

ANTI-CONVULSANT ISOQUINOLYL-BENZAMIDE DERIVATIVES

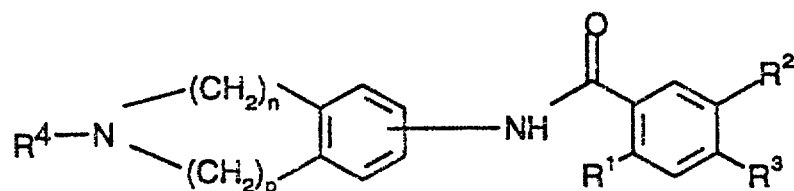
This invention relates to novel compounds, to processes for preparing them, and to their use as therapeutic agents.

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US-A-4022900 (Marion) discloses benzamido-tetrahydroisoquinolines having anti-hypertensive and vasodilator properties.

WO97/48683 (SmithKline Beecham), unpublished at the filing date of this application, discloses that benzamide compounds of formula (A) below possess anti-convulsant activity and are therefore believed to be useful in the treatment and/or prevention of anxiety, mania, and related depression disorders.

10



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(A)

where n and p are independently integers from 1 to 4 and $(n+p)$ is from 2 to 5;

R^1 is C_{1-6} alkylo-;

20 R^2 is hydrogen, halogen, CN, N_3 , trifluoromethyldiaziriny, CF_3 , CF_3O- , CF_3S- , CF_3CO- , C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl-, C_{1-6} alkylo-, C_{1-6} alkylCO-, C_{3-6} cycloalkylCO-, C_{3-6} cycloalkyl- C_{1-4} alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl- C_{1-4} alkyl-, C_{1-6} alkylS-, C_{1-6} alkylSO₂-, $(C_{1-4}$ alkyl)₂NSO₂- or
25 $(C_{1-4}$ alkyl)NHSO₂-;

R^3 is hydrogen, halogen, NO₂, CN, N_3 , trifluoromethyldiaziriny,

C_{1-6} alkylo-, C_{1-6} alkylS-, C_{1-6} alkyl, C_{3-6} cycloalkyl,

C_{3-6} cycloalkyl- C_{1-4} alkyl-, C_{1-6} alkenyl, C_{1-6} alkynyl, CF_3CO- ,

C_{1-6} alkylCO-, C_{3-6} cycloalkylCO-, C_{3-6} cycloalkyl- C_{1-4} alkylCO-,

30 phenyl, phenoxy, benzyloxy, benzoyl, phenyl- C_{1-4} alkyl-,

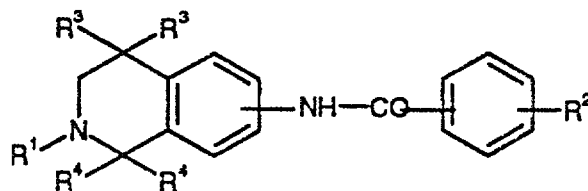
or $-NR^5R^6$ where R^5 is hydrogen or C_{1-4} alkyl, and

R^6 is hydrogen, C_{1-4} alkyl, $-CHO$, $-CO_2C_{1-4}$ alkyl or $-COC_{1-4}$ alkyl;

R^4 is hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, or C_{1-6} alkynyl.

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 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).

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



(I)

where R^1 is hydrogen, C_{1-6} alkyl (optionally substituted by hydroxy or C_{1-4} alkoxy), C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} alkylCO-, formyl, CF_3 CO- or C_{1-6} alkylSO₂-,
 R^2 is hydrogen or up to three substituents selected from halogen, NO₂, CN, N₃, CF_3 O-, CF_3 S-, CF_3 CO-, trifluoromethyldiaziriny, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} perfluoroalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl-, C_{1-6} alkylO-, C_{1-6} alkylCO-, C_{3-6} cycloalkylO-, C_{3-6} cycloalkylCO-, C_{3-6} cycloalkyl- C_{1-4} alkylO-, C_{3-6} cycloalkyl- C_{1-4} alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl- C_{1-4} alkyl-, C_{1-6} alkylS-, C_{1-6} alkylSO₂-, $(C_{1-4}$ alkyl)₂NSO₂-, $(C_{1-4}$ alkyl)NHSO₂-, $(C_{1-4}$ alkyl)₂NCO-, $(C_{1-4}$ alkyl)NHCO- or CONH₂;

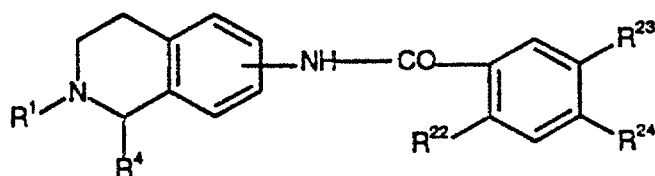
or $-NR^5R^6$ where R^5 is hydrogen or C_{1-4} alkyl, and R^6 is hydrogen, C_{1-4} alkyl, formyl, $-CO_2C_{1-4}$ alkyl or $-COC_{1-4}$ alkyl; or two R^2 groups together form a carbocyclic ring that is saturated or unsaturated and unsubstituted or substituted by $-OH$ or $=O$; and
 5 the two R^3 groups and the two R^4 groups are each independently hydrogen or C_{1-6} alkyl or the two R^3 groups and/or the two R^4 groups together form a C_{3-6} spiroalkyl group provided that at least one R^3 and R^4 group is not hydrogen.

10 The compounds of this invention are typically isoquinolinyl-carboxamides, especially (tetrahydroisoquinolin-7-yl)carboxamides. The carboxamide moiety may be a benzamide. When two R^2 groups form a carbocyclic ring, this is typically a 5-7 membered ring, and the carboxamide moiety may be a naphthalene carboxamide or an indane or indanone carboxamide.

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

It should be appreciated that compounds of the present invention possess chiral centres and as such may exist in different enantiomeric forms, the present invention extends to
 25 each enantiomeric form and mixtures thereof including diastereoisomers and racemates.

One suitable group of compounds of this invention are of formula (IA)



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(IA)

where

R^1 is hydrogen, C_{1-6} alkyl (optionally substituted by hydroxy or C_{1-4} alkoxy), C_{1-6} alkenyl, C_{1-6} alkynyl, formyl, C_{1-6} alkylCO, C_{1-6} alkylSO₂, or CF₃CO-;

R^{22} is C_{1-6} alkylO-, C_{3-6} cycloalkylO- or C_{3-6} cycloalkyl C_{1-4} alkylO-;

R^{23} is hydrogen, halogen, CN, N_3 , trifluoromethyldiaziriny, C_{1-6} perfluoroalkyl, CF_3O -, CF_3S -, CF_3CO -, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl-, C_{1-6} alkylO-, C_{1-6} alkylCO-, C_{3-6} cycloalkylCO-, C_{3-6} cycloalkyl- C_{1-4} alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl- C_{1-4} alkyl-, C_{1-6} alkylS-, C_{1-6} alkylSO₂-, (C_{1-4} alkyl)₂NSO₂-, (C_{1-4} alkyl)NHSO₂-, (C_{1-4} alkyl)₂NCO-, (C_{1-4} alkyl)NHCO- or CONH₂;

R^{24} is hydrogen, halogen, NO₂, CN, N_3 , trifluoromethyldiaziriny, C_{1-6} alkylO-, C_{1-6} alkylS-, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl-, C_{1-6} alkenyl, C_{1-6} alkynyl, CF_3CO -, C_{1-6} alkylCO-, C_{3-6} cycloalkylCO-, C_{3-6} cycloalkyl- C_{1-4} alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl- C_{1-4} alkyl-;

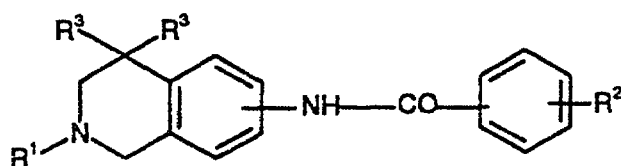
or -NR⁵R⁶ where R⁵ is hydrogen or C_{1-4} alkyl, and

R⁶ is hydrogen, C_{1-4} alkyl, formyl, -CO₂ C_{1-4} alkyl or -COC C_{1-4} alkyl;

or R^{23} and R^{24} together form a carbocyclic ring that is unsaturated or saturated and unsubstituted or substituted by carbonyl or hydroxyl;

R^4 is C_{1-6} alkyl.

Another suitable group is of formula (IB)



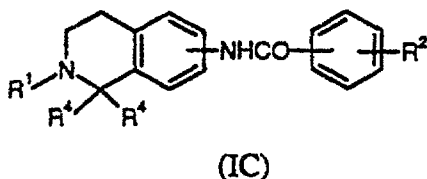
(IB)

where R^1 is hydrogen, C_{1-6} alkyl (optionally substituted by hydroxy or C_{1-4} alkoxy), C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} alkylCO-, formyl, CF_3CO - or C_{1-6} alkylSO₂-;

R^2 is hydrogen or up to three substituents selected from halogen, NO₂, CN, N_3 , CF_3O -, CF_3S -, CF_3CO -, trifluoromethyldiaziriny, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} perfluoroalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl-, C_{1-6} alkylO-, C_{1-6} alkylCO-, C_{3-6} cycloalkylO-, C_{3-6} cycloalkylCO-, C_{3-6} cycloalkyl- C_{1-4} alkylO-, C_{3-6} cycloalkyl- C_{1-4} alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl- C_{1-4} alkyl-, C_{1-6} alkylS-, C_{1-6} alkylSO₂-, (C_{1-4} alkyl)₂NSO₂-, (C_{1-4} alkyl)NHSO₂-, (C_{1-4} alkyl)₂NCO-, (C_{1-4} alkyl)NHCO- or CONH₂;

or $-NR^5R^6$ where R^5 is hydrogen or C_{1-4} alkyl, and
 R^6 is hydrogen, C_{1-4} alkyl, formyl, $-CO_2C_{1-4}$ alkyl or $-COC_{1-4}$ alkyl;
 or two R^2 groups together form a carbocyclic ring that is saturated or
 unsaturated and unsubstituted or substituted by $-OH$ or $=O$; and
 each R^3 is C_{1-6} alkyl.

A further suitable group is of formula (IC)



where R^1 is hydrogen, C_{1-6} alkyl (optionally substituted by hydroxy or C_{1-4} alkoxy),
 C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} alkylCO-, formyl, CF_3 CO- or
 C_{1-6} alkylSO₂-,
 R^2 is hydrogen or up to three substituents selected from halogen, NO₂, CN, N₃,
 CF_3 O-, CF_3 S-, CF_3 CO-, trifluoromethyldiaziriny, C_{1-6} alkyl, C_{1-6} alkenyl,
 C_{1-6} alkynyl, C_{1-6} perfluoroalkyl, C_{3-6} cycloalkyl,
 C_{3-6} cycloalkyl- C_{1-4} alkyl-, C_{1-6} alkylO-, C_{1-6} alkylCO-,
 C_{3-6} cycloalkylO-, C_{3-6} cycloalkylCO-, C_{3-6} cycloalkyl- C_{1-4} alkylO-,
 C_{3-6} cycloalkyl- C_{1-4} alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl,
 phenyl- C_{1-4} alkyl-, C_{1-6} alkylS-, C_{1-6} alkylSO₂-, $(C_{1-4}$ alkyl)₂NSO₂-,
 $(C_{1-4}$ alkyl)NHSO₂-, $(C_{1-4}$ alkyl)₂NCO-, $(C_{1-4}$ alkyl)NHCO- or CONH₂;
 or $-NR^5R^6$ where R^5 is hydrogen or C_{1-4} alkyl, and
 R^6 is hydrogen, C_{1-4} alkyl, formyl, $-CO_2C_{1-4}$ alkyl or $-COC_{1-4}$ alkyl;
 or two R^2 groups together form a carbocyclic ring that is saturated or
 unsaturated and unsubstituted or substituted by $-OH$ or $=O$; and
 each R^4 is C_{1-6} alkyl.

A suitable group of compounds of formula (I), (IB) and (IC) have

R^1 as hydrogen, methyl, ethyl, propyl, hydroxyethyl, methoxyethyl, formyl,
 acetyl, trifluoroacetyl or methanesulfonyl,

R^2 as hydrogen or one or more of methyl, ethyl, *n*-butyl, *iso*-propyl, *t*-butyl,
 phenyl, methoxy, ethoxy, *iso*-propoxy, cyclopropylmethoxy, *n*-butoxy,
 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,
R³ one or both is methyl,
R⁴ one or both is methyl.

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In compounds of formula (IA) groups R¹ and R⁴ are suitably selected from the above list, and R²², R²³ and R²⁴ are selected as appropriate values from the above listing for R².

A preferred group of compounds of formula (I) have

10 R¹ as hydrogen, methyl, ethyl,
R² as hydrogen or one or more of methyl, ethyl, *i*-propyl, *t*-butyl, methoxy, ethoxy, *i*-propoxy, bromo, chloro, cyano, trifluoromethyl,
R³ one or both is methyl,
R⁴ one or both is methyl.

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Examples of compounds of formula (I) are:

(±) N-(1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-ethoxy-2-methoxybenzamide
20 (±) N-(1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-2,4-dimethoxybenzamide
(±) N-(1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-ethoxy-2-methoxybenzamide
(±) N-(1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-*iso*-propoxy-2-methoxybenzamide
25 (±) N-(1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxybenzamide
(±) N-(1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-trifluoromethyl-2-methoxy-4-methylbenzamide
N-(2,4,4-trimethyl-4H-isoquinolin-7-yl)-4-methoxy-3-trifluoromethylbenzamide
30 N-(2,4,4-trimethyl-4H-isoquinolin-7-yl)-3-cyano-4-*iso*-propylbenzamide
N-(2,4,4-trimethyl-4H-isoquinolin-7-yl)-3-bromo-4-ethylbenzamide
N-(2,4,4-trimethyl-4H-isoquinolin-7-yl)-3-bromo-4-ethoxybenzamide
N-(2,4,4-trimethyl-4H-isoquinolin-7-yl)-3-chloro-4-*iso*-propoxybenzamide
(±) N-(1,2-dimethyl-4H-isoquinolin-7-yl)-3-bromo-4-ethylbenzamide
35 (±) N-(1,2-dimethyl-4H-isoquinolin-7-yl)-3-bromo-4-ethoxybenzamide
N-(1,1,2-trimethyl-4H-isoquinolin-7-yl)-4-methoxy-3-trifluoromethylbenzamide

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.

5 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.

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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,
15 100, 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
20 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 a unit dose oral, including sub-lingual, rectal, topical or parenteral (especially intravenous) composition.

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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
30 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,
35 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.

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

10 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 preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium
15 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 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
20 granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the 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
25 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 enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

30 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 surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

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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

5 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

10 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

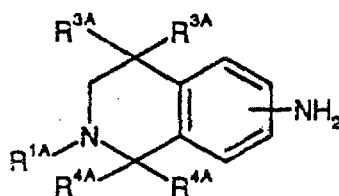
15 pharmaceutically acceptable salt or solvate, thereof as a therapeutic agent, in particular for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive

20 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,

25 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).

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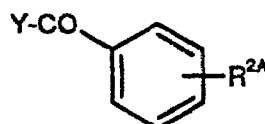
Another aspect of the invention is a process for the preparation of compounds of formula (I) as herein before described which comprises reacting a compound of formula (II)



(II)

where R^{1A} , R^{3A} , R^{4A} are R^1 , R^3 , R^4 as defined for formula (I) or a group or groups convertible to R^1 , R^3 , R^4

with a compound of formula (III)



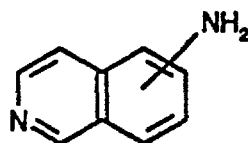
(III)

where Y is Cl or OH, and R^{2A} groups are independently R^2 as defined for formula (I) or a group or groups convertible to R^2 ,
 and where required converting an R^{1A} , R^{2A} , R^{3A} , R^{4A} group to a R^1 , R^2 , R^3 , R^4 group, converting one R^1 , R^2 , R^3 , R^4 group to another R^1 , R^2 , R^3 , R^4 group, or converting a salt product to the free base or another pharmaceutically acceptable salt, or separating any enantiomers, or converting a free base product to a pharmaceutically acceptable salt.

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

Conversions of an R^{1A} , R^{2A} , R^{3A} , R^{4A} group to a R^1 , R^2 , R^3 , R^4 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 , R^2 , R^3 , R^4 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 a more complex or reactive substituent at the end of a synthetic sequence.

Compounds of formula (II) when $R^4 = H$ or alkyl may be prepared from the corresponding isoquinoline of formula (IV)

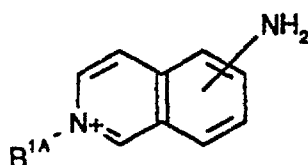


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(IV)

by reaction with a compound $R^{1A}Z$ where Z is a leaving group such as halogen, especially iodo, or tosylate to obtain an intermediate of formula (V)

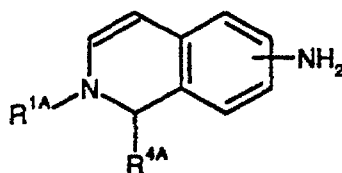
10



(V)

which is reacted with an R^{4A} containing Grignard reagent under conventional conditions to obtain a dihydroisoquinoline of formula (VI)

15



(VI)

20 which can be hydrogenated, for example using hydrogen and a palladium/activated carbon catalyst, to obtain a tetrahydroisoquinoline of formula (II) which is a precursor for compounds of formula (IA).

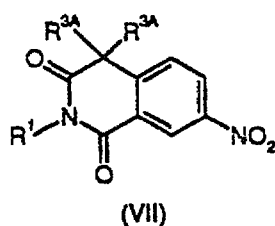
25 Alternatively the compound of formula (IV) may be a nitro-isoquinoline, and the nitro group is converted to an amino group in the hydrogenation step.

When the intended R^1 is hydrogen, the N of the isoquinoline is preferably protected conventionally, for example by making R^{1A} benzyl, or 4-methoxybenzyl during introduction of the R^4 group via the Grignard reagent. Again protection is preferably
30 provided prior to formation of the benzamide, for example by *tert.*-butoxycarbonyl and

then deprotected under standard conditions, for example using trifluoroacetic acid/methylene chloride.

Amino/nitro-isoquinolines of formulae (IV) and the reagents used are commercially available, or can be prepared from commercially available materials using conventional procedures described in the literature (eg. I.W. Matheson et al, J. Med. Chem. 1973, 16, 332).

Compounds of formula (II) which are precursors for compounds of formula (IB) may be prepared from the corresponding nitro-isoquinoline dione of formula (VII) with di- R^3 substitution, by converting the nitro group to amino by catalytic hydrogenation as above and subsequently removing the dione groups by reduction with diborane. The nitro-dione may be obtained by treating a di- R^3 isoquinoline dione [prepared using the procedure of H. Takechi *et al.*, Synthesis. 1992, 778] with fuming nitric acid. R^{1A} groups may be introduced as described above.



Compounds of formula (II) which are precursors for compounds of formula (IC) may be prepared from the corresponding nitro-3,4-dihydroisoquinoline by reduction with tin (II) chloride to the amino compound followed by quaternisation with an R^{1A} -X halide and subsequent treatment with an R^4 Grignard reagent. Compounds of formula (II) where both R_4 are alkyl may be prepared from the corresponding 1-alkyl-3,4-dihydroisoquinoline by nitration [using procedures by R.D. Larsen *et al.*, J. Org. Chem., 1991 56 6034 and A.P. Venkov and S.S. Abeghe, Syn. Commun., 1996 26 127] followed by quaternisation and treatment with an R^4 Grignard reagent as described above.

Compounds of formula (III) may be prepared by further substitution of commercially available benzoic 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.

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
- 5 Preparations, Descriptions and Examples. The utility of compounds of this invention is shown by the Pharmacological Data that follow the Examples.

Description 1**(±) 5-Amino-2-benzyl-1-methyl-1,2-dihydroisoquinoline**

5 To solution of 5-aminoisoquinoline (15g, 104mmol) in acetone (400ml) was added benzyl bromide (18.6ml, 156mmol). The mixture was stirred at room temp for 2 h before the precipitate was filtered off affording an orange solid (8.64g). A second crop (4.02g) was filtered after a further 2 h. To a solution of this 5-amino-2-benzyl-isoquinolinium bromide (8.46g, 26.8mmol) in THF (75ml) at 0°C under argon was added dropwise methyl
10 magnesium chloride (17.89ml, 56.6mmol). The mixture was allowed to warm up to room temperature and was stirred for 2 h. The mixture was then poured into ammonium chloride solution and extracted with ether. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford the title compound as a light brown solid (5.0g).

15

Description 2**(±) 5-Amino-1-methyl-1,2,3,4-tetrahydroisoquinoline**

20 5-Amino-2-benzyl-1-methyl-1,2-dihydroisoquinoline (4.5g, 17.9mmol) was dissolved in ethanol (250ml); 10% palladium catalyst on activated carbon (1g) was then added and the mixture hydrogenated at atmospheric pressure for 24 h. The catalyst was then removed by filtration through Kieselguhr and the solvent removed *in vacuo* to afford a brown solid. This residue was then subjected to column chromatography eluting with 5 to 10%
25 methanol - dichloromethane. The relevant fractions were combined and concentrated *in vacuo* to afford a brown solid (1.26g).

Description 3**(±) 5-Amino-2-(*t*-butoxycarbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline**

5-Amino-1-methyl-1,2,3,4-tetrahydroisoquinoline (0.39g, 2.4mmol) was dissolved in 1,4-dioxane (25ml) and sodium hydroxide solution (3M, 0.8ml) and cooled in an ice bath. The di-*t*-butyldicarbonate (0.53g, 2.4mmol) was added and the mixture stirred at room temp
35 for 2 h. The mixture was then poured into water and extracted with ether. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford a white solid. (0.251g)

Description 4**(±) 5-Amino-1,2-dihydro-1,2-dimethylisoquinoline**

5

5-Aminoisoquinoline (25g, 173mmol) was dissolved in acetone (500ml) and methyl iodide (25ml, 410mmol) was added. After stirring at room temperature for 1 h the orange precipitate was filtered off, washed with acetone and dried *in vacuo*, affording an orange solid (40.3g). A second crop was filtered off after 2 h affording an orange solid (0.84g).

10 To a solution of this 5-amino-2-methylisoquinolinium iodide (21.013g, 73.19mmol) in THF (150ml) at 0°C under argon was added methyl magnesium chloride (36.6ml 109.8mmol) dropwise. The mixture was allowed to stir at room temperature for 2 h before being poured into ammonium chloride and extracted with ether. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford a dark brown oil (8.52g).

15

Description 5**(±) 5-Amino-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline**

20 To an ice cold solution of 5-amino-1,2-dihydro-1,2-dimethyl isoquinoline (4g, 23.2mmol) in methanol (80ml) was added sodium borohydride (3.51g, 92.8mmol) portionwise. The mixture was allowed to stir at room temperature overnight before concentration *in vacuo*; the residue was then partitioned between water and dichloromethane. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford a light brown oil

25 (4.023g).

Description 6**7-Nitro-2,4,4-trimethyl-4H-isoquinoline-1,3-dione**

30

2,4,4-Trimethyl-4H-isoquinoline-1,3-dione (5g, 24.6mmol) [prepared according to H. Takechi *et al.*, Synthesis. 1992, 778] was dissolved in concentrated sulfuric acid (50ml) at 0°C. Fuming nitric acid (2.5ml) was added dropwise over 5 min and the reaction warmed to 25°C. After stirring for 30 min at 25°C the reaction mixture was poured into ice water

35 (100ml) and the organics extracted into dichloromethane (3x50ml). The combined organic extracts were dried over magnesium sulfate and evaporated *in vacuo* to give the title compound (5.31g, 86%).

¹H NMR (250 MHz, CDCl₃) δ: 1.70 (6H, s), 3.42 (3H, s), 7.69 (1H, d, J = 9 Hz), 8.46 (1H, dd, J = 9, 2 Hz), 9.07 (1H, d, J = 2 Hz); ^{m/z} (AP⁺): 249 (M+H)⁺

5 Description 7

7-Amino-2,4,4-trimethyl-4H-isoquinoline-1,3-dione

7-Nitro-2,4,4-trimethyl-4H-isoquinoline-1,3-dione (45g, 20mmol) was dissolved in a
10 methanol (500ml)/dichloromethane (100ml) mixture and treated with 10% Pd/C (0.5g).
The reaction mixture was hydrogenated for 2h before removal of the palladium catalyst by
filtration through Celite. The filtrate was evaporated to dryness *in vacuo* to give the title
compound (4.4g, quant).

15 ¹H NMR (250 MHz, CDCl₃) δ: 1.58 (6H, s), 3.36 (3H, s), 3.83 (2H, brs), 6.95 (1H, dd, J
= 6, 3 Hz), 7.24 (1H, d, J = 6 Hz), 7.48 (1H, d, J = 3 Hz); ^{m/z} (AP⁺): 219 (M+H)⁺

Description 8

20 7-Amino-2,4,4-trimethyl-4H-isoquinoline, hydrochloride

7-Amino-2,4,4-trimethyl-4H-isoquinoline-1,3-dione (4g, 18.3mmol) was dissolved in
tetrahydrofuran (400ml) and heated at reflux (~61°C). Borane-tetrahydrofuran complex
(88ml, 1M solution in THF) was added dropwise to the mixture and heating continued for
25 a further 3 h. The cooled reaction (0°C) was treated with methanol (400ml) dropwise to
destroy residual borane, followed by evaporation *in vacuo*. The resultant residue was
heated at reflux in 3N HCl (400ml) for 30 min. The mixture was cooled to 0°C and
treated with NaOH pellets until basic (pH 9). The free amine was extracted into
dichloromethane (4x100ml) before drying over magnesium sulfate and evaporation *in*
30 *vacuo*. The resulting light brown oil was dissolved in dichloromethane (50ml) and treated
with hydrogen chloride (1M solution in ether) until acidic (pH 2). Solvent removal *in*
vacuo followed by trituration with ether yielded the title compound as an off-white
powder (3.3g, 79%).

35 ¹H NMR (free base 250 MHz, CDCl₃) δ: 1.25 (6H, s), 2.37 (2H, s), 2.39 (3H, s), 3.43
(2H, s), 3.51 (2H, brs), 6.32 (1H, d, J = 2 Hz), 6.54 (1H, dd, J = 8, 2 Hz), 7.09 (1H, d, J =
8 Hz); ^{m/z} (AP⁺): 191 (M+H)⁺

Description 9**7-Amino-3,4-dihydroisoquinoline**

- 5 7-Nitro-3,4-dihydroisoquinoline (0.60g, 3.4mmol) [prepared according to the procedure of A.P. Venkov *et al*, Syn. Commun., 1996 26 127] was dissolved in ethanol (100ml) and heated to 60°C. This hot solution was treated with a solution of tin (II) chloride dihydrate (3.08g, 13.7mmol) in conc. HCl (10ml). The resultant mixture was heated at 60° for 1h. Upon cooling, the reaction mixture was poured into water (100ml) and
- 10 basified (pH 9) with KOH pellets, liberating an oily residue. This residue was extracted into dichloromethane and dried over magnesium sulfate. Purification by chromatography through silica gel, eluting with (0.5% conc. ammonia : 4.5% methanol : 95% dichloromethane) yielded the title compound as a dark yellow oil (0.44g, 88%).
- 15 ¹H NMR (250MHz, CDCl₃) δ: 2.63 (2H, t, J = 7 Hz), 3.67 (2H, brs), 3.73 (2H, dt, J = 7, 2 Hz), 6.62 (1H, d, J = 2 Hz), 6.70 (1H, dd, J = 8, 2 Hz), 6.95 (1H, d, J = 8 Hz), 8.24 (1H, s); ^{m/z} (API): 147 (M+H)⁺, 148 (M+2H)²⁺

Description 10

20

7-Amino-2-methyl-3,4-dihydroisoquinolinium iodide

- 7-amino-3,4-dihydroisoquinoline (0.40g, 2.74mmol) in acetone (125ml) was treated with iodomethane (0.50ml, 8.03mmol) and left stirring at room temperature for 18 h. The
- 25 resultant yellow precipitate was collected by filtration and dried *in vacuo* at ambient temperature (0.73g, 92%).

^{m/z} (API) = 161 (M)⁺

30 **Description 11****(±) 7-Amino-1,2-dimethyl-tetrahydroisoquinoline**

- (±) 7-Amino-2-methyl-3,4-dichloroisoquinolinium iodide (0.50g, 1.7mmol) was
- 35 suspended in anhydrous tetrahydrofuran (50ml) and cooled to -78°C. The cooled solution was treated with methyl magnesium chloride (2.14ml of a 3M solution in THF, 6.96mmol), added as a single portion. The reaction was allowed to reach room temperature over 18 h before being poured into water (50ml). The organic solvent was

removed *in vacuo* and the organic product extracted into dichloromethane. Drying over magnesium sulfate and evaporation *in vacuo* furnished the title compound as a pale yellow oil (0.3g, 98%). For ease of handling the product was converted into a monohydrochloride.

5

¹H NMR (250MHz, CDCl₃) δ: 1.37 (3H, d, J = 7 Hz), 2.46 (3H, s), 2.54 - 2.83 (3H, m), 3.00 (1H, m), 3.50 (3H, m), 6.45 (1H, d, J = 2 Hz), 6.51 (1H, dd, J = 8, 2 Hz), 6.88 (1H, d, J = 8 Hz); ^{m/z} (API): 177 (M+H)⁺

10 Description 12

(±) 1-Methyl-7-nitro-3,4-dihydroisoquinoline

A solution of (±) 1-methyl-3,4-dihydroisoquinoline (2.57g, 17.7mmol) in conc. sulfuric acid (10ml) was added dropwise to a stirred mixture of potassium nitrate (1.93g, 19.1mmol) in conc. sulfuric acid (10ml) at -5°C. The mixture was allowed to reach room temperature over 2 h and then heated at 60°C for 4 h. The reaction mixture was poured into ice-water (100ml) and basified (pH 9) with KOH pellets. Extraction into dichloromethane (3x50ml), drying over anhydrous sodium sulfate and evaporation *in vacuo* yielded the crude product. Purification by chromatography through silica gel, eluting with (0.5% 0.88 NH₃: 4.5% CH₃OH: 95% CH₂Cl₂) afforded the title compound as a dark brown oil (1.92g, 57%).

¹H NMR (250MHz, CDCl₃) δ: 2.48 (3H, s), 2.32 (2H, t, J = 8 Hz), 3.75 (2H, dt, J = 8, 1 Hz), 7.38 (1H, d, J = 8 Hz), 8.24 (1H, dd, J = 8, 2 Hz), 8.33 (1H, d, J = 2 Hz). ^{m/z} (API): 191 (M+H)⁺

Description 13

30 (±) 7-Amino-1-methyl-3,4-dihydroisoquinoline

(±) 1-Methyl-7-nitro-3,4-dihydroisoquinoline (2.0g, 10.5mmol) was dissolved in ethanol (150ml) and heated to 60°C, before treatment with a solution of tin (II) chloride dihydrate (9.5g, 42.1mmol) in conc. HCl (30ml). The resultant mixture was heated at 60°C for 1 h. After cooling, the reaction mixture was poured into water (200ml) and basified (pH 9) with KOH pellets, liberating an oily residue. This residue was extracted into dichloromethane and dried over magnesium sulfate. Purification by chromatography

through silica gel, eluting with (0.5% 0.88 NH₃: 4.5% CH₃OH: 95% CH₂Cl₂) yielded the title compound as a dark brown oil (0.93g, 55%).

¹H NMR (250MHz, CDCl₃) δ: 2.35 (3H, s), 2.59 (2H, t, J = 7 Hz), 3.62 (2H, t, J = 7 Hz),
5 3.60 (2H, brs), 6.71 (1H, dd, J = 8, 2 Hz), 6.83 (1H, d, J = 2 Hz), 6.98 (1H, d, J = 8 Hz).

Description 14

(±) 7-Amino-1,2-dimethyl-3,4-dihydroisoquinolinium iodide

10

(±) 7-Amino-1-methyl-3,4-dihydroisoquinoline (0.90g, 5.6mmol) in acetone (125ml) and iodomethane (1.0ml, 16mmol) was stirred at room temperature for 18 h. The resultant precipitate was collected by filtration and dried *in vacuo* at ambient temperature. The title compound was isolated as an orange powder (1.44g, 85%).

15

^{m/z} (API): 175 (M)⁺

Description 15

20 7-Amino-1,1,2-trimethyl-1,2,3,4-tetrahydroisoquinoline

7-Amino-1,2-dimethyl-3,4-dihydroisoquinolinium iodide (1.44g, 4.8mmol) was suspended in THF (200ml), cooled to -78°C and treated with methyl magnesium chloride (10ml of a 3M solution in THF) added as a single portion. The reaction was allowed to
25 reach room temperature over 18 h and poured into water (200ml). The organic solvent was removed *in vacuo* and the resultant oily residue extracted into dichloromethane (3x50ml). Evaporation *in vacuo* and chromatography through silica gel eluting with (0.5% 0.88 NH₃: 4.5% CH₃OH: 95% CH₂Cl₂) yielded the title compound as a yellow oil (0.07g, 8%). For ease of handling the product was converted into a monohydrochloride.

30

¹H NMR (250MHz, CDCl₃) δ: 1.45 (6H, s), 2.48 (3H, s), 2.80 (2H, t, J = 6 Hz), 2.96 (2H, t, J = 6 Hz), 6.51 (1H, dd, J = 8, 2 Hz), 6.57 (1H, d, J = 2 Hz), 6.86 (1H, d, J = 8 Hz).

Preparation 1**Methyl 3-Chloro-4-*iso*-propoxybenzoate**

- 5 Methyl 3-chloro-4-hydroxybenzoate (5g, 26.8mmol) in DMF (45ml) was treated with potassium carbonate (7.41g, 53.6mmol), 2-iodopropane (3.85ml, 40.2mmol) and then stirred at 25°C for 18h. Work-up with ethyl acetate gave the title compound (6.1g).

Preparation 2

10

3-Chloro-4-*iso*-propoxybenzoic acid

- Methyl 3-chloro-4-*iso*-propoxybenzoate (5.5g, 24.1mmol) was hydrolysed using 1M NaOH (36ml) in methanol (80ml). Extraction and work-up with ethyl acetate gave the
15 title compound (4.3g).

¹H NMR (DMSO) δ: 1.33 (6H, d), 4.79 (1H, m), 7.24 (1H, d), 7.87 (2H, m).

Preparation 3

20

3-Bromo-4-ethoxybenzoic acid

The title compound was prepared from 4-ethylbenzoic acid in a manner similar to that of Procedure 1.

25

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

Preparation 4

30

3-Bromo-4-ethylbenzoic acid

The title compound was prepared from 4-ethylbenzoic acid in a manner similar to that of Procedure 1.

35

¹H NMR (DMSO) δ: 1.20 (3H, t, J = 7 Hz), 2.78 (2H, q, J = 7Hz), 7.50 (1H, d, J = 8 Hz), 7.90 (1H, dd, J = 2, 8 Hz), 8.07 (1H, d, J = 8 Hz).

Preparation 5**3-Cyano-4-*iso*-propylbenzoic acid**

- 5 The title compound was prepared from 4-*iso*-propylbenzoic acid using a manner similar to that described in Procedures 1 and 5.

¹H NMR (DMSO) 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).

10

Preparation 6**4-Methoxy-3-trifluoromethylbenzoic acid**

15

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

¹H NMR (DMSO) 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)

20

Preparation 7**4-Methoxy-3-trifluoromethylbenzoyl chloride**

25

The title compound was prepared from 4-methoxy-3-trifluoromethylbenzoic acid with oxalyl chloride and DMF in chloroform at room temperature followed by evaporation *in vacuo*.

30 **Procedure 1**

5-Bromo-2,4-dimethoxybenzoic acid

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).

35

Procedure 2**5-Bromo-4-*iso*-propyl-2-methoxybenzoic acid**

- 5 To a solution of 2-methoxy-4-*iso*-propyl benzoic acid (7.0g, 36.0 mmol) in chloroform (100 ml) was added bromine (1.86 ml) in chloroform (20 ml) dropwise. The reaction was stirred at room temperature overnight. Evaporation *in vacuo* afforded an oil (9.27g).

m/z (CI): 275, 273 (MH⁺; 70%).

10

Procedure 3**Methyl-5-bromo-4-*iso*-propyl-2-methoxy benzoate**

- 15 5-Bromo-4-*iso*-propyl-2-methoxybenzoic acid (9.268g 34.0 mmol) was dissolved in ethanol (250 ml) and conc. H₂SO₄ (2 ml) added. The mixture was refluxed for 5h and concentrated *in vacuo*. Residual material was taken up into ethyl acetate and water, and the organic layer, dried (MgSO₄). Concentration *in vacuo* afforded an oil, which was
20 purified by Biotage Column Chromatography on silica gel using 10% ether in hexane to give an oil (5.5g).

Procedure 4**2,4-Dimethoxy-5-trifluoromethylbenzoic acid**

25

- 2,4-Dimethoxy-5-bromobenzoic 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. The mixture was allowed to cool,
30 poured into 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).

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

- 5 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
- 10 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%).

15

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

- 20 2N NaOH (1.25ml) was added to a solution of the methyl ester P5a (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
- 25 white solid (418mg).

¹H NMR (250MHz, CDCl₃) δ: 1.35 (6H, d, J=7Hz), 3.43 (1H, sep, J=7Hz), 4.14 (3H, s), 7.00 (1H, s), 8.41 (1H, s); m/z (API⁺): 220 (MH⁺, 100%).

Procedure 6a

30

Ethyl 2-ethoxy-4-*iso*-propyl-5-cyanobenzoate

- Ethyl 2-ethoxy-4-*iso*-propyl-5-bromobenzoate (1.2g, 3.8mmol) was treated with copper (I) cyanide (682mg, 7.6 mmol) in N-methyl-2-pyrrolidinone (40ml) as described in
- 35 Procedure 5 to give the title compound as an oil (400mg).

¹H NMR (250MHz, CDCl₃) δ: 1.12 (6H, d, J=7Hz), 1.30 (3H, t, J=7Hz), 1.84 (3H, t, J=7Hz), 3.17 (1H, sep, J=7Hz), 3.99 (2H, q, J=9Hz), 4.16 (2H, q, J=7Hz), 6.69 (1H, s), 7.86 (1H, s); m/z (API⁺): 262 (MH⁺, 100%).

5 Procedure 6b

2-Ethoxy-4-*iso*-propyl-5-cyanobenzoic acid

The ester P6a (370mg, 1.41mmol) was dissolved in methanol (5ml) and over a 24 h period
10 1N NaOH (2.1ml, 2.1mmol) was added. The solution was concentrated under vacuum, diluted with water and washed with ethyl acetate. The aqueous phase was acidified with 2N HCl and extracted with ethyl acetate. The extract was washed with brine, dried (Mg SO₄) and evaporated to give the title acid (306 mg).

15 ¹H NMR (250MHz CDCl₃) δ: 1.39 (3H, d, J=7Hz), 1.66 (3H, t, J=7Hz), 3.47 (1H, sep, J=7Hz), 4.46 (2H, q, J=7Hz), 7.03 (1H, s), 8.47 (1H, s);
m/z (API⁺): 234 (MH⁺, 100%).

Procedure 7

20

4-Ethoxy-2-methoxy-5-methylsulfonylbenzoic acid

4-Ethoxy-2-methoxy-5-chlorosulfonyl benzoic acid in a 49% yield. was prepared in 49%
yield using the procedure of M.W. Harrold *et al.*, J. Med. Chem., 1989, 32 874. This was
25 used according to the method of R.W. Brown, J. Org. Chem., 1991, 56, 4974, to the title compound in 19% yield.

¹H NMR (DMSO) δ: 1.30 (3H, t), 3.10 (3H, s), 3.83 (3H, s), 4.24 (2H, q), 6.73 (1H, s), 8.07 (1H, s).

30

Procedure 8

4-*iso*-Propyl-2-methoxy-5-methylsulfonylbenzoic acid

35 This was prepared in a similar manner to the procedure of C. Hansch, B. Schmidhalter, F. Reiter, W. Saltonstall. J. Org. Chem., 1956, 21, 265 to afford the intermediate 5-chlorosulfonyl-4-isopropyl-2-methoxybenzoic acid which was converted into the title compound using the method of Procedure 7.

¹H NMR (DMSO) δ : 1.30 (6H, d), 3.21 (3H, s), 3.80 (1H, m), 3.94 (3H, s), 7.26 (1H, s), 8.19 (1H, s).

5 Example 1

(a) ($\pm$) 2-(*t*-Butoxycarbonyl)-N-(1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-ethoxy-2-methoxybenzamide

10 To a solution of 5-amino-2-(*t*-butoxycarbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline (0.251g, 0.9mmol) in dichloromethane (8ml) and triethylamine (0.75ml) was added 5-chloro-4-ethoxy-2-methoxybenzoyl chloride (0.262g, 1.05mmol) and the mixture stirred at room temperature overnight. After diluting with more dichloromethane, the mixture was washed with sodium bicarbonate solution. The organic layer was dried over sodium sulfate
15 and concentrated *in vacuo* to afford a beige solid. This was then recrystallised from ethyl acetate and petrol to afford a white solid. (0.124g)

(b) ($\pm$) N-(1-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-ethoxy-2-methoxybenzamide, trifluoroacetate

20

To a solution of the above boc protected compound (0.124g, 0.47mmol) in dichloromethane (5ml) at 0°C was added trifluoroacetic acid (0.37ml) dropwise. The solution was stirred at room temperature for 3 h and then the solvent was removed *in vacuo* to afford a beige solid (0.192g).

25

¹H NMR (DMSO-*d*⁶) δ : 1.42 (3H, t, *J*=6Hz), 1.60 (3H, d, *J*=6Hz), 2.94 (2H, m), 3.48 (2H, m), 4.08 (3H, s), 4.28 (2H, m), 6.95 (1H, s), 7.19 (1H, d, *J*=6Hz), 7.32 (1H, t, *J*=6Hz), 7.28 (1H, d, *J*=6Hz), 7.48 (1H, s), 9.00 (1H, m), 9.30 (1H, m), 9.73 (1H, s); *m/z* (CI): 375 (MH⁺)

30

Example 2

($\pm$) N-(1,2-Dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-2,4-dimethoxybenzamide, hydrochloride.

35

The title compound was prepared in a similar fashion to Example 1 from 5-amino-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline and 2,4-dimethoxy-5-bromobenzoic acid. The

crude product was recrystallised from methanol and ethyl acetate to afford a white solid (101mg).

¹H NMR (DMSO-d⁶) δ: 1.62 (3H, m), 2.85 (3H, br.s), 3.00 (2H, m), 3.18 (2H, s), 4.02 (3H, s), 4.12 (3H, s), 4.63 (1H, m), 6.93 (1H, s), 7.15 (1H, d, J=6Hz), 7.35 (1H, t, J=6Hz), 7.88 (1H, d, J=6Hz), 8.09 (1H, s), 9.75 (1H, s), 10.91 (1H, br.s); m/z (CI): 419 (MH⁺)

Example 3

10

(±) N-(1,2-Dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-ethoxy-2-methoxybenzamide, hydrochloride.

The title compound was prepared in a similar fashion to Example 1 from 5-amino-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline and 5-chloro-4-ethoxy-2-methoxybenzoic acid. The crude product was recrystallised from methanol and ethyl acetate to afford a pale brown solid (319mg).

¹H NMR (DMSO-d⁶) δ: 1.42 (3H, t, J=6Hz), 1.56 (1H, d, J=6Hz), 1.70 (2H, d, J=6Hz) 2.80 (2H, m), 3.03 (2H, m), 3.32-3.62 (3H, m), 4.09 (3H, s), 4.29 (2H, m), 4.65 (1H, m), 6.96 (1H, s), 7.12 (1H, m), 7.35 (1H, t, J=6Hz), 7.90 (2H, m), 9.25 (1H, m), 11.42 (1H, br.s); m/z (CI): 389 (MH⁺)

The following Examples were prepared using methods similar to those outline above.

25

Example 4

(±) N-(1,2-Dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-*iso*-propoxy-2-methoxybenzamide, hydrochloride

30

¹H NMR (DMSO-d⁶) δ: 1.32 (6H, d), 1.6 (3H, m), 2.66 (3H, m), 3.02 (2H, m), 3.58 (2H, m), 4.04 (3H, s), 4.60 (1H, m), 4.97 (1H, m), 7.17 - 7.90 (5H, m), 9.75 (1H, m), 11.30 (1H, br s); m/z (CI): 403 (MH⁺).

Example 5

(±) N-(1,2-Dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxybenzamide, hydrochloride

5

¹H NMR (DMSO-d⁶) δ: 1.32 (9H, s), 1.61 (3H, m), 2.82 (3H, m), 3.07 (2H, m), 3.50 (2H, m), 4.05 (3H, s), 4.64 (1H, m), 7.12 (3H, m), 7.34 (1H, m), 7.88 (2H, m), 9.85 (1H, br s), 11.08 (1H, br s); m/z (CI): 367 (MH⁺).

10 **Example 6**

(±) N-(1,2-Dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-trifluoromethyl-2-methoxy-4-methyl benzamide, hydrochloride

15 ¹H NMR (DMSO-d⁶) δ: 1.60 (4H, m), 2.80 (4H, m), 3.00 (2H, m), 3.50 (3H, m), 4.06 (3H, s), 4.55 (1H, m), 7.20 (3H, m), 7.73 (1H, m), 8.08 (1H, m), 9.81 (1H, m), 11.27 (1H, m); m/z (CI): 393 (MH⁺).

Example 7

20

N-(2,4,4-Trimethyl-4H-isoquinolin-7-yl)-4-methoxy-3-trifluoromethylbenzamide, hydrochloride

25 The amine hydrochloride D8 (226mg, 1.0mmol) in dichloromethane (10ml) was sequentially treated with 4-methoxy-3-trifluoromethylbenzoyl chloride (283mg, 1.0mmol) and triethylamine (0.4ml, 2.9mmol). The mixture was stirred at 25°C for 18h and evaporated *in vacuo*. The resultant residue was purified by chromatography on silica gel eluting with dichloromethane : ammonia : methanol (0.5% conc. ammonia : 4.5% methanol: 95% dichloromethane). The title compound was obtained as an off-white foam
30 (337mg, 86%) which was converted into the hydrochloride.

¹H NMR (250 MHz, d⁶DMSO) δ: 1.26 (3H, s), 1.37 (3H, s), 2.43 (5H, overlapping DMSO), 3.91 (3H, s), 4.30 (2H, m), 7.36 (1H, d, J = 9 Hz), 7.42 (1H, d, J = 9 Hz), 7.58 (2H, m), 8.18 (1H, s), 8.23 (1H, d, J = 9 Hz), 9.80 (1H, brs); m/z (API⁺): 393 (M+H)⁺

Example 8**N-(2,4,4-Trimethyl-4H-isoquinolin-7-yl)-3-cyano-4-*iso*-propylbenzamide**

- 5 Prepared in a similar manner to Example 7, using 3-cyano-4-*iso*-propylbenzoyl chloride, and isolated in 70% yield.

¹H NMR (250 MHz, CDCl₃) δ: 1.31 (6H, s), 1.35 (6H, d, J = 7 Hz), 2.40 (2H, s), 2.42 (3H, s), 3.44 (1H, m), 3.55 (2H, s), 7.37 (3H, s), 7.53 (1H, d, J = 8 Hz), 7.67 (1H, brs),
10 8.02 (1H, d, J = 2 Hz), 8.09 (1H, d, J = 2 Hz); ^{m/z} (API⁺): 362 (M+H)⁺

Example 9**N-(2,4,4-Trimethyl-4H-isoquinolin-7-yl)-3-bromo-4-ethylbenzamide**

15

Prepared in a similar manner to Example 7, using 3-bromo-4-ethylbenzoyl chloride, and isolated in 89% yield.

¹H NMR (250 MHz, CDCl₃) δ: 1.26 (3H, t, J = 8 Hz), 1.30 (6H, s), 2.39 (2H, s), 2.42 (3H, s), 2.82 (2H, q, J = 8 Hz), 3.54 (2H, s), 7.37 (3H, m), 7.51 (1H, d, J = 2 Hz), 7.80 (1H, brs), 8.03 (1H, br s); ^{m/z} (API⁺): 402, 404 (M+H)⁺

Example 10**N-(2,4,4-Trimethyl-4H-isoquinolin-7-yl)-3-bromo-4-ethoxybenzamide**

25 The amine hydrochloride D8 (226mg, 1.0mmol) in dichloromethane (10ml) was sequentially treated with 3-bromo-4-ethoxybenzoyl chloride, (270mg, 1.0mmol) and triethylamine (0.4ml, 2.9mmol). The mixture was stirred at 25°C for 18h and evaporated
30 *in vacuo*. The resultant residue was purified by chromatography on silica gel eluting with ammonia : methanol : dichloromethane (0.5% 0.88 ammonia : 4.5% methanol: 95% dichloromethane). The title compound was obtained as an off-white foam (291mg, 70%).

¹H NMR [free base](250 MHz, CDCl₃) δ: 1.30 (6H, s), 1.51 (3H, t, J = 7 Hz), 2.39 (2H, s), 2.41 (3H, s), 3.53 (2H, s), 4.17 (2H, q, J = 7 Hz), 6.93 (1H, d, J = 9 Hz), 7.34 (3H, m), 7.65 (1H, brs), 7.80 (1H, dd, J = 9, 2 Hz), 8.04 (1H, d, J = 2 Hz); ^{m/z} (API⁺): 418, 420 (M+H)⁺

A portion of the title compound was converted into the hydrochloride salt.

¹H NMR (250 MHz, d⁶DMSO) δ: 1.21 (3H, s), 1.28 (3H, t, J = 7 Hz), 1.34 (3H, s), 2.34 - 2.44 (2H, brs), 2.83 (3H, d, J = 4 Hz), 4.10 (2H, q, J = 7 Hz), 4.15 - 4.37 (2H, m), 7.13 (1H, d, J = 9 Hz), 7.37 (1H, d, J = 8 Hz), 7.52 (1H, brs), 7.54 (1H, d, J = 9 Hz), 7.89 (1H, dd, J = 9, 2 Hz), 8.12 (1H, d, J = 2 Hz), 10.18 (1H, s), 10.35 (1H, brs).

Example 11

10 N-(2,4,4-Trimethyl-4H-isoquinolin-7-yl)-3-chloro-4-*iso*-propoxybenzamide

Prepared in a similar manner to Example 7, using 3-chloro-4-*iso*-propoxybenzoyl chloride, and isolated in 84% yield.

15 ¹H NMR (250 MHz, CDCl₃) δ: 1.30 (6H, s), 1.42 (6H, d, J = 6 Hz), 2.39 (2H, s), 2.41 (3H, s), 3.53 (2H, s), 4.66 (1H, septet, J = 6 Hz), 6.98 (1H, d, J = 9 Hz), 7.35 (3H, m), 7.68 (1H, brs), 7.74 (1H, dd, J = 9, 2 Hz), 7.87 (1H, d, J = 2 Hz).
m/z (AP⁺): 387, 389 (M+H)⁺

20

Example 12

(±) N-(1,2-Dimethyl-4H-isoquinolin-7-yl)-3-bromo-4-ethylbenzamide

25 (±) 7-Amino-1,2-dimethyl-tetrahydroisoquinoline mono hydrochloride (0.106g, 0.50mmol) in dichloromethane (10ml) was sequentially treated with 3-bromo-4-ethylbenzoyl chloride (0.124g, 0.50mmol) and triethylamine (0.3ml, 2.2mmol). The mixture was stirred at ambient temperature for 18 h. Evaporation *in vacuo* gave an oily residue which was purified by chromatography through silica gel eluting with (0.5%
30 conc. ammonia: 4.5% methanol: 95% dichloromethane). The title compound was obtained as an off-white foam (0.149g, 77%).

¹H NMR (250MHz, CDCl₃) δ: 1.23 (3H, t, J = 8 Hz), 1.36 (3H, d, J = 7 Hz), 2.46 (3H, s), 2.60 (1H, m), 2.80 (4H, m), 3.54 (1H, q, J = 7 Hz), 7.02 (1H, d, J = 8 Hz), 7.25 (1H, d, J = 8 Hz), 7.32 (1H, dd, J = 8, 2 Hz), 8.00 (1H, d, J = 2 Hz), 8.17 (1H, s);
35 m/z (AP⁺): 387, 389 (M+H)⁺

Example 13**(±) N-(1,2-Dimethyl-4H-isoquinolin-7-yl)-3-bromo-4-ethoxybenzamide**

- 5 Prepared as described in Example 12 using 3-bromo-4-ethoxybenzoyl chloride and isolated in 90% yield.

¹H NMR (250MHz, CDCl₃) δ: 1.36 (3H, d, J = 7 Hz), 1.49 (3H, t, J = 7 Hz), 2.46 (3H, s), 2.64 (1H, m), 2.80 (2H, m), 3.00 (1H, m), 3.55 (1H, q, J = 7 Hz), 4.13 (2H, q, J = 7 Hz),
10 6.85 (1H, d, J = 9 Hz), 7.02 (1H, d, J = 8 Hz), 7.32 (1H, d, J = 8, 2 Hz), 7.45 (1H, s), 7.77 (1H, dd, J = 9, 2 Hz), 8.06 (1H, s), 8.08 (1H, d, J = 2 Hz); ^{m/z} (API): 403, 405 (M+H)⁺

Example 14

15

N-(1,1,2-Trimethyl-4H-isoquinolin-7-yl)-4-methoxy-3-trifluoromethylbenzamide

The title compound was prepared from 7-amino-1,1,2-trimethyl-tetrahydroisoquinoline mono hydrochloride (0.077g, 0.3mmol) and 3-trifluoromethyl-4-methoxybenzoyl
20 chloride (0.083g, 0.3mmol) in a manner similar to that of Example 12 as an off-white foam (0.132g, 99%).

¹H NMR(250MHz, CDCl₃) δ: 1.40 (6H, s), 2.44 (3H, s), 2.78 - 2.93 (4H, m), 3.95 (3H, s), 7.00 (1H, s), 7.03 (1H, s), 7.33 (1H, dd, J = 8, 2 Hz), 7.59 (1H, d, J = 2 Hz), 8.03 -
25 8.10 (3H, m); ^{m/z} (API): 393 (M+H)⁺

PHARMACOLOGICAL DATA**1. Binding Assay Method**

30

WO 92/22293 (SmithKline Beecham) discloses compounds having anti-convulsant 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
35 obtainable from rat forebrain tissue, as described in WO 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 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 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 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 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 in this test. For example, compounds of Examples 1 to 14 gave pKi values greater than 7.

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.

5

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.

10
15

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.

20

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.

25

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. At a dose of 10 mg/kg/ p.o. at 2h, the compounds of Examples 4, 5, and 6 showed percentage increases of 47, 46, and 36% respectively.

30

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

35

5-20mA). The procedure is similar to that outlined above for mouse and full details are as published by Upton et al.,⁴

5 The percentage increase or decrease in CC₅₀ for each group compared to the control is calculated.

Drugs are suspended in 1% methyl cellulose.

Results

10

At a dosage of 2 mg/kg p.o. at 2h, the compounds of Examples 7 to 11 show the increases set out in the Table.

Table

15

Ex No	pKi			Rat MEST at 2 mg/kg p.o. at 2h
	Compound A			
E7	8.5			510
E8	8.0			120
E9	8.3			53
E10	8.2			294
E11	7.9			204

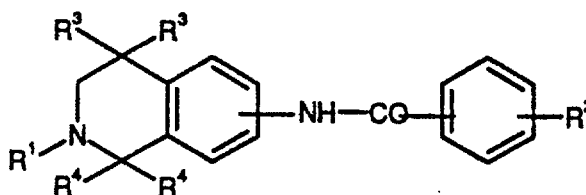
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 25 121, 1679-1686



Claims

1. A compound of formula (I) or pharmaceutically acceptable salt thereof:

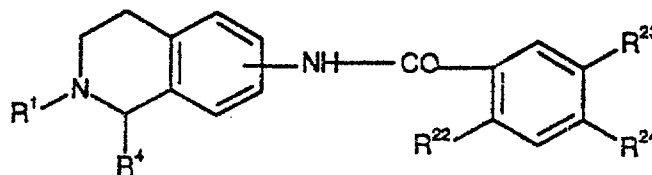


(I)

where R^1 is hydrogen, C_{1-6} alkyl (optionally substituted by hydroxy or C_{1-4} alkoxy), C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} alkylCO-, formyl, CF_3 CO- or C_{1-6} alkylSO₂-,

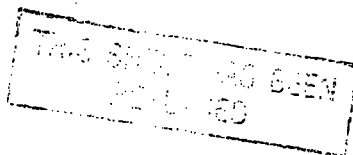
R^2 is hydrogen or up to three substituents selected from halogen, NO₂, CN, N₃, CF_3 O-, CF_3 S-, CF_3 CO-, trifluoromethyldiaziriny, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} perfluoroalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl-, C_{1-6} alkylO-, C_{1-6} alkylCO-, C_{3-6} cycloalkylO-, C_{3-6} cycloalkylCO-, C_{3-6} cycloalkyl- C_{1-4} alkylO-, C_{3-6} cycloalkyl- C_{1-4} alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl- C_{1-4} alkyl-, C_{1-6} alkylS-, C_{1-6} alkylSO₂-, $(C_{1-4}$ alkyl)₂NSO₂-, $(C_{1-4}$ alkyl)NHSO₂-, $(C_{1-4}$ alkyl)₂NCO-, $(C_{1-4}$ alkyl)NHCO- or CONH₂; or -NR⁵R⁶ where R⁵ is hydrogen or C_{1-4} alkyl, and R⁶ is hydrogen, C_{1-4} alkyl, formyl, -CO₂ C_{1-4} alkyl or -COC C_{1-4} alkyl; or two R^2 groups together form a carbocyclic ring that is saturated or unsaturated and unsubstituted or substituted by -OH or =O; and the two R^3 groups and the two R^4 groups are each independently hydrogen or C_{1-6} alkyl or the two R^3 groups and/or the two R^4 groups together form a C_{3-6} spiroalkyl group provided that at least one R^3 and R^4 group is not hydrogen.

2. A compound formula (IA)



(IA)





where

R^1 is hydrogen, C_{1-6} alkyl (optionally substituted by hydroxy or C_{1-4} alkoxy),
 C_{1-6} alkenyl, C_{1-6} alkynyl, formyl, C_{1-6} alkylCO-, C_{1-6} alkylSO₂-, or CF_3 CO-;

5 R^{22} is C_{1-6} alkylO-, C_{3-6} cycloalkylO- or C_{3-6} cycloalkyl C_{1-4} alkylO-;

R^{23} is hydrogen, halogen, CN, N_3 , trifluoromethyldiaziriny, C_{1-6} perfluoroalkyl,
 CF_3 O-, CF_3 S-, CF_3 CO-, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl-,
 C_{1-6} alkylO-, C_{1-6} alkylCO-, C_{3-6} cycloalkylCO-, C_{3-6} cycloalkyl- C_{1-4} alkylCO-,
 phenyl, phenoxy, benzyloxy, benzoyl, phenyl- C_{1-4} alkyl-, C_{1-6} alkylS-,
 10 C_{1-6} alkylSO₂-, (C_{1-4} alkyl)₂NSO₂, (C_{1-4} alkyl)NHSO₂, (C_{1-4} alkyl)₂NCO-,
 (C_{1-4} alkyl)NHCO- or CONH₂;

R^{24} is hydrogen, halogen, NO₂, CN, N_3 , trifluoromethyldiaziriny, C_{1-6} alkylO-,
 C_{1-6} alkylS-, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl-, C_{1-6} alkenyl,
 C_{1-6} alkynyl, CF_3 CO-, C_{1-6} alkylCO-, C_{3-6} cycloalkylCO-,
 15 C_{3-6} cycloalkyl- C_{1-4} alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl,
 phenyl- C_{1-4} alkyl-;

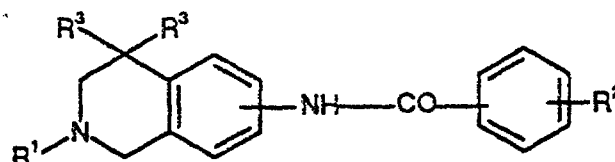
or -NR⁵R⁶ where R^5 is hydrogen or C_{1-4} alkyl, and

R^6 is hydrogen, C_{1-4} alkyl, formyl, -CO₂ C_{1-4} alkyl or -COC C_{1-4} alkyl;

or R^{23} and R^{24} together form a carbocyclic ring that is unsaturated or saturated
 20 and unsubstituted or substituted by carbonyl or hydroxyl;

R^4 is C_{1-6} alkyl.

3. A compound of formula (IB)



(IB)

where R^1 is hydrogen, C_{1-6} alkyl (optionally substituted by hydroxy or C_{1-4} alkoxy),
 30 C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} alkylCO-, formyl, CF_3 CO- or
 C_{1-6} alkylSO₂-,

R^2 is hydrogen or up to three substituents selected from halogen, NO₂, CN, N_3 ,
 CF_3 O-, CF_3 S-, CF_3 CO-, trifluoromethyldiaziriny, C_{1-6} alkyl, C_{1-6} alkenyl,
 C_{1-6} alkynyl, C_{1-6} perfluoroalkyl, C_{3-6} cycloalkyl,
 35 C_{3-6} cycloalkyl- C_{1-4} alkyl-, C_{1-6} alkylO-, C_{1-6} alkylCO-,



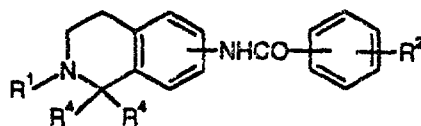


5

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 -NR⁵R⁶ where R⁵ is hydrogen or C₁₋₄ alkyl, and R⁶ 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; and each R³ is C₁₋₆ alkyl.

10

4. A compound of formula (IC)



(IC)

- 15 where R¹ is hydrogen, C₁₋₆ alkyl (optionally substituted by hydroxy or C₁₋₄alkoxy), C₁₋₆alkenyl, C₁₋₆alkynyl, C₁₋₆alkylCO-, formyl, CF₃CO- or C₁₋₆alkylSO₂-,
- R² is hydrogen or up to three substituents selected from halogen, NO₂, CN, N₃, CF₃O-, CF₃S-, CF₃CO-, trifluoromethyldiaziriny, 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 -NR⁵R⁶ where R⁵ is hydrogen or C₁₋₄ alkyl, and R⁶ 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; and
- each R⁴ is C₁₋₆ alkyl.

30

5. A compound selected from the group consisting of:





- (±) N-(1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-ethoxy-2-methoxybenzamide
 (±) N-(1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-2,4-dimethoxybenzamide
 5 (±) N-(1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-ethoxy-2-methoxybenzamide
 (±) N-(1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-*iso*-propoxy-2-methoxybenzamide
 (±) N-(1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxybenzamide
 10 (±) N-(1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-trifluoromethyl-2-methoxy-4-methylbenzamide
 N-(2,4,4-trimethyl-4H-isoquinolin-7-yl)-4-methoxy-3-trifluoromethylbenzamide
 N-(2,4,4-trimethyl-4H-isoquinolin-7-yl)-3-cyano-4-*iso*-propylbenzamide
 N-(2,4,4-trimethyl-4H-isoquinolin-7-yl)-3-bromo-4-ethylbenzamide
 15 N-(2,4,4-trimethyl-4H-isoquinolin-7-yl)-3-bromo-4-ethoxybenzamide
 N-(2,4,4-trimethyl-4H-isoquinolin-7-yl)-3-chloro-4-*iso*-propoxybenzamide
 (±) N-(1,2-dimethyl-4H-isoquinolin-7-yl)-3-bromo-4-ethylbenzamide
 (±) N-(1,2-dimethyl-4H-isoquinolin-7-yl)-3-bromo-4-ethoxybenzamide
 N-(1,1,2-trimethyl-4H-isoquinolin-7-yl)-4-methoxy-3-trifluoromethylbenzamide.
 20
6. 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
 25 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 Huntington's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy),
 30 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
 35 comprises a compound according to any one of the preceding claims and a pharmaceutically acceptable carrier.

7. A method of treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or

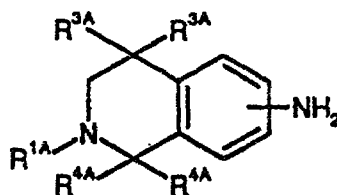


neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other
5 degenerative diseases such as Huntington'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
10 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 according to any one of claims 1 to 5.

15

8. Use of a compound according to any one of claims 1 to 5, 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
20 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 Huntington's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including
25 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
30 amyotrophic lateral sclerosis (ALS).

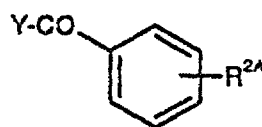
9. A process for the preparation of compounds according to any one of claims 1 to 5 which comprises reacting a compound of formula (II)



(II)

- 5 where R^{1A} , R^{3A} , R^{4A} are R^1 , R^3 , R^4 as defined for formula (I) or a group or groups convertible to R^1 , R^3 , R^4

with a compound of formula (III)



10

(III)

- 15 where Y is Cl or OH, and R^{2A} groups are independently R^2 as defined for formula (I) or a group or groups convertible to R^2 ,
 and where required converting an R^{1A} , R^{2A} , R^{3A} , R^{4A} group to a R^1 , R^2 , R^3 , R^4 group, converting one R^1 , R^2 , R^3 , R^4 group to another R^1 , R^2 , R^3 , R^4 group, or converting a salt product to the free base or another pharmaceutically acceptable salt, or separating any enantiomers, or converting a free base product to a pharmaceutically
 20 acceptable salt.