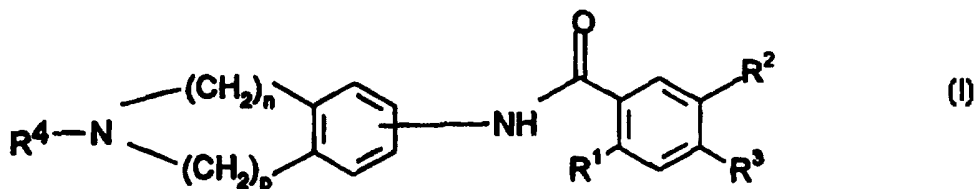




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(54) Title: **SUBSTITUTED BENZAMIDE DERIVATIVES AND THEIR USE AS ANTICONVULSANTS**

(57) Abstract

The invention relates to substituted benzamido-heterocyclic compounds of general formula (I) having an alkoxy substituent at the C2 position of the benzamido group and various substituents at positions C4 and C5, being optionally substituted on the N atom of the heterocyclic system, and where the unsaturated ring of the heterocyclic system is a 5, 6, 7 or 8-membered ring. Also to the use of these compounds as anticonvulsants in certain medical conditions, and to processes for making them.

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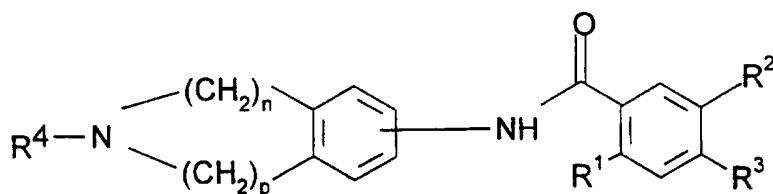
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SUBSTITUTED BENZAMIDE DERIVATIVES AND THEIR USE AS ANTICONVULSANTS

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

5 US-A-4022900 (Marion), FR-A-2004748 (Marion) and DE-A-2101691 (Marion) disclose benzamido-tetrahydroisoquinolines having anti-hypertensive and vasodilator properties, including the compound 5-(2,4,5-trimethoxy-benzamido)-2-methyl-1,2,3,4-tetrahydroisoquinoline, which can also be expressed as 2,4,5-trimethoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide.

10 It has now been surprisingly found that benzamide 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
 15 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,
 20 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, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).
 25 Accordingly, the present invention provides a compound of formula (I) or pharmaceutically acceptable salt thereof:



30

(I)

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

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

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- $C_{1-4}alkyl-$, $C_{1-6}alkylS-$, $C_{1-6}alkylSO_2-$, $(C_{1-4}alkyl)_2NSO_2-$ or $(C_{1-4}alkyl)NHSO_2-$;
 R^3 is hydrogen, halogen, NO_2 , 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 $-NR^5R^6$ 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 $C_{1-6}alkynyl$;
 but excluding the compound 2,4,5-trimethoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide.

The compounds of this invention are typically (tetrahydroisoquinolin-5-yl)benzamides, (tetrahydroisoquinolin-6-yl)benzamides, (tetrahydroisoquinolin-7-yl)benzamides or (tetrahydroisoquinolin-8-yl)benzamides, especially (tetrahydroisoquinolin-7-yl)benzamides, and most suitably (tetrahydroisoquinolin-5-yl)benzamides; or (dihydroisoindol-4-yl)benzamides; or (tetrahydro-3-benzazepin-6-yl)benzamides.

In the formula (I), R^1 alkoxy groups are typically based on straight chain alkyl groups, but in general alkyl groups may be straight chain or branched. Aromatic rings, especially the aromatic ring in the bicyclic heterocyclic moiety in formula (I) and phenyl groups, including phenyl groups that are part of other moieties, in R^2 and R^3 may optionally be substituted with one or more independently selected halogen or $C_{1-6}alkyl$, $C_{1-6}alkoxy$ or $C_{1-6}alkylcarbonyl$.

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 formula (I) have

R^1 as methoxy, ethoxy or *n*-propoxy

R^2 as hydrogen, methoxy, bromo, chloro, iodo, acetyl, pivaloyl, *iso*-butyroyl, benzoyl, trifluoromethyl, trifluoroacetyl, *n*-propylsulfonyl, isopropylsulfonyl or dimethylsulfamoyl

R³ as hydrogen, methyl, ethyl, *n*-butyl, *iso*-propyl, *t*-butyl, phenyl, methoxy, ethoxy, *iso*-propoxy, *n*-butoxy, phenoxy, benzyloxy, amino, acetylamino, nitro, benzoyl, iodobenzoyl, chloro or azido

R⁴ as hydrogen, methyl, ethyl or propyl.

- 5 In a special class of compounds of formula (I), suitable for use as mechanistic probes, R² or R³ are photolabile groups, such as N₃, benzoyl and trifluoromethyldiaziriny. Also radiolabels such as ¹²⁵I can be incorporated at R² or R³, and ³H and ¹²⁵I can be located at other suitable positions.

Examples of compounds of formula (I) are:

- 10 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-chloro-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2,4-dimethoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-chloro-2-methoxybenzamide
15 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-acetylamino-5-bromo-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-bromo-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-azido-5-iodo-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-acetylamino-5-chloro-2-
20 propoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-chloro-2-propoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-acetylamino-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-nitrobenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-iodo-2-methoxybenzamide
25 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-benzyloxy-5-chloro-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4,5-dichloro-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-2,4-dimethoxybenzamide
30 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-[3-(trifluoromethyl)-3H-diazirin-3-yl]-2-methoxybenzamide
N-(1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-methylbenzamide
N-(2-*n*-propyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide
35 N-(2-ethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-ethoxy-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2,5-dimethoxybenzamide

- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-2-methoxy-4-methylbenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-dimethylsulfamoyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-benzoyl-2-methoxybenzamide
5 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-benzoyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-4-acetylamino-5-chloro-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-4-amino-5-chloro-2-methoxybenzamide
N-(2,3-dihydro-2-methyl-1H-isoindol-4-yl)-5-chloro-2,4-dimethoxybenzamide.
10 N-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-6-yl)-4-*tert*-butyl-2-methoxybenzamide
N-(1,2,3,4-tetrahydroisoquinolin-6-yl)-4-*tert*-butyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-4-*tert*-butyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*n*-butyl-2-methoxy-5-chloro-benzamide
15 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethyl-2-methoxy-5-chloro benzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxy-5-chloro-benzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-4-phenylbenzamide
N-(1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxybenzamide
20 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*iso*-propyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-*iso*-propyl-2-methoxybenzamide
N-(1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-*tert*-butyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethyl-2-methoxybenzamide
25 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-4-*iso*-propoxy-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*iso*-propyl-5-trifluoromethyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*iso*-propoxy-2-methoxy-5-trifluoromethyl-benzamide
30 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-4-*iso*-propyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl) 5-*iso*-butyryl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-pivaloyl-2-methoxybenzamide
35 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-chloro-2-methoxy-4-*iso*-propoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-bromo-2,4-dimethoxybenzamide

- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-*tert*-butyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxy-4-methyl-5-trifluoromethylbenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxybenzamide
- 5 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2,4-dimethoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-chloro-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*iso*-propoxy-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-dimethylsulfamoyl-2,4-dimethoxybenzamide
- 10 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-*iso*-propylsulfonylbenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-phenylbenzamide
N-(1,2,3,4-Tetrahydroisoquinolin-5-yl)-5-bromo-2,4-dimethoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-*n*-propylsulfonylbenzamide
- 15 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2,4-dimethoxy-5-trifluoromethylbenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-4-methyl-5-trifluoromethylbenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-acetyl-2,4-dimethoxybenzamide
- 20 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-4-ethyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethyl-2-methoxy-5-trifluoromethylbenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*n*-butoxy-5-chloro-2-methoxybenzamide
- 25 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-4-*iso*-propyloxy-5-acetylbenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-*iso*-propoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-iodo-4-trifluoromethylbenzamide
- 30 N-(1,2,3,4-tetrahydroisoquinolin-5-yl)-4-azido-5-iodo-2-methoxybenzamide
N-(1,2,3,4-tetrahydroisoquinolin-5-yl)-5-iodo-2-methoxy-4-trifluoromethylbenzamide
N-(7-iodo-2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-benzoyl-2-methoxybenzamide
- 35 N-(7-iodo-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-benzoyl-2-methoxybenzamide
N-(5-iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-benzoyl-2-methoxybenzamide

- N-(5-iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxy-4-trifluoromethyl-diaziriny-benzamide
 N-(5-iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxy-5-trifluoromethyl-diaziriny-benzamide
- 5 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-trifluoroacetyl benzamide
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-4-trifluoromethyl-diaziriny-benzamide
 N-(1,2,3,4-tetrahydroisoquinolin-7-yl)-5-iodo-2-methoxy-4-trifluoromethyl-diaziriny-benzamide
- 10 N-(1,2,3,4-tetrahydroisoquinolin-5-yl)-5-(4-iodobenzoyl)-2-methoxybenzamide
 N-(7-iodo-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-trifluoromethyl-diaziriny-benzamide,
 N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-chloro-2-methoxybenzamide
 N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxy-4-methylthiobenzamide
- 15 N-(8-Fluoro-2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*t*-butyl-2-methoxybenzamide
 N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-*iso*-butyryl-4-*iso*-propoxy-2-methoxybenzamide, and
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*n*-butoxy-2-methoxybenzamide.
- A preferred group of these compounds is
- 20 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-chloro-2-methoxybenzamide
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-bromo-2-methoxybenzamide
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-iodo-2-methoxybenzamide
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-ethoxy-2-methoxybenzamide
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-bromo-2,4-dimethoxybenzamide
- 25 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxybenzamide
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-4-*iso*-propoxy-2-methoxybenzamide
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*iso*-propyl-5-trifluoromethyl-2-methoxybenzamide
- 30 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl) 5-*iso*-butyryl-2-methoxy-benzamide
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-pivaloyl-2-methoxybenzamide
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-4-*iso*-propyloxy-5-acetylbenzamide
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-*iso*-propoxybenzamide.
- 35 N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethyl-2-methoxy-5-chloro benzamide, hydrochloride

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethyl-2-methoxy-5-trifluoromethylbenzamide, hydrochloride

When synthesised, these compounds are often in salt form, typically 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-listed 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, 60, 80, 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 a unit dose oral, including sub-lingual, rectal, topical, nasal, 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 nasal sprays 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, colourants, 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 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 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 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 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 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 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, in a further aspect, the present invention 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, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS)

which comprises a compound of formula (I), without excluding 2,4,5-trimethoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide, 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, 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), without excluding 2,4,5-trimethoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide, or a pharmaceutically acceptable salt or solvate thereof.

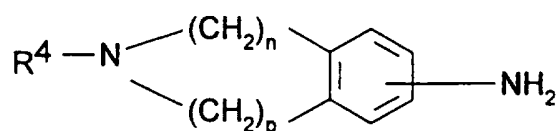
In a further aspect the invention provides the use of a compound of formula (I), without excluding 2,4,5-trimethoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis 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, 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, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

Another aspect of the invention provides a process for the preparation of compounds of formula (I), which comprises reacting a compound of formula (II)

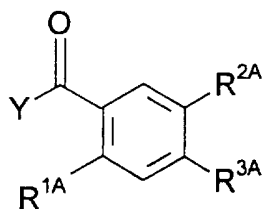
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(II)

where n and p are as defined for formula (I) and R^{4A} is R^4 as defined for formula (I) or a group convertible to R^4

with a compound of formula (III)



(III)

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where Y is Cl or OH, and R^{1A}, R^{2A}, and R^{3A} are respectively R¹, R², and R³ as defined for formula (I) or groups convertible to R¹, R², and R³,

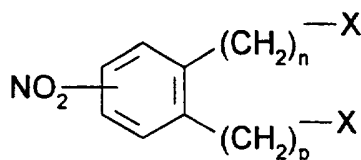
and where required converting a R^{1A}, R^{2A}, R^{3A} or R^{4A} group to a R¹, R², R³ or R⁴ group, converting one R¹, R², R³ or R⁴ group to another R¹, R², R³ or R⁴ group,

10 converting a hydrochloride salt product to the free base or another pharmaceutically acceptable salt 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 and tetrahydrofuran. When the compound of formula (III) is a benzoic acid derivative
15 (Y=OH), conventional conditions for condensation of aromatic acids with amines may be used, for example reacting the components in a mixture of (dimethylaminopropyl)-ethyl-carbodiimide and hydroxybenzotriazole in a suitable solvent such as dimethyl formamide.

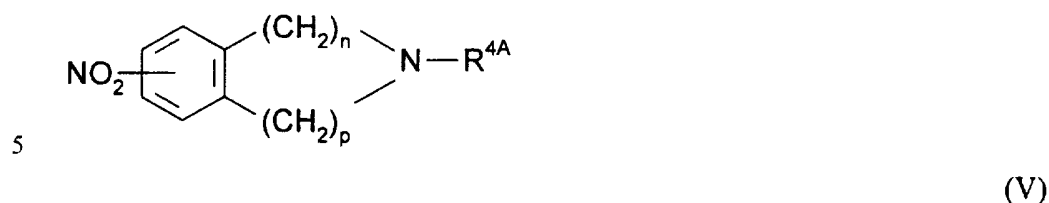
Conversions of an R^{1A}, R^{2A}, R^{3A} or R^{4A} group to a R¹, R², R³ or R⁴ group typically arise when a protecting group is needed during the above coupling reaction or
20 during the preparation of the reactants by the procedures described below. Interconversion of one R¹, R², R³ or R⁴ group to another 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.

25 Compounds of formula (II) may be prepared from a compound of formula (IV)



(IV)

where X is a leaving group, such as halogen, especially Br, or methanesulfonyl, which is reacted with $R^{4A}NH_2$, where R^{4A} is R^4 as defined above or an N-protecting group, to obtain compounds of formula (V)



and then reduced, for example using hydrogen/palladium, to obtain compounds of formula (II).

10 Alternatively, a compound of formula (VI)



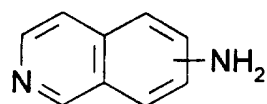
may be reduced directly, for example with lithium aluminium hydride, typically in tetrahydrofuran, to obtain a compound of formula (II) or a compound of formula (II) may be obtained in a two step procedure where a hydrogenation, typically with hydrogen/palladium, is followed by reduction, again suitably with lithium aluminium hydride.

When R^{4A} in formula (V) or (VI) is alkenyl or alkynyl, reagents for reduction of NO_2 must be selected so as to selectively reduce NO_2 without affecting the R^{4A} group. It may be more suitable that R^{4A} in formula (V) or (VI) is an N-protecting group, that may be removed at an appropriate point in the reaction and replaced by a desired R^4 group by conventional methods.

Compounds of formulae (IV) and (VI) and the reagents used are commercially available, or can be prepared from commercially available materials using conventional procedures described in the literature, and as illustrated below.

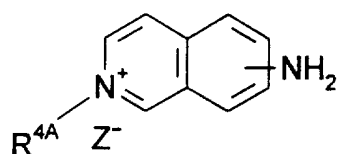
More specifically, compounds of formula (II) in which $n=1$ and $p=2$ or $n=2$ and $p=1$ are tetrahydroisoquinolines and may be prepared from the corresponding unsaturated compound of formula (VII)

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(VII)

by reaction with a compound $R^{4A}Z$ where Z is a leaving group such as halogen, especially
 5 iodo, or tosylate to obtain an intermediate of formula (VIII)



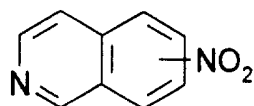
(VIII)

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which can be reduced, for example using sodium borohydride, to the compound of formula (II). Alternatively the compound of formula (VIII) can be hydrogenated, for example using hydrogen at 50psi in a solution of acetic/sulphuric acid with a platinum oxide catalyst.

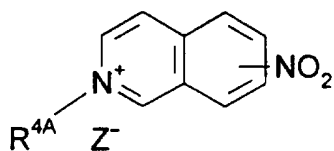
Another route is from a precursor of formula (IX)

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(IX)

which can be reacted with $R^{4A}Z$, preferably as a tosylate, to obtain the intermediate of
 20 formula (X)



(X)

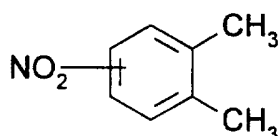
25 which can then be hydrogenated under the conditions previously described to prepare the compound of formula (II).

When R^{4A} is hydrogen, the compound of formula (II) can be obtained by direct hydrogenation of the compounds of formula (VII) or (IX), using the reagents already described. The NH may be protected conventionally, for example by making R^{4A} t-

butoxycarbonyl, prior to formation of the benzamide, and then deprotected under standard conditions, for example using trifluoroacetic acid/methylene chloride.

Compounds of formulae (VII) and (IX) and the reagents used are commercially available, or can be prepared from commercially available materials using conventional procedures described in the literature.

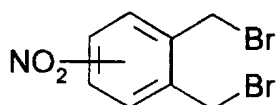
Compounds of formula (II) in which $n=1$ and $p=1$ are amino-dihydroisoindolines. Such compounds may be prepared from compounds of formula (XI)



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(XI)

by forming a leaving group, such as bromo, on the methyl groups, and reacting with an amine $R^{4A}NH_2$ to form the saturated heterocyclic ring, followed by reduction of the nitro group. For example, the compound of formula (XII)

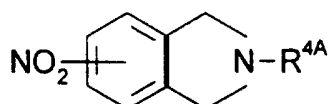


(XII)

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may be formed by refluxing the compound of formula (XI) with N-bromosuccinimide/carbon tetrachloride in the presence of a light source and/or a radical initiator such as t-butyl perbenzoate. The product (XII) can be reacted with $R^{4A}NH_2$ in methylene dichloride to obtain the compound of formula (XIII)

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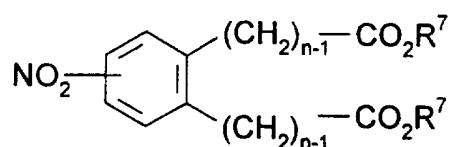
(XIII)

This can be converted to an aminoisoindoline of formula (II) by reduction with hydrogen and a palladium catalyst in ethanol. This route is based on the procedure disclosed in US-5436250.

Alternative routes to dihydroisoindolines of formula (II) via a compound of formula (VI) where $n=1$ and $p=1$ can be found in Wätjen *et al*, Biomed.Lett. 1994, 4(2), 371 and Knefeli *et al*, Arch.Pharm. 1989, 322, 419.

Compounds of formula (II) in which $(n+p)=4$ are amino-tetrahydrobenzazepines.

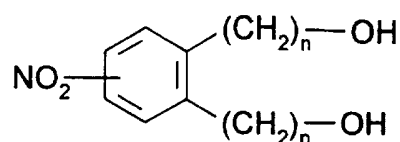
- 5 Such compounds may be prepared from a compound of formula (XIV)



(XIV)

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where R^7 is C_{1-4} alkyl, typically methyl or ethyl, which is reacted with diborane in a suitable solvent such as tetrahydrofuran to give a compound of formula (XV)

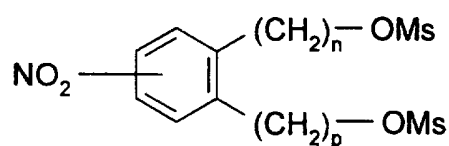


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(XV)

Further reaction with methanesulfonyl chloride in pyridine gives a compound of formula (XVI)

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(XVI)

- 25 which is a compound of formula (IV) in which X is methanesulfonyl (OMs). This can be reacted with $R^{4A}NH_2$ in a solvent such as dimethylformamide to obtain a compound of formula (V) with the appropriate n/p values for an amino-tetrahydrobenzazepine.

In this reaction R^{4A} is suitably a protecting group such as benzyl which is easily replaceable by desired R^4 groups. Further reaction with hydrogen and a palladium catalyst in acetic acid converts the NO_2 group to NH_2 and results in a compound of formula (II). If the R^{4A} group in formula (XVII) is benzyl then the corresponding formula (II) compound

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will contain a R⁴ hydrogen group, which can be used as a starting point for additional R⁴ groups by conventional interconversions. This reaction scheme is based on the disclosure of EP-A-0002624 to which reference is directed, and which specifically discloses preparation of aminotetrahydrobenzazepines of formula (II) in which n=1 and p=3 (or *vice versa*), or as described by R.M. DeMarinis *et al*, J. Med. Chem., 1984, 27, 918 for n=p=2.

Compounds of formula (III) can be prepared by further substitution of commercially available benzoic acid derivatives using conventional procedures, by analogy with the procedures set out in the Preparations below. Suitable starting materials are 2,4-dimethoxy benzoic acid, 2-methoxy 4-amino benzoic acid and 2-methoxy 4-chloro benzoic acid.

The preparation of compounds of this invention is further illustrated by the following Preparations and Examples. The utility of compounds of this invention is shown by the Pharmacological Data that follow the Examples.

15

Preparation 1

5-Amino-2-methylisoquinolinium iodide

To a solution of 5-aminoisoquinoline (14.4g, 100mmol) in acetone (300ml) was added iodomethane (14.4ml). The solution was briefly stirred and then allowed to stand for 2h. The yellow precipitate was then filtered, washed with acetone and dried to afford the title compound as a yellow solid (18.8g).

Preparation 2

5-Amino-2-methyl-1,2,3,4-tetrahydroisoquinoline

To an ice cold solution of 5-amino-2-methylisoquinolinium iodide (18.8g, 65mmol) in methanol (1.5L) and water (60ml) was added sodium borohydride (17.8g, 0.47mol) portionwise over 2h. The mixture was then allowed to stir at room temperature for 18h before concentration *in vacuo* and partitioning of the residue between water and dichloromethane. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford the title compound (8.87g).

Preparation 3

4-Azido-5-iodo-2-methoxybenzoic acid

To a solution of 4-amino-5-iodo-2-methoxybenzoic acid (300 mg, 1.02 mmol) in trifluoroacetic acid (4 ml) at 5°C, was added sodium nitrite (283 mg, 4.1 mmol) portionwise, and the mixture allowed to stir for 30 min. Sodium azide (200 mg, 3.07

mmol) was then added portionwise and the mixture stirred for a further 30 min at 0°C. The mixture was diluted with water, and a yellow solid precipitated. The solid was filtered, washed with cold water and dried, to afford the title compound (274 mg, 84%).

5 Preparation 4

4,5-Dichloro-2-methoxybenzoic acid

To an ice cold solution of 4-chloro-2-methoxybenzoic acid (1.0g, 5.36mmol) in trifluoroacetic acid (7ml) was added N-chloromorpholine (0.67g, 5.5mmol) dropwise, maintaining the internal temperature below 10°C. After stirring overnight at room temperature the trifluoroacetic acid was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulfate, concentrated *in vacuo* and the residue recrystallised from methanol to afford the title compound as a white solid (200mg).

15

Preparation 5

5-Chloro-2,4-dimethoxybenzoic acid

The title compound was prepared in an analogous fashion to Preparation 4 from 2,4-dimethoxybenzoic acid (1.3g). Recrystallisation of the crude product from methanol afforded the title compound as a white solid (1.3g).

Preparation 6

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).

30 Preparation 7

(5-Bromo-2-methoxybenzyloxy)-*tert*-butyldimethylsilane

To a solution of 5-bromo-2-methoxybenzyl alcohol (1.0 g, 4.6 mmol) and imidazole (470 mg, 7.01 mmol) in DMF (15 ml) was added *tert*-butyldimethylsilyl chloride (1.04 g, 6.91 mmol). The mixture was allowed to stir for 4 h, poured onto water (100 ml) and extracted with ether (3 x 30 ml). The combined organic phases were washed with water (50 ml), brine (50 ml), dried over sodium sulfate and evaporated under reduced pressure to leave a

pale yellow oil. This was purified by chromatography (SiO₂, 5% ether/petrol), to give the title compound (1.46g, 96%) as a colourless oil.

Preparation 8

5 (5-Trifluoroacetyl-2-methoxybenzyloxy)-*tert*-butyldimethylsilane

To a solution of 5-bromo-2-methoxybenzyloxy)-*tert*-butyldimethylsilane (1.0 g, 3.02 mmol) in THF (5 ml) at -78°C, was added *n*-BuLi (2.26 ml of a 1.6 M solution in pentane, 3.62 mmol) dropwise over 10 min. The solution was allowed to stir for a further 1 h at -78°C, to give a bright yellow solution. N,N-diethyltrifluoroacetamide (561 mg, 3.32 mmol) in THF (2 ml) was added dropwise over 30 min, and the solution was stirred for a further 1 h at -78°C. Saturated aqueous ammonium chloride (5 ml) was added and the mixture allowed to warm to room temperature, and extracted with ether (3 x 10 ml). The combined organic phases were washed with water (10 ml), brine (10 ml), dried over sodium sulfate and evaporated *in vacuo*. The resulting residue was purified by
15 chromatography (SiO₂, 5% ether/petrol) to give the title compound (0.99g, 94%) as a white solid.

Preparation 9

20 (E, Z)-1-[3-(*tert*-Butyldimethylsilanyloxymethyl)-4-methoxyphenyl]-2,2,2-trifluoroethanone oxime

A mixture of (5-trifluoroacetyl-2-methoxybenzyloxy)-*tert*-butyldimethylsilane (1.0 g, 2.87 mmol), hydroxylamine hydrochloride (240 mg, 3.44 mmol), pyridine (18 ml) and ethanol (9 ml) were heated at reflux for 4 h. The resulting mixture was evaporated *in vacuo* and the
25 residue purified by chromatography (SiO₂, 20% ether/petrol), to give an approximately 3:2 inseparable isomeric mixture of (E, Z)-1-[3-(*tert*-butyldimethylsilanyl oxymethyl)-4-methoxyphenyl]-2,2,2-trifluoroethanone oximes (1.02 g, 98%) as a colourless oil.

Preparation 10

30 (E, Z)-(4-Toluensulfonyl)-1-[3-(*tert*-butyldimethylsilanyloxymethyl)-4-methoxyphenyl]-2,2,2-trifluoroethanone oxime

To a solution of (E, Z)-1-[3-(*tert*-butyldimethylsilanyloxymethyl)-4-methoxyphenyl]-2,2,2-trifluoroethanone oximes (1.0 g, 2.75 mmol), triethylamine (340 mg, 3.36 mmol), DMAP (31 mg, 0.25 mmol) in dichloromethane (5 ml) at 0°C, was added tosyl chloride (627 mg, 3.29 mmol) portionwise. The mixture was stirred for 1 h at room temperature and then
35 poured onto water (10 ml). The layers were separated, and the aqueous phase extracted with dichloromethane (3 x 10 ml). The combined organic phases were washed with water

(10 ml), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by chromatography (SiO₂, 20% ether/petrol) to give an inseparable mixture of (E, Z)-(4-toluensulfonyl)-1-[3-(*tert*-butyldimethylsilanyloxymethyl)-4-methoxyphenyl]-2,2,2-trifluoroethanone oximes (1.39 g, 98%) as a colourless oil.

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Preparation 11

3-[3-(*tert*-Butyldimethylsilanyloxymethyl)-4-methoxyphenyl]-3-trifluoromethyl-diaziridine

A solution of (E, Z)-(4-toluensulfonyl)-1-[3-(*tert*-butyldimethylsilanyloxymethyl)-4-methoxyphenyl]-2,2,2-trifluoroethanone oximes (517 mg, 1 mmol) in ether (5 ml) was stirred with liquid NH₃ (15 ml) in a bomb for 4 h at room temperature. The mixture was then filtered and the solid washed with ether. The filtrate was evaporated *in vacuo* and the residue purified by chromatography (SiO₂, 20% ether/petrol) to give the title compound (350 mg, 97%) as a pale yellow oil.

15

Preparation 12

3-[3-(*tert*-Butyldimethylsilanyloxymethyl)-4-methoxyphenyl]-3-trifluoromethyl-3H-diazirine

A mixture of 3-[3-(*tert*-butyldimethylsilanyloxymethyl)-4-methoxyphenyl]-3-trifluoromethyl-diaziridine (200 mg, 0.55 mmol) and freshly prepared Ag₂O (255 mg, 1.1 mmol) in ether (3 ml) was stirred for 24 h. The solid was filtered, washed with ether, and the filtrate evaporated *in vacuo*. The resulting residue was purified by chromatography (SiO₂, 10% ether/petrol) to give the title compound (187 mg, 94%) as a colourless oil.

25

Preparation 13

2-Methoxy-5-(3-trifluoromethyl-3H-diazirin-3-yl)benzoic acid

A solution of 3-[3-(*tert*-butyldimethylsilanyloxymethyl)-4-methoxyphenyl]-3-trifluoromethyl-3H-diazirine (150 mg, 0.41 mmol) in methanol (5 ml) was stirred for 20 min with conc. HCl (2 drops). The solution was poured onto saturated aqueous sodium bicarbonate (10 ml) and extracted with dichloromethane (3 x 5 ml). The combined organic extracts were dried over sodium sulfate and evaporated under reduced pressure. The residue was taken up in dioxane (3 ml) and aqueous potassium hydroxide (2.5 ml of a 0.2M solution), potassium permanganate (98 mg, 0.62 mmol) was added and the mixture stirred for 4 h. The mixture was filtered through a pad of Celite and washed with water. The

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filtrate was extracted with ether (2 x 10 ml). The aqueous phase was brought to pH 1, extracted with ether (2 x 10 ml) and these extracts were dried over sodium sulfate and evaporated *in vacuo* to give the title compound (77 mg, 72%) as an off white solid.

5 **Preparation 14**

5-Amino-1,2,3,4-tetrahydroisoquinoline

A solution of 5-aminoisoquinoline (10g, 69mmol) in glacial acetic acid (150ml) and concentrated sulfuric acid (1ml) was hydrogenated over platinum oxide (1g) at 55psi for 20h. The acetic acid was then removed *in vacuo* and the residue treated with saturated aqueous potassium carbonate (100ml) and extracted with dichloromethane. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford the title compound (6.45g).

Preparation 15

15 **5-Amino-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline**

An ice cold solution of 5-amino-1,2,3,4-tetrahydroisoquinoline (6.45g, 44mmol) in 1,4-dioxane (250ml) was treated with 3M sodium hydroxide (14.7ml, 44mmol), and di-*tert*-butyl-dicarbonate (9.57ml, 44mmol) and the solution was stirred at room temperature overnight. The reaction mixture was then poured into water (400ml) and extracted with ether. The organic phases were dried over sodium sulfate and concentrated *in vacuo* to afford a brown oil which solidified on standing and was recrystallised from ethanol/petrol to afford the title compound as an off white crystalline solid (5.1g).

Preparation 16

25 **5-Chloro-2,4-dimethoxybenzoyl chloride**

A solution of 5-chloro-2,4-dimethoxybenzoic acid (6.4g) in dichloromethane (250ml) was treated with thionyl chloride (30ml) and the mixture heated at reflux for 18h. Removal of volatile material *in vacuo* afforded the title compound as a white solid (6.6g).

30 **Preparation 17**

5-Chloro-2,4-dimethoxy-N-[2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]benzamide

To a solution of 5-amino-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (1g, 4mmol) in dichloromethane (30ml) and triethylamine (3ml) was added 5-chloro-2,4-dimethoxybenzoyl chloride (1.03g, 4.4mmol). After stirring at room temperature for 2h the reaction mixture was diluted with dichloromethane (75ml) and washed with saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate,

concentrated *in vacuo* and the residue recrystallised from ethyl acetate/petrol to afford the title compound as a colourless crystalline solid (1.3g).

Preparation 18

5-Chloro-2-methoxy-4-methylbenzoic acid

The title compound was prepared in an analogous manner to Preparation 4 from 2-methoxy-4-methylbenzoic acid (3.0g, 0.018mol). Purification of the crude product using a chromatotron (SiO₂, 10% ethyl acetate in hexane) afforded the title compound as a white solid (0.40g)

10

Preparation 19

5-Amino-2-ethyl-1,2,3,4-tetrahydroisoquinoline

The title compound was prepared by treatment of 5-aminoisoquinoline with iodoethane followed by reduction with sodium borohydride using procedures analogous to those

described in Preparation 1 and Preparation 2.

Preparation 20

5-Amino-2-propyl-1,2,3,4-tetrahydroisoquinoline

The title compound was prepared by treatment of 5-aminoisoquinoline with iodopropane followed by reduction with sodium borohydride using procedures analogous to those described in Preparation 1 and Preparation 2.

Preparation 21

4-Benzyloxy-5-chloro-2-methoxybenzoic acid

A solution of chlorine (5.1g) in acetic acid (100ml) was added dropwise to a solution of methyl 4-benzyloxy-2-methoxybenzoate (10g) in acetic acid (40ml) whilst maintaining the temperature at 20-25°C. The mixture was poured into ice-water and extracted with

dichloromethane. The organic extract was dried over sodium sulfate and concentrated *in vacuo*. The resulting crude material was suspended in ethanol (500ml) and treated with 10% aqueous sodium hydroxide (16ml). The mixture was heated at reflux overnight and then concentrated *in vacuo*. The residue was treated with excess 5M HCl and extracted into dichloromethane. The extract was dried (sodium sulfate) and concentrated *in vacuo* to afford a white solid which was crystallised from ethanol to give the title compound (6.3g).

Preparation 22

4-Hydroxy-2-methoxybenzoic acid methyl ester.

4-Amino-2-methoxy benzoic acid methyl ester (15g, 82.7mmol) was dissolved in sulfuric acid (80ml of a 25% solution). The solution was cooled in an ice bath and diazotized with saturated sodium nitrite solution (8.57g, 124mmol) maintaining the temperature below 5°C. The diazonium solution was poured slowly into boiling sulphuric acid (1L of a 3% solution) and the mixture was heated for an additional 5 mins. The mixture was then allowed to cool before being extracted with dichloromethane. The organic extracts were combined, dried over sodium sulfate and concentrated *in vacuo* to afford a brown solid (9.7g).

10

Preparation 23**4-Ethoxy-2-methoxy-benzoic acid methyl ester**

To a solution of 4-hydroxy-2-methoxybenzoic acid methyl ester (4.17g, 22mmol) in DMF (50ml) under argon was added potassium carbonate (6.33g, 4.6mmol) followed by iodoethane (7.15g, 4.6mmol). The mixture was then heated to 50°C under argon for 12h. On cooling the mixture was poured into a large excess of water and extracted with ether. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to afford the title compound as a brown oil (4.8g).

20 **Preparation 24****5-Chloro-4-ethoxy-2-methoxybenzoic acid**

Trifluoroacetic acid (35ml) was cooled in an ice bath. 4-Ethoxy-2-methoxy-benzoic acid methyl ester (4.85g, 23mmol) was then added slowly. N-chloromorpholine (3.64g, 29.9mmol) was then added dropwise maintaining the reaction mixture temperature below 10°C. The ice bath was removed and the mixture stirred under argon for 12h at room temperature. The solvent was then removed *in vacuo* and the residue taken up in ethyl acetate and washed with water. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford a brown oil which was triturated with ether and 60/80 petrol. The resulting brown solid was then recrystallised from 60/80 petrol, taken up into ether and washed with sodium hydroxide solution (2M). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford the methyl ester as a pale yellow solid (0.9g). A mixture of this ester (0.9g, 3.6mmol), methanol (22ml) and sodium hydroxide solution (20ml, 2M) was heated to 70°C overnight. On cooling the mixture was acidified to pH 6-7 and the solvent was removed *in vacuo*. The residue was taken up in ethanol and the inorganic solid filtered off. The filtrate was concentrated *in vacuo* to afford the title compound as a pale brown solid (0.44g).

35

Preparation 25**5-Bromo-2-methoxy-4-methylbenzoic acid**

The title compound was prepared in an analogous manner to Preparation 6 from 2-methoxy-4-methylbenzoic acid (3.0g, 0.018mol). Recrystallisation of the crude product
5 from dichloromethane afforded the title compound as a white solid (0.99g).

Preparation 26**[4-(*tert*-Butyldimethylsilyloxyethyl)-3-methoxyphenyl]-phenylmethanol**

To 2-(*tert*-Butyldimethylsilyloxyethyl)-5-bromoanisole (500 mg, 1.51 mmol) in THF
10 (10 ml) at -78°C was added *n*-BuLi (1.13 ml of a 1.6M solution in pentane, 1.81 mmol) and the mixture allowed to stir for 1 h at -78°C. Benzaldehyde (176 mg, 1.66 mmol) was added and the mixture allowed to warm to room temperature and stirred for 1 h. Water (20 ml) was added and the mixture extracted with ether (3 x 10 ml). The combined extracts were washed with water (10 ml), brine (10 ml), dried (Na₂SO₄) and evaporated under
15 reduced pressure. The resulting residue was purified by chromatography (SiO₂, 50% ether/petrol) to give the title compound as a colourless oil (303 mg, 56%).

20 Preparation 27**[5-(*tert*-Butyldimethylsilyloxyethyl)-4-methoxyphenyl]-phenylmethanol**

The title compound was prepared in an analogous manner to Preparation 26 from 2-(*tert*-Butyldimethylsilyloxyethyl)-4-bromoanisole (500 mg, 1.51 mmol). The crude product was purified by chromatography (SiO₂, 50% ether/petrol) to give the title compound as a
25 colourless oil (63%).

Preparation 28**4-Benzoyl-2-methoxybenzoic acid**

A solution of 4-(*tert*-butyldimethylsilyloxyethyl)-3-methoxyphenyl]-phenylmethanol
30 (200 mg, 0.56 mmol) in THF (5 ml) was stirred with 5N HCl (5 ml) for 1 h. The mixture was poured onto saturated aqueous sodium bicarbonate (10 ml) and extracted with ether (3 x 10 ml). The combined organic extracts were dried (Na₂SO₄), and evaporated under reduced pressure. The residue was taken up in dioxane (4 ml) and aqueous KOH (5.6 ml of a 0.2M solution), potassium permanganate (266 mg, 1.68 mmol) was added and the
35 mixture stirred for 4 h. The mixture was filtered through a pad of Celite and washed with water. The filtrate was extracted with ether (2 x 10 ml) and the aqueous phase was brought

to pH 1 and extracted with ether (2 x 10 ml). These extracts were dried over sodium sulfate and evaporated *in vacuo* to afford the title compound as a white foam (102 mg, 71%).

Preparation 29

5 5-Benzoyl-2-methoxybenzoic acid

The title compound was prepared in an analogous manner to Preparation 28 from [5-(*tert*-butyldimethylsilanyloxymethyl)-4-methoxyphenyl]-phenylmethanol (200mg, 0.56mmol). The title compound was obtained as a white foam (74%).

10 Preparation 30

3-Nitro-N-methylphthalimide

A solution of 3-nitrophthalimide (Aldrich)(1.78g, 0.01mol) in dry N,N-dimethylformamide (20ml) was added dropwise to a stirred suspension of sodium hydride (0.36g of an 80% dispersion in oil; 0.012mol) in dry N,N-dimethylformamide (10ml) under argon. The
15 mixture was stirred at room temperature for 30min and then treated with iodomethane (0.75ml, 0.012mol). After stirring overnight the reaction was poured into ice-water and extracted with dichloromethane (4x50ml). The combined extracts were washed with water followed by brine, then dried over sodium sulfate and concentrated *in vacuo*. The residue was treated with water, and the resulting precipitate was removed by filtration and washed
20 with water. After drying in a vacuum dessicator over silica gel the title compound was obtained as a yellow solid (1.64g).

Preparation 31

4-Amino-2,3-dihydro-2-methyl-1H-isoindole

25 A solution of 3-nitro-N-methylphthalimide (0.58g, 2.8mmol) in dry tetrahydrofuran (10ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.64g, 16.8mmol) under argon. The mixture was stirred at room temperature for 2h and then heated under gentle reflux for 2.5h. The reaction was quenched by addition of wet diethyl ether followed by a minimum amount of water. The precipitated aluminium salts were
30 removed by filtration. The filtrate was concentrated *in vacuo* to give the title compound as a brown oil (400mg) which was used directly in the next stage (Example 31).

Preparation 32

6-Amino-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

35 9-Amino-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, prepared according to R.M. DeMarinis *et al*, J. Med. Chem., 1984, 27, 918, (0.190g, 0.90 mmol) was dissolved in 10% acetic acid in methanol (50ml) and 10% Pd/C (150mg) added. The mixture was stirred

at room temperature, under hydrogen/atmos pressure for 4h, then filtered through Kieselguhr and evaporated *in vacuo*. Residual material was taken up into dichloromethane and 5% NaHCO₃ solution; the organic layer was washed with brine, dried (Na₂SO₄) and evaporated *in vacuo* to afford the title compound as a colourless oil (133mg).

5

Preparation 33

6-Amino-2-(*t*-butyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline

A solution of 6-amino-1,2,3,4-tetrahydroisoquinoline (0.74g, 5 mmol) in 1,4-dioxan (50ml) containing 5M-NaOH (1ml) was stirred at 5°C and treated with di-*t*-butyl dicarbonate
10 (1.09g, 5 mmol). After 20 min at room temperature the product was extracted with ethyl acetate and the material in the organic layer gave a brown gum which was chromatographed on Kieselgel 60 in 5% methanol:dichloromethane. The title compound was obtained as a pale gum (0.55g).

15 ¹H NMR (CDCl₃) δ: 1.49 (9H, s), 2.74 (2H, t), 3.60 (4H, br), 4.46 (2H, s), 6.47 (1H, d), 6.55 (1H, dd), 6.90 (1H, d).

20 Preparation 34

4-*tert*-Butyl-phenoxyacetate

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
25 combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to afford the acetate compound as an oil (33.33g).

Preparation 35

4-*tert*-Butyl-2-hydroxy acetophenone

30 A mixture of the acetate of Preparation 34 (33.23g, 0.173 mole) and AlCl₃ (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 steam distil the product (bath temp 190-200°C). The distillate was extracted with ether and
35 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 36**4-*tert*-Butyl-2-methoxy acetophenone**

A suspension of 4-*tert*-butyl-2-hydroxy acetophenone (12.65g), potassium carbonate (13.14g) and dimethyl sulphate (8.99ml) in acetone (200ml) was refluxed for 48h. After
5 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 sodium sulphate and concentrated *in vacuo* to afford a yellow oil (12.05g).

Preparation 37**4-*tert*-Butyl-2-methoxybenzoic acid**

The acetophenone of Preparation 36 (11.0g, 53 mmol) was added to a solution of sodium 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
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).

¹H NMR (DMSO-d⁶) 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).

20

Preparation 38**4-*n*-Butyl-2-methoxybenzoic acid**

A mixture of 4-bromo-2-methoxybenzoic acid methyl ester (3.0g, 0.0122 mole), lithium chloride (1.56g), tetra butyl tin (4.51g) and bis (triphenyl phosphine palladium (II) chloride
25 (214mg, 0.3 mmol) were heated at 100°C for 24h. The solvent was then removed *in vacuo* and the residue taken up in dichloromethane. The black solid was removed by filtration and the filtrate concentrated *in vacuo* to give a yellow oil. The oil was purified by column chromatography (Biotage) on silica gel using 10% ether in hexane to afford a colourless oil (1.63g). A portion of the foregoing 4-*n*-butyl-2-methoxybenzoic acid methyl ester (1.50g)
30 was dissolved in methanol (35 ml) with sodium hydroxide solution (2N, 30ml). The mixture was allowed to stir at room temperature overnight. Then added dil. HCl until pH-5. The solvent was then removed *in vacuo* and the residue taken up in ethyl acetate and washed with brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford an oil (1.02g).

35

Preparation 39**4-*n*-Butyl-2-methoxy-5-chlorobenzoic acid**

4-*n*-Butyl-2-methoxybenzoic acid (0.5g; 2.9 mmol) and N-chloromorpholine (356mg; 2.9 mmol) were treated in a similar manner to that described in Preparation 24 to give the title compound as a white solid (0.4g).

5 **Preparation 40**

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

To a solution of 2-methoxy-4-*iso*-propyl benzoic acid (prepared in an analogous manner to Preparation 37, 4-*tert*-butyl-2-methoxy 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%).

Preparation 41

15 **Methyl-5-bromo-4-*iso*-propyl-2-methoxy benzoate**

5-Bromo-4-*iso*-propyl-2-methoxybenzoic acid (9.268g 34.0 mmol) was dissolved in ethanol (250 ml) and conc. H_2SO_4 (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 ($MgSO_4$). Concentration *in vacuo* afforded an oil, which was purified by Biotage Column Chromatography on silica gel using 10% ether in hexane. An oil (5.5g) was obtained.

Preparation 42

Methyl-4-*iso*-propyl-2-methoxy-5-trifluoromethyl benzoate

25 A mixture of methyl-5-bromo-4-*iso*-propyl-2-methoxy benzoate (5.43g, 0.0189 mole), potassium trifluoroacetate (5.75g, 0.0378 mole) and copper (I) iodide (7.92g, 0.042 mole) in DMF (100ml) and toluene (30ml) were heated at 170°C under argon to remove water (Dean-Stark Trap) and then heated to 155°C overnight. On cooling, after concentration *in vacuo*, the mixture was poured into ether (300ml) and water (300ml). After filtration through Kieselguhr, the organic layer was separated, washed with brine and dried (Na_2SO_4). Concentration *in vacuo* afforded a brown yellow solid (4.85g).

Preparation 43

4-*iso*-Propyl-2-methoxy-5-trifluoromethyl benzoic acid

35 Methyl-4-*iso*-propyl-2-methoxy-5-trifluoromethyl benzoate was dissolved in methanol (100ml), containing sodium hydroxide solution (2N, 100ml). The mixture was allowed to stir at 25°C overnight and then dil. HCl added until pH~5. The solvent was then removed

in vacuo and the residue taken up in ethyl acetate and washed with brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford a crude solid which was recrystallised with dichloromethane and hexane to give a solid (2.59g).

5 **Preparation 44**

5-Pivaloyl-2-methoxy benzoic acid

5-Pivaloyl-2-methoxy benzyl alcohol (1.19g, 5.35 mmol) was dissolved in dioxane (20ml). A solution of KOH (0.449g, 8.025 mmol in water (5ml) was added followed by KMnO₄ (1.69g, 10.7 mmol). The mixture was allowed to stir at room temperature over the
10 weekend. The solution was filtered through Celite and extracted with ether. The aqueous phase was acidified with dil. HCl and extracted with ether (3x50ml). The organic layer was dried over magnesium sulphate and concentrated *in vacuo* to afford the title compound as a white solid (1.06g).

15 **Preparation 45**

5-Pivaloyl-2-methoxy benzyl alcohol

5-Pivaloyl-2-methoxy benzyl TBDMS ether (1.8g, 5.35 mmol) was dissolved in methanol (30ml); conc. HCl (20 drops) was added and the whole allowed to stir at room temperature for 4h. Saturated NaHCO₃ solution was added and the mixture extracted with ether
20 (2x100ml). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford the title compound as a colourless oil (1.19g).

Preparation 46

5-Pivaloyl-2-methoxy benzyl TBDMS Ether

25 n-Butyllithium (11.43ml, 0.0183 mole, 1.6M in hexane) was slowly added to a solution of 5-bromo-2-methoxy benzyl TBDMS ether in tetrahydrofuran (30ml) over 45 mins at -78°C. The reaction mixture was maintained under argon at -78°C for 1h. Then N,O-dimethylhydroxy pivaloyl amide (2.43g, 0.0167 mole) was added dropwise with stirring at -78°C. The resulting mixture was allowed to stir at -78°C for 2.5h, quenched with NH₄Cl
30 solution and allowed to warm to room temperature. The mixture was extracted with ether (2x50ml), the combined organics were dried (Na₂SO₄) and concentrated *in vacuo* to give an oil. The oil was purified by Biotage column chromatography on silica gel using 5% ether in hexane to afford the title compound as a colourless oil (2.95g).

35 **Preparation 47**

5-Bromo-2-methoxy benzyl TBMS ether

To a solution of 5-bromo-2-methoxy benzyl alcohol (20.87g, 0.096 mole) in dichloromethane (300ml), Et₃N (20.90 ml, 0.15 mole) was added *tert*-butyldimethylsilyl chloride (15.94g, 0.10 mole) dropwise. The mixture was allowed to stir at room temperature overnight, then water (300ml) was added. The organic layer was washed with
5 brine, dried (Na₂SO₄) and evaporated to give a white solid. The title compound was purified by dry flash column chromatography on silica gel using 20% ether in hexane to give a white solid (20.1g).

Preparation 48

10 2,4-Dimethoxy-5-trifluoromethylbenzoic acid

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,
15 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).

20

Preparation 49

2-Methoxy-4-(3-trifluoromethyl-3H-diaziriny)benzoic acid

The title compound was prepared from 4-bromo-2-methoxybenzyl alcohol using a method
25 similar to that described in Preparations 7 to 13.

Preparation 50

5-Iodo-2-methoxy-4-(3-trifluoromethyl-3H-diaziriny)benzoic acid

30 The benzoic acid of Preparation 49 (100mg) in triflic acid (2ml) containing N-iodosuccinimide (104mg) was stirred at room temperature overnight. The mixture was poured onto ice/water and extracted into ether. The combined organic extracts were washed with aqueous sodium thiosulfate, dried (MgSO₄) and evaporation *in vacuo* gave the title compound as an off-white solid (115mg; 78%).

35

Preparation 51

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 as a pale yellow solid (19.04g).

Preparation 52

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

The nitro compound of Preparation 51 (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 according to the procedure of G.E. Stokker., Tet. Lett., 1996, **37**, 5453. Work up afforded the title compound 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⁺)

Preparation 53

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

The trifluoroacetamide of Preparation 52 (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).

Preparation 54

2-Methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline

The amine of Preparation 53 (2.08g; 11.7 mmol) was treated with 88% formic acid (3.45ml) and 37% aqueous formaldehyde (5.88ml) at 80°C for 2h according to the procedure of G.M. Carrera and D.S. Garvey, J. Het. Chem., 1992, **29**, 847. Basification with 10% sodium hydroxide followed by work-up with ethyl acetate afforded an orange gum (2.3g). Chromatography on Kiesegel 60 in 0-3% methanol - ethyl acetate gave the title compound as an orange solid (1.7g).

m/z (CI): 193 (MH^+).

Preparation 55

7-Amino-2-methyl-1,2,3,4-tetrahydroisoquinoline

5

The 7-nitro compound of Preparation 54 (0.25g; 1.3 mmol) in methanol (40ml) was hydrogenated over 10% palladium on carbon (100mg) at atmospheric pressure overnight. The catalyst was removed by filtration through a pad of Kieselguhr and evaporation *in vacuo* gave the title compound as a white solid (213mg).

10

m/z (CI): 163 (MH^+)

Preparation 56

7-Amino-2-(*t*-butyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline

15

The title compound was prepared from the compound of Preparation 53 using di *t*-butyl dicarbonate in 10% aqueous hydroxide in dioxan at 25°C followed by catalytic hydrogenation according to the procedures described for Preparations 15 and 55.

20

Preparation 57

7-Amino-1,2,3,4-tetrahydro-2-trifluoroacetyl-isoquinoline

The 7-nitro compound of Preparation 52 (0.99g; 3.6 mmol) in ethanol (50ml) was
25 hydrogenated over 10% palladium on carbon (450mg) at atmospheric pressure for 4h. The catalyst was removed by filtration through a pad of Celite and evaporation *in vacuo* gave the title compound as a white solid (840mg).

1H NMR (250MHz, $CDCl_3$) δ : 2.84 (2H, t), 3.23 (2H, br s), 3.82 (2H, m), 4.66
30 (2H, d, restricted rotation around C-1), 6.47 (1H, m), 6.57 (1H, m), 6.96 (1H, m)

Preparation 58

2-Methyl-5-nitro-1,2,3,4-tetrahydroisoquinoline

35 5-Nitroisoquinoline was quaternized with methyl iodide and then reduced using sodium borohydride according to the procedures of Preparations 1 and 2 to give the title compound.

Preparation 59**7-Iodo-2-methyl-5-nitro-1,2,3,4-tetrahydroisoquinoline**

- 5 The nitro compound of Preparation 58 (100mg; 0.52 mmol) and N-iodosuccinimide (118mg) in triflic acid (3ml) was stirred at 25°C overnight. 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 1% methanol -
10 dichloromethane gave the title compound (101mg; 61%).

m/z (API⁺): 319 (MH⁺; 100%).

Preparation 60**5-Amino-7-iodo-2-methyl-1,2,3,4-tetrahydroisoquinoline**

- A solution of the nitro compound of Preparation 59 (101mg) in ethanol (20ml) at 50°C was treated with a solution of tin (II) chloride (243mg) in conc. hydrochloric acid (1ml). The resultant yellow solution was basified with 10% aqueous sodium hydroxide and the
20 product extracted into dichloromethane. Flash chromatography on Kieselgel 60 (5% methanol - dichloromethane) gave the title compound (65mg; 70%).

¹H NMR (CDCl₃): δ 2.40 (3H, s), 2.46 (2H, t), 2.68 (2H, t), 2.90 - 3.50 (2H, br), 3.42 (2H, s), 6.75 (1H, d, J = 1.5 Hz), 6.81 (1H, d, J = 1.5 Hz). m/z (API): 289(MH⁺; 100%).

25 Preparation 61**7-Amino-5-iodo-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline**

The title compound was prepared from the nitro compound of Preparation 52 using a procedure similar to that of Preparations 59 and 60.

30

Preparation 62**5-Amino-7-iodo-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline**

- The title compound was prepared from 5-nitro-1,2,3,4-tetrahydroisoquinoline using
35 procedures similar to those outlined in Preparations 51, 59 and 60.

Preparation 63

8-Fluoro-1,2,3,4-tetrahydroisoquinoline

The title compound was prepared using a method similar to that described by W.L. Mendelson *et al*; Tetrahedron Lett., 1980, **21**, 1393.

5

Preparation 64**5-Nitro-8-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinoline**

The compound of Preparation 63 was nitrated using potassium nitrate and conc. sulfuric acid using standard conditions to give 5-nitro-8-fluoro-1,2,3,4-tetrahydroisoquinoline. This was treated with 88% formic acid and 37% aqueous formaldehyde at 80°C for 2h according to the procedure of G.M. Carrera and D.S. Garvey, J. Het. Chem., 1992, **29**, 847 to give the title compound.

15

20 **Preparation 65****5-Amino-8-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinoline**

The title compound was prepared by hydrogenation of 5-nitro-8-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinoline (Preparation 64) using a method similar to that of Preparation 55 with ethyl acetate as solvent.

25

m/z (API⁺): 181 (MH⁺; 80%)

Example 130 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-chloro-2-methoxybenzamide Hydrochloride**

4-Amino-5-chloro-2-methoxybenzoic acid (2.08g, 11.1mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.77g 9.24mmol) and 1-hydroxybenzotriazole (1.25g, 9.24mmol) were dissolved in dry DMF (40ml) and stirred at room temperature under argon for 0.5h before 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline (1.5g, 9.24mmol) was added. The mixture was then stirred for 18 h under argon at room temperature. The DMF

35

was removed *in vacuo* and the residue taken up into ethyl acetate and washed with water, saturated aqueous sodium bicarbonate and brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford a yellow solid. This was then passed through a short pad of silica eluting with dichloromethane to afford a white solid which was then taken up into methanol and treated with hydrogen chloride (1M in ether, 1 equivalent). The solvent was removed *in vacuo* and the residue recrystallised from methanol and ethyl acetate to afford the title compound as a white solid (0.775g).

¹H NMR(DMSO-d₆) δ: 2.93 (3H, s), 3.10 (2H, s), 3.30 (2H, s), 3.90 (3H, s), 4.30-4.50 (2H, brs), 6.10 (2H, s), 6.60 (1H, s), 6.97 (1H, d, J=6Hz), 7.28 (1H, t, J=6Hz), 7.80 (1H, s), 8.00 (1H, d, J=6Hz), 9.63 (1H, s), 10.89 (1H, s).

Example 2

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2,4-dimethoxybenzamide

Hydrochloride

To a solution of 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.25g, 1.54mmol) in ethyl acetate (5ml) was added 2,4-dimethoxybenzoyl chloride (0.263g 1.54mmol). The mixture was stirred under argon for 2 h before the precipitate was filtered off and dried to afford the title compound as white solid.

¹H NMR (DMSO-d₆) δ: 2.90 (3H, s), 3.05 (2H, br. s), 3.35 (2H,s),3.85 (3H, s), 4.03 (3H, s), 4.25-4.55 (2H, m), 6.70 (1H, dd, J's=1,6Hz), 6.75 (1H, m), 7.00 (1H, d, J=6Hz), 7.30 (1H, t, J=6Hz), 7.95 (2H, m), 9.75 (1H, s), 11.25 (1H, br. s); m/z (M+H)⁺ 327.

Example 3

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxybenzamide Hydrochloride

The title compound was prepared in an analogous fashion to Example 2 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 2-methoxybenzoyl chloride.

¹H NMR (DMSO-d₆) δ: 2.90 (3H, s), 3.08 (2H, m), 3.38 (1H, m), 3.75 (1H, m), 4.00 (3H, s), 4.30 (1H, m), 4.50 (1H, m), 7.05 (1H, d, J=8Hz), 7.11 (1H, t, J=8Hz), 7.23 (1H, d, J=8Hz), 7.31 (1H, t, J=8Hz), 7.55 (1H, t, J=8Hz), 7.85 (2H, m), 9.85 (1H, s), 10.95 (1H, br, s); m/z (M+H)⁺ 297.

Example 4

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

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 5-chloro-2-methoxybenzoic acid.

- 5 ^1H NMR (DMSO- d_6) δ : 2.36 (3H, s), 2.67 (2H, m), 2.73 (2H, m), 3.51 (2H, s), 3.98 (3H, s), 6.92 (1H, d, $J=6\text{Hz}$), 7.16 (1H, t, $J=7\text{Hz}$), 7.28 (1H, d, $J=8\text{Hz}$), 7.61 (1H, dd, $J's=3,10\text{Hz}$), 7.71 (1H, d, $J=8\text{Hz}$), 7.83 (1H, d, $J=3\text{Hz}$), 9.79 (1H, s); m/z ($M+H$) $^+$ 331.

10 **Example 5**

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

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-chloro-2-methoxybenzoic acid.

- 15 ^1H NMR (DMSO- d_6) δ : 2.40 (3H, s), 2.78 (4H, br. s), 3.60 (2H, br. s), 4.02 (3H, s), 6.93 (1H, d, $J=5\text{Hz}$), 7.18 (1H, dd, $J's=1,5\text{Hz}$), 7.35 (1H, d, $J=1\text{Hz}$), 7.74 (1H, d, $J=5\text{Hz}$), 7.89 (1H, d, $J=5\text{Hz}$), 9.71 (1H, s); m/z ($M+H$) $^+$ 331.

Example 6

- 20 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-acetylamino-5-bromo-2-methoxybenzamide**

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-acetylamino-5-bromo-2-methoxybenzoic acid.

- 25 ^1H NMR (DMSO- d_6) δ : 2.15 (3H, s), 2.35 (3H, s), 2.61-2.81 (4H, m), 3.50 (2H, m), 3.98 (3H, s), 6.90 (1H, d, $J=6\text{Hz}$), 7.15 (1H, t, $J=6\text{Hz}$), 7.72 (1H, s), 7.78 (1H, d, $J=8\text{Hz}$), 8.07 (1H, s), 9.22 (1H, s), 9.53 (1H, s); m/z ($M+H$) $^+$ 432.

30

Example 7**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-bromo-2-methoxybenzamide**

- 35 To a solution of 4-acetylamino-5-bromo-2-methoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide (0.888g, 2mmol) in ethanol (30ml) and water (10ml) was added 10% aqueous sodium hydroxide (1.25ml). The mixture was heated at reflux for

1.25h before pouring into water and extracting with chloroform. The organic layer was dried over sodium sulfate, concentrated *in vacuo* and the residue recrystallised from ethyl acetate to afford the title compound as a brown solid (0.062g).

- 5 ¹H NMR (DMSO-d₆) δ: 2.34 (3H, s), 2.68 (4H, m), 3.45 (2H, s), 3.95 (3H, s), 6.08 (2H, s), 6.57 (1H, s), 6.80 (1H, d, J=6Hz), 7.12 (1H, t, J=6Hz), 7.95 (1H, d, J=6Hz), 7.99 (1H, s), 9.60 (1H, s); m/z (M+H)⁺ 390.

Example 8

- 10 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinol-5-yl)-4-azido-5-iodo-2-methoxybenzamide**

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-azido-5-iodo-2-methoxybenzoic acid.

- 15 ¹H NMR (CDCl₃) δ: 2.48 (3H, s), 2.75-2.85 (4H, m), 3.62 (2H, s), 4.10 (3H, s), 6.74 (1H, s), 6.87 (1H, d, J=7Hz), 7.22 (1H, t, J=7Hz), 8.08 (1H, d, J=7Hz), 8.69 (1H, s), 9.50 (1H, br. s); m/z (M+H)⁺ 464.

Example 9

- 20 **N-(2-Methyl-1,2,3,4-tetrahydroiso quinolin-5-yl)-4-acetylamino-5-chloro-2-propoxy-benzamide**

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-acetylamino-5-chloro-2-propoxybenzoic acid.

- 25 ¹H NMR (DMSO-d₆) δ: 0.96 (3H, t, J=6Hz), 1.84 (2H, m), 2.18 (3H, s), 2.37 (3H, s), 2.65 (2H, m), 2.75 (2H, m), 3.53 (2H, s), 4.14 (2H, t, J=6Hz), 6.92 (1H, d, J=6Hz), 7.15 (1H, t, J=6Hz), 7.65 (1H, d, J=6Hz), 7.85 (1H, s), 7.90 (1H, s), 9.58 (1H, s), 9.64 (1H, s); m/z (M+H)⁺ 416.

30

Example 10

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-chloro-2-propoxy-benzamide

- 35 4-Acetylamino-5-chloro-2-propoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide (0.877g, 2mmol) was added to a mixture of 10% sodium hydroxide (1.25ml) and water (5ml) in ethanol (30ml) and heated at reflux for 1.25h. The mixture was then

cooled, poured into a large volume of water and extracted with chloroform. The organic layer was dried over sodium sulfate, concentrated *in vacuo* and the residue recrystallised from ethyl acetate to afford the title compound as a yellow crystalline solid (387mg).

- 5 ^1H NMR (DMSO- d_6) δ : 0.98 (3H, t, $J=6\text{Hz}$), 1.85 (2H, m), 2.35 (3H, s), 2.64 (2H, m), 2.70 (2H, m), 3.50 (2H, s), 4.15 (2H, t, $J=6\text{Hz}$), 6.10 (2H, s), 6.60 (1H, s), 6.85 (1H, d, $J=6\text{Hz}$), 7.12 (1H, t, $J=6\text{Hz}$), 7.80 (1H, s), 7.96 (1H, s), 9.42 (1H, s); m/z (M+H)+374.

Example 11

10 N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-acetylamino-2-methoxybenzamide

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-acetylamino-2-methoxybenzoic acid.

15

^1H NMR(DMSO- d_6) δ : 2.08 (3H, s), 2.52 (3H, s), 2.87 (4H, br. s), 3.71 (2H, br.s), 3.99 (3H, s), 6.90 (1H, d, $J=8\text{Hz}$), 7.17 (1H, t, $J=7\text{Hz}$), 7.35 (1H, d, $J=8\text{Hz}$), 7.70 (1H, s), 7.91 (2H, m), 9.75 (1H, s), 10.71 (1H, s); m/z (M+H)+ 354.

20 Example 12

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-nitrobenzamide

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 5-chloro-2-methoxy-4-nitrobenzoic acid.

25

^1H NMR (DMSO- d_6) δ : 2.35 (3H, s), 2.63 (2H, m), 2.77 (2H, m), 3.51 (2H, s), 3.99 (3H, s), 6.99 (1H, d, $J=5\text{Hz}$), 7.17 (1H, t, $J=5\text{Hz}$), 7.54 (1H, d, $J=5\text{Hz}$), 7.91 (1H, s), 7.99 (1H, s), 9.77 (1H, s); m/z (M+H)+ 376.

30

Example 13

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-iodo-2-methoxybenzamide

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-amino-5-iodo-2-methoxybenzoic acid.

35

^1H NMR (DMSO- d_6) δ : 2.35 (3H, s), 2.70 (4H, m), 3.50 (2H, s), 3.95 (3H, s), 5.95

(2H, s), 6.55 (1H, s), 6.82 (1H, d, J=6Hz), 7.13 (1H, t, J=6Hz), 7.95 (1H, d, J=6Hz), 8.18 (1H, s), 9.58 (1H, s); m/z (M+H)⁺ 438.

Example 14

5 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-benzyloxy-5-chloro-2-methoxy benzamide**

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-benzyloxy-5-chloro-2-methoxybenzoic acid.

10

¹H NMR (DMSO-d₆) δ: 2.35 (3H, s), 2.68 (2H, m), 2.76 (2H, m), 3.49 (2H, s), 4.08 (3H, s), 5.39 (2H, s), 6.88 (1H, d, J=7Hz), 7.09 (1H, s), 7.16 (1H, t, J=7Hz), 7.37-7.57 (5H, m), 7.85 (1H, d, J=7Hz), 7.95 (1H, s), 9.68 (1H, s); m/z (M+H)⁺ 437.

15

Example 15

20 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4,5-dichloro-2-methoxybenzamide**

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4,5-dichloro-2-methoxybenzoic acid

25 ¹H NMR (DMSO-d₆) δ: 2.34 (3H, s), 2.65 (2H, m), 2.76 (2H, m), 3.50 (2H, s), 4.03 (3H, s), 6.92 (1H, d, J=7Hz), 7.16 (1H, t, J=7Hz), 7.55 (1H, s), 7.67 (1H, d, J=8Hz), 7.98 (1H, s), 9.70 (1H, s); m/z (M+H)⁺ 365.

Example 16

30 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide**

5-Chloro-2,4-dimethoxybenzoic acid (0.245g, 1.1 mmol), 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (0.186g, 0.94mmol) and 1-hydroxybenzotriazole (0.144g, 0.94mmol) were dissolved in dry DMF (10ml) and stirred at room temperature under argon
35 for 25mins before 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.153g, 0.94mmol) was added. The mixture was then stirred for 24h under argon at room temperature. The DMF was removed *in vacuo* and the residue taken up into ethyl acetate and washed with

water. The organic layer was dried over magnesium sulfate, concentrated *in vacuo* and the residue recrystallised from ethyl acetate/ hexane to afford the title compound as a solid (0.069g).

- 5 ¹H NMR (DMSO-d₆) δ: 2.34 (3H, s), 2.67 (2H, m), 2.75 (2H, m), 3.49 (2H, s), 3.99 (3H, s), 4.10 (3H, s), 6.87 (1H, d, J=5Hz), 6.95 (1H, s), 7.15 (1H, t, J=5Hz), 7.89 (1H, d, J=5Hz), 7.94 (1H, s), 9.70 (1H, s); m/z (M+H)⁺ 361.

Example 17

- 10 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-2,4-dimethoxybenzamide**

- 5-Bromo-2,4-dimethoxybenzoic acid (0.296g, 1.1 mmol), 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (0.186g, 0.94mmol) and 1-hydroxybenzotriazole (0.144g, 0.94mmol) were dissolved in dry DMF (10ml) and stirred at room temperature under argon
15 for 25mins before 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.153g, 0.94mmol) was added. The mixture was then stirred overnight under argon at room temperature. The DMF was removed *in vacuo* and the residue taken up into ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate, concentrated *in vacuo* and the residue recrystallised from ethyl acetate/ hexane to afford the title compound as a solid
20 (0.106g)

- ¹H NMR (DMSO-d₆) δ: 2.35 (3H, s), 2.68 (2H, m), 2.75 (2H, d, m), 3.49 (2H, s), 3.99 (3H, s), 4.12 (3H, s), 6.89 (2H, m), 7.15 (1H, t, J=7Hz), 7.85 (1H, d, J=7Hz), 8.09 (1H, s), 9.68 (1H, s); m/z (M+H)⁺ 405.

25

Example 18

N-(2-Methyl-1,2,3,4-tetrahydroisoquinol-5-yl)-5-[3-(trifluoromethyl)-3H-diazirin-3-yl]-2-methoxybenzamide

- 30 The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 5-[3-(trifluoromethyl)-3H-diazirin-3-yl]-2-methoxybenzoic acid.

- ¹H NMR, (CDCl₃) δ: 2.40 (3H, s), 2.65-2.78 (4H, m), 3.54 (2H, s), 4.00 (3H, s), 6.80 (1H, d, J=7Hz), 7.02 (1H, d, J=7Hz), 7.14 (1H, t, J=7Hz), 7.36 (1H, dd, J's=2,7Hz), 7.98-8.12 (2H, m), 9.50 (1H, s); m/z (M+H)⁺ 405.

35

Example 19**N-(1,2,3,4-Tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide**

To a solution of 5-chloro-2,4-dimethoxy-N-[2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]benzamide (1g) in dichloromethane (30ml) at 0°C was added trifluoroacetic acid (3ml). The mixture was then stirred at room temperature for 3h before pouring into saturated aqueous sodium bicarbonate (100ml) and extracting with dichloromethane. The organic phase was dried over sodium sulfate and concentrated *in vacuo* to afford the title compound as an off white solid (700mg).

¹H NMR (DMSO-d₆) δ: 2.62 (2H, m), 3.06 (2H, m), 3.85 (2H, s), 4.00 (3H, s), 4.10 (3H, s), 6.86 (1H, d, J=7Hz), 6.96 (1H, s), 7.13 (1H, t, J=7Hz), 7.86 (1H, d, J=7Hz), 7.94 (1H, s), 9.70 (1H, s); m/z (M+H)⁺347.

Example 20**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-methylbenzamide**

5-Chloro-2-methoxy-4-methylbenzoic acid (0.202g, 1 mmol), 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (0.200g, 1mmol) and 1-hydroxy-benzotriazole (0.155g, 1mmol) were dissolved in dry DMF (10ml) and stirred at room temperature under argon for 25mins before 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.163g, 1mmol) was added. The mixture was then stirred for 24 h under argon at room temperature. The DMF was removed *in vacuo* and the residue suspended in ethyl acetate and washed with water. The insoluble white precipitate was filtered off, washed with water then dried to afford the title compound (149mg).

¹H NMR (methanol-d₄) δ: 2.48 (3H, s), 3.07 (3H, s), 3.16 (2H, m), 3.63 (2H, m), 4.09 (3H, s), 4.46 (2H, s), 7.13 (1H, d, J=9Hz), 7.22 (1H, s), 7.38 (1H, t, J=9Hz), 7.78 (1H, d, J=9Hz), 7.98 (1H, s); m/z (M+H)⁺ 345.

Example 21

N-(2-*n*-Propyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide Hydrochloride

The title compound was prepared in an analogous manner to Example 2 from 5-amino-2-*n*-propyl-1,2,3,4-tetrahydroisoquinoline and 5-chloro-2,4-dimethoxybenzoyl chloride.

¹H NMR (DMSO-d₆) δ: 0.95 (3H, t, J=7Hz), 1.82 (2H, m), 3.10 (3H, m), 3.35 (1H, m), 3.50 (1H, m), 3.77 (1H, m), 4.00 (3H, s), 4.11 (3H, s), 4.34 (1H, m), 4.54 (1H, m), 6.95 (1H, s), 7.05 (1H, d, J=6Hz), 7.32 (1H, t, J=6Hz), 7.89 (2H, m), 9.75 (1H, s), 10.93 (1H, br. s); m/z (M+H)⁺ 389.

Example 22

N-(2-Ethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide Hydrochloride

The title compound was prepared in an analogous manner to Example 2 from 5-amino-2-ethyl-1,2,3,4-tetrahydroisoquinoline and 5-chloro-2,4-dimethoxybenzoyl chloride.

¹H NMR (DMSO-d₆) δ: 1.36 (3H, t, J=7Hz), 3.09 (2H, m), 3.12-3.85 (4H, m), 4.00 (3H, s), 4.10 (3H, s), 4.30 (1H, m), 4.55 (1H, m), 6.94 (1H, s), 7.06 (1H, d, J=6Hz), 7.32 (1H, t, J=6Hz), 7.89 (2H, m), 9.76 (1H, s), 10.85 (1H, br.s); m/z (M+H)⁺ 375.

Example 23

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-ethoxy-2-methoxybenzamide

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 5-chloro-4-ethoxy-2-methoxybenzoic acid.

¹H NMR (DMSO-d₆) δ: 1.42 (3H, t, J=6Hz), 2.34 (3H, s), 2.70 (4H, m), 3.50 (2H, s), 4.08 (3H, s), 4.28 (2H, m), 6.87 (1H, d, J=6Hz), 6.93 (1H, s), 7.15 (1H, t J=6Hz), 7.86 (1H, d, J=6Hz), 7.94 (1H, s), 9.70 (1H, s); m/z (M+H)⁺ 375.

Example 24

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2,5-dimethoxybenzamide

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 2,5-dimethoxybenzoic acid.

¹H NMR (DMSO-d₆) δ: 2.94 (2H, m), 3.04 (3H, s), 3.34 (2H, m), 3.58 (2H, m), 3.77 (3H, s), 3.95 (3H, s), 7.16 (2H, m), 7.35 (1H, m), 7.40 (1H, d, J=4Hz), 7.75 (1H, d, J=9Hz), 7.92 (1H, d, J=9Hz), 10.00 (1H, s); m/z (M+H)⁺ 327.

Example 25

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-2-methoxy-4-methylbenzamide

5-Bromo-2-methoxy-4-methylbenzoic acid (0.245g, 1 mmol), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (0.200g, 1mmol) and 1-hydroxy-benzotriazole (0.155g, 1mmol) were dissolved in dry DMF (10ml) and stirred at room temperature under argon for 25mins before 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline (0.163g, 1mmol) was added. The mixture was then stirred for 24 h under argon at room temperature. The DMF was removed *in vacuo* and the residue suspended in ethyl acetate and washed with water. The insoluble white precipitate was filtered off, washed with water then dried to afford the title compound (210mg).

¹H NMR (methanol-d₄) δ: 2.49 (3H, s), 3.05 (2H, m), 3.07 (3H, s), 3.15 (2H, m), 3.62 (2H, m), 4.08 (3H, s), 4.47 (2H, s), 7.13 (1H, d, J=8Hz), 7.22 (1H, s), 7.38 (1H, t, J=7Hz), 7.77 (1H, d, J=8Hz), 8.14 (1H, s); m/z (M+H)⁺ 389

Example 26

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-dimethylsulfamoyl-2-methoxybenzamide

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 5-dimethylsulfamoyl-2-methoxybenzoic acid.

¹H NMR (DMSO-d₆) δ: 2.36 (3H, s), 2.60 (6H, s), 2.65 (2H, m), 2.79 (2H, m), 3.51 (2H, s), 4.08 (3H, s), 6.92 (1H, d, J=7Hz), 7.17 (1H, t, J=7Hz), 7.48 (1H, d, J=7Hz), 7.79 (1H, d, J=7Hz), 7.90 (1H, dd, J's=1,7Hz), 8.15 (1H, d, J=1Hz), 9.74 (1H, s); m/z (M+H)⁺ 404.

Example 27

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-benzoyl-2-methoxybenzamide

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-benzoyl-2-methoxybenzoic acid.

5

¹H NMR (CDCl₃) δ: 2.6 (3H, s), 2.70-2.87 (4H, m), 3.54 (2H, s), 4.06 (3H, s), 6.70 (1H, d, J=7Hz), 7.23 (1H, d, J=7Hz), 7.62-7.30 (5H, m), 7.68-7.83 (2H, m), 8.10 (1H, d, J=7Hz), 8.32 (1H, d, J=7Hz), 9.7 (1H, br s); m/z (M+H)⁺ 401

10 **Example 28****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-benzoyl-2-methoxybenzamide**

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 5-benzoyl-2-methoxybenzoic acid.

15

¹H NMR (CDCl₃) δ: 2.50 (3H, s), 2.72-2.92 (4H, m), 3.63 (2H, s), 4.16 (3H, s), 6.87 (1H, d, J=7Hz), 7.15-7.26 (2H, m), 7.45-7.65 (3H, m), 7.76-7.85 (2H, m), 8.08-8.19 (2H, m), 8.75 (1H, d, J=2Hz), 9.60 (1H, br s); m/z (M+H)⁺ 401.

20

Example 29**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-4-acetylamino-5-chloro-2-methoxybenzamide**

25 To a cooled solution of 4-acetylamino-5-chloro-2-methoxybenzoyl chloride, (prepared from 4-acetylamino-5-chloro-2-methoxybenzoic acid, 3.19g) in dichloromethane was added 8-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline (2.1g) and triethylamine (4ml). After stirring at room temperature for 2.5h, the mixture was basified with 10% sodium hydroxide. The organic layer was separated, dried and concentrated *in vacuo*. The residue
30 was purified by chromatography on alumina eluting with chloroform, and then crystallised from ethyl acetate to give the title compound.

Example 3035 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-4-amino-5-chloro-2-methoxybenzamide**

To a solution of 4-acetylamino-5-chloro-2-methoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)benzamide (0.95g) in ethanol (20ml) and water (10ml) was added sodium hydroxide (0.1g) and the mixture was heated on a steam bath for 45min. The reaction was concentrated *in vacuo* and the residue partitioned between methylene chloride and water. The organic phase was dried and concentrated *in vacuo*. Purification by chromatography on alumina eluting with chloroform followed by crystallisation from ethyl acetate afforded the title compound (0.51g) m.p. = 192 -193°C.

¹H NMR δ: 2.50 (3H, s), 2.50 - 2.99 (4H, m), 3.51 (2H, s), 3.95 (3H, s), 4.48 (2H, br s), 6.31 (1H, s), 6.86 - 7.27 (2H, m), 7.90 - 8.00 (1H, m), 8.17 (1H, s), 9.30 (1H, br s).

Example 31

N-(2,3-Dihydro-2-methyl-1H-isoindol-4-yl)-5-chloro-2,4-dimethoxybenzamide hydrochloride

A solution of freshly prepared 4-amino-2,3-dihydro-2-methyl-1H-isoindole (400mg, 3.0mmol) in dry ethyl acetate (40ml) under argon was treated dropwise with a solution of 5-chloro-2,4-dimethoxybenzoyl chloride (700mg, 3.0mmol) in a mixture of ethyl acetate (10ml) and dichloromethane (10ml). The reaction was stirred at room temperature for 6h and then concentrated *in vacuo*. The residue was triturated with diethyl ether/ethyl acetate and then crystallised twice from methanol/ diethyl ether to give the title compound as a pale grey solid (0.11g).

¹H NMR (DMSO-d₆) δ: 3.01 (3H, s), 4.02 (3H, s), 4.06 (3H, s), 4.4-4.8 (4H, br m), 6.93 (1H, s), 7.26 (1H, d, J=8Hz), 7.42 (1H, t, J= 8Hz), 7.56 (1H, d, J=8Hz), 7.82 (1H, s), 9.98 (1H, s), 11.88 (1H, br s); m/z (M+H)⁺ 347.

Example 32

N-(3-Methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-6-yl)-4-tert-butyl-2-methoxybenzamide, hydrochloride

The title compound was prepared from 6-amino-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine and 4-tert-butyl-2-methoxybenzoic acid.

¹H NMR (DMSO-d₆) δ: 1.32 (9H, s), 2.79 (3H, s), 3.08 (5H, m), 3.33 (1H, m), 3.60 (2H, m), 3.96 (3H, s), 7.28 (5H, m), 7.65 (1H, d, J = 10 Hz), 9.84 (1H, s), 10.82 (1H, br s). m/z (CI): 367 (MH⁺)

Example 33**N-(1,2,3,4-Tetrahydroisoquinolin-6-yl)-4-*t*-butyl-2-methoxybenzamide, trifluoroacetate**

- 5 The title compound was prepared from amine Preparation 33 (190mg; 0.77 mmol) and 4-*t*-butyl-2-methoxybenzoic acid (174mg; 0.84 mmol) according to the procedure of Example 1. The product (350mg) in dichloromethane (20ml) containing trifluoroacetic acid (1ml) was kept at 25°C for 18hr and evaporation *in vacuo* followed by crystallisation of the residue from ethyl acetate:ether gave the title compound as off-white crystals (295mg),
10 m.p. 207-211°C.

¹H NMR (DMSO-d₆) δ: 1.33 (9H, s), 3.00 (2H, t), 3.39 (2H, t), 3.94 (3H, s), 4.25 (2H, s), 7.10 (2H, m), 7.18 (1H, d), 7.55 (1H, dd), 7.60 (1H, d), 7.69 (1H, s), 9.03 (2H, br), 10.05 (1H, s); Found: M⁺ 338.1998 calc for C₂₁H₂₆N₂O₂ 338.2010

15

Example 34**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-4-*t*-butyl-2-methoxybenzamide, trifluoroacetate**

- 20 The compound of Example 33 (168mg; 0.37 mmol) and paraformaldehyde (224mg; 7.4 mmol) in dry tetrahydrofuran (5ml) was stirred at 25°C under argon and treated with sodium borohydride (152mg; 4 mmol) and trifluoroacetic acid (2ml) according to the procedure of G.W. Gribble, Synthesis 1987, 709. Work-up gave a yellow gum (62mg).

- 25 ¹H NMR (CDCl₃) δ: 1.36 (9H, s), 2.50 (3H, s), 2.75 (2H, t), 2.97 (2H, t), 3.63 (2H, s), 4.06 (3H, s), 7.00 (2H, d), 7.16 (1H, dd), 7.35 (1H, dd), 7.56 (1H, br s), 8.20 (1H, d), 9.76 (1H, s).

- Treatment with trifluoroacetic acid followed by crystallisation from ethyl acetate:ether
30 gave the title compound as white crystals (64mg), m.p. 205-8°C.; Found: M⁺ 352.21549
Calc for C₂₂H₂₈N₂O₂ 352.21666.

Example 35

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

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-*tert*-butyl-2-methoxybenzoic acid.

¹H NMR (DMSO-d₆) δ: 1.32 (9H, s), 2.91 (3H, s), 3.06 (2H, m), 3.35 (1H, m), 3.70 (1H, m), 4.02 (3H, s), 4.45 (2H, m), 7.04 (1H, d, J = 10 Hz), 7.15 (2H, m), 7.31 (1H, m), 7.82 (1H, d, J = 12 Hz), 7.90 (1H, d, J = 12 Hz), 9.83 (1H, s), 10.82 (1H, s). m/z CI: 353 (MH⁺).

Example 36

10 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*n*-butyl-2-methoxy-5-chloro-benzamide, hydrochloride**

The title compound was prepared in a similar manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-*n*-butyl-2-methoxy-5-chlorobenzoic acid.

15

¹H NMR (DMSO-d₆) δ: 0.93 (3H, m), 1.38 (2H, m), 1.58 (2H, m), 2.63 (2H, m), 2.90 (3H, s), 3.07 (2H, m), 3.35 (1H, m), 3.70 (1H, m), 4.00 (3H, s), 4.34 (1H, m), 4.48 (1H, m), 7.06 (1H, d, J = 12 Hz), 7.23 (1H, s), 7.33 (1H, m), 7.80 (2H, m), 9.83 (1H, s), 11.90 (1H, br s). m/z (CI): 387 (MH⁺)

20

Example 37**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethyl-2-methoxy-5-chloro benzamide, hydrochloride**

- 5 The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-ethyl-2-methoxy-5-chlorobenzoic acid.

¹H NMR (DMSO d⁶)δ: 1.24 (3H, m), 2.77 (2H, m), 2.91 (3H, s), 3.15 (2H, m), 3.35 (1H, m), 3.65 (1H, m), 4.02 (3H, s), 4.40 (2H, m), 7.07 (1H, d, J = 9 Hz), 7.26 (1H, s), 7.34 (1H, m), 7.77 (2H, m), 9.85 (1H, s), 10.72 (1H, br s) m/z (CI): 359 (MH⁺).

Example 38**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxy-5-chloro-benzamide, hydrochloride**

15

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-*tert*-butyl-2-methoxy-5-chlorobenzoic acid.

¹H NMR (DMSO-d⁶) δ: 1.49 (9H, s), 2.91 (3H, s), 3.05 (2H, m), 3.18 (2H, s), 3.35 (1H, m), 4.03 (3H, s), 4.42 (1H, m), 7.08 (1H, d, J = 8 Hz), 7.20 (1H, s), 7.33 (1H, m), 7.79 (2H, m), 9.82 (1H, s), 10.66 (1H, br s). m/z (CI): 387 (MH⁺, 90%)

Example 39**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-4-phenylbenzamide, hydrochloride**

25

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 2-methoxy-4-phenylbenzoic acid.

30 ¹H NMR (DMSO-d⁶)δ: 2.94 (3H, d), 3.11 (2H, m), 3.40 (1H, m), 3.78 (1H, m), 4.14 (3H, s), 4.35 (1H, m), 4.55 (1H, m), 7.08 (1H, d, J = 9 Hz), 7.35 (1H, m), 7.50 (5H, m), 7.81 (2H, m), 7.89 (1H, d), 7.99 (1H, m), 9.92 (1H, s), 10.80 (1H, br s). m/z (CI): 373 (MH⁺, 100%).

Example 40**N-(1,2,3,4-Tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxybenzamide hydrochloride**

5 The title compound was prepared in an analogous manner to Example 19.

^1H NMR (DMSO- d_6) δ : 1.31 (9H, s), 2.97 (2H, m), 3.37 (2H, m), 3.44 (2H, m), 4.06 (3H, s), 4.31 (2H, m), 7.08 (1H, d, $J = 9$ Hz), 7.16 (2H, m), 7.28 (1H, m), 7.84 (2H, m), 9.55 (2H, br s), 9.83 (1H, s). m/z (CI): 339 (MH^+ ; 80%).

10

Example 41**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*iso*-propyl-2-methoxybenzamide, hydrochloride**

15 The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-*iso*-propyl-2-methoxybenzoic acid.

^1H NMR (DMSO- d_6) δ : 1.26 (6H, d), 2.92 (3H, s), 2.99 (1H, m), 3.09 (1H, m), 3.39 (1H, m), 3.73 (1H, m), 4.02 (3H, s), 4.33 (1H, m), 4.50 (1H, m), 7.03 (2H, m), 7.10 (1H, s),
20 7.31 (1H, m), 7.83 (2H, m), 9.83 (1H, s), 10.97 (1H, br s). m/z (CI): 339 (MH^+).

Example 42**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-*iso*-propyl-2-methoxybenzamide, hydrochloride**

25

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 5-chloro-4-*iso*-propyl-2-methoxybenzoic acid.

^1H NMR (DMSO- d_6) δ : 1.28 (6H, d), 2.91 (3H, m), 3.07 (2H, m), 3.33 (1H, m), 3.70 (1H, m), 4.03 (3H, s), 4.30 (1H, m), 4.52 (1H, m), 7.06 (1H, d, $J = 9$ Hz), 7.16 (1H, s), 7.32 (1H, m), 7.76 (2H, m), 9.86 (1H, s), 10.68 (1H, br s). m/z (CI): 373 (MH^+ ; 90%).

30

Example 43**N-(1,2,3,4-Tetrahydroisoquinolin-5-yl)-5-chloro-4-*tert*-butyl-2-methoxybenzamide, Hydrochloride**

35

The title compound was prepared in an analogous manner to Examples 19, 20.

¹H NMR (DMSO-d⁶) δ: 1.50 (9H, s), 2.95 (2H, m), 3.42 (2H, m), 4.05 (3H, s), 4.30 (2H, m), 7.10 (1H, d), 7.20 (1H, s), 7.30 (1H, m), 7.76 (2H, m), 9.50 (2H, br s), 9.81 (1H, s). m/z (CI): 373 (MH⁺; 100%)

5

Example 44

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethyl-2-methoxybenzamide, hydrochloride

- 10 The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 4-ethyl-2-methoxybenzoic acid.

¹H NMR (DMSO-d⁶) δ: 1.23 (3H, t), 2.68 (2H, q), 2.91 (3H, s), 3.06 (2H, m), 3.35 (1H, m), 3.71 (1H, m), 4.00 (3H, s), 4.40 (2H, m), 7.0 (2H, m), 7.10 (1H, s), 7.30 (1H, m), 15 7.87 (2H, m), 9.80 (1H, s), 10.83 (1H, s). m/z (CI): 325 (MH⁺; 100%).

Example 45

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-4-*iso*-propoxy-2-methoxybenzamide, hydrochloride

20

¹H NMR (DMSO-d⁶) δ: 1.36 (6H, d), 2.92 (3H, m), 3.05 (2H, m), 3.49 (1H, m), 3.77 (1H, m), 4.06 (3H, s), 4.33 (1H, m), 4.55 (1H, m), 4.93 (1H, m), 6.91 (1H, s), 7.05 (1H, d, J = 9 Hz), 7.31 (1H, m), 7.84 (1H, d, J = 10 Hz), 8.02 (1H, s), 9.76 (1H, s), 10.57 (1H, br s). m/z (CI): 435 (MH⁺)

25

Example 46

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*iso*-propyl-5-trifluoromethyl-2-methoxybenzamide, hydrochloride

- 30 ¹H NMR (DMSO-d⁶) δ: 1.30 (6H, d), 2.90 (3H, s), 3.05 (2H, m), 3.30 (1H, m), 3.50 (2H, m), 4.07 (3H, s), 4.39 (2H, m), 7.06 (1H, d, J = 9 Hz), 7.31 (2H, m), 7.74 (1H, d, J = 10 Hz), 8.02 (1H, s), 9.86 (1H, s), 11.00 (1H, br s). m/z (CI): 407 (MH⁺; 90%).

Example 47

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*iso*-propoxy-2-methoxy-5-trifluoromethyl-benzamide, hydrochloride

- 5 ^1H NMR (DMSO- d_6) δ : 1.33 (6H, d), 2.91 (3H, s), 3.06 (2H, m), 3.35 (1H, m), 3.69 (1H, m), 4.11 (3H, s), 4.40 (2H, m), 5.06 (1H, m), 7.04 (2H, m), 7.31 (1H, m), 7.82 (1H, d, $J = 10$ Hz), 8.10 (1H, s), 9.75 (1H, s), 11.00 (1H, br s). m/z (CI): 423 (MH^+ ; 100%).

Example 48

- 10 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-4-*iso*-propyl-2-methoxy benzamide, hydrochloride**

- ^1H NMR (DMSO- d_6) δ : 1.22 (6H, d), 2.90 (3H, s), 3.06 (2H, m), 3.33 (3H, m), 4.03 (3H, s), 4.43 (2H, m), 7.05 (1H, d, $J = 8$ Hz), 7.17 (1H, s), 7.31 (1H, m), 7.70 (1H, d, $J = 10$ Hz), 7.94 (1H, s), 9.82 (1H, s), 10.94 (1H, br s). m/z (CI): 419 (MH^+)
- 15

Example 49

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl) 5-*iso*-butyroyl-2-methoxy-benzamide hydrochloride

20

The title compound was prepared in a similar manner to that of Example 50.

- ^1H NMR (DMSO- d_6) δ : 1.06 (6H, d), 2.84 (3H, s), 3.04 (2H, m), 3.31 (1H, m), 3.62 (2H, m), 3.97 (3H, s), 4.37 (2H, m), 7.02 (1H, d, $J = 10$ Hz), 7.30 (2H, m), 7.66 (1H, d, $J = 10$ Hz), 8.12 (1H, dd, $J = 12, 3$ Hz), 8.30 (1H, d, $J = 3.3$ Hz), 9.80 (1H, s), 10.91 (1H, br s). m/z (CI): 367 (MH^+)
- 25

Example 50

- N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-pivaloyl-2-methoxybenzamide, hydrochloride**
- 30

The title compound was prepared in an analogous manner to Example 1 from 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline and 5-pivaloyl-2-methoxy benzoic acid.

- ^1H NMR (DMSO- d_6) δ : 1.40 (9H, s), 2.95 (3H, s), 3.13 (2H, m), 3.35 (2H, m), 4.10 (3H, s), 4.47 (2H, m), 7.14 (1H, d, $J = 10$ Hz), 7.39 (2H, m), 7.80 (1H, d, $J = 10$ Hz), 8.14 (1H, d, $J = 12$ Hz), 8.54 (1H, s), 9.93 (1H, s), 10.65 (1H, br s). m/z (CI): 381 (MH^+)
- 35

Example 51

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

5

m.p. 164-9°C

Free base: ^1H NMR (CDCl_3) δ : 1.44 (6H, d), 2.46 (3H, s), 2.70 (2H, t), 2.91 (2H, t), 3.60 (2H, s), 4.04 (3H, s), 4.66 (1H, m), 6.56 (1H, s), 7.08 (1H, d), 7.28 (1H, dd), 7.46 (1H, d), 8.27 (1H, s), 9.53 (1H, s). m/z (CI): 389 (MH^+ ; 50%).

10

Example 52

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-bromo-2,4-dimethoxybenzamide, hydrochloride salt

15

^1H NMR (250MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ : 2.89 - 3.19 (4H, m and overlapping s at 2.98 and HOD signal), 3.27 (1H, m), 3.46 (1H, m, overlapping with CHD_2OD signal), 3.70 (1H, m), 4.00 (3H, s), 4.11 (4H, overlapping s and d), 4.58 (1H, br d), 6.54 (1H, s), 7.18 (1H, d), 7.38 (1H, d), 7.61 (1H, br s), 8.36 (1H, s), 9.69 (partially exchanged 1H, br s).

20

Example 53

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-*tert*-butyl-2-methoxybenzamide

^1H NMR (250MHz, CDCl_3) δ : 1.35 (9H, s), 2.46 (3H, s), 2.68 (2H, t), 2.89 (2H, s), 3.59 (2H, s), 4.06 (3H, s), 7.01 (1H, d), 7.07 (1H, d), 7.15 (1H, dd), 7.31 (1H, dd), 7.50 (1H, d), 8.19 (1H, d), 9.74 (1H, br s)

25

Example 54

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxy-4-methyl-5-trifluoromethylbenzamide

30

^1H NMR (250MHz, CDCl_3) δ : 2.47 (3H, s), 2.54 (3H, s), 2.70 (2H, t), 2.91 (2H, t), 3.60 (2H, s), 4.10 (3H, s), 6.91 (1H, s), 7.09 (1H, d), 7.30 (1H, dd), 7.48 (1H, d), 8.54 (1H, s), 9.55 (1H, br s).

35

Example 55

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxybenzamide, hydrochloride salt

- 5 ^1H NMR (250MHz, CD_3OD) δ : 3.00 - 3.53 (6H, m and overlapping s at 3.07 and CHD_2OD signal), 3.69 - 3.86 (1H, br m), 4.02 (3H, s), 4.36 (1H, d), 4.57 (1H, d), 7.10 (1H, t), 7.20 (1H, d), 7.28 (1H, d), 7.48 - 7.60 (2H, overlapping signals), 7.73 (1H, s), 7.88 (1H, dd).

10 **Example 56**

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2,4-dimethoxybenzamide, hydrochloride salt

- 15 ^1H NMR (200MHz, CD_3OD) δ : 2.90 - 3.60 (6H, m overlapping with s at 3.09 and CHD_2OD signal), 3.60 - 3.95 (4H, m overlapping with s at 3.91), 4.08 (3H, s), 4.38 (1H, d), 4.60 (1H, d), 6.67 - 6.78 (2H, m, overlapping signals), 7.30 (1H, d), 7.53 (1H, dd), 7.73 (1H, s), 7.99 (1H, d).

Example 57

- 20 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-chloro-2-methoxybenzamide**

^1H NMR (250MHz, CDCl_3) δ : 2.46 (3H, s), 2.69 (2H, t), 2.89 (2H, t), 3.60 (2H, s), 4.04 (3H, s), 6.97 (1H, d), 7.09 (1H, d), 7.30 (1H, dd), 7.39 - 7.49 (2H, m, overlapping signals), 8.24 (1H, d), 9.65 (1H, br s).

25

Example 58

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

- 30 ^1H NMR ($\text{DMSO}-d^6$) δ : 1.31 (6H, d, $J = 7$ Hz), 3.42 (3H, s), 3.04 (2H, m), 3.29 - 3.78 (2H, br m), 4.02 (3H, s), 4.24 - 4.56 (2H, m), 4.78 (1H, m), 6.35 (1H, m), 6.70 (2H, m), 7.02 (1H, m), 7.32 (1H, t, $J = 6$ Hz), 7.95 (2H, m), 9.73 (1H, s), 10.83 (1H, br s).
 m/z (CI): 355 (MH^+)

Example 59

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-dimethylsulfamoyl-2,4-dimethoxybenzamide, hydrochloride

- 5 ^1H NMR (DMSO- d^6) δ : 2.72 (6H, s), 2.91 (2H, m), 3.05 (2H, m), 3.38 (1H, m), 3.72 (1H, m), 4.05 (3H, s), 4.15 (3H, s), 4.35 (1H, m), 4.56 (1H, m), 7.95 (1H, s), 7.06 (1H, d, $J = 6$ Hz), 7.33 (1H, t, $J = 6$ Hz), 7.80 (1H, d, $J = 6$ Hz), 8.28 (1H, s), 9.72 (1H, s), 10.82 (1H, s).

10 **Example 60**

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-*iso*-propylsulfonylbenzamide, hydrochloride

- ^1H NMR (DMSO d^6) δ : 1.18 (6H, d, $J = 6$ Hz), 2.90 (3H, s), 3.11 (2H, m), 3.25 - 3.42 (2H, m), 3.70 (1H, m), 4.06 (3H, s), 4.34 (1H, m), 4.51 (1H, m), 7.08 (1H, d, $J = 6$ Hz),
15 7.34 (1H, d, $J = 6$ Hz), 7.47 (1H, d, $J = 6$ Hz), 8.00 (1H, d, $J = 6$ Hz), 8.15 (1H, s), 9.95 (1H, s), 11.22 (1H, br s). m/z (CI): 403 (MH^+)

Example 61

- 20 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-phenylbenzamide, hydrochloride**

- ^1H NMR (DMSO- d^6) δ : 2.93 (3H, d), 3.10 (2H, br m), 3.35 (1H, br m), 3.70 (1H, br, overlapped), 4.04 (3H, s), 4.33 (1H, dd), 4.55 (1H, d), 7.10 (1H, d), 7.25 (1H, s), 7.36 (1H, t),
25 7.55 (5H, br s), 7.78 (1H, d), 7.93 (1H, s). m/z (CI): 407 (MH^+ , 100%).

Example 62

N-(1,2,3,4-Tetrahydroisoquinolin-5-yl)-5-bromo-2,4-dimethoxybenzamide, trifluoroacetate

- 30 ^1H NMR (400 MHz, $\text{CDCl}_3 + \text{MeOH}-d^4$) δ : 2.99 (2H, t, overlapping HOD), 3.48 (2H, t), 4.00 (3H, s), 4.11 (3H, s), 4.34 (2H, s), 6.58 (1H, s), 7.02 (1H, d), 7.27 - 7.36 (1H, m, overlapping CHCl_3), 7.75 (1H, d), 8.38 (1H, s).

Example 63

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-n-propylsulfonylbenzamide, hydrochloride

- 5 ^1H NMR (DMSO- d_6) δ : 0.92 (3H, t, J = 8 Hz), 1.56 (2H, m), 2.90 (3H, s), 3.09 (2H, m), 3.36 (3H, m), 3.73 (1H, m), 4.02 (3H, s), 4.33 (1H, m), 4.52 (1H, m), 7.09 (1H, d, J = 7 Hz), 7.32 (1H, t, J = 7 Hz), 7.47 (1H, d, J = 8 Hz), 7.67 (1H, d, J = 8 Hz), 8.03 (1H, dd, J = 7, 1 Hz), 8.20 (1H, d, J = 1 Hz), 9.92 (1H, s), 11.0 (1H, br s). m/z (CI): 403 (MH^+).

10 **Example 64**

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2,4-dimethoxy-5-trifluoromethylbenzamide, hydrochloride

- 15 ^1H NMR (DMSO- d_6) δ : 2.41 (3H, s), 3.04 (2H, m), 3.30 - 3.78 (2H, m), 4.03 (3H, s), 4.13 (3H, s), 4.40 (2H, m), 7.05 (2H, m), 7.32 (1H, t, J = 6 Hz), 7.85 (1H, d, J = 6 Hz), 8.12 (1H, s), 9.72 (1H, s), 11.32 (1H, br s). m/z (CI): 395 (MH^+)

20 **Example 65**

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-4-methyl-5-trifluoromethylbenzamide, hydrochloride

- 25 ^1H NMR (DMSO- d_6) δ : 2.94 (3H, s), 3.08 (2H, m), 3.42 (1H, m), 3.70 (1H, m), 4.06 (3H, s), 4.40 (2H, m), 7.09 (1H, d, J = 6 Hz), 7.34 (2H, m), 7.75 (1H, d, J = 6 Hz), 8.08 (1H, s), 9.82 (1H, s), 10.83 (1H, s). m/z (CI): 379 (MH^+)

Example 66

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-acetyl-2,4-dimethoxybenzamide, hydrochloride

- 30 ^1H NMR (DMSO- d_6) δ : 2.48 (3H, s), 2.58 (3H, s), 2.92 (2H, m), 3.02 (2H, m), 3.38 (2H, m), 4.06 (3H, s), 4.12 (3H, s), 7.06 (1H, d, J = 8 Hz), 7.33 (1H, t, J = 8 Hz), 7.78 (1H, d, J = 8 Hz), 8.28 (1H, s), 9.70 (1H, s). m/z (CI): 369 (MH^+ ; 100%).

Example 67

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-4-ethyl-2-methoxybenzamide, hydrochloride

- 5 ^1H NMR (DMSO- d_6) δ : 1.21 (3H, t, $J = 8$ Hz), 2.50 (3H, s), 2.78 (2H, q, $J = 8$ Hz), 2.92 (4H, m), 3.05 (2H, m), 4.00 (3H, s), 7.06 (1H, d, $J = 7$ Hz), 7.25 (1H, s), 7.32 (1H, t, $J = 7$ Hz), 7.74 (1H, d, $J = 7$ Hz), 7.93 (1H, s), 9.82 (1H, s), 10.40 (1H, br s).
 m/z (CI): 405, 403 (MH^+ , 100%).

10 **Example 68**

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethyl-2-methoxy-5-trifluoromethylbenzamide, hydrochloride

- ^1H NMR (DMSO- d_6) δ : 1.40 (3H, t, $J = 8$ Hz), 2.94 (2H, m), 2.99 (3H, s), 3.17 (2H, m), 3.45 (3H, s), 3.75 (1H, m), 4.11 (1H, m), 4.24 (3H, s), 4.50 (2H, m), 7.17 (1H, d, $J = 7$ Hz), 7.42 (2H, m), 7.86 (1H, d, $J = 7$ Hz), 8.16 (1H, s), 9.94 (1H, s), 11.26 (1H, br s)
15 m/z (CI): 393 (MH^+)

Example 69

- 20 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*n*-butoxy-5-chloro-2-methoxybenzamide, hydrochloride**

- ^1H NMR (DMSO- d_6) δ : 0.98 (3H, t, $J = 6$ Hz), 1.48 (2H, m), 1.29 (2H, m), 2.89 (3H, s), 3.06 (2H, m), 3.70 (1H, m), 4.10 (3H, s), 4.24 (2H, t, $J = 6$ Hz), 4.48 (1H, m), 6.95 (1H, s), 7.04 (1H, d, $J = 6$ Hz), 7.32 (1H, t, $J = 6$ Hz), 7.79 (2H, m), 9.75 (1H, s), 11.20 (1H, br s).
25 m/z (CI): 403 (MH^+)

Example 70

- 30 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-4-*iso*-propyloxy-5-acetylbenzamide, hydrochloride**

- ^1H NMR (free base; CDCl_3) δ : 1.39 (6H, d, $J = 7$ Hz), 2.48 (3H, s), 2.59 (3H, s), 2.79 (4H, m), 3.61 (2H, s), 4.09 (3H, s), 4.76 (1H, s), 6.51 (1H, s), 6.84 (1H, d, $J = 8$ Hz), 7.20 (1H, t, $J = 8$ Hz), 8.13 (1H, d, $J = 8$ Hz), 8.73 (1H, s), 9.36 (1H, br s).
35 m/z (CI): 397 (MH^+ ; 100%).

Example 71

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-*iso*-propoxybenzamide, hydrochloride

- 5 ^1H NMR (DMSO d^6) δ : 1.37 (6H, d, $J = 6$ Hz), 2.92 (3H, s), 3.05 (2H, m), 3.37 (1H, m), 3.73 (1H, m), 4.08 (3H, s), 4.32 (1H, m), 4.51 (1H, m), 4.96 (1H, m), 6.95 (1H, s), 7.06 (1H, d, $J = 6$ Hz), 7.32 (1H, t, $J = 6$ Hz), 7.89 (2H, m), 9.27 (1H, s), 11.20 (1H, br s).
 m/z (CI): 389 (MH^+ , 80%)

10 **Example 72**

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-iodo-4-trifluoromethyldiaziriny benzamide

- ^1H NMR (200 MHz, CDCl_3) δ : 2.48 (3H, s), 2.81 (4H, br s), 3.64 (2H, br s), 4.13
15 (3H, s), 6.88 (1H, d), 7.20 (1H, t), 7.23 (1H, s), 8.05 (1H, d), 8.77 (1H, s), 9.50 (1H, br s).
 m/z (CI): 531 (MH^+)

Example 73

- N-(1,2,3,4-Tetrahydroisoquinolin-5-yl)-4-azido-5-iodo-2-methoxybenzamide,**
20 **trifluoroacetate**

- ^1H NMR (200 MHz, $\text{MeOD}-d^4$) δ : 3.13 (2H, t), 3.53 (2H, t), 4.14 (3H, s), 4.38 (2H, s),
6.89 (1H, s), 7.12 (1H, d), 7.37 (1H, t), 7.65 (1H, s), 7.70 (1H, d), 8.48 (1H, s).
 m/z (CI): 450 (MH^+ ; 100%).
25

Example 74

N-(1,2,3,4-Tetrahydroisoquinolin-5-yl)-5-iodo-2-methoxy-4-trifluoromethyldiaziriny benzamide, trifluoroacetate

- 30 ^1H NMR (250 MHz, $\text{MeOD}-d^4$) δ : 3.11 (2H, t), 3.59 (2H, t), 4.14 (3H, s), 4.40 (2H, s), 7.18 (1H, d), 7.38 (1H, t), 7.55 (1H, s), 7.69 (1H, d), 8.42 (1H, s).
 m/z (CI): 517 (MH^+ ; 80%).

Example 75

N-(7-Iodo-2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-benzoyl-2-methoxybenzamide

- 5 ^1H NMR (CDCl_3) δ : 2.41 (3H, s), 2.70 (4H, s), 3.50 (2H, s), 4.10 (3H, s), 7.12 - 7.23 (2H, m), 7.41 - 7.68 (3H, m), 7.74 - 7.85 (2H, m), 8.12 (1H, dd), 8.55 (1H, s), 8.72 (1H, d), 9.61 (1H, br s).

Example 76

- 10 **N-(7-Iodo-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-benzoyl-2-methoxybenzamide, trifluoroacetate**

- ^1H NMR (250 MHz, DMSO-d^6) δ : 2.92 (2H, br s), 3.46 (2H, br s), 4.08 (3H, s), 4.32 (2H, br s), 7.42 (1H, d), 7.54 - 7.76 (6H, m), 7.98 (1H, d), 8.10 (1H, s), 8.21 (1H, s), 9.26
15 (2H, br s), 9.98 (1H, s). m/z (CI, API-): 511 ($\text{M}^+ - \text{H}$).

Example 77

N-(5-Iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-benzoyl-2-methoxybenzamide, trifluoroacetate

- 20 ^1H NMR (250 MHz, DMSO-d^6) δ : 2.82 (2H, t), 3.44 (2H, br s), 4.01 (3H, s), 4.31 (2H, br s), 7.38 (1H, d), 7.57 - 7.72 (6H, m), 7.95 - 8.00 (2H, m), 8.22 (1H, s), 9.15 (2H, br s), 10.35 (1H, s). m/z (CI): 513 (MH^+ ; 100%).

25 **Example 78**

N-(5-Iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxy-4-trifluoromethyldiazirinybenzamide, trifluoroacetate

- ^1H NMR (250MHz, DMSO-d^6) δ : 2.82 (2H, br s), 3.50 (2H, br s), 3.93 (3H, s), 4.30
30 (2H, br s), 7.24 (1H, d), 7.34 (1H, d), 7.41 - 7.48 (1H, m), 7.64 - 7.78 (2H, m), 8.22 (1H, s), 9.20 (2H, br s), 10.25 (1H, s). m/z (CI): 517 (MH^+ ; 100%).

Example 79

N-(5-Iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxy-5-trifluoromethyldiazirinybenzamide, trifluoroacetate

- 5 ^1H NMR (250 MHz, DMSO- d_6) δ : 2.82 (2H, br s), 3.43 (2H, br s), 3.91 (3H, s), 4.30 (2H, br s), 6.86 (1H, s), 7.12 (1H, d), 7.68 - 7.71 (2H, m), 8.20 (1H, s), 9.18 (2H, br s), 10.33 (1H, s).

Example 80

- 10 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-trifluoroacetyl benzamide**

- ^1H NMR (DMSO- d_6) δ : 2.54 (3H, s), 2.82 (4H, s), 3.73 (2H, s), 4.29 (3H, s), 6.91 (1H, d), 7.18 (1H, t), 7.31 (1H, d), 8.04 (1H, d), 8.41 (1H, d), 8.96 (1H, s), 9.61 (1H, br s). m/z
15 (CI): 393 (MH^+)

Example 81

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-4-trifluoromethyldiaziriny benzamide

- 20 ^1H NMR (DMSO- d_6) δ : 2.52 (3H, s), 2.83 (4H, s), 3.69 (2H, s), 4.09 (3H, s), 6.78 (1H, s), 6.86 (1H, d), 6.97 (1H, d), 7.21 (1H, t), 8.08 (1H, d), 8.37 (1H, d), 9.56 (1H, br s).

Example 82

- 25 **N-(1,2,3,4-Tetrahydroisoquinolin-7-yl)-5-iodo-2-methoxy-4-trifluoromethyldiazirinybenzamide, trifluoroacetate**

m/z (CI): 517 (MH^+ ; 100%).

30 **Example 83**

N-(1,2,3,4-Tetrahydroisoquinolin-5-yl)-5-(4-iodobenzoyl)-2-methoxybenzamide, trifluoroacetate

- 35 ^1H NMR (250 MHz, DMSO- d_6) δ : 2.98 (2H, t), 3.42 (2H, br s), 4.08 (3H, s), 4.35 (2H, br s), 7.12 (1H, d), 7.33 (1H, t), 7.41 (1H, d), 7.52 (2H, d), 7.65 (1H, d), 7.95 - 8.03 (3H, m), 8.16 (1H, d), 9.09 (2H, br s), 9.90 (1H, s).

Example 84

N-(7-Iodo-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-trifluoromethyldiaziriny benzamide, trifluoroacetate

- 5 ^1H NMR (250 MHz, DMSO- d_6) δ : 2.90 (2H, br s), 3.45 (2H, br s), 4.01 (3H, s), 4.32 (2H, br s), 7.38 (1H, d), 7.50 - 7.54 (2H, m), 7.70 (1H, s), 8.11 (1H, s), 9.28 (2H, br s), 9.91 (1H, s). m/z (CI): 517 (MH^+ ; 100%).

Example 85

- 10 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-chloro-2-methoxybenzamide**

^1H NMR (CDCl_3) δ : 2.47 (3H, s), 2.70 (2H, t), 2.90 (2H, t), 3.61 (2H, s), 4.06 (3H, s), 7.03 (1H, s), 7.11 (1H, t), 7.47 (1H, s), 8.22 (1H, d, $J = 7$ Hz), 9.55 (1H, br s). m/z (API^+): MH^+ at 333 (37%) and 331 (100%)

15

Example 86

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxy-4-methylthiobenzamide

- 20 ^1H NMR (CDCl_3) δ : 2.53 (3H, s); 2.54 (3H, s), 2.69 (2H, t), 2.88 (2H, t), 3.60 (2H, s), 4.05 (3H, s), 6.86 (1H, d), 6.95 (1H, dd), 7.08 (1H, d, $J = 7$ Hz), 7.28 (1H, dd), 7.49 (1H, d), 8.22 (1H, d, $J = 7$ Hz), 9.64 (1H, br s). m/z (API^+): 343 (MH^+ ; 100%).

Example 87

- 25 **N-(8-Fluoro-2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*t*-butyl-2-methoxybenzamide**

m/z (API^+): 371 (MH^+ ; 80%).

Example 88

- 30 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-*iso*-butyroyl-4-*iso*-propoxy-2-methoxybenzamide**

- 35 ^1H NMR (CDCl_3) δ : 1.15 (6H, d, $J = 6.6$ Hz), 1.51 (6H, d, $J = 6$ Hz), 2.48 (3H, s), 2.73 (2H, t), 2.84 (2H, t), 3.46 (1H, m), 3.61 (2H, s), 3.94 (3H, s), 4.90 (1H, m), 6.54 (1H, s), 6.88 (1H, d, $J = 7$ Hz), 7.20 (1H, t, $J = 7$ Hz), 7.90 (1H, d, $J = 7$ Hz), 8.58 (1H, s), 9.29 (1H, br s).

PHARMACOLOGICAL DATA

1. Binding Assay Method

5 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
10 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

15 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
20 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.
25 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
30 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
35 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, 7, 10, 13, 16, 17, 19, 20, 23, 25, 35, 37, 45, 46, 49, 50, 52, 68, 70 and 71 gave pKi values greater than 7.

2. MEST Test

The maximal electroshock seizure threshold (MEST) 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.

20 Method

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.

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

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.

Drugs are suspended or dissolved in 1% methyl cellulose.

5

References

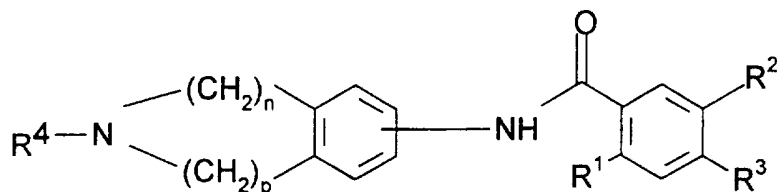
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Results

15 Compounds of this invention dosed by the oral route as a suspension in methyl cellulose and tested one hour post dosing showed an increase in seizure threshold. All compounds tested showed significant % increase at 30 mg/kg po. Preferred compounds are hereinafter mentioned.

CLAIMS

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



(I)

- 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-;

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 $(C_{1-4}$ 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-, 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, -CO₂ C_{1-4} alkyl or -COC C_{1-4} alkyl;

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

but excluding the compound 2,4,5-trimethoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide.

2. A compound according to Claim 1 in which R^1 is methoxy, ethoxy or n -propoxy

3. A compound according to Claim 1 or 2 in which R^2 as hydrogen, methoxy, bromo, chloro, iodo, acetyl, pivaloyl, *iso*-butyryl, benzoyl, trifluoromethyl, trifluoroacetyl, n -propylsulfonyl, isopropylsulfonyl or dimethylsulfamoyl.

4. A compound according to any one of claims 1 to 3 in which R^3 as hydrogen, methyl, ethyl, *n*-butyl, *iso*-propyl, *t*-butyl, phenyl, methoxy, ethoxy, *iso*-propoxy, *n*-butoxy, phenoxy, benzyloxy, amino, acetylamino, nitro, benzoyl, iodobenzoyl, chloro or azido
5. A compound according to any one of claims 1 to 3 in which R^4 is hydrogen, methyl, ethyl or propyl.
6. A compound as defined in Claim 1 or 2 where R^2 or R^3 are photolabile groups and all other variables are as defined in Claim 1.
7. N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-chloro-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2,4-dimethoxybenzamide
- 15 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-chloro-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-acetylamino-5-bromo-2-methoxybenzamide
- 20 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-bromo-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-azido-5-iodo-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-acetylamino-5-chloro-2-propoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-chloro-2-propoxybenzamide
- 25 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-acetylamino-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-nitrobenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-amino-5-iodo-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-benzyloxy-5-chloro-2-methoxybenzamide
- 30 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4,5-dichloro-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-2,4-dimethoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-[3-(trifluoromethyl)-3H-diazirin-3-yl]-2-methoxybenzamide
- 35 N-(1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-methylbenzamide
N-(2-*n*-propyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide

- N-(2-ethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-ethoxy-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2,5-dimethoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-2-methoxy-4-methylbenzamide
5 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-dimethylsulfamoyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-benzoyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-benzoyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-4-acetylamino-5-chloro-2-
10 methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-4-amino-5-chloro-2-methoxybenzamide
N-(2,3-dihydro-2-methyl-1H-isoindol-4-yl)-5-chloro-2,4-dimethoxybenzamide.
N-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-6-yl)-4-*tert*-butyl-2-methoxy-benzamide
N-(1,2,3,4-tetrahydroisoquinolin-6-yl)-4-*tert*-butyl-2-methoxybenzamide
15 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-4-*tert*-butyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*n*-butyl-2-methoxy-5-chloro-benzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethyl-2-methoxy-5-chloro benzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxy-5-chloro-
20 benzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-4-phenylbenzamide
N-(1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*iso*-propyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-*iso*-propyl-2-methoxy-
25 benzamide
N-(1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-*tert*-butyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-4-*iso*-propoxy-2-methoxy-
benzamide
30 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*iso*-propyl-5-trifluoromethyl-2-methoxybenzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*iso*-propoxy-2-methoxy-5-trifluoromethyl-benzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-4-*iso*-propyl-2-methoxy
35 benzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl) 5-*iso*-butyryl-2-methoxy-benzamide
N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-pivaloyl-2-methoxybenzamide

- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-chloro-2-methoxy-4-*iso*-propoxybenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-bromo-2,4-dimethoxybenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-*tert*-butyl-2-methoxybenzamide
- 5 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxy-4-methyl-5-trifluoromethylbenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxybenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2,4-dimethoxybenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-chloro-2-methoxybenzamide
- 10 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*iso*-propoxy-2-methoxybenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-dimethylsulfamoyl-2,4-dimethoxybenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-*iso*-propylsulfonylbenzamide
- 15 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-phenylbenzamide
- N-(1,2,3,4-Tetrahydroisoquinolin-5-yl)-5-bromo-2,4-dimethoxybenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-*n*-propylsulfonylbenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2,4-dimethoxy-5-trifluoromethylbenzamide
- 20 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-4-methyl-5-trifluoromethylbenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-acetyl-2,4-dimethoxybenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-bromo-4-ethyl-2-methoxybenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-ethyl-2-methoxy-5-
- 25 trifluoromethylbenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*n*-butoxy-5-chloro-2-methoxybenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-4-*iso*-propyloxy-5-acetylbenzamide
- 30 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-*iso*-propoxybenzamide
- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-iodo-4-trifluoromethyldiaziriny benzamide
- N-(1,2,3,4-tetrahydroisoquinolin-5-yl)-4-azido-5-iodo-2-methoxybenzamide
- 35 N-(1,2,3,4-tetrahydroisoquinolin-5-yl)-5-iodo-2-methoxy-4-trifluoromethyldiaziriny benzamide
- N-(7-iodo-2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-benzoyl-2-methoxybenzamide

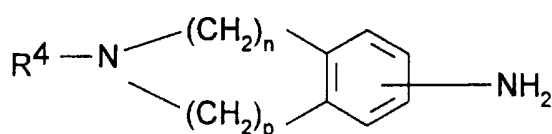
- N-(7-iodo-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-benzoyl-2-methoxybenzamide
 N-(5-iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-benzoyl-2-methoxybenzamide
 N-(5-iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxy-4-trifluoromethyldiazirinybenzamide
 5 N-(5-iodo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxy-5-trifluoromethyldiazirinybenzamide
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-trifluoroacetyl benzamide
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-trifluoroacetyl benzamide
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-4-trifluoromethyldiaziriny
 10 benzamide
 N-(1,2,3,4-tetrahydroisoquinolin-7-yl)-5-iodo-2-methoxy-4-trifluoromethyldiazirinybenzamide
 N-(1,2,3,4-tetrahydroisoquinolin-5-yl)-5-(4-iodobenzoyl)-2-methoxybenzamide
 N-(7-iodo-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxy-5-trifluoromethyldiaziriny
 15 benzamide,
 N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-chloro-2-methoxybenzamide
 N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methoxy-4-methylthiobenzamide
 N-(8-Fluoro-2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*t*-butyl-2-methoxybenzamide
 N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-*iso*-butyryl-4-*iso*-propoxy-2-
 20 methoxybenzamide, and
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*n*-butoxy-2-methoxybenzamide.
8. A pharmaceutical composition for use in the treatment and/or prophylaxis of of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from
 25 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
 30 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, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint
 35 dysfunction, and amyotrophic lateral sclerosis (ALS) which comprises a compound of formula (I), as defined in claim 1, without excluding 2,4,5-trimethoxy-N-(2-methyl-

1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

9. A method of treatment and/or prophylaxis of 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, 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), as defined in claim 1, without excluding 2,4,5-trimethoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide, or a pharmaceutically acceptable salt or solvate thereof.

10. A compound of formula (I), as defined in claim 1, without excluding 2,4,5-trimethoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of 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, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

11. A compound of formula (I), as defined in Claim 1, or a pharmaceutically acceptable salt or solvate, thereof as a therapeutic agent, in particular for the treatment and/or prophylaxis of of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects
- 5 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
- 10 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, MS and motor neurone disease, ataxias, muscular rigidity (spasticity),
- 15 temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).
12. A process for the preparation of compounds of formula (I), which comprises reacting a compound of formula (II)

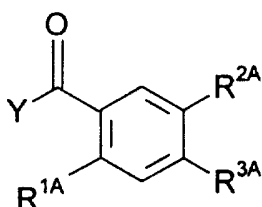


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(II)

where n and p are as defined for formula (I), as defined in Claim 1, and R^{4A} is R^4 as defined for formula (I) or a group convertible to R^4

- 25 with a compound of formula (III)



(III)

- where Y is Cl or OH, and R^{1A} , R^{2A} , and R^{3A} are respectively R^1 , R^2 , and R^3 as defined
- 30 for formula (I) or groups convertible to R^1 , R^2 , and R^3 ,
and where required converting a R^{1A} , R^{2A} , R^{3A} or R^{4A} group to a R^1 , R^2 , R^3 or R^4 group, converting one R^1 , R^2 , R^3 or R^4 group to another R^1 , R^2 , R^3 or R^4 group,

converting a hydrochloride salt product to the free base or another pharmaceutically acceptable salt or converting a free base product to a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

Intern. Application No.

PCT/EP 97/03131

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D217/04 C07D217/02 C07D209/44 C07D223/16 A61K31/47
 A61K31/40 A61K31/495 C07D401/12

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 022 900 A (MATHISON IAN WILLIAM) 10 May 1977 cited in the application see the whole document ---	1-6,8-11
X	GB 984 517 A (VEB ARNEIMITTELWERK DRESDEN) 24 February 1965 see the whole document ---	1,8-11
X	W.MATHISON ET AL: "Synthesis and hypotensive properties of tetrahydroisoquinolines" JOURNAL OF MEDICINAL CHEMISTRY., vol. 16, no. 4, 1973, WASHINGTON US, pages 332-336, XP002040786 see the whole document -----	1-6,8-11

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

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "&" document member of the same patent family

Date of the actual completion of the international search

16 September 1997

Date of mailing of the international search report

26.09.97

Name and mailing address of the ISA

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Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 97/03131

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 9
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/03131

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4022900 A	10-05-77	BE 763149 A	16-07-71
		CH 550797 A	28-06-74
		DE 2101691 A	16-03-72
		FR 2106399 A	05-05-72
		GB 1312205 A	04-04-73

GB 984517 A		BE 634851 A	
