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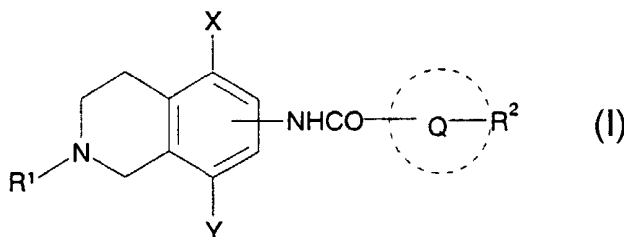
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(54) Title: NOVEL COMPOUNDS



(57) Abstract: Compounds of formula (I) wherein Q is a monocyclic or bicyclic aryl or heteroaryl ring; R¹ is hydrogen; R² is hydrogen or up to three substituents selected from halogen, NO₂, CN, N₃, CF₃O-, CF₃S-, CF₃SO₂-, CF₃CO-, C₁₋₆alkyl, C₁₋₆alkenyl, C₁₋₆alkynyl, C₁₋₆perfluoroalkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl-, C₁₋₆alkylO-C₁₋₆alkylCO-, C₃₋₆cycloalkylO-, C₃₋₆cycloalkylCO-, C₃₋₆cycloalkyl-C₁₋₄alkylO-, C₃₋₆cycloalkyl-C₁₋₄alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C₁₋₄alkyl-, C₁₋₆alkylS-, C₁₋₆alkylSO₂-, (C₁₋₄alkyl)₂NSO₂-, (C₁₋₄alkyl)NHSO₂-, (C₁₋₄alkyl)₂NCO-, (C₁₋₄alkyl)NHCO-, or CONH₂, or -NR³R⁴ where R³ is hydrogen or C₁₋₄alkyl, and R⁴ is hydrogen, C₁₋₄alkyl, formyl, -CO₂C₁₋₄alkyl, or -COC₁₋₄alkyl, or two R² groups together form a carbocyclic ring that is saturated or unsaturated and unsubstituted or substituted by -OH or =O; X is halogen, C₁₋₆alkoxy, C₁₋₆alkyl, or C₁₋₆perfluoroalkyl, and; Y is hydrogen, halogen, C₁₋₆alkoxy, C₁₋₆alkyl, or C₁₋₆perfluoroalkyl; but excluding the compounds N-(5-Iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-azidobenzamide and N-(5-iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-benzoyl-2-methoxybenzamide; and pharmaceutically acceptable salts or solvates thereof possess anticonvulsant activity and are useful in the treatment of a variety of disorders.

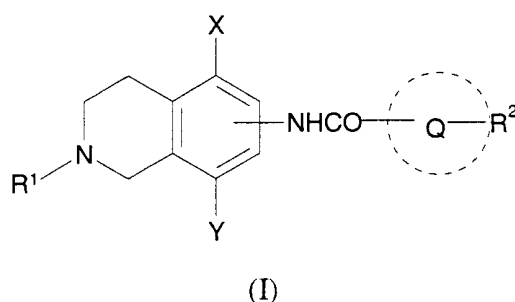
NOVEL COMPOUNDS

This invention relates to novel compounds, to processes for preparing them, and to their use as therapeutic agents.

5 Prior art document United States patent 4,022,900 (Marion Laboratories Inc.) discloses benzamido-1,2,3,4-tetrahydroisoquinolines having anti-hypertensive properties. Prior art documents International Application Publication Numbers WO 97/48683, WO98/41507, WO 98/41508, WO 97/48683, WO 99/21836 and WO 99/31068 (SmithKline Beecham) disclose isoquinolinyl benzamide derivatives and their use as
10 anticonvulsants.

It has now been surprisingly found that carboxamide compounds of formula (I) below possess anti-convulsant activity and are therefore believed to be useful in the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the
15 effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological
20 deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity
25 (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

Accordingly, in a first aspect, the present invention provides a compound of formula (I) or pharmaceutically acceptable salt thereof:



wherein:

5 Q is a monocyclic or bicyclic aryl or heteroaryl ring;

R¹ is hydrogen;

R² is hydrogen or up to three substituents selected from halogen, NO₂, CN, N₃, CF₃O-, CF₃S-, CF₃SO₂-, CF₃CO-, C₁₋₆alkyl, C₁₋₆alkenyl, C₁₋₆alkynyl, C₁₋₆perfluoroalkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl-, C₁₋₆alkylO-, C₁₋₆alkylCO-, C₃₋₆cycloalkylO-, C₃₋₆cycloalkylCO-, C₃₋₆cycloalkyl-C₁₋₄alkylO-, C₃₋₆cycloalkyl-C₁₋₄alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C₁₋₄alkyl-, C₁₋₆alkylS-, C₁₋₆alkylSO₂-, (C₁₋₄alkyl)₂NSO₂-,

(C₁₋₄alkyl)NHSO₂-, (C₁₋₄alkyl)₂NCO-, (C₁₋₄alkyl)NHCO-, or CONH₂, or -NR³R⁴

where R³ is hydrogen or C₁₋₄ alkyl, and R⁴ is hydrogen, C₁₋₄alkyl, formyl, -CO₂C₁₋

15 4alkyl, or -COC₁₋₄alkyl, or two R² groups together form a carbocyclic ring that is saturated or unsaturated and unsubstituted or substituted by -OH or =O;

X is halogen, C₁₋₆ alkoxy, C₁₋₆ alkyl, or C₁₋₆ perfluoroalkyl, and;

Y is hydrogen, halogen, C₁₋₆ alkoxy, C₁₋₆ alkyl, or C₁₋₆ perfluoroalkyl;

with the proviso that the following compounds are excluded:

20 N-(5-Iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-azidobenzamide, and;

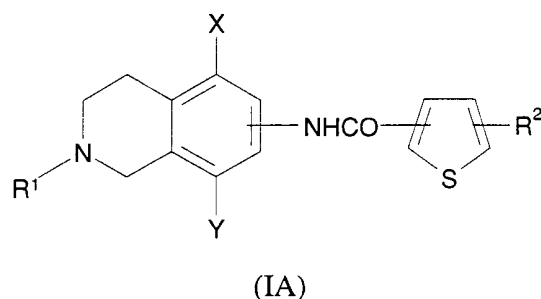
N-(5-iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-benzoyl-2-methoxybenzamide.

The compounds of this invention are typically (tetrahydroisoquinolin-7-yl) carboxamides.

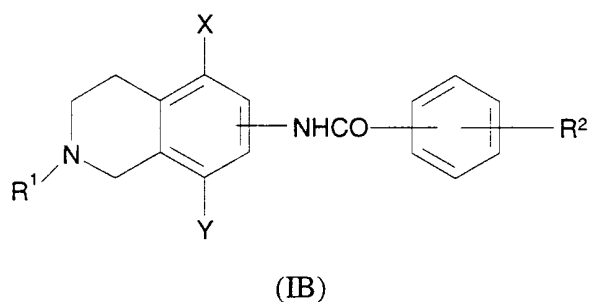
The ring system Q is typically unsubstituted or substituted phenyl or unsubstituted or substituted thiophenyl. When two R² groups form a carbocyclic ring, this is typically a 5-7-membered ring, and Q may be a naphthalene, indane, or indanone ring system.

Alkyl groups of formula (I), including alkyl groups that are part of other moieties such as alkoxy or acyl, may be straight or branched chain. Phenyl groups in R^2 , including phenyl groups that are part of other moieties, may be substituted independently with one or more groups selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} alkylcarbonyl. Suitable C_{3-6} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Suitable halo substituents include fluoro, chloro, iodo and bromo.

A suitable group of compounds of this invention consists of compounds of formula (IA):



another suitable group of compounds consists of compounds of formula (IB):



wherein R^1 , R^2 , X, and Y are as hereinbefore defined.

A suitable group of compounds of formula (I) are those wherein;

R^1 is hydrogen;

R^2 is hydrogen or one or more of the following groups;

methyl, ethyl, *n*-butyl, *iso*-propyl, *t*-butyl, phenyl, methoxy, ethoxy, *iso*-propoxy, *n*-butoxy, cyclopropylmethoxy, phenoxy, benzyloxy, amino, acetylamino, nitro, azido,

cyano, bromo, chloro, fluoro, iodo, acetyl, pivaloyl, *iso*-butyryl, benzoyl, iodobenzoyl, trifluoromethyl, perfluoroethyl, trifluoromethoxy, trifluoroacetyl, methanesulfonyl, *n*-propylsulfonyl, isopropylsulfonyl, dimethylsulfamoyl, or two R² groups form a benzene, cyclopentane or cyclopentanone ring;

5 X is chloro, bromo, iodo, fluoro C₁₋₆ perfluoroalkyl, and;

Y is hydrogen, halogen, C₁₋₆ alkoxy, C₁₋₆ alkyl, or, C₁₋₆ perfluoroalkyl.

A preferred group of compounds of formula (I) are those wherein;

R¹ is hydrogen;

R² is hydrogen or one or more of the following groups;

10 methyl, ethyl, *iso*-propyl, *n*-butyl, *t*-butyl, phenyl, methoxy, ethoxy, *iso*-propoxy, phenoxy, acetoxy, nitro, cyano, bromo, chloro, fluoro, iodo, acetyl, pivaloyl, trifluoromethyl, pentafluoroethyl, azido, trifluoromethoxy;

X is iodo, chloro, bromo or trifluoromethyl, and;

Y is hydrogen, chloro, bromo, iodo or trifluoromethyl.

15 The following compounds are examples of compounds of formula (I), but do not limit the invention in any way:

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-chlorothiophene-2-carboxamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-ethoxy benzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-*iso*-propyl benzamide

20 N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethyl benzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-methoxybenzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-methoxybenzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-ethoxybenzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-*iso*-propoxybenzamide

25 N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-ethylbenzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-ethylbenzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-*iso*-propoxybenzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-ethoxy-3-trifluoromethyl benzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-ethoxy benzamide

30 N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-ethoxy benzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-ethyl-3-trifluoromethyl benzamide

- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethylbenzamide
- N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-methoxybenzamide
- N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-fluoro-4-methoxybenzamide
- 5 N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-*iso*-propoxybenzamide
- N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-pentafluoroethyl benzamide
- N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-*iso*-propoxy-3-trifluoromethyl benzamide
- 10 N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-methoxybenzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethyl benzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-ethoxy-3-trifluoromethyl benzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-ethoxybenzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-ethoxybenzamide
- 15 N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-*iso*-propoxybenzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-ethoxybenzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-ethoxybenzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-*iso*-propylbenzamide
- N-(5-Trifluoromethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-ethoxybenzamide
- 20 N-(5-Trifluoromethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethylbenzamide
- N-(5-Trifluoromethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-fluoro-4-methoxy-benzamide
- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-ethoxybenzamide
- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-ethoxybenzamide
- 25 N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-ethoxybenzamide
- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-ethoxybenzamide
- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-fluoro-4-methoxybenzamide
- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-methoxybenzamide
- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-*iso*-propoxybenzamide
- 30 N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-*iso*-propoxybenzamide.

When synthesised these compounds are often in salt form such as the hydrochloride or trifluoroacetate, and such salts also form part of this invention. Such salts may be used in preparing pharmaceutically acceptable salts. The compounds and

their salts may be obtained as solvates such as hydrates, and these also form part of this invention.

The above compounds and pharmaceutically acceptable salts thereof, especially the hydrochloride, and pharmaceutically acceptable solvates, especially hydrates, form a preferred aspect of the present invention.

The administration of such compounds to a mammal may be by way of oral, parenteral, sub-lingual, nasal, rectal, topical or transdermal administration.

An amount effective to treat the disorders hereinbefore described depends on the usual factors such as the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 1 to 1000 mg, suitably 1 to 500 mg, for example an amount in the range of from 2 to 400 mg such as 2, 5, 10, 20, 30, 40, 50, 100, 200, 300 and 400 mg of the active compound. Unit doses will normally be administered once or more than once per day, for example 1, 2, 3, 4, 5 or 6 times a day, more usually 1 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 1 to 1000 mg, for example 1 to 500 mg, that is in the range of approximately 0.01 to 15 mg/kg/day, more usually 0.1 to 6 mg/kg/day, for example 1 to 6 mg/kg/day.

It is greatly preferred that the compound of formula (I) is administered in the form of a unit dose composition, such as an oral unit dose including sub-lingual, rectal, topical or parenteral (especially intravenous) composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colorants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art. Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch

glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to
5 distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid
10 preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of
15 glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents. Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the
20 compound and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To
25 enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a
30 surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

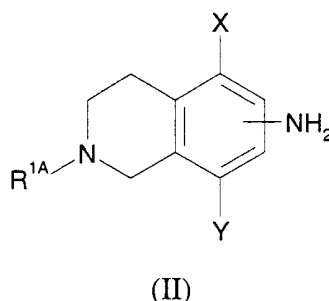
Accordingly, the present invention further provides a pharmaceutical composition for use in the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesis in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS) which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides a method of treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesis in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS) comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof.

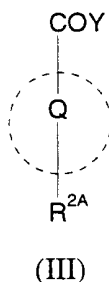
In a further aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

In a further aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate, thereof as a therapeutic agent, in particular for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

In a further aspect, the present invention provides a process for the preparation of compounds of formula (I) as hereinbefore defined which process comprises reacting a compound of formula (II);



wherein R^{1A} is R¹ or preferably a group convertible to R¹, and R¹, X, and Y are as hereinbefore defined, with a compound of formula (III)



wherein Q is as hereinbefore defined;

15 Y is a leaving group such as Cl or OH, and;

R^{2A} represents hydrogen or up to three substituents as hereinbefore defined for R²

wherein the R^{2A} groups may independently be R² groups or groups convertible to R²;

and where required converting an R^{1A} or R^{2A} group to a R¹ or R² group respectively;

converting one R¹ or R² group to another R¹ or R² group;

20 converting a salt product to the free base or a pharmaceutically acceptable salt, or
converting a free base product to a pharmaceutically acceptable salt.

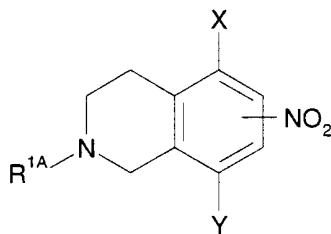
Reaction of a compound of formula (III) which is an acid chloride (Y=Cl) will lead directly to the hydrochloride salt. Suitable solvents include ethyl acetate or dichloromethane, optionally in the presence of a base such as triethylamine. When the

compound of formula (III) is an aromatic acid ($Y=OH$), conventional conditions for condensation of such acids with amines may be used, for example reacting the components in a mixture of (dimethylaminopropyl)-ethyl-carbodiimide/hydroxybenzotriazole in a suitable solvent such as dimethyl formamide.

- 5 Conversions of an R^{1A} or R^{2A} group-to a R^1 or R^2 group typically arise when a protecting group is needed during the above coupling reaction or during the preparation of the reactants by the procedures described below. Interconversion of one R^1 or R^2 group to another typically arises when one compound of formula (I) is used as the immediate precursor of another compound of formula (I) or when it is easier to introduce
10 a more complex or reactive substituent at the end of a synthetic sequence.

The compound of formula (II), wherein R^{1A} is hydrogen or trifluoroacetyl and X and Y are both chloro may be prepared from the compound of formula (II) wherein R^{1A} is hydrogen or trifluoroacetyl, X is chloro, and Y is hydrogen by reaction with N-chloromorpholine in glacial acetic acid.

- 15 The compound of formula (II) wherein R^{1A} is hydrogen or trifluoroacetyl, X is chloro, and Y is hydrogen may be prepared from the compound of formula (IV) wherein R^{1A} is hydrogen or trifluoroacetyl, X is chloro and Y is hydrogen by reduction with tin (II) chloride in concentrated hydrochloric acid.



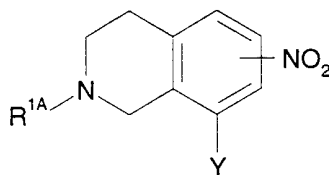
20

(IV)

- The compound of formula (IV) wherein R^{1A} is hydrogen or trifluoroacetyl, X is chloro and Y is hydrogen may be prepared from the compound of formula (IV) wherein
25 X is iodo and Y is hydrogen by heating in the presence of copper (I) chloride in an inert atmosphere.

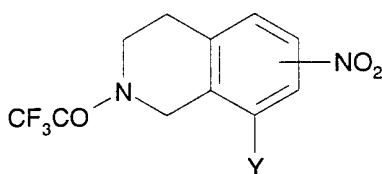
The compound of formula (IV) wherein R^{1A} is hydrogen or trifluoroacetyl, X is iodo and Y is hydrogen may be prepared from the compound of formula (V) wherein R^{1A}

is hydrogen or trifluoroacetyl and Y is hydrogen by reaction with N-iodosuccinimide in triflic acid according to the procedure of G.A.Olah *et al.*, J.Org.Chem., 1993, 58, 3194.



(V)

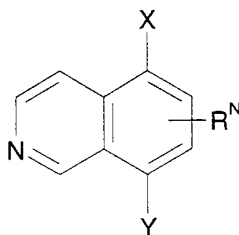
The compound of formula (V) wherein R^{1A} is hydrogen and Y is hydrogen may be prepared from the compound of formula (VI) wherein Y is hydrogen by hydrolysis with potassium carbonate in methanol.



(VI)

The compound of formula (VI) wherein Y is hydrogen may be prepared by reaction of N-(nitrophenyl)ethyl trifluoroacetamide and paraformaldehyde in acidic conditions using the procedure of Stokker, Tet.Lett.,1996, 37, 5453. N-(nitrophenyl)ethyl trifluoroacetamides can be prepared from readily available materials by reaction of trifluoroacetic anhydride with lutidine and nitrophenethylamine hydrochloride, as illustrated in the Descriptions below.

Compounds of formula (II) may also be prepared from the corresponding aminoisoquinoline (or its nitro-analogue) of formula (VII)

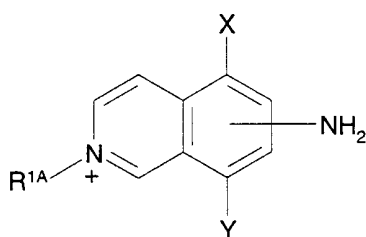


(VII)

where R^N is NH_2 or NO_2 and X and Y are as hereinbefore defined

by reaction with a compound $R^{1A}Z$ where Z is a leaving group such as halogen,

- 5 especially iodo, or tosylate and R^{1A} is benzyl or 4-methoxybenzyl to obtain an intermediate of formula (VIII).



(VIII)

10

which can be reduced, for example using sodium borohydride, or hydrogenated, for example using hydrogen and a palladium/activated carbon catalyst, to obtain a tetrahydroisoquinoline of formula (II). When the compound of formula (VIII) is replaced by a nitroisoquinoline, the nitro group is converted to an amino group in the

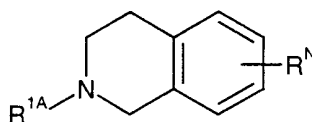
15 hydrogenation step.

- When the intended R^1 is hydrogen, the nitrogen atom of the tetrahydroisoquinoline or isoquinoline molecule is preferably protected conventionally, prior to the coupling step that forms the carboxamide of formula (I), for example by *tert.*-butoxycarbonyl, trifluoroacetyl or benzyl. The compound can be deprotected under
- 20 standard conditions, for example using trifluoroacetic acid/methylene chloride or potassium carbonate in aqueous methanol, catalytic hydrogenolysis.

Amino/nitro-isoquinolines of formula (VIII) and the reagents used are commercially available, or can be prepared from commercially available materials using conventional procedures described in the literature.

- 25 The substituents X and Y may be introduced during any of the procedures above, for example by conventional substitution of the aromatic ring of compounds of formula (IV), (V) or (VIII) or may be present on commercially available starting materials usable

in the above described procedures. Most suitably the substituents X and Y are introduced to a compound of formula (IX)



(IX)

5

where R^N and R^{1A} are as hereinbefore defined. For example X as halogen may be incorporated by reaction with a halosuccinimide, or X = CF₃ may be introduced by displacement of iodo with copper(I)trifluoroacetate as illustrated in the descriptions below.

10

Compounds of formula (III) may be prepared by further substitution of commercially available benzoic acid or thiophene carboxylic acid derivatives using conventional procedures, or by oxidation of corresponding substituted benzyl alcohols. Alternatively benzoic acids can be prepared from correspondingly substituted phenols, for example by formation of the acetate, conversion to an acetophenone and then to the desired acid. Examples of these procedures are documented in WO 98/41507 and WO98/41508.

15

Where the above described intermediates are novel compounds, they also form part of this invention.

The preparation of compounds of this invention is further illustrated by the following Descriptions and Examples, which do not limit the invention in any way:

20

Description 1

N-2-(4-Nitrophenyl)ethyl-trifluoroacetamide

A solution of trifluoroacetic anhydride (10.6ml) in dichloromethane (100ml) was added dropwise to a stirred solution of 2,6-lutidine (17.44ml) and 4-nitrophenethylamine hydrochloride (15.2g; 75 mmol) at 0°C. The mixture was stirred at 25°C overnight under argon and then washed with dilute citric acid (x2), brine and dried over Na₂SO₄. The material in the organic phase gave the title compound D1 as a pale yellow solid (19.04g).

30

Description 2**7-Nitro-1,2,3,4-tetrahydro-2-trifluoroacetyl-isoquinoline**

The product from Description 1 (2.26g; 9.15 mmol) and paraformaldehyde (0.45g; 14.4 mmol) in acetic acid (10ml) and conc. H₂SO₄ (15ml) were stirred at 25°C for 20h

- 5 according to the procedure of G.E. Stokker., Tet. Lett., 1996, **37**, 5453. Work up afforded the title compound D2 as a white solid (2.17g).

¹H NMR (CDCl₃) δ: 3.10 (2H, m), 3.92 (2H, m), 4.85 + 4.92 (2H, 2xs), 7.38 (1H, t), 8.10 (2H, m); m/z (EI): 274 (M⁺)

10 **Description 3**

7-Nitro-1,2,3,4-tetrahydroisoquinoline

The product from Description 2 (17.22g; 63 mmol) was hydrolysed at room temperature using a solution of potassium carbonate (46.6g) in 10% aqueous methanol (660ml).

Work-up with dichloromethane gave the title compound (11g).

15

Description 4**5-Iodo-7-nitro-1,2,3,4-tetrahydroisoquinoline**

The product from Description 3 (750mg; 3.9mmol) and N-iodosuccinimide (1.13g) in triflic acid (5ml) was stirred at 25°C overnight according to the procedure of G.A.Olah *et*
20 *al.*, J.Org.Chem., 1993, 58, 3194. The mixture was poured cautiously into saturated NaHCO₃ and then extracted into ether (2x). The combined organic extracts were washed with aqueous sodium thiosulfate, dried (MgSO₄) and evaporation *in vacuo* gave a residue. Chromatography on Kieselgel 60 in 2% methanol - dichloromethane gave the title compound (650mg).

25

Description 5**7-Amino-5-iodo-1,2,3,4-tetrahydroisoquinoline**

A solution of the product from Description 4 (650mg, 2.14mmol) in ethanol (20ml) at 50°C was treated with a solution of tin (II) chloride (1.42g) in c. HCl (3ml). The resultant
30 yellow solution was basified with 10% aqueous sodium hydroxide and the product extracted into dichloromethane. Flash chromatography on Kieselgel 60 (5% methanol - dichloromethane) gave the title compound (428mg; 73%).

Description 6**5-Iodo-7-nitro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline**

The title compound was prepared from the product from Description 2 using a procedure similar to that of Description 4.

m/z (API⁺): 401 (MH⁺; 45%).

Description 7**5-Chloro-7-nitro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline**

The product from Description 6 (810mg) in dry DMF (15ml) was treated with copper (I) chloride (605mg) and heated at 125°C under argon for 18h. After cooling, the mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was then washed with water (x 3), aqueous sodium thiosulfate, brine and dried (MgSO₄). Evaporation *in vacuo* gave the title compound as a red gum (519mg).

¹H NMR (CDCl₃) δ: 3.09 (2H, m), 3.96 (2H, m), 4.85, 4.92 (2H, 2s, rotamers), 7.99 (1H, m), 8.20 (1H, m).

Description 8**7-Amino-5-chloro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline**

A solution of the product from Description 7 (2.14mmol) in ethanol (20ml) at 50°C was treated with a solution of tin (II) chloride (1.42g) in c. HCl (3ml). The resultant yellow solution was basified with 10% aqueous sodium hydroxide and the product extracted into dichloromethane. Flash chromatography on Kieselgel 60 (5% methanol - dichloromethane) gave the title compound.

¹H NMR (CDCl₃) δ: 2.84 (2H, m), 3.67 (2H, brs), 3.83 (2H, m), 4.61, 4.67 (2H, 2s, rotamers), 6.33 (1H, m), 6.65 (1H, m).

Description 9**7-Amino-5,8-dichloro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline**

Chlorination of the product from Description 8 (150mg; 0.54 mmol) with N-chloromorpholine (100mg; 0.89 mmol) in glacial acetic acid (6ml) for 30 min at 25°C

followed by basic work-up similar to that of Description 8 gave the title compound (70mg).

m/z (API⁺): 315, 313 (MH⁺; 50% expected isotope pattern)

5 Description 10

7-Amino-5-bromo-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline

The title compound was prepared from the product from Description 6 and copper (II) bromide using a method similar to that of Description 7 followed by tin (II) chloride reduction according to the procedure used in Description 8.

- 10 ¹H NMR (CDCl₃) δ: 2.86 (2H, m), 3.68 (2H, brs), 3.85 (2H, m), 4.62, 4.69 (2H, 2s, rotamers), 6.39 (1H, m), 6.85 (1H, m).

Description 11

7-Amino-5-trifluoromethyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline

- 15 The title compound was prepared from the product from Description 6 and potassium trifluoroacetate using a method similar to that of Preparation 6 followed by hydrogenation over 10% palladium on carbon (100mg) in ethanol at atmospheric pressure overnight. The catalyst was removed by filtration through a pad of Kieselguhr and evaporation *in vacuo* gave the title compound.

- 20 ¹H NMR (CDCl₃) δ: 2.98 (2H, brm), 3.82 (4H, m), 4.67, 4.72 (2H, 2s, rotamers), 6.60 (1H, m), 6.88 (1H, m).

Preparation 1

4-tert-Butyl-phenoxyacetate

- 25 A mixture of 3-tert-butylphenol (25.25g, 0.1680 mole), acetic anhydride (34.31g, 0.336 mole) and sodium acetate (13.78g, 0.1680 mole) was heated at 100°C for 2h. On cooling the mixture was poured into water (200ml) and extracted with ethyl acetate (200ml). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to afford the acetate compound as an oil (33.33g).

30

Preparation 2

4-tert-Butyl-2-hydroxy acetophenone

A mixture of the acetate of Preparation 1 (33.23g, 0.173 mole) and AlCl_3 (25.61g, 0.192 mole) was placed in an oil bath preheated to 120°C and stirred mechanically. Then the oil bath temperature was raised to 165°C and maintained for 45 min before being allowed to cool to 120°C. Then water was added dropwise into the reaction mixture (4x250ml) to
5 steam distil the product (bath temp 190-200°C). The distillate was extracted with ether and the combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to afford 4-*tert*-butyl-2-hydroxy acetophenone as an oil (18.05g).

Preparation 3

10 4-*tert*-Butyl-2-methoxy acetophenone

A suspension of 4-*tert*-butyl-2-hydroxy acetophenone (12.65g), potassium carbonate (13.14g) and dimethyl sulfate (8.99ml) in acetone (200ml) was refluxed for 48h. After cooling, the mixture was filtered. The solvent was then removed *in vacuo* and the residue taken up in dichloromethane and washed with brine. The organic layer was dried over
15 sodium sulfate and concentrated *in vacuo* to afford a yellow oil (12.05g).

Preparation 4

4-*tert*-Butyl-2-methoxybenzoic acid

The acetophenone of Preparation 3 (11.0g, 53 mmol) was added to a solution of sodium
20 hydroxide (28.68g), sodium hypochlorite (182ml, 12% w/w) and water (70ml) at 80°C with stirring. After heating for 1.25h, the mixture was cooled to 0°C and a solution of sodium metabisulphite (41.1g) in water (170ml) was added. The mixture was stirred for 15 min and then acidified (pH1) with conc. HCl (45ml). Work-up with ethyl acetate gave the title compound as a white solid (8.9g).

25 ^1H NMR ($\text{DMSO}-d_6$) δ : 1.30 (9H, s), 3.85 (3H, s), 6.96 - 7.12 (2H, m), 7.60 (1H, d), 12.30 - 12.60 (1H, br).

Preparation 5

5-Bromo-2,4-dimethoxybenzoic acid

30 To a solution of 2,4-dimethoxybenzoic acid (4.0g, 0.022mol) in chloroform (60ml) was added bromine (1.13ml, 0.022mol) in chloroform (20ml) dropwise. After stirring

overnight at room temperature the precipitate was filtered off and dried to afford the title compound as a white solid (2.87g).

Preparation 6

5 2,4-Dimethoxy-5-trifluoromethylbenzoic acid

5-Bromo-2,4-dimethoxybenzoic acid methyl ester (1.5g; 5.4 mmol) in DMF (25ml) and toluene (8ml) under argon was treated with potassium trifluoroacetate (1.53g; 10.1 mmol) and copper (I) iodide (2.1g, 10.9 mmol). The mixture was heated to 170°C with removal of water (Dean/Stark), and then at 155°C overnight; then allowed to cool, poured into
10 ether and water and filtered through Kieselguhr. The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to give a brown solid. Chromatography on Kieselgel 60 with 1:1 ether/petrol gave a white solid (1.03g) which was hydrolysed in 1:1 methanolic: aqueous NaOH (50ml) at 50°C. Work-up gave the title compound as a white solid (1g).

15 Preparation 7

3-Bromo-4-ethoxybenzoic acid

The title compound was prepared from 4-ethoxybenzoic acid in a manner similar to that of Preparation 5.

¹H NMR (DMSO-D₆) δ: 1.45 (3H, t, J = 7 Hz), 4.26 (2H, q, J = 7 Hz), 7.26 (1H, d, J = 9
20 Hz), 7.98 (1H, dd, J = 2, 9 Hz), 8.12 (1H, d, J = 2 Hz)

Preparation 8

4-Methoxy-3-trifluoromethylbenzoic acid

The title compound was prepared from 3-bromo-4-methoxybenzoic acid and potassium
25 trifluoroacetate in a manner similar to that of Preparation 6.

¹H NMR (DMSO-D₆) δ: 3.78 (3H, s), 7.18 (1H, d, J = 9 Hz), 7.90 (1H, d, J = 2 Hz), 8.00
(1H, dd, J = 2, 9 Hz), 12.70 - 13.10 (1H, br,exchangeable)

Preparation 9

30 4-Methoxy-3-trifluoromethylbenzoyl chloride

The title compound was prepared from 4-methoxy-3-trifluoromethylbenzoic acid with oxalyl chloride and DMF in chloroform at room temperature [D. Levin, Chem. Br., 1977, 20] followed by evaporation *in vacuo*.

5 Preparation 10

3-Bromo-4-ethylbenzoic acid

The title compound was prepared from 4-ethylbenzoic acid.

^1H NMR (DMSO- D_6) δ : 1.20 (3H, t, $J = 7$ Hz), 2.78 (2H, q, $J = 7\text{Hz}$), 7.50 (1H, d, $J = 8$ Hz), 7.90 (1H, dd, $J = 2, 8$ Hz), 8.07 (1H, d, $J = 8$ Hz)

10

Preparation 11

4-*iso*-Propyl-3-trifluoromethylbenzoic acid

Prepared as described in Preparation 6 from methyl 3-bromo-4-*iso*-propylbenzoate and isolated as a white solid.

15 m/z (API): 231.1 [M-H].

Preparation 12

3-Cyano-4-*iso*-propylbenzoic acid

20 The title compound was prepared from 4-*iso*-propylbenzoic acid similar to that described in Procedure 1.

^1H NMR (DMSO- D_6) δ : 1.07 (6H, d, $J = 7$ Hz), 3.13 (1H, m, overlapped), 7.48 (1H, d, $J = 7$ Hz), 7.96 (1H, dd, $J = 2, 8$ Hz), 8.00 (1H, d, $J = 2$ Hz).

Preparation 13

25 Methyl 3-bromo-4-*iso*-propoxybenzoate

Methyl 3-bromo-4-hydroxybenzoate (2.5g, 10.8mmol) in DMF (35ml) was treated with potassium carbonate (3.0g, 21.6mmol), 2-iodopropane (2.76, 21.6mmol) and then stirred at 25°C for 48h. Work-up with ethyl acetate gave the title compound (3.0g).

30 ^1H NMR (250MHz, CDCl_3) δ : 1.41 (6H, d, $J=7$ Hz), 3.89 (3H, s), 4.66 (1H, m), 6.90 (1H, d, $J = 8$ Hz), 7.93 (1H, dd, $J = 8, 2$ Hz), 8.22 (1H, d, $J = 2$ Hz)

Preparation 14

Methyl 3-cyano-4-*iso*-propoxybenzoate

Methyl 3-bromo-4-*iso*-propoxybenzoate (2.0g, 7.3mmol) and copper(I)cyanide in N-methyl pyrrolidone (50ml) were heated under vigorous reflux for 4h. Work-up with ethyl acetate gave the title compound (1.0g).

- 5 ^1H NMR (250MHz, CDCl_3) δ : 1.56 (6H, d, $J=7$ Hz), 4.05 (3H, s), 4.88 (1H, m), 7.13 (1H, d, $J = 8$ Hz), 8.31 (1H, dd, $J = 8, 2$ Hz), 8.38 (1H, d, $J = 2$ Hz)

Preparation 15**3-Cyano-4-*iso*-propoxybenzoic acid.**

- 10 Saponification of **P14** gave the acid as an off white solid.

^1H NMR (250MHz, CDCl_3) δ : 1.35 (6H, d, $J=7$ Hz), 4.67 (1H, m), 6.90 (1H, d, $J = 8$ Hz), 8.11 (1H, dd, $J = 8, 2$ Hz), 8.19 (1H, d, $J = 2$ Hz)

Preparation 16

- 15 ***iso*-Propyl 3-acetyl-4-*iso*-propoxybenzoate**

The bromo ester (2.5g, 8.3mmol) in dry dioxan (30ml) was treated with (1-ethoxyvinyl)-tributyl tin (3.58g, 9.9mmol) followed by tetrakis triphenylphosphine palladium(o) (0.48g, 0.4mmol) and heated at 100° for 18h. After cooling, the mixture was acidified and aqueous work-up and extraction into ethyl acetate gave a coloured oil (5.6g). Flash

- 20 chromatography on Kieselgel 60 [hexane to 20% EtAc/hexane gave the title compound as a yellow oil (2.3g).

m/z (API^+): 265.2 (MH^+ , 90%).

Preparation 17

- 25 **3-Acetyl-4-*iso*-propoxybenzoic acid**

Saponification of the ester **P16** (2.3g) gave the title compound as a white solid (1.3g).

^1H NMR (250MHz, CDCl_3) δ : 1.48 (6H, d, $J=7$ Hz), 2.63 (3H, s), 4.80 (1H, m), 7.00 (1H, d, $J = 8$ Hz), 8.17 (1H, dd, $J = 8, 2$ Hz), 8.46 (1H, d, $J = 2$ Hz)

- 30 **Preparation 18**

Methyl 3-cyano-4-ethoxybenzoate

¹H NMR (250MHz, CDCl₃) δ: 1.53 (3H, d, J=7 Hz), 3.91 (3H, s), 4.25 (2H, q, J=7 Hz), 7.02 (1H, d, J = 8 Hz), 8.25 (1H, dd, J = 8, 2 Hz), 8.32 (1H, d, J = 2 Hz).

Preparation 19

5 3-Acetyl-4-ethoxybenzoic acid

Prepared in a similar manner to that described for Preparations 16 and 17.

¹H NMR (250MHz, CDCl₃) δ: 1.53 (3H, t, J=7 Hz), 2.65 (3H, s), 4.23 (2H, q, J=7 Hz), 7.01 (1H, d, J = 8 Hz), 8.19 (1H, dd, J = 8, 2 Hz), 8.48 (1H, d, J = 2 Hz).

10 Preparation 20

3-Chloro-4-ethoxybenzoic acid

¹H NMR (DMSO-D₆) δ: 1.39 (3H, t, J = 7 Hz), 4.20 (2H, q, J = 7 Hz), 7.22 (1H, d, J = 7 Hz), 7.87 (2H, m).

15 Procedure 1a

Methyl 2-methoxy-5-cyano-4-*iso*-propylbenzoate

Copper (I) cyanide (550mg, 6mmol) was added to a solution of methyl 2-methoxy-5-bromo-4-*iso*-propylbenzoate (861mg) in N-methyl-2-pyrrolidinone (30ml). The mixture was stirred under argon and boiled under reflux for 4h. The mixture was cooled, poured into excess ice/water and ethyl acetate and filtered. The organic phase was separated, washed with water, brine and dried(MgSO₄). Evaporation gave a crude brown solid which was purified by chromatography on silica gel eluting with ethyl acetate/n-hexane (1:4). The product was obtained as a white solid (523 mg).

¹H NMR (250MHz, CDCl₃) δ: 1.33 (6H, d, J=7Hz), 3.38 (1H, sep, J=7Hz), 3.89 (3H, s), 3.98 (3H, s), 6.91 (1H, s), 8.08 (1H, s); m/z (API⁺): 234 (MH⁺, 30%).

Procedure 1b

2-Methoxy-5-cyano-4-*iso*-propylbenzoic acid

2N NaOH (1.25ml) was added to a solution of the methyl ester **P1a** (490mg) in methanol (10ml). The solution was stirred overnight at room temperature. The solution was then diluted with water, concentrated *in vacuo* and washed with ethyl acetate. The aqueous

phase was then acidified with 2N HCl and extracted with ethyl acetate. The extract was washed with brine, dried (MgSO₄) and evaporated to dryness giving the product as a white solid (418mg).

¹H NMR (250MHz, CDCl₃) δ: 1.35 (6H, d, J=7Hz), 3.43 (1H, sep, J=7Hz), 4.14 (3H,s),

5 7.00 (1H, s), 8.41 (1H, s); m/z (API⁺): 220 (MH⁺, 100%).

Procedure 2

N-(5-Chloro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-chlorothiophene-2-carboxamide

10 5-Chloro-2-thenoic acid (90mg, 0.55mmol) and oxalyl chloride (0.05ml, 0.6mmol) in dichloromethane (2ml) was treated with 2 drops of DMF and stirred at at 25°C for 30min. Evaporation *in vacuo* gave a solid which was added to a solution of **D8** (155mg, 0.55mmol) in dichloromethane (10ml) containing triethylamine (0.1ml). After 20h at room temperature, the mixture was diluted with ethyl acetate (100ml) and washed with
15 1N HCl (100ml), water (100ml), brine (50ml) and dried (MgSO₄). Evaporation *in vacuo* gave the title compound as a white solid (148mg).

¹H NMR (CDCl₃) δ: 2.96 (2H, m), 3.88 (2H, m), 4.73, 4.77 (2H, 2s, rotamers), 6.95 (1H, d, J = 5 Hz), 7.20 - 7.60 (3H, m), 7.70 (1H, br); m/z (API⁺): 424.8, 422.9 (MH⁺; 100%).

20

Example 1

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-chlorothiophene-2-carboxamide

A suspension of the compound of Procedure 2 (148mg, 0.35mmol) and potassium carbonate (800mg, 5.8mmol) in 20% aqueous methanol (50ml) was stirred at 25°C for
25 18h. Work-up similar to Description 3 gave the title compound as a white solid (68mg).
¹H NMR (d⁶DMSO) δ: 2.57 (2H, t), 2.97 (2H, t), 3.81 (2H, s), 7.28 (1H, d, J = 5 Hz), 7.35 (1H, d, J = 2 Hz), 7.68 (1H, d, J = 2 Hz), 7.89 (1H, d, J = 5 Hz), 10.31 (1H, s);
m/z (API⁺): 329.1, 327.1 (MH⁺; 30%).

30 The following Examples were prepared using the methods previously described in the Descriptions, Preparations, Procedures, and Example 1.

Example 2**N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-ethoxy benzamide**

¹H NMR (270MHz, CDCl₃) δ: 1.51 (3H, t, J = 7 Hz), 2.73 (2H, t, J = 7 Hz), 3.16 (2H, t, J = 7 Hz), 3.97 (2H, s), 4.17 (2H, q, J = 7 Hz), 6.95 (1H, d, J = 8 Hz), 7.50 (1H, d, J = 1 Hz), 7.74 (1H, dd, J = 8, 1 Hz), 7.82 (1H, s), 7.87 (1H, d, J = 1 Hz);
m/z (API⁺): 365 (MH⁺)

Example 3**N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-iso-propyl benzamide**

¹H NMR (270MHz, CDCl₃) δ: 1.31 (6H, d, J = 7 Hz), 2.74 (2H, t, J = 7 Hz), 3.16 (2H, t, J = 7 Hz), 3.44 (1H, m), 3.88 (2H, s), 7.29 (1H, d, J = 1 Hz), 7.51 (2H, m), 7.87 (1H, s), 8.04 (1H, dd, J = 7, 1 Hz), 8.10 (1H, d, J = 1 Hz); m/z (API⁺): 328 (MH⁺).

Example 4**N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethyl benzamide**

¹H NMR (250MHz, CDCl₃) δ: 2.71 - 2.76 (2H, m), 3.14 - 3.19 (2H, m), 3.98 (ca 5H, s), 7.09 (1H, d, J = 9 Hz), 7.29 (ca 1H, brs), 7.50 (1H, d, J = 2 Hz), 7.80 (1H, br), 8.05 - 8.07 (2H, m); m/z (API⁺): 385 (MH⁺)

Example 5**N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-methoxybenzamide**

¹H NMR (250MHz, CDCl₃-d₄ MeOH): δ: *inter alia* 2.76 - 2.81 (2H, m), 3.13 - 3.18 (2H, m), 3.97 (2H, s), 4.03 (3H, s), 7.14 (1H, d, J = 8 Hz), 7.34 (1H, s), 7.43 (1H, m), 7.64 (1H, s), 8.19 - 8.23 (2H, m); m/z (API⁺): 342 (MH⁺)

Example 6**N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-methoxybenzamide**

¹H NMR (250MHz, d₄ MeOH) δ: *inter alia* 2.69 - 2.74 (2H, m), 3.03 - 3.08 (2H, m), 3.88 (2H, s), 3.91 (3H, s), 7.14 (1H, d, J = 8.5 Hz), 7.28 (1H, d, J = 2 Hz), 7.63 (1H, d, J = 2 Hz), 7.84 (1H, dd, J = 8, 2 Hz), 7.93 (1H, d, J = 2 Hz); m/z (API⁺) 351, 353 (MH⁺)

5 **Example 7**

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-ethoxybenzamide

¹H NMR (250 MHz, d₄ MeOH) δ: 1.34 (3H, t, J = 7 Hz), 2.61 - 2.66 (2H, m), 2.96 - 3.00 (2H, m), 3.80 (2H, s), 4.06 (2H, q, J = 7 Hz), 6.98 (1H, d, J = 7.5 Hz), 7.21 (1H, brs), 7.55 (1H, d, J = 2 Hz), 7.78 (1H, dd, J = 8, 2 Hz), 8.01 (1H, d, J = 2 Hz);

10 m/z (API⁺) 409, 411 (MH⁺)

Example 8

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-*iso*-propoxybenzamide

¹H NMR (250MHz, d₄ MeOH) δ: 1.16 (6H, d, J = 6 Hz), 2.35 (3H, s), 2.46 - 2.51 (2H, m), 2.81 - 2.86 (2H, m), 3.66 (2H, s), 6.96 (1H, d, J = 8.5 Hz), 7.06 (1H, d, J = 2 Hz), 7.41 (1H, d, J = 2 Hz), 7.79 (1H, dd, J = 8.5, 2 Hz), 7.95 (1H, d, J = 2 Hz);
15 m/z (API⁺): 387 (MH⁺)

Example 9

20 **N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-ethylbenzamide**

¹H NMR (250MHz, d₄MeOH) δ: 1.03 (3H, t, J = 7 Hz), 2.45 (3H, s), 2.57 (2H, m), 2.92 (2H, m), 3.75 (2H, s), 7.17 (1H, d, J = 2 Hz), 7.25 (1H, d, J = 8.5 Hz), 7.51 (1H, d, J = 2 Hz), 7.82 (1H, dd, J = 8.5, 2 Hz), 8.07 (1H, d, J = 2 Hz); m/z (API⁺): 357 (MH⁺)

25 **Example 10**

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-ethylbenzamide

¹H NMR (CDCl₃) δ: 1.26 (3H, t), 2.77 (4H, m), 3.17 (2H, t), 3.98 (2H, s), 7.28 (1H, d), 7.34 (1H, d), 7.52 (1H, d), 7.72 (1H, dd), 7.81 (1H, s), 8.01 (1H, d);
30 m/z (API⁺): 393.1 (M⁺; 95%)

Example 11**N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-*iso*-propoxybenzamide**¹H NMR (CDCl₃) δ: 1.42 (6H, d), 2.74 (2H, t), 3.17 (2H, t), 3.99 (2H, s), 4.67 (1H, m), 6.99 (1H, d), 7.28 (1H, d), 7.50 (1H, d), 7.69 (1H, s), 7.74 (1H, dd), 7.87 (1H, d);5 m/z (API+): 379.2 (MH⁺;100%)**Example 12****N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-ethoxy-3-trifluoromethyl benzamide**10 ¹H NMR (CDCl₃) δ: 1.49 (3H, t), 2.74 (2H, t), 3.17 (2H, t), 4.00 (2H, s), 4.21 (2H, q), 7.07 (1H, d), 7.29 (1H, d), 7.51 (1H, d), 7.69 (1H, s), 8.03 (2H, m);m/z (API+): 399.1 (MH⁺; 100%).**Example 13**15 **N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-ethoxy benzamide**¹H NMR (CDCl₃) δ: 1.53 (3H, t), 2.75 (2H, t), 3.17 (2H, t), 4.00 (2H, s), 4.24 (2H, q), 7.06 (1H, d), 7.27 (1H, d), 7.50 (1H, d), 7.66 (1H, s), 8.07 (2H, m);m/z (API+): 356.2 (MH⁺;100%).20 **Example 14****N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-ethoxy benzamide**¹H NMR (CDCl₃) δ: 1.54 (3H, t), 2.68 (3H, s), 2.74 (2H, t), 3.17 (2H, t), 4.00 (2H, s), 4.24 (2H, q), 7.07 (1H, d), 7.29 (1H, d), 7.56 (1H, d), 7.91 (1H, s), 8.14 (1H, dd), 8.18 (1H, d); m/z (API+): 373.3 (MH⁺;100%).

25

Example 15**N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-ethyl-3-trifluoromethyl benzamide**30 ¹H NMR (CDCl₃) δ: 1.29 (3H, t), 2.75 (2H, t), 2.90 (2H, q), 3.18 (2H, t), 4.00 (2H, s), 7.31 (1H, d), 7.49 (1H, d), 7.53 (1H, d), 7.78 (1H, s), 7.97 (1H, dd), 8.08 (1H, d);

m/z (API+): 383.2 (MH⁺; 100%).

Example 16

5 **N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethylbenzamide**

¹H NMR (d⁶DMSO) δ: 2.46 (2H, t), 2.78 (2H, t), 3.66 (2H, s), 3.82 (3H, s), 7.27 (1H, d, J = 8 Hz), 7.38 (1H, s), 8.08 (1H, d, J = 1 Hz), 8.10 (1H, dd, J = 8, 1 Hz), 10.07 (1H, s);
m/z (API+): 420.9, 419.0, (MH⁺, 100% expected isotope pattern).

10

Example 17

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-methoxybenzamide

¹H NMR (CD₃OD) δ: 2.68 (2H, m), 3.01 (2H, m), 3.84 (2H, s), 3.86 (3H, s), 7.06 (1H, d, J = 8 Hz), 7.29 (1H, d, J = 1 Hz), 7.59 (1H, d, J = 1 Hz), 7.84 (1H, dd, J = 8, 2 Hz), 8.05
15 (1H, d, J = 2 Hz); m/z (API+): 396.9 (MH⁺;90%), 395.0 (MH⁺;60%).

Example 18

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-fluoro-4-methoxybenzamide

¹H NMR (CD₃OD) δ: 2.67 (2H, t, J = 7 Hz), 3.01 (2H, t, J = 7 Hz), 3.81 (2H, s), 3.85
20 (3H, s), 7.11 (1H, t, J = 10 Hz), 7.23 (1H, d, J = 1 Hz), 7.58 – 7.63 (2H, m), 7.67 (1H, dd, J = 8, 2 Hz); m/z (API+): 335 (MH⁺;100%).

Example 19

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-iso-propoxybenzamide

25 ¹H NMR (CDCl₃) δ: 1.42 (6H, d, J = 7 Hz), 2.73 (2H, t, J = 7 Hz), 3.16 (2H, t, J = 7 Hz), 3.97 (2H, s), 4.66 (2H, m), 6.94 (1H, d, J = 8 Hz), 7.28 (1H, d, J = 2 Hz), 7.49 (1H, d, J = 2 Hz), 7.74 (1H, s), 7.80 (1H, dd, J = 8, 2 Hz), 8.03 (1H, d, J = 2 Hz);
m/z (API+): 424.9, 423.0 (MH⁺;100%).

30 **Example 20**

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-pentafluoroethyl benzamide

¹H NMR (400 MHz, CDCl₃) δ: 2.73 (2H, t), 3.16 (2H, t), 3.95 (3H, s), 3.98 (2H, s), 7.1 (1H, d), 7.29 (1H, d), 7.50 (1H, d), 7.81 (1H, s), 8.01 (1H, d), 8.07 (1H, d)

5 m/z (API⁺): 435 (M+H)⁺

Example 21

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-*iso*-propoxy-3-trifluoromethyl benzamide

10 ¹H NMR (400MHz, CDCl₃) δ: 1.40 (6H, d, J = 6 Hz), 2.71 (2H, t), 3.14 (2H, t), 4.10 (2H, s), 4.72 (1H, m), 7.04 (1H, d), 7.47 (1H, d), 8.02 (3H, m); m/z (API⁺): 413 (MH⁺; 90%).

Example 22

N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-methoxybenzamide

15 ¹H NMR (250MHz, d₆ DMSO) δ: 2.56 (2H, t), 2.98 (2H, t), 3.83 (2H, s), 3.94 (3H, s), 7.26 (1H, d), 7.49 (1H, s), 7.93 (1H, s), 8.01 (1H, d), 8.23 (1H, d), 10.19 (1H, s); m/z (API⁺): 440.8 (MH⁺100%).

Example 23

20 **N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethyl benzamide**

¹H NMR (250MHz, CDCl₃) δ: 2.73 (2H, t), 3.19 (2H, t), 3.99 (*ca* 5H, s), 7.08 (1H, d, J = 9 Hz), 7.35 (1H, d), 7.70 (1H, d, J = 2 Hz), 7.90 (1H, s), 8.07 (2H, m);

m/z (API⁺): 428.2 (MH⁺)

25

Example 24

N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-ethoxy-3-trifluoromethyl benzamide

¹H NMR (CDCl₃) δ: 1.49 (3H, t), 2.73 (2H, t), 3.19 (2H, t), 3.98 (2H, s), 4.20 (2H, q),

30 7.05 (1H, d), 7.33 (1H, d), 7.70 (1H, d), 7.91 (1H, s), 8.03 (2H, m);

m/z (API⁺): 443 (MH⁺; 100%).

Example 25**N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-ethoxybenzamide**

¹H NMR (250MHz, d₆ DMSO) δ: 1.46 (3H, t), 2.63 (2H, t), 3.06 (2H, t), 3.91 (2H, s),
5 4.36 (2H, q), 7.45 (1H, d), 7.54 (1H, d), 7.97 (1H, d), 8.29 (1H, dd), 8.41 (1H, d), 10.29
(1H, s); m/z (API⁺): 400 (MH⁺; 100%).

Example 26**N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-ethoxybenzamide**

10 ¹H NMR (CDCl₃) δ: 1.54 (3H, t), 2.67 (3H, s), 2.70 (2H, t), 3.16 (2H, t), 3.98 (2H, s),
4.23 (2H, q), 7.07 (1H, d), 7.35 (1H, d), 7.72 (1H, d), 8.02 (1H, s), 8.13 (1H, dd), 8.19
(1H, d); m/z (API⁺): 417 (MH⁺; 100%).

Example 27**N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-*iso*-propoxybenzamide**

15 ¹H NMR (250MHz, CDCl₃) δ: 1.46 (6H, d, J = 6 Hz), 2.66 (3H, s), 2.71 (2H, t), 3.16
(2H, t), 3.99 (2H, s), 4.81 (1H, m), 7.07 (1H, d, J = 8.5 Hz), 7.35 (1H, d, J = 2 Hz), 7.72
(1H, d, J = 2 Hz), 7.90 (1H, s), 8.12 (1H, dd, J = 8.5, 2 Hz), 8.16 (1H, d, J = 2 Hz);
m/z (API⁺): 431 (MH⁺)

20

Example 28**N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-ethoxybenzamide**

¹H NMR (270MHz, CDCl₃) δ: 1.51 (3H, t, J = 7 Hz), 2.71 (2H, t, J = 7 Hz), 3.16 (2H, t,
J = 7 Hz), 3.98 (2H, s), 4.18 (2H, q, J = 7 Hz), 6.98 (1H, d, J = 8 Hz), 7.35 (1H, d, J = 1
25 Hz), 7.66 (1H, d), 7.70 (1H, s), 7.74 (1H, dd, J = 8, 1 Hz), 7.87 (1H, d, J = 1 Hz);
m/z (API⁺): 409 (MH⁺)

Example 29**N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-ethoxybenzamide**

^1H NMR (270MHz, CDCl_3) δ : 1.52 (3H, t, $J = 7$ Hz), 2.71 (2H, t, $J = 7$ Hz), 3.17 (2H, t, $J = 7$ Hz), 3.98 (2H, s), 4.18 (2H, q, $J = 7$ Hz), 6.94 (1H, d, $J = 8$ Hz), 7.35 (1H, d, $J = 1$ Hz), 7.66 (1H, d), 7.71 (1H, s), 7.79 (1H, dd, $J = 8, 1$ Hz), 8.04 (1H, d, $J = 1$ Hz);
 m/z (API^+): 454.9 (MH^+ 100%)

5

Example 30**N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-iso-propylbenzamide**

^1H NMR (270MHz, CDCl_3) δ : 1.35 (6H, d, $J = 7$ Hz), 2.73 (2H, t, $J = 7$ Hz), 3.18 (2H, t, $J = 7$ Hz), 3.44 (1H, m), 3.99 (2H, s), 7.35 (1H, d, $J = 1$ Hz), 7.53 (1H, d), 7.70 (1H, d),
10 7.95 (1H, s), 8.05 (1H, dd, $J = 7, 1$ Hz), 8.11 (1H, d, $J = 1$ Hz); m/z (API^+): 398 (MH^+).

Example 31**N-(5-Trifluoromethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-ethoxybenzamide**

15 ^1H NMR (270MHz, CDCl_3) δ : 1.52 (3H, t, $J = 7$ Hz), 2.91 (2H, m), 3.14 (2H, m), 4.07 (2H, s), 4.17 (2H, q, $J = 7$ Hz), 6.98 (1H, d, $J = 8$ Hz), 7.59 (1H, d, $J = 1$ Hz), 7.66 (1H, d), 7.79 (2H, m), 7.88 (1H, d, $J = 1$ Hz); m/z (API^+): 399 (MH^+ 90%)

Example 32

20 **N-(5-Trifluoromethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethylbenzamide**

^1H NMR (270MHz, CDCl_3) δ : 2.88 (2H, m), 3.10 (2H, m), 3.98 (3H, s), 4.05 (2H, m),
7.07 (1H, m), 7.61 (2H, m), 8.01 (1H, m), 8.08 (2H, m); m/z (API^+): 419 (MH^+ 85%)

25 **Example 33**

N-(5-Trifluoromethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-fluoro-4-methoxybenzamide

^1H NMR (270MHz, CDCl_3) δ : 2.91 (2H, m), 3.15 (2H, m), 3.97 (3H, s), 4.08 (2H, s),
7.03 (1H, t, $J = 7$ Hz), 7.61 (4H, m), 7.78 (1H, brs); m/z (API^+): 369 (MH^+ 85%)

30

Example 34**N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-ethoxybenzamide**

¹H NMR (CDCl₃) δ: 1.52 (3H, t), 2.76 (2H, t), 3.14 (2H, t), 4.00 (2H, s), 4.20 (2H, q), 7.00 (1H, d), 7.78 (1H, dd), 7.93 (1H, d), 8.29 (1H, s), 8.51 (1H, s);

5 m/z (AP⁺): 399.0 (M⁺; 100%)

Example 35**N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-ethoxybenzamide**

¹H NMR (CDCl₃) δ: 1.53 (3H, t), 2.78 (2H, t), 3.16 (2H, t), 4.05 (2H, s), 4.19 (2H, q), 6.97 (1H, d), 7.83 (1H, dd), 8.11 (1H, d), 8.28 (1H, s), 8.52 (1H, s);

10 m/z (AP⁺): 445.0 (MH⁺; 100%)

Example 36**N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-ethoxybenzamide**

15 ¹H NMR (CDCl₃) δ: 1.54 (3H, t), 2.77 (2H, t), 3.15 (2H, t), 4.05 (2H, s), 4.26 (2H, q), 7.09 (1H, d), 8.10 (2H, m), 8.27 (1H, s), 8.49 (1H, s); m/z (AP⁺): 390.1 (M⁺; 100%)

Example 37**N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-ethoxybenzamide**

20 ¹H NMR (CDCl₃) δ: 1.54 (3H, t), 2.68 (3H, s), 2.75 (2H, t), 3.14 (2H, t), 4.03 (2H, s), 4.25 (2H, q), 7.09 (1H, d), 8.12 (1H, dd), 8.25 (1H, d), 8.40 (1H, s), 8.48 (1H, s); m/z (AP⁺): 407.1 (M⁺; 100%)

Example 38**N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-fluoro-4-methoxybenzamide**

¹H NMR (CDCl₃) δ: 2.75 (2H, t), 3.14 (2H, t), 3.97 (3H, s), 4.02 (2H, s), 7.06 (1H, t), 7.66 (2H, m), 8.33 (1H, s), 8.50 (1H, s); m/z (AP⁺): 369.0 (M⁺; 70%), 410.3 (M+K⁺, 100%)

Example 39**N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-methoxybenzamide**

^1H NMR (CDCl_3) δ : 2.76 (2H, t), 3.14 (2H, t), 3.99 (3H, s), 4.03 (2H, s), 7.00 (1H, d), 7.86 (1H, dd), 8.11 (1H, d), 8.29 (1H, s), 8.51 (1H, s); m/z (API^+): 452.9 ($\text{M}+\text{Na}^+$; 100%)

5

Example 40

N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-iso-propoxybenzamide

^1H NMR (CDCl_3) δ : 1.46 (6H, d, $J = 6$ Hz), 2.67 (3H, s), 2.75 (2H, t), 3.14 (2H, t), 4.03 (2H, s), 4.82 (1H, m), 7.09 (1H, d), 8.11 (1H, dd), 8.23 (1H, d), 8.40 (1H, s), 8.48 (1H, s); m/z (API^+): 421.0 (M^+ ; 100%)

10

Example 41

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-iso-propoxybenzamide

m/z (API^+): 370.0 (MH^+ ; 100%, expected isotope pattern for M^+ $\text{C}_{20}\text{H}_{20}\text{ClN}_3\text{O}_2$)

15

PHARMACOLOGICAL DATA

1. Binding Assay Method

- 5 WO 92/22293 (SmithKline Beecham) discloses compounds having anticonvulsant activity, including *inter alia* the compound *trans*-(+)-6-acetyl-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (hereinafter referred to as Compound A). It has been found that the compounds of WO 92/22293 bind to a novel receptor obtainable from rat forebrain tissue, as described in WO
- 10 96/18650 (SmithKline Beecham). The affinity of test compounds to the novel receptor site is assessed as follows.

Method

Whole forebrain tissue is obtained from rats. The tissue is first homogenised in

15 buffer (usually 50mM Tris/HCl, pH 7.4). The homogenised tissue is washed by centrifugation and resuspension in the same buffer, then stored at -70°C until used.

To carry out the radioligand binding assay, aliquots of tissue prepared as above (usually at a concentration of 1-2mg protein/ml) are mixed with aliquots of [3H]-Compound A dissolved in buffer. The final concentration of [3H]-Compound A in the

20 mixture is usually 20nM. The mixture is incubated at room temperature for 1 hour. [3H]-Compound A bound to the tissue is then separated from unbound [3H]-Compound A by filtration through Whatman GF/B glass fibre filters. The filters are then washed rapidly with ice-cold buffer. The amount of radioactivity bound to the tissue trapped on the filters is measured by addition of liquid scintillation cocktail to the filters followed by counting

25 in a liquid scintillation counter.

In order to determine the amount of "specific" binding of [3H]-Compound A, parallel assays are carried out as above in which [3H]-Compound A and tissue are incubated together in the presence of unlabelled Compound A (usually 3 µM). The amount of binding of [3H]-Compound A remaining in the presence of this unlabelled

30 compound is defined as "non-specific" binding. This amount is subtracted from the total amount of [3H]-Compound A binding (i.e. that present in the absence of unlabelled compound) to obtain the amount of "specific" binding of [3H]-Compound A to the novel site.

The affinity of the binding of test compounds to the novel site can be estimated by incubating together [3H]-Compound A and tissue in the presence of a range of concentrations of the compound to be tested. The decrease in the level of specific [3H]-Compound A binding as a result of competition by increasing concentrations of the compound under test is plotted graphically, and non-linear regression analysis of the resultant curve is used to provide an estimate of compound affinity in terms of pKi value.

Results

Compounds of this invention were active ($pK_i > 6$) in this test. For example, compounds of Examples 1, 10-12, 15, 38 gave pKi values greater than 7 and those of Examples 2-9, 13, 14, 16, 22-37, 39-41 gave values greater than 8.

2. MEST Test

The maximal electroshock seizure (MEST) threshold test in rodents is particularly sensitive for detecting potential anticonvulsant properties¹. In this model, anticonvulsant agents elevate the threshold to electrically-induced seizures whilst proconvulsants lower the seizure threshold.

Method for mouse model

Mice (naive male, Charles River, U.K. CD-1 strain, 25 - 30g) are randomly assigned to groups of 10 - 20 and dosed orally or intraperitoneally at a dose volume of 10 ml/kg with various doses of compound (0.3 - 300 mg/kg) or vehicle. Mice are then subjected at 30 or 60 min post dose to a single electroshock (0.1 sec, 50Hz, sine wave form) administered via corneal electrodes. The mean current and standard error required to induce a tonic seizure in 50% (CC₅₀) of the mice in a particular treatment group is determined by the 'up and down' method of Dixon and Mood (1948)². Statistical comparisons between vehicle- and drug-treated groups are made using the method of Litchfield and Wilcoxon (1949)³.

In control animals the CC₅₀ is usually 14 - 18 mA. Hence the first animal in the control group is subjected to a current of 16 mA. If a tonic seizure does not ensue, the current is increased for a subsequent mouse. If a tonic convulsion does occur, then the current is decreased, and so on until all the animals in the group have been tested.

Studies are carried out using a Hugo Sachs Elektronik Constant Current Shock Generator with totally variable control of shock level from 0 to 300 mA and steps of 2 mA are usually used.

5 Results

Compounds of this invention dosed at 10 mg/kg by the oral route as a suspension in methyl cellulose and tested one hour post dosing showed an increase in seizure threshold.

10 Method for rat model

The threshold for maximal (tonic hindlimb extension) electroshock seizures in male rats (Sprague Dawley, 80 - 150g, 6 weeks old) was determined by a Hugo Sachs Elektronik stimulator which delivered a constant current (0.3 sec duration; from 1-300mA in steps of 5-20mA). The procedure is similar to that outlined above for mouse and full

15 details are as published by Upton et al.,⁴

The percentage increase or decrease in CC₅₀ for each group compared to the control is calculated. Drugs are suspended in 1% methyl cellulose.

Results

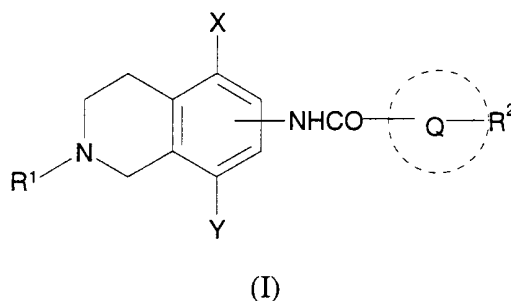
20 At a dosage of 2 mg/kg p.o. at 2h, the compounds of Examples 2, 3, 5, 7 and 8 gave significant increases of 390, 140, 210, 410 and 114% respectively.

References

1. Loscher, W. and Schmidt, D. (1988). *Epilepsy Res.*, **2**, 145-181
- 25 2. Dixon, W.J. and Mood, A.M. (1948). *J. Amer. Stat. Assn.*, **43**, 109-126
3. Litchfield, J.T. and Wilcoxon, F.(1949). *J. Pharmacol. exp. Ther.*, **96**, 99-113
4. N.Upton, T.P.Blackburn, C.A.Campbell, D.Cooper, M.L.Evans, H.J.Herdon, P.D.King, A.M.Ray, T.O.Stean, W.N.Chan, J.M.Evans and M.Thompson. (1997). *B. J. Pharmacol.*,
30 **121**, 1679-1686

CLAIMS

1. A compound of formula (I):



wherein:

Q is a monocyclic or bicyclic aryl or heteroaryl ring;

10 R¹ is hydrogen;

R² is hydrogen or up to three substituents selected from halogen, NO₂, CN, N₃, CF₃O-, CF₃S-, CF₃SO₂-, CF₃CO-, C₁₋₆alkyl, C₁₋₆alkenyl, C₁₋₆alkynyl, C₁₋₆perfluoroalkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl-, C₁₋₆alkylO-, C₁₋₆alkylCO-, C₃₋₆cycloalkylO-, C₃₋₆cycloalkylCO-, C₃₋₆cycloalkyl-C₁₋₄alkylO-, C₃₋₆cycloalkyl-C₁₋₄alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C₁₋₄alkyl-, C₁₋₆alkylS-, C₁₋₆alkylSO₂-, (C₁₋₄alkyl)₂NSO₂-,

15 (C₁₋₄alkyl)NHSO₂-, (C₁₋₄alkyl)₂NCO-, (C₁₋₄alkyl)NHCO-, or CONH₂, or -NR³R⁴ where R³ is hydrogen or C₁₋₄ alkyl, and R⁴ is hydrogen, C₁₋₄alkyl, formyl, -CO₂C₁₋₄alkyl, or -COC₁₋₄alkyl, or two R² groups together form a carbocyclic ring that is

20 saturated or unsaturated and unsubstituted or substituted by -OH or =O;

X is halogen, C₁₋₆ alkoxy, C₁₋₆ alkyl, or C₁₋₆ perfluoroalkyl, and;

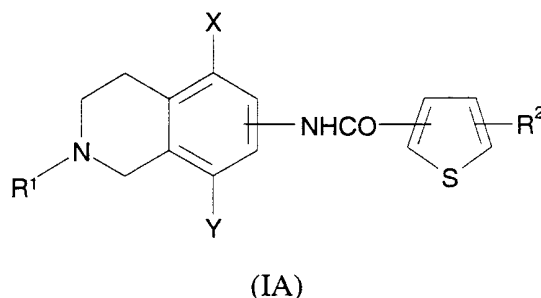
Y is hydrogen, halogen, C₁₋₆ alkoxy, C₁₋₆ alkyl, or C₁₋₆ perfluoroalkyl;

but excluding the compounds N-(5-Iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-azidobenzamide and N-(5-iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-benzoyl-2-methoxybenzamide;

25 or a pharmaceutically acceptable salt or solvate thereof.

2. A compound of formula (I) according to claim 1 which is a (tetrahydroisoquinolin-7-yl) carboxamide.

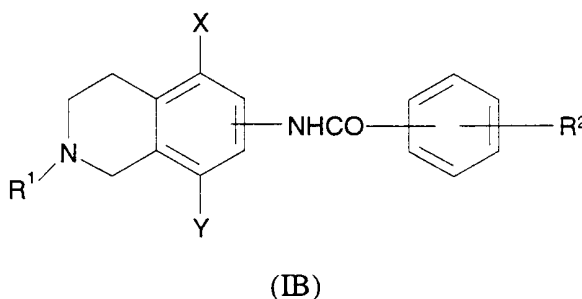
5 3. A compound of formula (I) according to claim 1 which is a compound of formula (IA):



10

wherein R^1 , R^2 , X, and Y are as hereinbefore defined.

4. A compound of formula (I) according to claim 1 which is a compound of formula (IB):



15

wherein R^1 , R^2 , X, and Y are as hereinbefore defined.

20 5. A compound according to any one of claims 1 to 4, in which

R^1 is hydrogen;

R^2 is hydrogen or one or more of the following groups;

methyl, ethyl, *n*-butyl, *iso*-propyl, *t*-butyl, phenyl, methoxy, ethoxy, *iso*-propoxy, *n*-butoxy, cyclopropylmethoxy, phenoxy, benzyloxy, amino, acetylamino, nitro, azido,

cyano, bromo, chloro, fluoro, iodo, acetyl, pivaloyl, *iso*-butyryl, benzoyl, iodobenzoyl, trifluoromethyl, perfluoroethyl, trifluoromethoxy, trifluoroacetyl, methanesulfonyl, *n*-propylsulfonyl, isopropylsulfonyl, dimethylsulfamoyl, or two R² groups form a benzene, cyclopentane or cyclopentanone ring;

5 X is chloro, bromo, iodo, fluoro C₁₋₆ perfluoroalkyl, and;

Y is hydrogen, halogen, C₁₋₆ alkoxy, C₁₋₆ alkyl, or , C₁₋₆ perfluoroalkyl.

6. A compound according to any one of claims 1 to 4, in which

R¹ is hydrogen;

10 R² is hydrogen or one or more of the following groups;

methyl, ethyl, *iso*-propyl, *n*-butyl, *t*-butyl, phenyl, methoxy, ethoxy, *iso*-propoxy, phenoxy, acetoxy, nitro, cyano, bromo, chloro, fluoro, iodo, acetyl, pivaloyl, trifluoromethyl, pentafluoroethyl, azido, trifluoromethoxy;

X is iodo, chloro, bromo or trifluoromethyl, and;

15 Y is hydrogen , chloro, bromo, iodo or trifluoromethyl.

7. A compound of formula (I) according to claim 1 which is:

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-chlorothiophene-2-carboxamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-ethoxy benzamide

20 N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-*iso*-propyl benzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethyl benzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-methoxybenzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-methoxybenzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-ethoxybenzamide

25 N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-*iso*-propoxybenzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-ethylbenzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-ethylbenzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-*iso*-propoxybenzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-ethoxy-3-trifluoromethyl benzamide

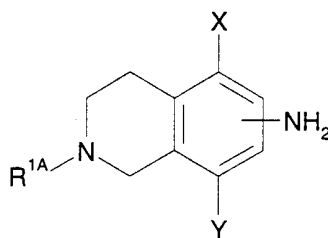
30 N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-ethoxy benzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-ethoxy benzamide

N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-ethyl-3-trifluoromethyl benzamide

- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethylbenzamide
- N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-methoxybenzamide
- N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-fluoro-4-methoxybenzamide
- 5 N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-*iso*-propoxybenzamide
- N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-pentafluoroethyl benzamide
- N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-*iso*-propoxy-3-trifluoromethyl benzamide
- 10 N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-methoxybenzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethyl benzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-ethoxy-3-trifluoromethyl benzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-ethoxybenzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-ethoxybenzamide
- 15 N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-*iso*-propoxybenzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-ethoxybenzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-ethoxybenzamide
- N-(5-Bromo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-*iso*-propylbenzamide
- N-(5-Trifluoromethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-ethoxybenzamide
- 20 N-(5-Trifluoromethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethylbenzamide
- N-(5-Trifluoromethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-fluoro-4-methoxy-benzamide
- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-ethoxybenzamide
- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-ethoxybenzamide
- 25 N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-ethoxybenzamide
- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-ethoxybenzamide
- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-fluoro-4-methoxybenzamide
- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-methoxybenzamide
- N-(5,8-Dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-acetyl-4-*iso*-propoxybenzamide, or
- 30 N-(5-Chloro-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-*iso*-propoxybenzamide; or a pharmaceutically acceptable salt or solvate thereof.

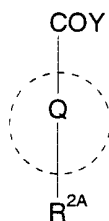
8. A process for the preparation of a compound according to any one of claims 1 to 7, which comprises reacting a compound of formula (II):



(II)

5

wherein R^{1A} is R^1 or preferably a group convertible to R^1 , and R^1 , X, and Y are as hereinbefore defined, with a compound of formula (III):



(III)

10

wherein Q is as hereinbefore defined;

Y is a leaving group such as Cl or OH, and;

R^{2A} represents hydrogen or up to three substituents as hereinbefore defined for R^2

wherein the R^{2A} groups may independently be R^2 groups or groups convertible to R^2 ;

15 and where required converting an R^{1A} or R^{2A} group to a R^1 or R^2 group respectively;

converting one R^1 or R^2 group to another R^1 or R^2 group;

converting a salt product to the free base or a pharmaceutically acceptable salt, or

converting a free base product to a pharmaceutically acceptable salt.

- 20 9. A pharmaceutical composition for use in the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-

traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesis in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and/or amyotrophic lateral sclerosis (ALS), which comprises a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

10. A method of treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesis in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and/or amyotrophic lateral sclerosis (ALS), comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof.

11. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from

substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea,

5 schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesis in diseases such as diabetes,

10 multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and/or amyotrophic lateral sclerosis (ALS).