to give the title compound as a pale yellow oil (320mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.46 (d, 3H), 3.90 (d, 2H), 4.00 (s, 3H), 4.21 (q, 1H), 6.75-6.80 (m, 1H), 6.84–6.90 (m, 1H), 7.48-7.53 (m, 2H), 7.80 (t, 1H), 8.01 (d, 1H). LRMS (ESI & APCI) m/z 307 $[MH]^+$

Preparation 20

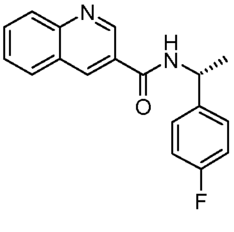
Methyl 6-({[(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)pyridine-2-carboxylate



The title compound was prepared according to the method of preparation 13 from (1S)-1-(4-fluorophenyl)ethanamine (100mg, 0.719mmol) and methyl 6-formylpyridine-2-carboxylate (119mg, 0.719mmol) to give the title compound as a viscous oil (195mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.39 (d, 3H), 3.78-3.84 (m, 3H), 4.00 (s, 3H), 6.97-7.03 (m, 2H), 7.29-7.35 (m, 2H), 7.47 (d, 2H), 7.78 (t, 1H), 7.99 (d, 1H). LRMS (ESI) m/z 289 $[MH]^+$.

Preparation 21

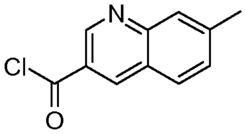
N-[(1R)-1-(4-fluorophenyl)ethyl]quinoline-3-carboxamide



A suspension of quinoline-3-carbonyl chloride (500mg, 2.19mmol) in dichloromethane (5mL) was treated with (1R)-1-(4-fluorophenyl)ethanamine (277mg, 1.99mmol) followed by triethylamine (611µL, 4.38mmol). The reaction mixture was stirred at room temperature overnight. Dichloromethane (5mL) was added to the reaction mixture and the mixture was washed with a saturated $NaHCO_3$ aqueous solution (10mL). The organic layer was dried through a phase separating cartridge and concentrated in vacuo to afford the title compound as a white solid, (535mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.66 (d, 3H), 5.36-5.43 (m, 1H), 6.56 (d, 1H), 7.03 - 7.08 (m, 2H), 7.38-7.43 (m, 2H), 7.59 - 7.63 (m, 1H), 7.79 - 7.83 (m, 1H), 7.87-7.90 (m, 1H), 8.14 (d, 1H), 8.56 (d, 1H), 9.26 (d, 1H); LRMS (ESI & APCI) m/z 295 $[MH]^+$, 293 $[M-H]^-$

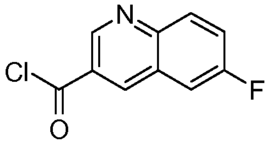
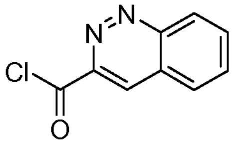
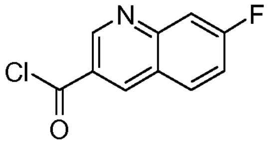
Preparation 22

7-methylquinoline-3-carbonyl chloride



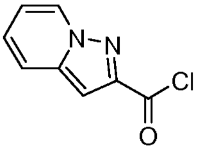
7-methylquinoline-3-carboxylic acid (50mg, 0.267mmol) in thionyl chloride (0.45mL) was heated at reflux for 1h 30mins. After this time the reaction mixture was concentrated in vacuo and azeotroped with dichloromethane three times to give the title compound as a white solid (55mg 100%) which was used straight away.

Preparations 23-25 were similarly prepared according to the method described above for preparation 22, starting from the appropriate acid, compounds were used straight away.

Preparation	Compound
Preparation 23	
Preparation 24	
Preparation 25	

Preparation 26

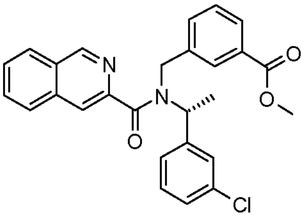
Pyrazolo[1,5-a]pyridine-2-carbonyl chloride



Pyrazolo[1,5-a]pyridine-2-carboxylic acid (44.4mg, 0.274mmol) was suspended in dichloromethane (1mL) and treated with 1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (109uL, 0.823mmol). The mixture was stirred at room temperature for 30 minutes during this time a solution was given. This solution was then used straight away.

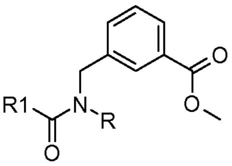
Preparation 27

Methyl 3-({[(1R)-1-(3-chlorophenyl)ethyl](isoquinolin-3-ylcarbonyl)amino} methyl)benzoate

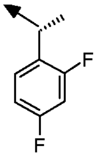
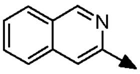
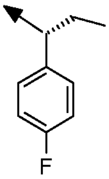
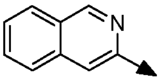
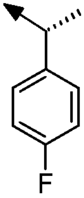
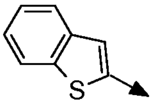
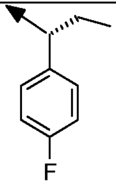
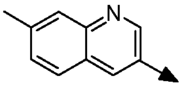
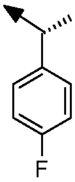
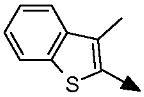
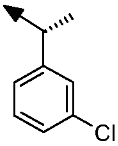
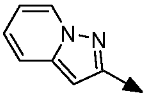
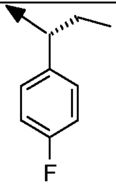
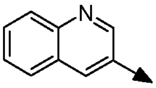
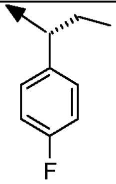
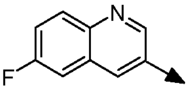
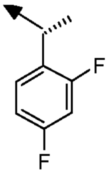
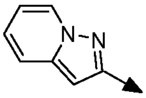


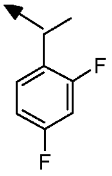
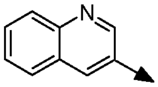
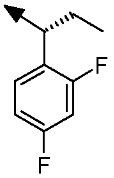
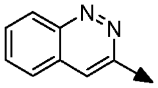
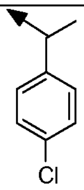
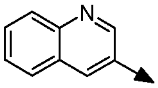
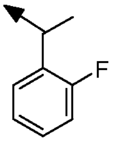
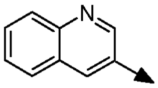
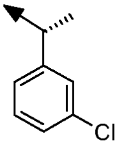
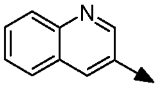
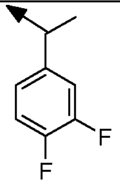
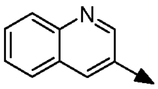
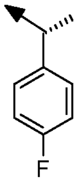
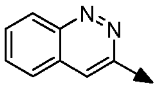
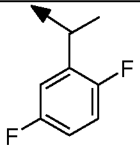
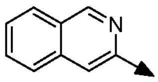
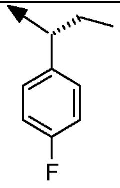
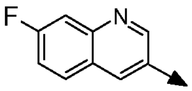
The amine from preparation 1 (1.12g, 3.687mmol) was dissolved in dichloromethane (30mL) and triethylamine (1.8mL, 12.9mmol) was added. A suspension of isoquinoline-3-carbonyl chloride (0.706g, 3.687mmol) in dichloromehtane (20mL) was then added over 2 minutes. The solution was stirred to room temperature and left overnight. The reaction was concentrated in vacuo and the residue partitioned between ethyl acetate (40mL) and water (2x 25mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the desired compound as a pale yellow foam (1.69g, 100%). LCMS Rt 1.55mins, (ES) m/z 459 $[MH]^+$ (Analysis System 11).

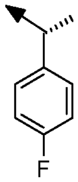
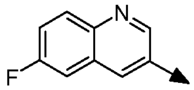
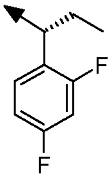
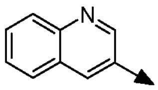
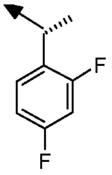
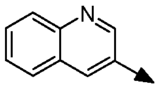
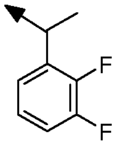
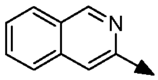
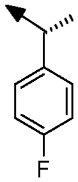
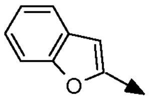
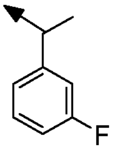
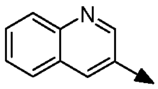
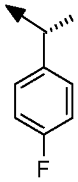
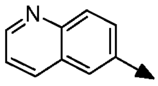
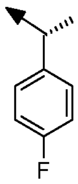
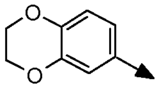
Preparations 28-60 were similarly prepared according to the method described above for preparation 27, starting from the appropriate amine from preparations 1-3,9-16,100 and the appropriate acid chloride.

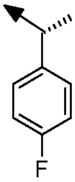
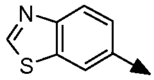
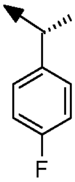
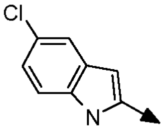
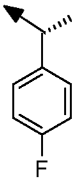
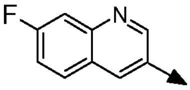
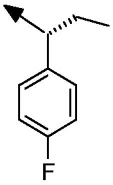
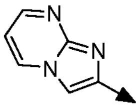
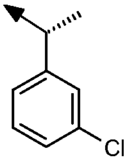
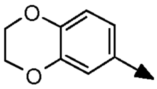
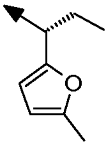
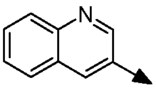


Preparation	R	R1	Precursor	Data

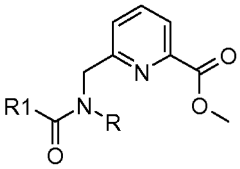
28			Preparation 2	LCMS Rt 1.50mins, (APCI) m/z 461[MH]$^+$ (Analysis System 11)
29			Preparation 3	LCMS Rt 1.87 mins, (ESI & APCI) m/z 479 [M+Na]$^+$ (Analysis System 4)
30			Preparation 100	LCMS Rt 3.68mins, (ESI & APCI) m/z 448 [MH]$^+$, 470 [M+Na]$^+$ (Analysis System 12)
31			Preparation 3 & 22	LCMS Rt 1.73 mins, (ESI & APCI) m/z 471 [MH]$^+$ (Analysis System 4)
32			Preparation 100	LCMS Rt 3.77mins, (ESI & APCI) m/z 462 [MH]$^+$, 484 [M+Na]$^+$ (Analysis System 12)
33			Preparation 1 & Preparation 26	No data obtained as compound used straight away
34			Preparation 3	LCMS Rt 1.75 mins, (ESI & APCI) m/z 457 [MH]$^+$ (Analysis System 4)
35			Preparation 3 & 23	LCMS Rt 1.74 mins, (ESI & APCI) m/z 475 [MH]$^+$ (Analysis System 4)
36			Preparation 2 & Preparation 26	No data obtained as compound used straight away

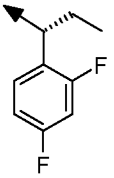
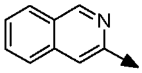
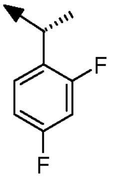
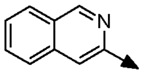
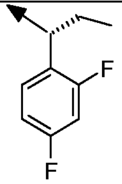
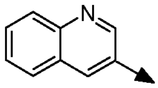
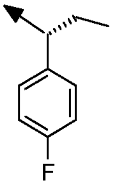
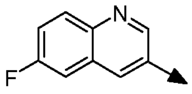
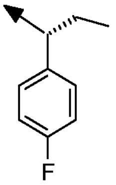
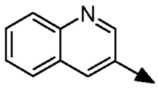
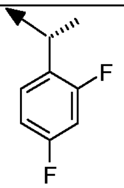
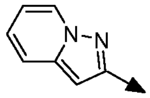
37			Preparation 9	LCMS Rt 3.04 mins, (ESI) m/z 461 $[MH]^+$ (Analysis System 7)
38			Preparation 4 & 24	LCMS Rt 3.29mins, (ESI & APCI) m/z 476 $[MH]^+$, 498 $[M+Na]^+$, 474 $[M]^-$ (Analysis System 12)
39			Preparation 10	LCMS Rt 3.19 mins, (ESI) m/z 459/461 $[MH]^+$ (Analysis System 7)
40			Preparation 11	LCMS Rt 2.94 mins, (ESI) m/z 443 $[MH]^+$ (Analysis System 7)
41			Preparation 1	No data obtained as compound used straight away
42			Preparation 12	LCMS Rt 3.05 mins, (ESI) m/z 461 $[MH]^+$ (Analysis System 7)
43			Preparation 100 & 24	LCMS Rt 3.38mins, (ESI & APCI) m/z 444 $[MH]^+$, 466 $[M+Na]^+$, 443 $[M]^-$ (Analysis System 12)
44			Preparation 13	No data obtained as compound used straight away
45			Preparation 3 & 25	LCMS Rt 1.74 mins, (ESI & APCI) m/z 475 $[MH]^+$ (Analysis System 4)

46			Preparation 100 & 23	LCMS Rt 1.69 mins, (ESI & APCI) m/z 461 $[MH]^+$ (Analysis System 4)
47			Preparation 4	LCMS Rt 1.69 mins, (ESI & APCI) m/z 475 $[MH]^+$ (Analysis System 4)
48			Preparation 2	No data obtained as compound used straight away
49			Preparation 14	No data obtained as compound used straight away
50			Preparation 100	^{1}H NMR (400 MHz, DMSO–d6, 90°C) δ ppm: 1.63 (d, 3H); 3.83 (s, 3H); 4.69 (dd, 2H); 5.73-5.81 (m, 1H); 7.07-7.12 (m, 2H); 7.26-7.57 (m, 8H); 7.61-7.80 (m, 3H). LRMS (ESI & APCI) m/z 432 $[MH]^+$, 454 $[M+Na]^+$
51			Preparation 15	LCMS Rt 3.06 mins, (ESI) m/z 443 $[MH]^+$ (Analysis System 7)
52			Preparation 100	^{1}H NMR (400 MHz, CD_3OD) δ ppm: 1.60-1.69 (m, 3H), 3.87 (bs, 3H), 4.47-4.55 (m, 1H), 4.59-4.76 (m, 1H), 6.98-9.00 (m, 15H), LRMS (ESI & APCI) m/z 443 $[MH]^+$
53			Preparation 100	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.45 (d, 3H), 3.89 (s, 3H), 4.05-4.15 (m, 2H), 4.26 (s, 4H), 4.68-4.78 (m, 1H), 6.85-6.90 (m, 1H), 6.97-7.06 (m, 4H), 7.19-7.25 (m, 2H), 7.28-7.41 (m,

				2H), 7.72 (s, 1H), 7.85 (dt, 1H). LRMS (ESI & APCI) m/z 450 [MH]$^+$
54			Preparation 100	LCMS Rt 1.67 mins, (ES) m/z 449 [MH]$^+$ (Analysis System 11)
56			Preparation 100	LCMS Rt 3.32 mins, (ESI & APCI) m/z 465 [MH]$^+$ (Analysis System13)
57			Preparation 100 & 25	LCMS Rt 1.69 mins, (ESI) m/z 461 [MH]$^+$ (Analysis System 4)
58			Preparation 3	^{1}H NMR (400 MHz, CD$_3$OD) Rotamers δ ppm: 1.15 (t, 3H), 2.16-2.23 (m, 2H), 2.82 (q, 2H), 3.85 (s, 3H), 5.80 (t, 1H), 6.96-7.02 (m, 2H), 7.19-7.25 (m, 3H), 7.45-7.50 (m, 3H), 7.71 (dt, 1H), 7.98-8.02 (m, 1H), 8.69 (dd, 1H), 9.35 (dd, 1H). LRMS (ESI & APCI) m/z 447 [MH]$^+$
59			Preparation 1	^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 1.52 (d, 3H), 3.91 (s, 3H), 4.04-4.16 (m, 1H), 4.25-4.37 (m, 5H), 4.71-4.90 (m, 1H), 6.87-7.43 (m ,9H), 7.74-7.80 (m, 1H), 7.84-7.88 (m, 1H).
60			Preparation 16	LCMS Rt 1.75 mins, (ESI & APCI) m/z 443 [MH]$^+$ (Analysis System 4)

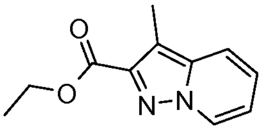
Preparations 61-66 were similarly prepared according to the method described above for preparation 27, starting from the appropriate amine from preparations 17-19 and the appropriate acid chloride.



Preparation	R	R1	Precursor	Data
61			Preparation 18	LCMS Rt 1.69mins, (ESI & APCI) m/z 476 $[MH]^+$ (Analysis System 14)
62			Preparation 19	^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 1.75 (d, 3H), 3.99 (s, 3H), 4.82 (dd, 2H), 5.68-5.73 (m, 1H), 6.52-6.57 (m, 1H), 6.74-6.79 (m, 1H), 7.31–7.36 (m, 1H), 7.66-7.81 (m, 4H), 7.92-7.98 (m, 2H), 8.06 (d, 1H), 8.23 (s, 1H), 9.30 (s, 1H). LRMS (ESI & APCI) m/z 462 $[MH]^+$ 484 $[M+Na]^+$
63			Preparation 18	LCMS Rt 1.56 mins, (APCI 7 ESI) m/z 476 $[MH]^+$ (Analysis System 4)
64			Preparation 17 & Preparation 23	LCMS Rt 1.63 mins, (ESI) m/z 476 $[MH]^+$ (Analysis System 4)
65			Preparation 17	LCMS Rt 1.56 mins, (ESI) m/z 458 $[MH]^+$ (Analysis System 4)
66			Preparation 19 & Preparation 26	No data obtained as compound used straight away

Preparation 67

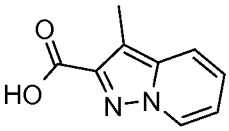
Ethyl 3-methylpyrazolo[1,5-a]pyridine-2-carboxylate



1-Amino-2-ethylpyridinium iodide (3.40g, 13.6mmol) in pyridine (5mL) was treated with ethyl chlorooxoacetate (3.0mL, 27.2mmol) and refluxed for 45mins. The reaction was diluted with water, then extracted with ethyl acetate/hexane (1:1, 3x 50mL) and the combined extracts were washed with 1M HCl, water, and saturated aqueous NaCl, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane 2:3). The title compound was then recrystallized from hexane to give a solid (1.252g, 45%). ^{1}H NMR ($CDCl_3$) δ ppm: 1.5 (t, 3H), 2.55 (s, 3H), 4.5 (q, 2H), 6.8 (t, 1H), 7.15 (t, 1H), 7.55 (d, 1H), 8.5 (d, 1H). Anal: Calc'd for $C_{11}H_{12}N_2O_2$: C 64.69, H 5.92, N 13.72 Found: C 64.49, H 5.88, N 13.46

Preparation 68

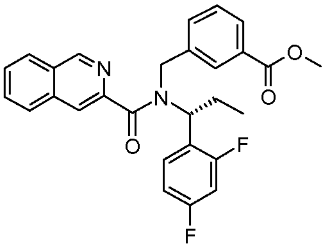
3-Methylpyrazolo[1,5-a]pyridine-2-carboxylic acid



The ester from preparation 67 (1.0g, 4.90mmol) was dissolved in methanol (10mL) and 2.5M aqueous lithium hydroxide (5.88mL, 14.7mmol) was added, the reaction mixture was then stirred at room temperature over night. The methanol was removed in vacuo and the residue dissolved in water (7.5mL), acidified with 2M aqueous HCl to pH4 and the solid collected by filtration. The solid was washed with water and dried to give the title compound as a white solid (580mg, 56%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 2.49 (s, 3H), 6.96 (dt, 1H), 7.16-7.23 (m 1H), 7.62 (d, 1H), 8.44 (d, 1H). LRMS (ESI & APCI) m/z 177 $[MH]^+$

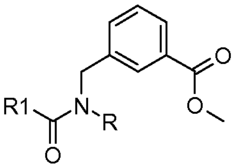
Preparation 69

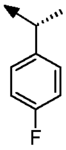
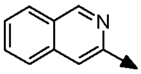
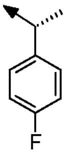
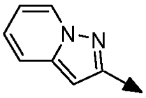
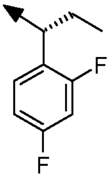
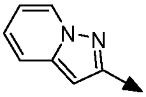
Methyl 3-({[(1R)-1-(2,4-difluorophenyl)propyl](isoquinolin-3-ylcarbonyl)amino} methyl)benzoate

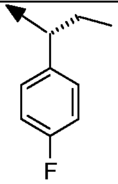
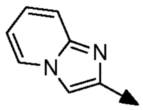
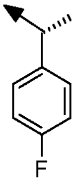
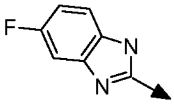
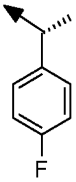
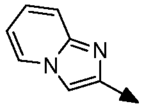
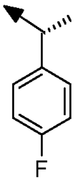
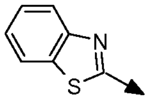
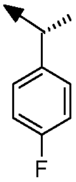
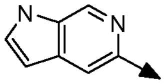
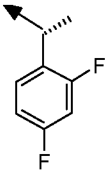
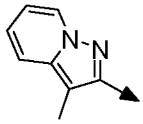
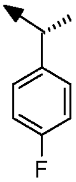
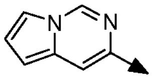
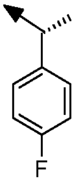
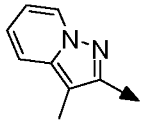


Isoquinoline-3-carboxylic acid (32.6mg, 0.188mmol) was dissolved in dichloromethane (4mL) and HBTU (77.4mg, 0.204mmol) was added followed by triethylamine (65.7μL, 0.471mmol). The resulting solution was allowed to stir at room temperature for 10mins prior to the addition of amine from preparation 4 (50mg, 0.16mmol). The resulting reaction mixture was then allowed to stir at room temperature over night. The crude mixture was diluted with dichloromethane (20mL) and washed with water (20mL), the aqueous phase was then re-extracted with dichloromethane (20mL) and the combined organics dried ($MgSO_4$) and concentrated in vacuo to give the title compound as a clear oil (74mg, 100%) which was used . LCMS Rt 1.77mins, (ES & APCI) m/z 497 $[M+Na]^+$ (Analysis System 4).

Preparations 70-80 were similarly prepared according to the method described above for preparation 69, starting from the appropriate amine from preparations 2-4,100 and the appropriate acid.

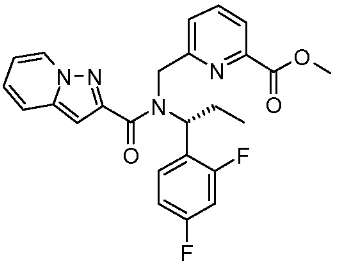


Preparation	R	R1	Precursor	Data
70			Preparation 100	LCMS Rt 1.80 mins, (ESI & APCI) m/z 443 $[MH]^+$ (Analysis System 14)
71			Preparation 100	LCMS Rt 1.78 mins, (ESI) m/z 432 $[MH]^+$ (Analysis System 14)
72			Preparation 4	LCMS Rt 3.48 mins, (ESI) m/z 486 $[M+Na]^+$ (Analysis System 12)

73			Preparation 3	LCMS Rt 1.61 mins, (APCI) m/z 446 $[MH]^+$ 468 $[M+Na]^+$ (Analysis System 4)
74			Preparation 100	LCMS Rt 1.74mins, (ESI & APCI) m/z 450 $[MH]^+$, 448 $[M]^-$ (Analysis System 4)
75			Preparation 100	LCMS Rt 1,58 mins, (APCI) m/z 432 $[MH]^+$ (Analysis System 14)
76			Preparation 100	LCMS Rt 3.86mins, (ESI & APCI) m/z 471 $[M+Na]^+$ (Analysis System 12)
77			Preparation 100	LCMS Rt 1.45mins, (ESI & APCI) m/z 432 $[MH]^+$, 430 $[M]^-$ (Analysis System 4)
78			Preparation 2 & 68	LCMS Rt 3.44 mins, (APCI & ESI) m/z 486 $[M+Na]^+$ (Analysis System 12)
79			Preparation 100	LCMS Rt 1.69 mins, (APCI & ESI) m/z 454 $[M+Na]^+$ (Analysis System 4)
80			Preparation 100 & 68	LCMS Rt 3.41 mins, (APCI & ESI) m/z 468 $[M+Na]^+$ (Analysis System 12)

Preparation 81

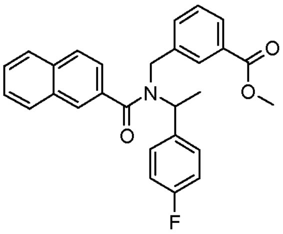
Methyl 6-({[(1R)-1-(2,4-difluorophenyl)propyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)pyridine-2-carboxylate



The title compound was prepared according to the method of Preparation 69 from Preparation 18 (50mg, 0.16mmol) and pyrazolo[1,5-a]pyridine-2-carboxylic acid (30.3mg, 0.187mmol) to give a colourless oil (74mg, 100%). LCMS Rt 1.58 mins, (APCI & ESI) m/z 465 $[MH]^+$ (Analysis System 4).

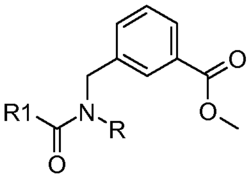
Preparation 82

Methyl 3-({[1-(4-fluorophenyl)ethyl](2-naphthoyl)amino}methyl)benzoate

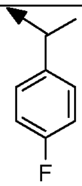
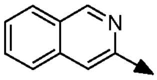
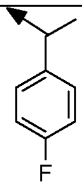
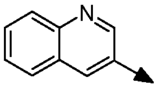
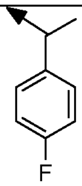
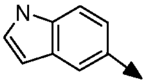
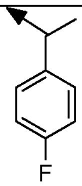
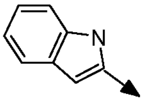
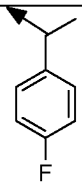
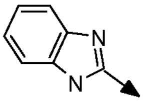
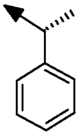
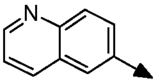
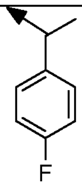
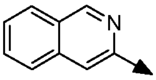
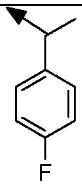
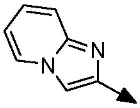
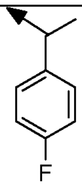
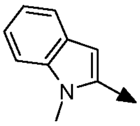
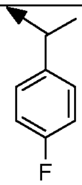
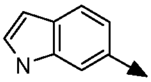


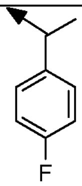
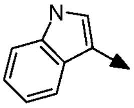
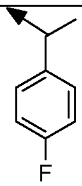
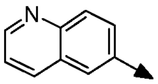
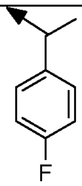
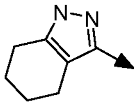
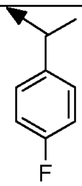
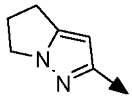
A solution of the amine from preparation 5 (35.9mg, 0.125mmol), 2-naphthoic acid (25.8mg, 0.150mmol) and 2-chloro-1,3-dimethylimidazolinium chloride (23.1mg (0.137mmol) in anhydrous dimethylacetamide (0.6mL) was shaken at 65°C for 16 h. The reaction was then concentrated in vacuo and the residue taken up in water (1mL) and extracted with dichloromethane (3x 1mL) the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give the title compound. No data obtained as compound used straight away.

Preparations 83-96 were similarly prepared according to the method described above for Preparation 82, starting from the appropriate amine from Preparations 5-7 and the appropriate acid.



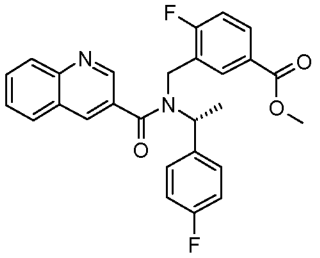
Preparation	R	R1	Precursor	Data

83			Preparation 5	No data obtained as compound used straight away
84			Preparation 5	No data obtained as compound used straight away
85			Preparation 5	No data obtained as compound used straight away
86			Preparation 5	No data obtained as compound used straight away
87			Preparation 5	No data obtained as compound used straight away
88			Preparation 7	No data obtained as compound used straight away
89			Preparation 5	No data obtained as compound used straight away
90			Preparation 5	No data obtained as compound used straight away
91			Preparation 5	No data obtained as compound used straight away
92			Preparation 5	No data obtained as compound used straight away

93			Preparation 5	No data obtained as compound used straight away
94			Preparation 5	No data obtained as compound used straight away
95			Preparation 5	No data obtained as compound used straight away
96			Preparation 5	No data obtained as compound used straight away

Preparation 97

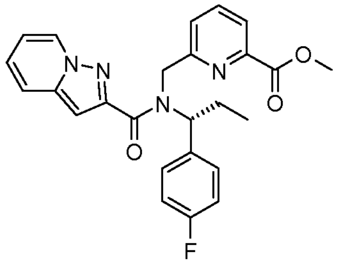
Methyl 4-fluoro-3-({[(1R)-1-(4-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino} methyl)]benzoate



The amide from preparation 21 (60mg, 0.20mmol) dissolved in THF (500µL) in a Reacti vial was treated with NaH 60% suspension in oil (12.2mg, 0.306mmol) and the mixture was stirred at room temperature for 1h. Methyl 3-(chloromethyl)-4-fluorobenzoate (62mg, 0.306mmol) was then added and the mixture was stirred at reflux for 1 h. More NaH 60% suspension in oil (8mg, 0.204mmol) was added and the mixture was stirred at room temperature of 1hr. Methyl 3-(chloromethyl)-4-fluorobenzoate (41mg, 0.204mmol) was added and the mixture was stirred at reflux overnight. The reaction mixture was diluted with dichloromethane (5mL) and washed with a 2N hydrochloric solution (5mL). The aqueous was extracted with dichloromethane (5mL) and the combined organic layers were dried through a phase separating cartridge and concentrated under reduce pressure. Used straight away without further purification.

Preparation 98

Methyl 6-({[(1R)-1-(4-fluorophenyl)propyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)pyridine-2-carboxylate



To a stirred solution of amine from Preparation 17 (42mg, 0.14mmol) in dichloromethane (1mL) was added pyrazolo[1,5-a]pyridine-2-carboxylic acid (22.5mg, 0.14mmol) followed by triethylamine (39µL, 0.278mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (26.6mg, 0.14mmol). The reaction was stirred at room temperature for 40 hrs after this time TLC showed only a small amount of conversion. O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (52.7mg, 0.14mmol) was added along with triethylamine (39µL, 0.278mmol). The reaction mixture was stirred over the weekend. The reaction was then washed with aqueous citric acid, followed by saturated aqueous NaHCO3, dried (MgSO4) and concentrated in vacuo. The residue was purified by column chromatography (silica, 50% ethyl acetate in pentane as eluent) to give the title compound (10mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$): the compound appears to exist as two non-interconverting rotameric forms in CDCl3 in the ratio ca. 2:1. Data for these rotamers are listed separately.

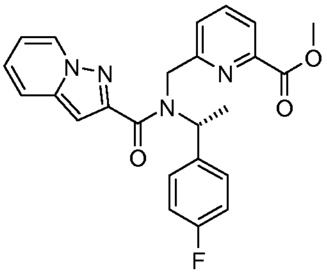
Major: δ ppm: 1.96-2.07 (m, 2H) 3.99 (s, 3H) 4.68 (d, 1H) 4.92 (d, 2H) 6.07 (t, 1H) 6.78-6.85 (m, 3H) 6.98 (s, 1H) 7.12-7.21 (m, 2H) 7.29-7.37 (m, 1H) 7.40-7.52 (m, 2H) 7.56-7.62 (m, 1H) 7.86 (d, 1H) 8.50 (d, 1H)

Minor: δ ppm: 2.08-2.19 (m, 2H) 3.99 (s, 3H) 5.00 (d, 1H) 5.43 (d, 2H) 6.00 (t, 1H) 6.71 (t, 1H) 6.78-6.85 (m, 3H) 7.08 (t, 1H) 7.29-7.37 (m, 1H) 7.40-7.52 (m, 2H) 7.56-7.62 (m, 1H) 7.80 (d, 1H) 8.16 (d, 1H).

LRMS (ESI) m/z 469 $[M+Na]^+$

Preparation 99

Methyl 6-({[(1R)-1-(4-fluorophenyl)ethyl](pyrazolo[1,5-a]pyridin-2-ylcarbonyl)amino}methyl)pyridine-2-carboxylate



To a stirred solution of the amine from Preparation 20 (49mg, 0.17mmol) in dichloromethane (1mL) was added pyrazolo[1,5-a]pyridine-2-carboxylic acid (27.6mg, 0.17mmol) followed by N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (32.6mg, 0.17mmol) and the reaction mixture was stirred for 23 hours. Saturated aqueous $NaHCO_3$ solution (2mL) was added and the mixture was stirred vigorously for 10 minutes before filtering through a phase separation cartridge. The solvent was removed in vacuo and the residue purified by column chromatography (silica 50-100% ethyl acetate in pentane as eluent). The solvent was removed in vacuo to give the title compound as a clear gum (37mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): the compound appears to exist as two non-interconverting rotameric forms in CDCl3 in the ratio ca. 2:1. Data for these rotamers are listed separately.

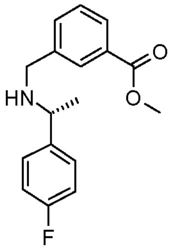
Major: δ ppm: 1.62 (d, 3H), 3.99 (s, 3H), 4.56 (d, 1H), 4.94 (d, 1H), 6.21-6.35 (m, 1H), 6.82-6.99 (m, 4H), 7.17 (t, 1H), 7.28-7.39 (m, 2H), 7.50 (d, 1H), 7.59 (d, 1H), 7.70 (t, 1H), 7.92 (d, 1H), 8.47 (d, 1H).

Minor: δ ppm: 1.56 (d, 3H), 3.99 (s, 3H), 5.05 (d, 1H), 5.31 (d, 1H), 6.21-6.35 (m, 1H), 6.72 (t, 1H), 6.82-6.99 (m, 3H), 7.08 (t, 1H), 7.28-7.39 (m, 3H), 7.50 (d, 1H), 7.58 (d, 1H), 7.86 (d, 1H), 8.16 (d, 1H).

LRMS (ESI) m/z 433 $[MH]^+$

Preparation 100

Methyl 3-({[(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoate

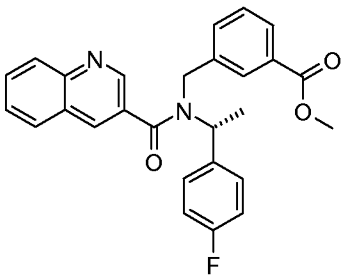


To a solution of methyl 3-formylbenzoate (103g, 627mmol) in 2-methyltetrahydrofuran (900mL) was added (1R)-1-(4-fluorophenyl)ethanamine (85mL, 629mmol) over 5mins. The reaction mixture was stirred for several hours at room temperature then sodium triacetoxyborohydride (340.3g, 1.53mol) was added.

After the initial exotherm was controlled below 36°C, the reaction mixture was stirred at 20°C overnight. It was then cooled to 15°C prior to the addition of a 5M aqueous sodium hydroxide (1L, 5mol) over 1 hour at such a rate the internal temperature was kept below 35°C. The layers were separated and the organic solution was washed with water (1L) before being dried ($MgSO_4$). The inorganics were filtered off and washed twice with methyl tertiary butyl ether (500mL). 4M hydrochloric acid in dioxane (230mL, 920mmol) was added to the liquors and the resulting solution was stirred at 20°C for 45mins prior to being seeded with some methyl-3-({[(1R)-1-(4-fluorophenyl)ethyl]amino}methyl)benzoate hydrochloride to affect precipitation. The slurry was stirred at 20°C over night before being filtered off. The isolated solid was washed three times with methyl tertiary butyl ether (250mL) to give the title compound as the hydrochloride salt as a white solid (145.83g, 72% yield). ^{1}H NMR (400 MHz, DMSO–d6) δ ppm: 1.63 (d, 3H), 3.87 (s, 3H), 3.85-3.93 (m, 1H), 4.11-4.19 (m, 1H), 4.38-4.47 (m, 1H), 7.26-7.33 (m, 2H), 7.56 (t, 1H), 7.62-7.68 (m, 2H), 7.78 (dt, 1H), 7.97 (dt, 1H), 8.06 (t, 1H), 9.65 (br s, 1H), 9.96 (br s, 1H).

Preparation 101

Methyl 3-({[(1R)-1-(4-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl) benzoate



A slurry of the amine hydrochloride from Preparation 100 (0.64g, 1.98mmol), quinoline-3-carboxylic acid (343mg, 1.98mmol), diisopropylethylamine (1.2mL, 6.88mmol) and 1-propanephosphoric acid cyclic anyhydride 40% in ethyl acetate (2.3mL, 3.83mmol) was stirred at 60°C overnight. The reaction mixture was cooled to 20°C prior to being quenched with water (2mL). The biphasic mixture was stirred for 30mins prior to being diluted with ethyl acetate (3mL) and basified with 5M aqueous sodium hydroxide (1.5mL) to pH 8. The layers were separated and the organic solution was washed with water (3mL) prior to being dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. This material was redissolved into ethyl acetate and stirred in presence of silica gel (2.12g) for 4hrs. The inorganics were filtered off, washed with some ethyl acetate. The liquors were concentrated in vauco to give the title compound as a yellow oil (761mg, 87% yield). ^{1}H NMR (400 MHz, DMSO–d6, 90°C) δ ppm: 1.61 (d, 3H), 3.84 (s, 3H), 4.49 (d, 1H), 4.72 (d, 1H), 5.45 (br m, 1H), 7.11 (m, 2H), 7.30-7.44 (m, 4H), 7.60-7.70 (m, 2H), 7.74 (m, 1H), 7.82 (m, 1H), 8.03 (m, 2H), 8.45 (s, 1H), 8.90 (s, 1H).

The ability of the compounds of formula (I) to block TRPM8 were assessed using the invitro assay described below.

Transient Receptor Potential (subfamily M, member 8), TRPM8, is a ligand-gated ion channel that is expressed in sensory neurons and has multiple modes of activation, including cooling chemicals such as menthol, WS-12 or icilin, cold and voltage changes. Upon activation it permits entry of Na^+ and Ca^{2+} ions to the cell that results in depolarization and the generation of action potential.

The method below details a channel activator-induced calcium mobilisation assay utilising recombinant cells. The assay was performed using Chinese Hamster Ovary (CHO) T-rex cells recombinantly expressing the human TRPM8 ion channel. Prior to conducting the assays, a large batch of cells was prepared, cells frozen in aliquots and stored in liquid nitrogen ($2x10^7$ cells/mL) prior to use in individual experiments.

Cell plate preparation

Each frozen cell vial was rapidly defrosted (by immersion in a water bath at 37°C). Inducing medium (Dulbecco's Modified Eagle Medium (DMEM) with supplements of 4500mg/L glucose, 10% v/v foetal bovine serum (FBS), 25mM, HEPES, 1x non-essential amino acids, 1mM sodium pyruvate, 2mM GlutaMAX™ (Invitrogen) and 1mg/mL doxycycline (in dH_2O)) was added dropwise to each vial, to avoid hypotonic shock, up to a volume of 1mL media per vial. Cells were then resuspended in inducing medium to achieve a final concentration of $1x10^6$ cells/mL, and plated out by addition of 20µL cell suspension/well in a 384-black squared-bottom plate. Cell plates were stored at 37°C for 24 hours in a humidified atmosphere with 5% CO_2 present.
Cells were subsequently loaded by addition of concentrated (2X) Calcium-4 dye in dye loading buffer (Hank's Balanced Salt Solution (HBSS) with $CaCl_2$ and $MgCl_2$, 20mM HEPES and 2.5mM probenecid, pH adjusted to 7.4) after media removal. Plates were then incubated for 1 hour at 37°C/5% C O_2.

Inhibitor compound plate preparation

Compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 1mM and serially diluted in DMSO, in 2 fold dilution increments. The resulting 11-point compound concentration range was added to designated wells of a 384-well plate. Two standard reference compounds were included in each plate for subsequent quality control (QC) and data validation purposes. Compound plates were diluted 25 fold, sealed and kept in an incubator at 37°C/5% CO_2 until required.

Assay conduction

For each assay, one dye-loaded cell plate was utilised to determine the EC_{50} value of the menthol analogue, WS-12, with addition of 11-point activator compound concentration range to cell plate performed utilising a Functional Drug Screening System (FDSS, Hamamatsu) and the EC_{80} calculated for use as a challenging concentration in the subsequent inhibitor format assay.

After the loading incubation time, concentration ranges of inhibitor compounds were added to their respective cell plate using the FDSS. Cell plates were then incubated at 37°C/5% CO_2 for 20 minutes, prior to challenging them with addition of a single concentration of WS-12 (final assay concentration corresponding to the calculated EC_{80} as detailed above).

Data analysis

The assay window per plate corresponded to the ratio data calculated by the FDSS in terms of fluorescence emission of the control wells. For each compound the % inhibition was then plotted against the concentration of the compound tested and a concentration effect curve was fitted to the data using a four-parameter logistic equation, and free-fitting parameters whenever possible, to generate an IC_{50} value. The term IC_{50} refers to the concentration of compound required to inhibit 50% of the agonist stimulation challenge.

Following individual determination of individual IC_{50} values for compounds tested, a geometric mean value was calculated together with 95% confidence intervals and n values, where n is the total number of individual IC_{50} values generated.

Compounds of the Examples were tested in the assay described above and found to have the EIC_{50} values specified in the table below.

Example number	TRPM8 IC50	Example number	TRPM8 IC50

1	55.7 nM	58	1790 nM
2	59.7 nM	59	1930 nM
3	60.5 nM	60	329 nM
4	74.7 nM	61	446 nM
5	90.4 nM	62	181 nM
6	93.8 nM	63	217 nM
7	123 nM	64	244 nM
8	145 nM	65	291 nM
9	147 nM	66	734 nM
10	164 nM	67	775 nM
11	184 nM	68	778 nM
12	199 nM	69	827 nM
13	203 nM	70	993 nM
14	207 nM	71	181 nM
15	221 nM	72	108
16	222 nM	73	181
17	234 nM	74	203
18	266 nM	75	1060
19	267 nM	76	1160
20	269 nM	77	1220
21	281 nM	78	1770
22	286 nM	79	2110
23	304 nM	80	2380
24	307 nM	81	2390
25	317 nM	82	2500
26	337 nM	83	2520
27	341 nM	84	2590
28	346 nM	85	2620
29	362 nM	86	2980
30	120 nM	87	3040
31	373 nM	88	3280
32	388 nM	89	3620
33	388 nM	90	3660
34	448 nM	91	4100
35	456 nM	92	4460

36	582 nM	93	4490
37	640 nM	94	4930
38	703 nM	95	5000
39	716 nM	96	5000
40	748 nM	97	5190
41	786 nM	98	5310
42	834 nM	99	5840
43	951 nM	100	6740
44	960 nM	101	6790
45	1010 nM	102	8190
46	1050 nM	103	8530
47	1150 nM	104	8640
48	1160 nM	105	>10000
49	1160 nM	106	>10000
50	1170 nM	107	>10000
51	1190 nM	108	>10000
52	1240 nM	109	>10000
53	1290 nM	110	>10000
54	1350 nM	111	>10000
55	1520 nM	112	>10000
56	1750 nM	113	>10000
57	1780 nM	114	>10000

In vivo analysis

The effects of Example 71 were investigated in discontinuous cystometry using menthol in the anaesthetised guinea pig. Menthol is an activator of the TRPM8 channel, and *in vivo* has been shown to reduce bladder capacity. The effects of the TRPM8 antagonist Example 71 on this menthol induced reduction in bladder capacity were examined *in vivo* in the anaesthetised guinea pig.

MATERIALS AND METHODS

Female guinea pigs (Dunkin-Hartley, B&K Universal) were used in this study. Animals were group housed in standard conditions under a 12h light/dark cycle with food and water available *ad libitum*.

Materials and Formulation

The vehicle used was 18% glycerol formerol (SIGMA, lot 1350392), 17% solutol (BASF) in saline. Where serial dilutions were carried out, these were done using this vehicle to give appropriate dosing solutions. Urethane (SIGMA) was prepared as a 0.2g/mL solution in saline. Chloralose (FLUKA) was prepared as a 10mg/mL solution in a 5mg/mL borax solution in saline. Example 71 or vehicle was prepared on each experimental day. Doses were prepared for an infusion rate of 100uL/kg/min.

Method

Anaesthesia was induced in an anaesthetic chamber with halothane (4%) in oxygen (4L/minute) for approximately 90 seconds after the righting reflex was lost, followed by i.p urethane injection (1.2g/kg of 0.2g/ml solution) to achieve surgical anaesthesia. The guinea pig was placed on a heated blanket and a rectal temperature probe inserted to maintain body temperature throughout the experiment. The jugular vein was cannulated for drug/vehicle infusions and anaesthetic infusions. The carotid artery was cannulated in order to record blood pressure. The trachea was cannulated and the animal artificially ventilated for the duration of the experiment. Chloralose (44mg/kg was infused into the jugular vein over a 2 minute period (approximately 0.5ml/30seconds) and supplementary doses of urethane were given if necessary (0.05g/kg i.v.).

Post laparotomy both ureters were dissected and tied rostral to the ligature. The bladder was cannulated with a double lumen catheter (to detect pressure and to infuse through), which was tied in place. Electrodes were inserted into the external urethral sphincter to record EMG activity.

After an hour acclimatization post surgery, the infusion pump, set at 36ml/hour (600μl/min), was started to initiate saline discontinuous cystometry. After the guinea pig voided the pump was stopped and 1-1.5 minutes later (to allow EUS EMG activity to be recorded) the bladder was drained to gravity and residual volume measured. This pattern was repeated at 15 min intervals until 3 voids were within 10% of each other, as measured by the micturition interval (seconds). The mean of the 3 saline voids was utilised as the control value.

0.2mM menthol was subsequently infused intravesically at 36ml/hr for 2 discontinuous voids, to ensure there was a response to menthol and to check its consistency. Intravenous Example 71 or vehicle infusion was then initiated to coincide with the 3rd intravesical menthol infusion post baseline; ensuring time was left to clear the 0.1ml dead space in the intravenous cannula, such that the drug was *in vivo* at the exact time that the intravesical infusion was initiated. A final saline fill was initiated to show that the bladder response to menthol could be 'washed out.'

Where blood samples were taken, these were taken 1 minute prior to the start intravesical infusion. Blood samples were centrifuged and plasma removed. 2µl phosphoric acid per 100µl plasma was added to stabilise the sample and samples frozen at -20°C. At the end of the study the guinea pig was culled by an overdose of pentobarbitone anaesthetic and a CSF sample taken, as well as brain.

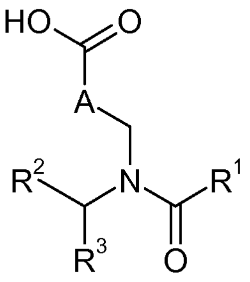
Data collected on Spike 2 software included micturition interval (MI) and threshold volume (TV). This data was used to determine the PKPD relationship.

The results are shown in Figure 1 which demonstrates the Effects of Example 71 at 16.3, 46.67 and 153.33ug/kg/min on Menthol Induced Reduction in Bladder Capacity in the Anaesthetised Guinea Pig. Data from anaesthetised guinea pigs showing the effects of vehicle (n=4, ■ - grey bars) or Example 71 (n=5, ■ - black bars) on the menthol induced reduction in bladder capacity. Example 71 or vehicle was administered at a rate of 0.1mL/kg/min. Example 71 was administered at doses of 16.3 (dose 1), 46.67 (dose 2) and 153.33ug/kg/min (dose 3). The initial 2 doses of Example 71 were administered over 30 min each, whilst the final dose of Example 71 was administered over 45 min to incorporate the final saline reading. *, *** $p< 0.05$ and 0.001 respectively (repeated measures ANOVA).

The results show that menthol consistently reduced bladder capacity when compared with baseline responses across a number of studies. Mean baseline capacity following menthol was 1.4 ± 0.1mL, compared to a saline baseline of 2.7 ± 0.2mL in animals treated with Example 71 (n=14), whilst baseline capacity following menthol was 1.1 ± 0.1mL, compared with a saline baseline of 2.3 ± 0.2mL in vehicle treated animals (n=12). In vehicle treated animals, this reduction was maintained throughout the experiment, and was reversed during saline cystometry at the end of the experiment. In animals treated with Example 71 reversal of the menthol induced reduction in bladder capacity was recorded, with an EC_{50} of 200nM and an EC_{90} of 425nM free plasma concentration.

CLAIMS

1. A compound of the formula (I):



(I)

wherein

A is (i) phenyl substituted at the 1 position by the carboxylic acid and the 3 position by the alkyl amido group and having either no further substituents or a halo group at the 4 position, or
(ii) pyridyl substituted at the 6 position by the carboxylic acid and the 2 position by the alkyl amido group;

R^1 is an 8 to 12 membered unsaturated or partially unsaturated fused bicyclic carbocycle or an 8 to 12 membered unsaturated or partially unsaturated fused bicyclic heterocycle containing 1, 2 or 3 heteroatoms each independently selected from nitrogen, oxygen and sulphur, said R^1 being optionally substituted with one or more substituents each independently selected from the group consisting of halo, $(C_1\text{-}C_3)$alkyl, halo$(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, and halo$(C_1\text{-}C_3)$alkoxy;

R^2 is methyl or ethyl; and

R^3 is: (i) phenyl optionally substituted by one or more halo atoms, or
(ii) furanyl optionally substituted with $(C_1\text{-}C_3)$alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 wherein A is phenyl and has no further substituents.

3. A compound according to claim 1 or claim 2 wherein R^1 is quinolin-3-yl, which is optionally substituted by one or more $(C_1\text{-}C_3)$alky groups.

4. A compound according to any one of claims 1 to 3 wherein R^2 is methyl.

5. A compound according to any one of claims 1 to 4 wherein R^3 is phenyl substituted by one or more fluoro atoms.

6. A compound according to Claim 1 which is 3-({[(1R)-1-(4-fluorophenyl)ethyl](quinolin-3-ylcarbonyl)amino}methyl)benzoic acid, or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a compound according to any of Claims 1 to 6 and a pharmaceutically acceptable excipient.

8. A pharmaceutical composition according to Claim 7 further comprising a second pharmacologically active agent.

9. A pharmaceutical composition according to claim 7 or claim 8 which is specifically adapted for topical administration.

10. A compound according to any one of Claims 1 to 6, or a pharmaceutical composition according to any one of claims 7 to 9, for use as a medicament.

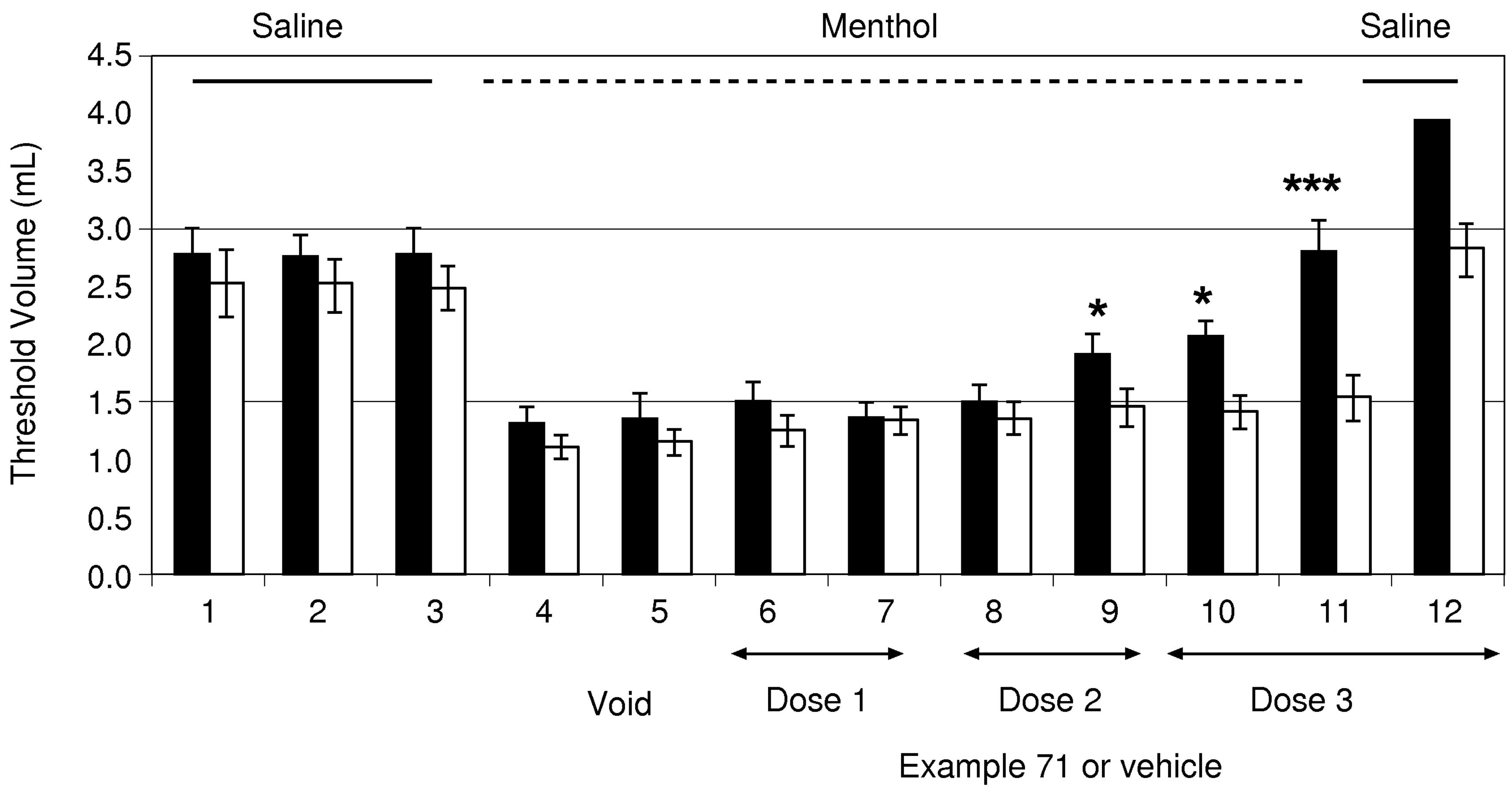
11. A compound according to any one of Claims 1 to 6, or a pharmaceutical composition according to any one of claims 7 to 9, for use in the treatment of a pain condition.

12. A compound according to any one of claims 1 to 6, or a pharmaceutical composition according to any one of claims 7 to 9, as claimed in claim 11, for use in the treatment of a pain condition selected from cold allodynia and Raynauld's syndrome.

13. The use of a compound according to any one of Claims 1 to 6, or a pharmaceutical composition according to any one of claims 7 to 9, for the manufacture of a medicament for the treatment of a pain condition, preferably cold allodynia or Reynauld's syndrome.

14. A method of treating a pain condition, preferably cold allodynia or Reynauld’s syndrome, in a mammal, including administering to said mammal an effective amount of a compound according to any one of Claims 1 to 6, or a pharmaceutical composition according to any one of Claims 7 to 9.

FIG. 1


Saline
Menthol
Saline
Threshold Volume (mL)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
***
*
*
1
2
3
4
5
6
7
8
9
10
11
12
Void
Dose 1
Dose 2
Dose 3
Example 71 or vehicle

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2012/050834

A. CLASSIFICATION OF SUBJECT MATTER

INV.	C07D209/08	C07D209/42	C07D215/48	C07D215/54	C07D217/26
	C07D231/56	C07D235/08	C07D235/16	C07D237/28	C07D241/42
	C07D241/44	C07D249/18	C07D271/12	C07D277/62	C07D277/68

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D C07C

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/040136 A1 (BAYER HEALTHCARE AG [DE]; LAMPE THOMAS [DE]; ALONSO-ALIJA CRISTINA [DE) 20 April 2006 (2006-04-20) cited in the application claims 1, 5-9 examples 38-40 -----	1-14
A	WO 2010/125831 A1 (ANDO K) 4 November 2010 (2010-11-04) cited in the application claims 1, 3, 4, 10-12 examples 115-117, 121-122 -----	1-14

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search 4 May 2012	Date of mailing of the international search report 15/05/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Brandstetter, T

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/050834

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006040136 A1	20-04-2006	CA 2583015 A1	20-04-2006
		JP 2008515950 A	15-05-2008
		US 2008214654 A1	04-09-2008
		WO 2006040136 A1	20-04-2006
WO 2010125831 A1	04-11-2010	CA 2757761 A1	04-11-2010
		CN 102427810 A	25-04-2012
		EP 2424517 A1	07-03-2012
		US 2012094964 A1	19-04-2012
		WO 2010125831 A1	04-11-2010