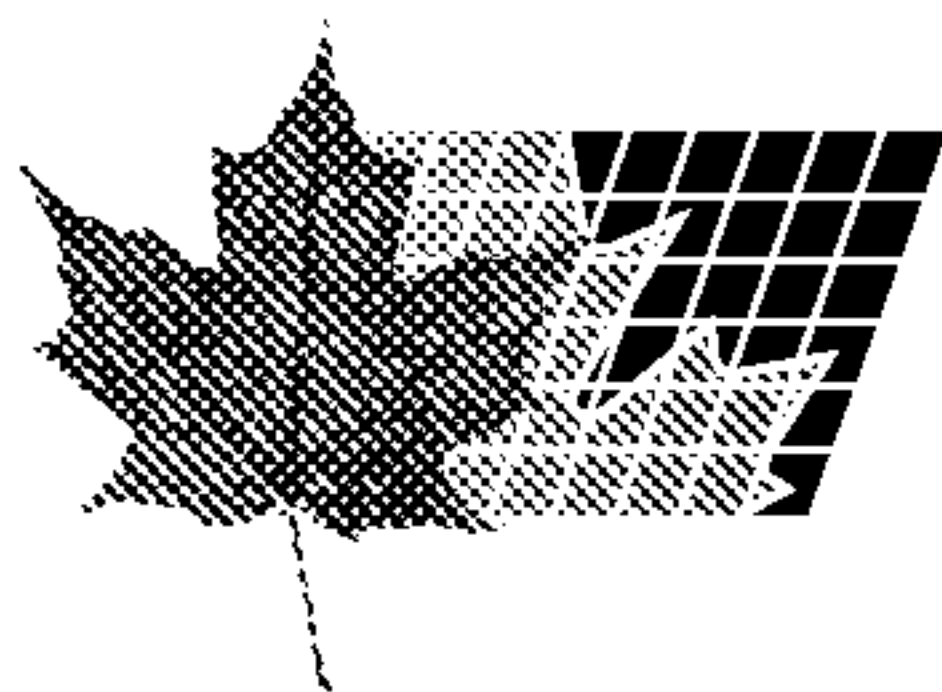




(72) THOMPSON, MERVYN, GB

(72) PORTER, RODERICK ALAN, GB

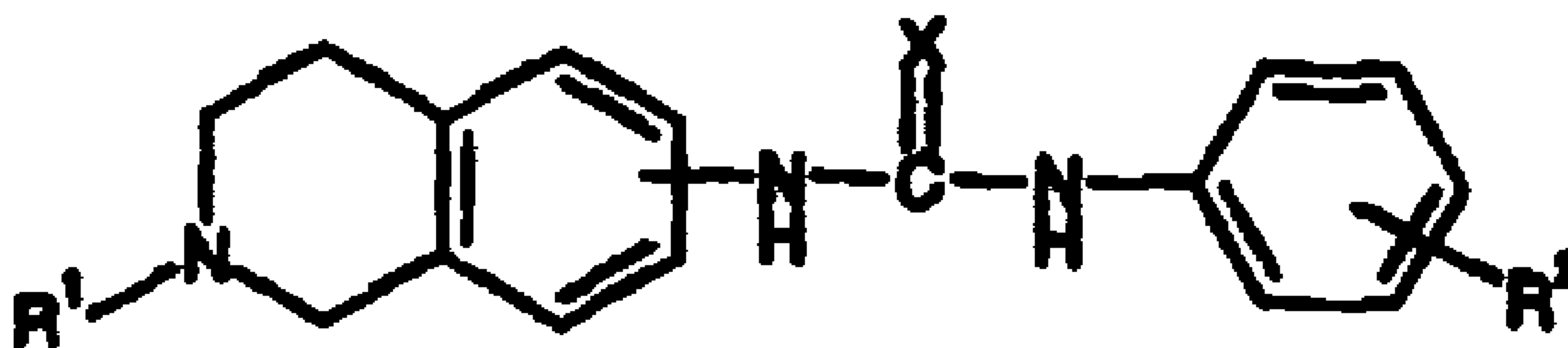
(71) SMITHKLINE BEECHAM P.L.C., GB

(51) Int.Cl.<sup>7</sup> C07D 217/04, A61K 31/47, C07D 413/12, C07D 401/12,  
C07D 217/02

(30) 1997/09/12 (9719530.9) GB

(54) **ISOQUINOLEINES SUBSTITUEES EN TANT  
QU'ANTICONVULSIFS**

(54) **SUBSTITUTED ISOQUINOLINES AS ANTICONVULSIVANTS**



(I)

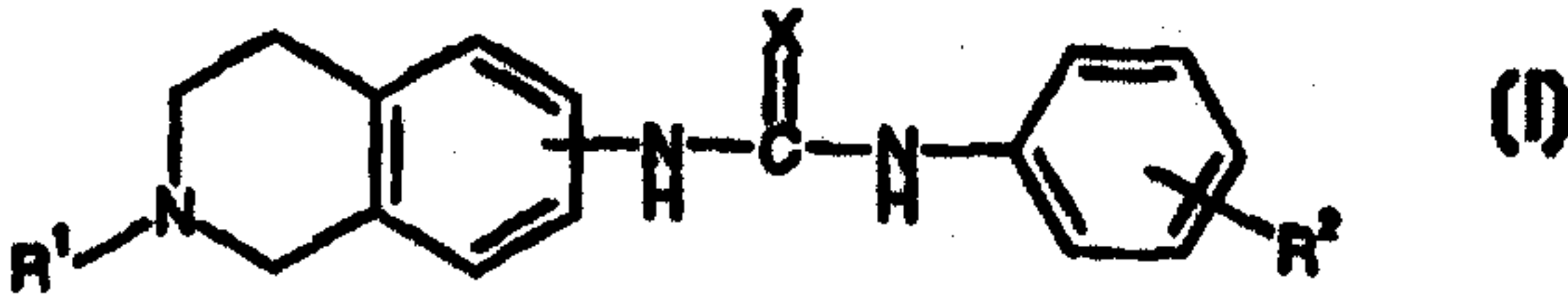
(57) N-(tétrahydroisoquinoléinyl)-N'-phénylurées/thiourées représentés par la formule suivante (I) utiles pour le traitement ou la prophylaxie de l'anxiété, de la manie, de la dépression ou de l'agression, de maladies associées à une hémorragie subarachnoïde ou à un choc nerveux, des effets associés à l'arrêt de la consommation de substances toxiques, telles que la cocaïne, la nicotine, l'alcool et les benzodiazépines, de maladies pouvant être traitées ou prévenues par des agents anticonvulsifs, telles que l'épilepsie, y compris l'épilepsie post-traumatique, la maladie de Parkinson, la psychose, la migraine, l'ischémie cérébrale, la maladie d'Alzheimer et d'autres maladies dégénératives, telles que la chorée d'Huntingdon, la schizophrénie, les maladies compulsives obsessionnelles (OCD), les déficiences neurologiques associées au SIDA, les troubles du sommeil (y compris les problèmes du rythme circadien, l'insomnie et la narcolepsie), les tics (par exemple, le syndrome de Gilles de la Tourette), la lésion cérébrale traumatique, l'acouphène, la névralgie, particulièrement, la névralgie faciale, la douleur neuropathique, la douleur dentaire, la douleur provoquée par le cancer, l'activité neuronale inadéquate conduisant vers des neurodysthésies dans des maladies, telles que le diabète, la sclérose en plaques (MS) et les troubles moteurs neuronaux, les ataxies, la rigidité musculaire (hypertonie spastique), le syndrome de Costen et la sclérose latérale amyotrophique (ALS).

(57) N-(tetrahydroisoquinoliny)-N'-phenyl-ureas/thioureas of general formula (I) are useful 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 and narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).



**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |           |                                                                                                                                                                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>(51) International Patent Classification <sup>6</sup> :</b><br><b>C07D 217/04, 217/02, A61K 31/47, C07D 401/12, 413/12</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <b>A1</b> | <b>(11) International Publication Number:</b> <b>WO 99/14197</b><br><b>(43) International Publication Date:</b> 25 March 1999 (25.03.99)                                                                 |
| <b>(21) International Application Number:</b> PCT/GB98/02728<br><b>(22) International Filing Date:</b> 9 September 1998 (09.09.98)<br><br><b>(30) Priority Data:</b><br>9719530.9      12 September 1997 (12.09.97)      GB<br><br><b>(71) Applicant (for all designated States except US):</b> SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).<br><br><b>(72) Inventors; and</b><br><b>(75) Inventors/Applicants (for US only):</b> THOMPSON, Mervyn [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). PORTER, Roderick, Alan [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).<br><br><b>(74) Agent:</b> WEST, Vivien; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |           | <b>(81) Designated States:</b> CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).<br><br><b>Published</b><br><i>With international search report.</i> |
| <b>(54) Title:</b> SUBSTITUTED ISOQUINOLINES AS ANTICONVULSIVANTS<br><br><div style="text-align: center;">  <p>(I)</p> </div><br><b>(57) Abstract</b><br><p>N-(tetrahydroisoquinoliny)-N'-phenyl-ureas/thioureas of general formula (I) are useful 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 and narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesis in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).</p> |           |                                                                                                                                                                                                          |

## SUBSTITUTED ISOQUINOLINES AS ANTICONVULSIVANTS

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

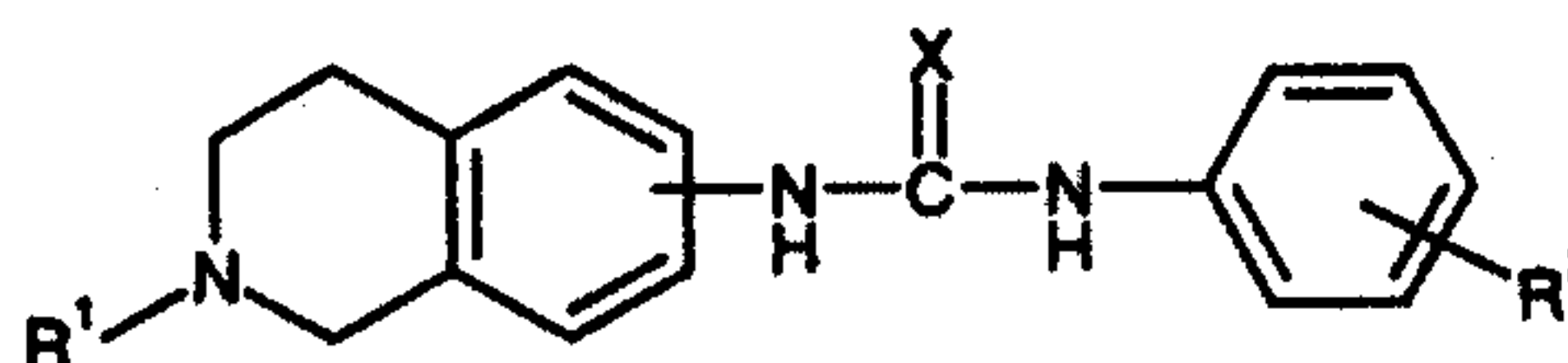
5

WO96/39382 (Fujisawa) discloses the preparation of N-heterocycl-ureas as 5-HT antagonists, including the compound N-(1-methyl-1H-indol-5-yl)-N'-(1,2,3,4-tetrahydro-7-isoquinoliny)-urea.

- 10 It has now been surprisingly found that urea 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 neurodysthesis in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

25

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



30

(I)

where X is O or S

- 35 R¹ is hydrogen, phenylC<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkyl,

- $R^4$  is hydrogen or up to three substituents independently selected from halogen,  $NO_2$ ,  $CN$ ,  $N_3$ ,  $C_{1-6}$  alkylO-,  $C_{1-6}$  alkylS-,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl- $C_{1-4}$  alkyl-,  $C_{1-6}$  alkenyl,  $C_{1-6}$  alkynyl,  $C_{1-6}$  haloalkylCO-,  $C_{1-6}$  alkylCO-,  $C_{3-6}$  cycloalkylCO-,  $C_{3-6}$  cycloalkyl- $C_{1-4}$  alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl- $C_{1-4}$  alkyl-, O- $C_{1-6}$  haloalkyl,  $CO_2C_{1-4}$  alkyl,  $S(O)_2C_{1-6}$  alkyl,  $C_{1-4}$  alkylsulfamoyl or heterocyclyl, or  $-NR^6R^7$  where  $R^6$  is hydrogen,  $C_{1-4}$  alkyl or  $S(O)_2C_{1-6}$  alkyl, and  $R^7$  is hydrogen,  $C_{1-4}$  alkyl,  $-CHO$ ,  $S(O)_2C_{1-6}$  alkyl  $-CO_2C_{1-4}$  alkyl or  $-COC_{1-4}$  alkyl, or an adjacent pair of  $R^2$  groups together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring.

- The compounds of this invention are typically N-(tetrahydroisoquinolyl)-N'-optionally substituted phenyl-ureas/thioureas. The compounds of the invention may be (tetrahydroisoquinolin-5-yl), (tetrahydroisoquinolin-6-yl), (tetrahydroisoquinolin-7-yl) or (tetrahydroisoquinolin-8-yl) ureas/thioureas, especially (tetrahydroisoquinolin-5-yl) and (tetrahydroisoquinolin-7-yl) ureas/thioureas.

- The phenyl moiety may be substituted by up to three, preferably 2 or 1, groups.

In the formula (I), alkyl groups, including alkyl groups that are part of another moiety, may be straight chain or branched. Alkyl groups are typically  $C_{1-6}$  alkyl, especially  $C_{1-4}$  alkyl, such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *t*-butyl.

- Aromatic rings, such as the aromatic ring in the bicyclic heterocyclic moiety in formula (I) and phenyl groups, including phenyl groups that are part of other moieties, in  $R^2$  may optionally be substituted with one or more independently selected substituents such as halogen or  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy or  $C_{1-6}$  alkylcarbonyl groups, or other optional substituents indicated below.

Suitable  $C_{3-6}$  cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

- Suitable halo substituents include fluoro, chloro, iodo and bromo, which may also appear in haloalkyl, haloalkyloxy and haloalkyl carbonyl groups mentioned above, examples of which are trifluoromethyl, trifluoromethoxy and trifluoroacetyl.

When any  $R^2$  represents heterocyclyl, this group is preferably a 5- to 10-membered monocyclic or bicyclic ring, which may be saturated or unsaturated, for example containing 1, 2 or 3 heteroatoms selected from oxygen, nitrogen or sulphur, for example oxazolyl, thienyl or piperidinyl. The heterocyclyl group may contain up to 5, more preferably 1, 2 or 3 optional substituents.

Preferably a substituent for a heterocyclyl group is selected from halogen, (C<sub>1-6</sub>)alkyl, aryl(C<sub>1-6</sub>)alkyl, (C<sub>1-6</sub>)alkoxy, (C<sub>1-6</sub>)alkoxy(C<sub>1-6</sub>)alkyl, halo(C<sub>1-6</sub>)alkyl, hydroxy, amino, mono- and di-N-(C<sub>1-6</sub>)alkyl-amino, acylamino, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-N-(C<sub>1-6</sub>)alkylcarbonyl, aryloxycarbonyl, (C<sub>1-6</sub>)alkoxycarbonyl(C<sub>1-6</sub>)alkyl, aryl, oxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, (C<sub>1-6</sub>)alkylthio, (C<sub>1-6</sub>)alkylsulphinyl, (C<sub>1-6</sub>)alkylsulphonyl, heterocyclyl and heterocyclyl(C<sub>1-6</sub>)alkyl.

When an adjacent pair of  $R^2$  together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic ring, it is preferably a 5- to 7-membered ring, which may be aromatic or non-aromatic. Heterocyclic rings preferably contain 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur; for example, pyrrole or pyrrolidine. A carbocyclic or heterocyclic ring formed by an adjacent pair of  $R^2$  together with the carbon atoms to which they are attached may be optionally substituted on carbon or nitrogen by one or more substituents, e.g. up to 3 substituents. Examples of suitable substituents for the carbocyclic or heterocyclic ring include; halogen, (C<sub>1-6</sub>)alkyl, aryl(C<sub>1-6</sub>)alkyl, (C<sub>1-6</sub>)alkoxy, (C<sub>1-6</sub>)alkoxy(C<sub>1-6</sub>)alkyl, halo(C<sub>1-6</sub>)alkyl, hydroxy, amino, mono- and di-N-(C<sub>1-6</sub>)alkyl-amino, acylamino, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-N-(C<sub>1-6</sub>)alkylcarbonyl, aryloxycarbonyl, (C<sub>1-6</sub>)alkoxycarbonyl(C<sub>1-6</sub>)alkyl, aryl, oxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, (C<sub>1-6</sub>)alkylthio, (C<sub>1-6</sub>)alkylsulphinyl, (C<sub>1-6</sub>)alkylsulphonyl, heterocyclyl and heterocyclyl(C<sub>1-6</sub>)alkyl.

A suitable group of compounds of formula (I) have

$R^1$  as hydrogen, benzyl, methyl, ethyl, *iso*-propyl or *t*-butyl

$R^2$  as hydrogen, methyl, ethyl, *n*-butyl, *iso*-propyl, *t*-butyl, phenyl, benzyl, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, phenoxy,

benzyloxy, bromo, chloro, iodo, fluoro, nitro, cyano, acetyl,

pivaloyl, *iso*-butyryl, benzoyl, trifluoromethyl, trifluoromethoxy,

trifluoroacetyl, carbomethoxy, carboethoxy, methylthio,

*n*-propylsulfonyl, isopropylsulfonyl, dimethylsulfamoyl or oxazolyl,

$R^6$  and  $R^7$  are hydrogen, acetyl or methanesulfonyl,  
or two  $R^2$  groups linked to form naphthyl, indolyl or indolinyl, optionally substituted by  
acetyl or methyl.

5 In a particular group of compounds of formula (I),

$R^1$  is hydrogen or methyl,

$R^2$  is hydrogen, methyl, ethyl, *t*-butyl, methoxy, ethoxy, *iso*-propoxy, phenoxy,  
benzyloxy, methylthio, bromo, chloro, fluoro, nitro, cyano, acetyl, benzoyl,  
trifluoromethyl, trifluoromethoxy, carbomethoxy, carboethoxy, amino,

10 acetylamino, methanesulphonylamino or oxazolyl,

or two  $R^2$  groups form methylindolyl or acetylmindolyl or naphthyl.

Examples of compounds of formula (I) are:

N-(1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-nitrophenyl) urea

15 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-nitrophenyl) urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-ethoxyphenyl) urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(4-ethoxyphenyl) urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-trifluoromethylphenyl)thiourea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-trifluoromethylphenyl)urea

20 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-methoxyphenyl)urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-bromophenyl) urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-trifluoromethylphenyl)urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(5-chloro-2,4-dimethoxyphenyl) urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-*tert*-butyl, 2-methoxyphenyl)urea

25 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(phenyl) urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-acetylphenyl)urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-methylphenyl)urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-methoxyphenyl)urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-chlorophenyl)urea

30 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-chloro-6-methoxyphenyl)urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3,5-di-trifluoromethylphenyl)urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-trifluoromethoxyphenyl)urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-chloro-4-methylphenyl)urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-trifluoromethylphenyl)urea

35 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(5-chloro-2,4-dimethoxyphenyl)urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-nitrophenyl)urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-bromophenyl) urea

N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-methoxyphenyl)urea

- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(4-trifluoromethoxyphenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(4-trifluoromethylphenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(phenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-acetylphenyl)urea  
 5 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-chloro-4-methylphenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-chloro-6-methoxyphenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-chlorophenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(2-methoxyphenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(2-methylphenyl)urea  
 10 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3,5-di-trifluoromethylphenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-trifluoromethylphenyl)thiourea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-carbomethoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2, 3-dimethylphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-methoxy-3-chlorophenyl) urea  
 15 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(1-naphthyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-methyl-3-nitrophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-cyanophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-cyano-3-methylphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(1-acetylinolin-7-yl) urea  
 20 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-cyanophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-ethylphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3, 5-dinitrophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2, 3-dichlorophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-chloro-4-fluorophenyl) urea  
 25 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-chloro-5-trifluoromethylphenyl)  
 urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-isopropoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-ethoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-*tert*butylphenyl) urea  
 30 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-[3-(1,3-oxazol-5-yl)phenyl] urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-benzyloxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-phenoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-fluorophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-fluorophenyl) urea  
 35 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-methylthiophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-carboethoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-fluorophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3, 4-difluorophenyl) urea

- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-benzoylphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-methoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-bromo-4-methoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-bromo-4-methoxyphenyl) urea  
 5 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(2,3-dichlorophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(2-chloro-5-trifluoromethylphenyl)  
 urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-chloro-4-fluorophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(4-methoxyphenyl) urea  
 10 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-ethylphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3, 5-dinitrophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-cyanophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-bromo-4-methoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-aminophenyl) urea  
 15 N-{3-[3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)ureido]phenyl} acetamide  
 N-{3-[3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)ureido]phenyl} bis  
 methanesulphonimide  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(1-methylindol-5-yl) urea.

- 20 When synthesised, these compounds may be in salt form, such as the hydrochloride or  
 trifluoroacetate, and such salts also form part of this invention. Such salts may be used in  
 preparing pharmaceutically acceptable salts. The compounds and their salts may be  
 obtained as solvates, such as hydrates, and these also form part of this invention.
- 25 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.

- 30 Where compounds of the present invention possess chiral centres and as such may exist in  
 different enantiomeric forms, the present invention extends to each enantiomeric form and  
 mixtures thereof including diastereoisomers and racemates.

- 35 The compounds of this invention possess anti-convulsant activity and are therefore  
 believed to be useful for administration to mammals in the treatment and/or prevention of  
 the disorders mentioned above, especially for humans, but also as a veterinary treatment.  
 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,  
5 100, 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.

10

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, nasal, rectal, topical or parenteral (especially intravenous) composition.

15 Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for  
20 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  
25 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.  
30 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  
35 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, 5 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.

- 10 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 15 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.

20

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 25 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.

- 30 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 35 anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including

- circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS) which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.
- 10 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,
- 15 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,
- 20 especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS) comprising administering to the sufferer in need thereof an effective or prophylactic amount of a
- 25 compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof.

In a further aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as

30 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

35

pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

- 5 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,
- 10 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,
- 15 insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

20

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

25

(II)

where  $R^{1A}$  is  $R^1$  as defined for formula (I) or a group convertible to  $R^1$ , and  
P is  $NH_2$  or  $NCX$ , X being as defined for formula (I),

- 30 with a compound of formula (III)

35

(III)

where Q is  $NCX$  or  $NH_2$  and different from P, X being as defined for formula (I), and  
 $R^{2A}$  is  $R^2$  as defined for formula (I) or a group or groups convertible to  $R^2$ ,

and where required converting a  $R^1A$  or  $R^2A$  group to a  $R^1$  or  $R^2$  group, converting one  $R^1$  or  $R^2$  group to another  $R^1$  or  $R^2$  group, converting a salt product to the free base or another pharmaceutically acceptable salt, or converting a free base product to a pharmaceutically acceptable salt.

5

Conventional conditions for condensation of isocyanates or isothiocyanates with amines may be used, for example treatment in an inert solvent such as toluene, DMF or dichloromethane at ambient or elevated temperature.

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

Compounds of formula (II) in which P is  $NH_2$  may be prepared from the corresponding unsaturated compound of formula (IV)

20

(IV)

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

25

(V)

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

Another route is from a precursor of formula (VI)

35

(VI)

which can be reacted with  $R^1AZ$ , preferably as a tosylate, to obtain the intermediate of formula (VII)

(VII)

5

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

- 10 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.

Alternatively, a compound of formula (II) in which P is  $NH_2$  may be prepared directly from the corresponding nitro compound by catalytic hydrogenation. More specifically 7-amino-tetrahydroisoquinolines may be prepared by the procedure of G E Stokker, Tet. Lett. 1996, 37, 5453.

When  $R^1A$  is hydrogen, the compound of formula (II) can be obtained by direct hydrogenation of the compounds of formula (IV) or (VI), using the reagents already described. The NH may be protected conventionally, for example by making  $R^1A$  *t*-butoxycarbonyl, prior to formation of the urea, and then deprotected under standard conditions, for example using trifluoroacetic acid/methylene chloride.

25 Compounds of formula (III) in which Q is iso(thio)cyanate are commercially available or may be prepared by formation of iso(thio)cyanates from commercially available substituted phenyl compounds using conventional procedures such as described by I T Forbes *et al*, J.Med.Chem., 1993, 36, 1104, and in Fieser and Fieser, Reagents for Organic Synthesis Vol I. For example an isocyanate may be prepared by stirring a relevant amine with one equivalent of carboxyl diimidazole in a suitable solvent such as dichloromethane at room temperature, and then evaporated to dryness *in vacuo*. Isothiocyanates may be prepared by reaction of the relevant amine with carbon disulphide in pyridine in the presence of dicyclohexylcarbodiimide.

35 Compounds of formula (II) in which P is iso(thio)cyanate may be similarly prepared starting from the amines of formula (II) described above.

Compounds of formula (III) in which Q is amino are commercially available or may be prepared by formation of amines on commercially available substituted phenyl compounds using conventional procedures.

- 5 Where intermediates disclosed for the above processes are novel compounds, they also form part of this invention.

The compounds of the present invention may contain a chiral centre, and therefore the above processes may produce a mixture of diastereoisomers. A single diastereoisomer may  
10 be prepared by separating such a mixture of diastereoisomers which has been synthesised using a racemic starting material, or by synthesis using an optically pure starting material.

The compounds of this invention may be in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. When some of the compounds of this  
15 invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be present in the crystalline product. Crystallisation procedures will usually produce stoichiometric hydrates. Compounds containing variable  
20 amounts of water may be produced by processes such as lyophilisation.

The compounds according to the invention are suitably provided in substantially pure form, for example at least 50% pure, suitable at least 60% pure, advantageously at least 75% pure, preferably at least 85% pure, more preferably at least 95% pure, especially at least  
25 98% pure, all percentages being calculated as weight/weight. An impure or less pure form of a compound according to the invention may, for example, be used in the preparation of a more pure form of the same compound or of a related compound (for example a corresponding derivative) suitable for pharmaceutical use.

- 30 The present invention also includes pharmaceutically acceptable salts and derivatives of the compounds of the invention. Salt formation may be possible when one of the substituents carries an acidic or basic group. Salts may be prepared by salt exchange in conventional manner.

Acid-addition salts may be pharmaceutically acceptable or non-pharmaceutically acceptable. In the latter case, such salts may be useful for isolation and purification of the compound of the invention, or intermediates thereto, and will subsequently be converted  
5 into a pharmaceutically acceptable salt or the free base.

The preparation of compounds of formula (II) is illustrated by the following Descriptions; the preparation of compounds of this invention is illustrated by the following Examples. The utility of compounds of this invention is shown by the Pharmacological Data that  
10 follow the Examples.

### Description 1

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

15

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 Na<sub>2</sub>SO<sub>4</sub>. The  
20 material in the organic phase gave the title compound as a pale yellow solid (19.04g).

### Description 2

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

25

The nitro compound D1 (2.26g; 9.15 mmol) and paraformaldehyde (0.45g; 14.4 mmol) in acetic acid (10ml) and conc. H<sub>2</sub>SO<sub>4</sub> (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).

30

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sup>+</sup>)

### Description 3

35

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

The trifluoroacetamide D2 (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).

5

#### Description 4

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

10 The amine D3 (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  
15 (1.7g).

$m/z$  (CI): 193 (MH<sup>+</sup>).

#### Description 5

20

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

The 7-nitro compound D4 (0.25g; 1.3 mmol) in methanol (40ml) was hydrogenated over 10% palladium on carbon (100mg) at atmospheric pressure overnight. The catalyst was  
25 removed by filtration through a pad of Kieselguhr and evaporation *in vacuo* gave the title compound as a white solid (213mg).

$m/z$  (CI): 163 (MH<sup>+</sup>)

#### 30 Description 6

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

The title compound was prepared from the compound of Description D3 using di *t*-butyl  
35 dicarbonate in 10% aqueous hydroxide in dioxan at 25°C followed by catalytic hydrogenation according to the procedure described for D5.

#### Description 7

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

The 7-nitro compound D2 (0.99g; 3.6 mmol) in ethanol (50ml) was hydrogenated over  
5 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).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.84 (2H, t), 3.23 (2H, b. s.), 3.82 (2H, m), 4.66 (2H,d,  
10 restricted rotation around C-1), 6.47 (1H, m), 6.57 (1H,m ), 6.96 (1H, m)

**Description 8****5-Amino-2-methylisoquinolinium iodide**

15

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).

20

**Description 9****5-Amino-2-methyl-1,2,3,4-tetrahydroisoquinoline**

25 Sodium borohydride (17.8g, 0.47mol) was added portionwise over 2h to an ice cold solution of 5-amino-2-methylisoquinolinium iodide D8 (18.8g, 65mmol) in methanol (1.5L) and water (60ml). The mixture was then stirred at 25°C for 18h. and concentrated *in vacuo*. The residue was extracted into water and dichloromethane. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentration *in vacuo* gave the title compound (8.87g).

30

**Description 10****2-Methyl-1,2,3,4-tetrahydroisoquinoline-7-isocyanate**

35 The amine D5 (0.25g) and carbonyl di-imidazole (0.24g) in dichloromethane were stirred at 25°C for 1h. Solvent was removed at reduced pressure below 40°C.

**Example 1****(a) N-(1,2,3,4-Tetrahydro-2-trifluoroacetyl-isoquinolin-7-yl)-N'-(3-nitrophenyl) urea**

- 5 A solution of amine D7 (400mg; 1.64 mmol) in dichloromethane (5ml) was treated with a solution of 3-nitrophenylisocyanate (295mg; 1.80 mmol) in toluene (10ml) and the mixture kept at room temperature under argon. After 20h., the resultant cream precipitate was removed by filtration and washed well with ether/hexane and dried *in vacuo*. Cream solid (612mg; 91%).

10

m/z (API+): 408 (MH+; 100%)

**(b) N-(1,2,3,4-Tetrahydroisoquinolin-7-yl)-N'-(3-nitrophenyl) urea**

- 15 The urea (a) (540mg; 1.32 mmol) in 10% aqueous methanol(80ml) and potassium carbonate (1g) was stirred at room temperature overnight. The mixture was partitioned between chloroform and water and the organic phase dried over magnesium sulfate. Evaporation *in vacuo* gave a pale yellow solid which was recrystallised from chloroform:hexane (300mg, 72%). m.p. 232-5 °C.

20

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.48 (2H, t), 2.78 (2H, t), 3.67 (2H, s), 6.83 (1H, d), 7.01 (1H, dd), 7.05 (1H, s), 7.42 (1H, t), 7.53 (1H, d), 7.67 (1H, dd), 8.43 (1H, t), 8.58 (1H, s), 9.07 (1H, s)

**25 Example 2****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-nitrophenyl) urea**

- 30 The title compound was prepared from amine D5 and 3-nitrophenylisocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.40 (3H, s), 2.58 (2H, t), 2.75 (2H, t), 3.44 (2H, s), 7.01 (1H, dd), 7.02 (1H, d), 7.20 (1H, s), 7.53 (1H, m), 7.68 (1H, m), 7.80 (2H, m), 8.57 (1H, s), 9.19 (1H, s); <sup>m</sup>/<sub>z</sub> (API+): 327 (MH+; 100%)

35

**Example 3****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-ethoxyphenyl) urea**

The title compound (262mg) was prepared from amine D5 and 4-ethoxyphenylisocyanate using a method similar to that of Example 1(a).

5 m.p. 189-193 °C.

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 1.31 (3H, t), 2.33 (3H, s), 2.56 (2H, t), 2.73 (2H, t), 3.43 (2H, s), 3.97 (2H, q), 7.01 (1H, dd), 6.84 and 7.34 (4H, ABq), 6.98 (1H, d), 7.16 (2H, m), 8.40 (1H, s), 8.44 (1H, s); <sup>m/z</sup> (API+): 326 (MH+; 100%)

10

#### Example 4

##### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(4-ethoxyphenyl) urea

15 The title compound was prepared from amine D9 (162mg; 1mmol) in dichloromethane (8ml) and 4-ethoxyphenyl isocyanate (166mg; 1mmol) in toluene (4ml) using a method similar to that of Example 1(a). White powder (210mg).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 1.42 (3H, t), 2.45 (3H, s), 2.62 (2H, br), 2.76 (2H, br), 20 3.57 (2H, s), 4.08 (2H, q), 6.83 (1H, d, J=6.5Hz), 6.96 and 7.45 (4H, Abq, J=7.5Hz), 7.19 (1H, t, J=6.5Hz), 7.82 (1H, d, J=6.5Hz), 7.86 (1H, s), 8.95 (1H, s); <sup>m/z</sup> (API+): 326 (MH+; 50%)

#### Example 5

25

##### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-trifluoromethylphenyl)thiourea

The title compound was prepared in 47% yield from amine D5 and 3-trifluoromethylphenyl isothiocyanate using a method similar to that of Example 1(a).

30

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.28 (3H, s), 2.53 (2H, t, J = 6 Hz), 2.74 (2H, t, J = 6 Hz), 3.40 (2H, s), 7.04 (2H, m), 7.13 (1H, dd, J = 2 and 8 Hz), 7.40 (1H, d, J = 8 Hz), 7.50 (1H, t, J = 8 Hz), 7.70 (1H, d, J = 8 Hz), 7.90 (1H, s), 9.87 (2H, b s); <sup>m/z</sup> (API): 366 (MH+; %)

35

#### Example 6

##### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-trifluoromethylphenyl)urea

The title compound was prepared in 21% yield from amine D5 and 3-trifluoromethylphenyl isocyanate using a method similar to that of Example 1(a).

- 5 <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.42 (3H, s), 2.64 (2H, t, J = 6 Hz), 2.84 (2H, t, J = 6 Hz), 3.45 (2H, s), 6.90 - 7.06 (3H, b. m.), 7.09 (1H, s), 7.22 - 7.44 (3H, b. m.), 7.51 (1H, d, J = 8 Hz), 7.58 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>): 350 (MH<sup>+</sup>; 100%).

#### Example 7

10

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-methoxyphenyl)urea

The title compound was prepared in 74% yield from amine D5 and 3-methoxyphenyl isocyanate using a method similar to that of Example 1(a).

15

- <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.35 (3H, s), 2.58 (2H, t, J = 6 Hz), 2.77 (2H, t, J = 6 Hz), 3.32 (2H, s), 3.68 (3H, s), 6.53 (1H, d, J = 8 Hz), 6.76 - 6.96 (3H, b. m.), 7.00 - 7.13 (3H, b. m.), 7.82 (1H, s), 7.93 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>): 312 (MH<sup>+</sup>; 100%).

#### 20 Example 8

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-bromophenyl) urea

- 25 The title compound was prepared in 90% yield from amine D5 and 3-bromophenyl isocyanate using a method similar to that of Example 1(a).

- <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.44 (3H, s), 2.67 (2H, t, J = 6 Hz), 2.87 (2H, t, J = 6 Hz), 3.50 (2H, s), 6.74 (1H, s), 6.97 (2H, m), 7.02 (2H, d, J = 5 Hz), 7.08 (1H, d, J = 3 Hz), 7.76 (2H, m), 7.53 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>): 360, 362 (MH<sup>+</sup>; 100%).

30

#### Example 9

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-trifluoromethylphenyl) urea

- 35 The title compound was prepared in 90% yield from amine D5 and 4-trifluoromethylphenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.41 (3H, s), 2.63 (2H, t, J = 6 Hz), 2.84 (2H, t, J = 6 Hz), 3.44 (2H, s), 6.93 (2H, m), 7.01 (2H, m), 7.37 (2H, m), 7.45 (3H, m);  
<sup>m/z</sup> (AP<sup>+</sup>): 350 (MH<sup>+</sup>; 100%).

5 **Example 10**

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(5-chloro-2,4-dimethoxy-phenyl) urea**

10 The title compound was prepared in 93% yield from amine D5 and 5-chloro-2,4-dimethoxyphenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.42 (3H, s), 2.66 (2H, t, J = 6 Hz), 2.85 (2H, t, J = 6 Hz), 3.48 (2H, s), 3.80 (3H, s), 3.86 (3H, s), 6.45 (1H, s), 7.00 (1H, d, J = 8 Hz), 7.06 - 7.12  
15 (2H, m), 7.32 (1H, s), 7.40 (1H, s), 8.08 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>): 376 (MH<sup>+</sup>; 100%).

**Example 11**

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-tert-butyl, 2-methoxyphenyl)urea**  
20

The title compound was prepared in 52% yield from amine D5 and 4-tert-butyl-2-methoxyphenyl isocyanate using a method similar to that of Example 1(a).

25 <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 1.30 (9H, s), 2.44 (3H, s), 2.67 (2H, t, J = 6 Hz), 2.87 (2H, t, J = 6 Hz), 3.52 (2H, s), 3.81 (3H, s), 6.81 (1H, s), 6.87 (1H, d, J = 2 Hz), 6.96 (1H, dd, J = 2 and 8 Hz), 7.07 (3H, m), 7.16 (1H, s), 7.94 (1H, d, J = 8 Hz);  
<sup>m/z</sup> (AP<sup>+</sup>): 368 (MH<sup>+</sup>; 100%)

30 **Example 12**

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(phenyl) urea**

The title compound was prepared in 94% yield from amine D5 and phenyl isocyanate using  
35 a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.41 (3H, s), 2.63 (2H, t, J = 6 Hz), 2.64 (2H, t, J = 6 Hz), 3.45 (2H, s), 6.90 - 7.13 (6H, b. m.), 7.22 - 7.34 (4H, b. m.); <sup>m/z</sup> (AP<sup>+</sup>): 282 (MH<sup>+</sup>; 100%).

**Example 13****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-acetylphenyl)urea**

5

The title compound was prepared in 59% yield from amine D5 and 3-acetylphenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.39 (3H, s), 2.55 (3H, s), 2.62 (2H, t, J = 6 Hz), 2.82 (2H, t, J = 6 Hz), 3.42 (2H, s), 6.92 - 7.13 (3H, m), 7.31 (1H, t, J = 8 Hz), 7.44 (1H, d, J = 8 Hz), 7.79 (3H, m), 7.95 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>): 324 (MH<sup>+</sup>; 100%).

10

**Example 14****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-methylphenyl)urea**

15

The title compound was prepared in 98% yield from amine D5 and 2-methylphenyl isocyanate using a method similar to that at Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.18 (3H, s), 2.39 (3H, s), 2.61 (2H, t, J = 6 Hz), 2.81 (2H, t, J = 6 Hz), 3.41 (2H, s), 6.88 (1H, s), 6.92 - 7.20 (6H, b. m.), 7.26 (1H, s), 7.54 (1H, d, J = 8 Hz); <sup>m/z</sup> (AP<sup>+</sup>): 296 (MH<sup>+</sup>; 100%).

20

**Example 15**

25

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-methoxyphenyl)urea**

The title compound was prepared in 45% yield from amine D5 and 2-methoxyphenyl isocyanate using a method similar to that of Example 1(a).

30

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.42 (3H, s), 2.67 (2H, t, J = 6 Hz), 2.85 (2H, t, J = 6 Hz), 3.48 (2H, s), 3.78 (3H, s), 6.68 - 7.03 (4H, b. m.), 7.09 - 7.22 (2H, b. m.), 7.46 - 7.68 (2H, b. m.), 8.10 (1H, d, J = 7 Hz); <sup>m/z</sup> (AP<sup>+</sup>): 312 (MH<sup>+</sup>; 100%)

**Example 16**

35

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-chlorophenyl)urea**

The title compound was prepared in 92% yield from amine D5 and 3-chlorophenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.47 (3H, s), 2.64 (2H, t, J = 6 Hz), 2.85 (2H, t, J = 6 Hz),  
5 3.46 (2H, s), 6.90 - 7.06 (4H, b. m.), 7.13 - 7.23 (4H, b. m.), 7.37 (1H, s);  
<sup>m/z</sup> (AP<sup>+</sup>): 316 (MH<sup>+</sup> 100%)

#### Example 17

10 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-chloro-6-methoxyphenyl)urea**

The title compound was prepared in 98% yield from amine D5 and 3-chloro-6-methoxyphenyl isocyanate using a method similar to that of Example 1(a).

15 <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.42 (3H, s), 2.66 (2H, t, J = 6 Hz), 2.85 (2H, t, J = 6 Hz),  
3.47 (2H, s), 3.77 (3H, s), 6.73 (1H, m), 6.90 (1H, dd, J = 2 and 9 Hz), 7.00 - 7.17 (3H, b.  
m.), 7.43 (1H, s), 7.60 (1H, s), 8.23 (1H, d, J = 2 Hz); <sup>m/z</sup> (AP<sup>+</sup>): 346 (100%)

#### Example 18

20

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3,5-ditrifluoromethylphenyl)urea**

The title compound was prepared in 41% yield from amine D5 and 3,5-  
25 ditrifluoromethylphenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.42 (3H, s), 2.66 (2H, t, J = 6 Hz), 2.82 (2H, t, J = 6 Hz),  
3.43 (2H, s), 6.89 (1H, s), 6.95 (2H, s), 7.46 (2H, s), 7.81 (2H, s), 8.23 (1H, s);  
<sup>m/z</sup> (AP<sup>+</sup>): 418 (100%)

30

#### Example 19

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-trifluoromethoxyphenyl)urea**

35 The title compound was prepared in 92% yield from amine D5 and 4-trifluoromethoxyphenyl isocyanate using a method similar to that at Example 1(a).

$^1\text{H}$  NMR (250MHz,  $\text{d}^6\text{-DMSO}$ )  $\delta$ : 2.49 (3H, s), 2.74 (2H, t,  $J = 6$  Hz), 2.92 (2H, t,  $J = 6$  Hz), 3.61 (2H, s), 7.18 (1H, d,  $J = 9$  Hz), 7.33 (2H, m), 7.45 (2H, d,  $J = 9$  Hz), 7.72 (2H, d,  $J = 9$  Hz), 8.77 (1H, s), 9.03 (1H, s);  $m/z$  (AP $^+$ ): 366 ( $\text{MH}^+$ ; 100%).

**Example 20****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-chloro-4-methylphenyl)urea**

- 5 The title compound was prepared in 98% yield from amine D5 and 3-chloro-4-methylphenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.28 (3H, s), 2.41 (3H, s), 2.64 (2H, t, J = 6 Hz), 2.84 (2H, t, J = 6 Hz), 3.44 (2H, s), 6.97 (1H, s), 7.01 - 7.16 (4H, b. m.), 7.19 (1H, s), 7.34 (2H, m);  
10 <sup>m/z</sup> (AP<sup>+</sup>): 330 (MH<sup>+</sup>; 100%).

**Example 21****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-trifluoromethylphenyl)urea**

15

The title compound was prepared from the amine D9 and 3-trifluoromethylphenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.41 (3H, s), 2.72 (4H, m), 3.54 (2H, s), 6.85 (1H, d, J = 7 Hz), 7.16 (1H, dd, J = 7 and 8 Hz), 7.37 (1H, d, J = 7 Hz), 7.61 (2H, m), 7.74 (1H, d, J = 8 Hz), 8.02 (1H, s), 8.10 (1H, s), 9.44 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>): 350 (MH<sup>+</sup>; 100%).  
20

**Example 22**

- 25 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(5-chloro-2,4-dimethoxyphenyl)urea**

The title compound was prepared in 54% yield from the amine D9 and 5-chloro-2,4-dimethoxyphenyl isocyanate using a method similar to that of Example 1(a).

30

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.32 (3H, s), 2.64 (4H, m), 3.46 (2H, s), 3.84 (3H, s), 3.94 (3H, s), 6.75 (1H, d, J = 7 Hz), 6.85 (1H, s), 7.06 (1H, dd, J = 7 and 8 Hz), 7.67 (1H, d, J = 8 Hz), 8.16 (1H, s), 8.36 (1H, s), 8.62 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>): 376 (MH<sup>+</sup>; 100%)

- 35 **Example 23**

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-nitrophenyl)urea**

The title compound was prepared in 73% yield from amine D9 and 3-nitrophenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.24 (3H, s), 2.57 (4H, m), 3.37 (2H, s), 6.70 (1H, d, J = 7 Hz), 7.02 (1H, t, J = 8 Hz), 7.47 (1H, t, J = 8 Hz), 7.58 (2H, m), 7.73 (1H, m), 7.89 (1H, s), 8.46 (1H, m), 9.43 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>); 327 (MH<sup>+</sup>; 100%).

#### Example 24

#### 10 N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-bromophenyl) urea

The title compound was prepared in 71% yield from amine D9 and 3-bromophenyl isocyanate using a method similar to that of Example 1(a).

15 <sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.15 (3H, s), 2.48 (4H, m), 3.27 (2H, s), 6.57 (1H, d, J = 7 Hz), 6.85 - 7.10 (4H, b. m.), 7.46 (1H, d, J = 8 Hz), 7.69 (1H, s), 7.71 (1H, s), 9.03 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>): 360, 362 (MH<sup>+</sup>; 100%).

#### Example 25

20

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-methoxyphenyl)urea

The title compound was prepared in 47% yield from amine D9 and 3-methoxyphenyl isocyanate using a method similar to that of Example 1(a).

25

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.36 (3H, s), 2.69 (4H, m), 3.52 (2H, s), 3.73 (3H, s), 6.56 (1H, d, J = 10 Hz), 6.76 (1H, d, J = 8 Hz), 6.94 (1H, d, J = 10 Hz), 7.14 (3H, m), 7.72 (1H, d, J = 8 Hz), 7.86 (1H, s), 9.08 (1H, s); <sup>m/z</sup> (APD): 312 (MH<sup>+</sup>; 100%)

#### 30 Example 26

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(4-trifluoromethoxy-phenyl)urea

The title compound was prepared in 74% yield from amine D9 and 4-trifluoromethoxyphenyl isocyanate using a method similar to Example 1(a).

35

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.59 (3H, s), 2.84 (2H, t, J = 5 Hz), 3.03 (2H, t, J = 5 Hz), 3.84 (2H, s), 6.82 (1H, d, J = 7 Hz), 7.15 (1H, s), 7.30 (2H, d, J = 8 Hz), 7.58 (2H, d, J = 8 Hz), 7.74 (1H, d, J = 7 Hz), 8.24 (1H, s), 9.59 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>): 366 (MH<sup>+</sup>; 100%)

5 **Example 27**

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(4-trifluoromethyl-phenyl)urea**

The title compound was prepared in 69% yield from amine D9 and 4-trifluoromethylphenyl  
10 isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.332 (3H, s), 2.58 (2H, t, J = 5 Hz), 2.74 (2H, t, J = 5 Hz), 3.58 (2H, s), 6.60 (1H, d, J = 7 Hz), 6.93 (1H, dd, J = 7 and 8 Hz), 7.45 (5H, m), 8.03 (1H, s), 9.52 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>): 350 (MH<sup>+</sup>; 100%)

15

**Example 28**

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(phenyl)urea**

20 The title compound was prepared in 79% yield from amine D9 and phenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.35 (3H, s), 2.66 (4H, m), 3.48 (2H, s), 6.76 (1H, d, J = 8 Hz), 6.95 (1H, t, J = 8 Hz), 7.08 (1H, t, J = 8 Hz), 7.28 (2H, t, J = 8 Hz), 7.46 (2H, d, J =  
25 8 Hz), 7.71 (1H, d, J = 8 Hz), 7.83 (1H, s), 9.03 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>): 282 (MH<sup>+</sup>; 100%).

**Example 29**

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-acetylphenyl)urea**

30

The title compound was prepared in 74% yield from amine D9 and 3-acetylphenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.43 (3H, s), 2.61 (5H, m), 2.78 (2H, b. m.), 3.56 (2H, s),  
35 6.74 (1H, s), 6.92 (1H, d, J = 7 Hz), 7.16 (1H, t, J = 8 Hz), 7.35 (3H, m), 7.59 (1H, d, J = 8 Hz), 7.80 (2H, m); <sup>m/z</sup> (AP<sup>+</sup>): 324 (MH<sup>+</sup>; 100%)

**Example 30**

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-chloro-4-methylphenyl)urea**

The title compound was prepared in 98% yield from amine D9 and 3-chloro-4-methylphenyl isocyanate using a method similar that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.29 (3H, s), 2.44 (3H, s), 2.65 (2H, t, J = 6 Hz), 2.76 (2H, t, J = 6 Hz), 3.57 (2H, s), 6.37 (1H, s), 6.71 (1H, s), 6.94 (1H, d, J = 8 Hz), 7.04 - 7.22 (3H, b. m.), 7.33 (2H, m); <sup>m/z</sup> (AP<sup>+</sup>): 330 (MH<sup>+</sup>; 100%).

**Example 31****N--(2-Methyl-1,2,3,4--tetrahydroisoquinolin-5-yl)-N'-(3-chloro-6-methoxyphenyl)urea**

The title compound was prepared in 61% yield from amine D9 and 3-chloro-6-methoxyphenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.45 (3H, s), 2.69 (2H, t, J = 6 Hz), 2.82 (2H, t, J = 6 Hz), 3.59 (2H, s), 3.73 (3H, s), 6.41 (1H, s), 6.70 (1H, d, J = 9 Hz), 6.93 (2H, t, J = 6 Hz), 7.18 (1H, t, J = 8 Hz), 7.35 (2H, m), 8.25 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>): 346 (MH<sup>+</sup>; 100%)

**Example 32****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-chlorophenyl)urea**

The title compound was prepared in 83% yield from amine D9 and 3-chlorophenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.42 (3H, s), 2.60 (2H, t, J = 6 Hz), 2.73 (2H, t, J = 6 Hz), 3.53 (2H, s), 6.70 (1H, s), 6.89 (1H, d, J = 8 Hz), 6.98 (1H, m), 7.04 - 7.20 (4H, m), 7.31 (1H, d, J = 8 Hz), 7.37 (1H, s); <sup>m/z</sup> (AP<sup>+</sup>): 316 (MH<sup>+</sup>; 100%).

**Example 33****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(2-methoxyphenyl)urea**

The title compound was prepared in 58% yield from amine D9 and 2-methoxyphenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.45 (3H, s), 2.68 (2H, t, J = 6 Hz), 2.81 (2H, t, J = 6 Hz), 3.59 (2H, s), 3.75 (3H, s), 6.38 (1H, s), 6.82 (1H, d, J = 7 Hz), 6.88 - 7.04 (3H, b. m.), 7.18 (1H, t, J = 8 Hz), 7.27 (1H, m), 7.40 (1H, d, J = 8 Hz), 8.12 (1H, d, J = 6 Hz); <sup>m/z</sup> (AP<sup>+</sup>): 312 (MH<sup>+</sup>; 100%)

#### Example 34

##### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(2-methylphenyl)urea

10

The title compound was prepared in 88% yield from amine D9 and 2-methylphenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>NMR (250MHz, CDCl<sub>3</sub>) δ: 1.71 (3H, s), 2.43 (3H, s), 2.66 (4H, m), 3.55 (2H, s), 6.40 (1H, s), 6.89 (1H, d, J = 8 Hz), 7.05 - 7.28 (5H, m), 7.48 (1H, d, J = 8 Hz), 7.61 (1H, d, J = 8 Hz); <sup>m/z</sup> (AP<sup>+</sup>): 296 (MH<sup>+</sup>; 100%)

#### Example 35

##### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3,5-di-trifluoromethylphenyl)urea

The title compound was prepared in 58% yield from amine D9 and 3,5-di-trifluoromethylphenyl isocyanate using a method similar to that of Example 1(a).

25

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.46 (3H, s), 2.67 (2H, t, J = 6 Hz), 2.81 (2H, t, J = 6 Hz), 3.59 (2H, s), 6.49 (1H, s), 6.86 (2H, d, J = 8 Hz), 7.16 - 7.34 (2H, b. m.), 7.51 (1H, s), 7.83 (2H, s); <sup>m/z</sup> (AP<sup>+</sup>): 418 (MH<sup>+</sup>; 100%).

#### Example 36

##### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-trifluoromethylphenyl)thiourea

The title compound was prepared in 57% yield from amine D9 and 3-trifluoromethylphenyl isothiocyanate using a method similar to that of Example 1(a).

35

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.46 (3H, s), 2.63 (2H, t, J = 6 Hz), 2.79 (2H, t, J = 6 Hz), 3.54 (2H, s), 7.00 (1H, dd, J = 3 and 6 Hz), 7.14 (2H, m), 7.45 (1H, d, J = 8 Hz), 7.55

(1H, t, J = 8 Hz), 7.79 (1H, d, J = 8 Hz), 8.00 (1H, s), 9.56 (1H, bs), 9.94 (1H, bs);  $m/z$  (AP $^+$ ): 366 (MH $^+$ ; 95%)

### Example 37

5

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-carbomethoxyphenyl) urea

The title compound was prepared in 69% yield from amine D5 and 2-carbomethoxyphenyl isocyanate using a method similar to that of Example 1(a).

10

$^1\text{H}$  NMR (250MHz, CDCl $_3$ )  $\delta$ : 2.46 (3H, s), 2.68 (2H, t, J = 6 Hz), 2.89 (2H, t, J = 6 Hz), 3.57 (2H, s), 6.53 (1H, br. s.), 7.00 (1H, t), 7.09 (2H, m), 7.19 (1H, s), 7.52 (1H, t), 7.99 (1H, d), 8.54 (1H, d), 10.52 (1H, bs);  $m/z$  (AP $^+$ ): 340 (MH $^+$ ; 95%)

15

### Example 38

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2, 3-dimethylphenyl) urea

20 The title compound was prepared in 16% yield from amine D5 and 2, 3-dimethylphenyl isocyanate using a method similar to that of Example 1(a).

$^1\text{H}$  NMR (250MHz, CDCl $_3$ )  $\delta$ : 2.19 (3H, s), 2.31 (3H, s), 2.43 (3H, s), 2.66 (2H, t, J = 6 Hz), 2.86 (2H, t, J = 6 Hz), 3.53 (2H, s), 6.22 (1H, br. s.), 6.38 (br. s. 1H), 7.02 - 7.27 (6H, m);  $m/z$  (AP $^+$ ): 310 (MH $^+$ ; 95%)

25

### Example 39

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-methoxy-3-chlorophenyl) urea

30

The title compound was prepared in 61% yield from amine D5 and 2-methoxy-3-chlorophenyl isocyanate using a method similar to that of Example 1(a).

$^1\text{H}$  NMR (250MHz, CDCl $_3$ )  $\delta$ : 2.31 (3H, s), 2.56 (2H, t, J = 6 Hz), 2.70 (2H, t, J = 6 Hz), 3.44 (2H, s), 3.77 (3H, s), 6.97 - 7.16 (5H, m), 8.14 (1H, dd), 8.43 (s, 1H) and 9.22 (s, 1H);  $m/z$  (AP $^+$ ): 346 (MH $^+$ ; 95%)

35

### Example 40

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(1-naphthyl) urea**

The title compound was prepared in 54% yield from amine D5 and 1-naphthyl isocyanate  
5 using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.42 (3H, s), 2.56 (2H, t, J = 6 Hz), 2.85 (2H, t, J = 6 Hz),  
3.51 (2H, s), 6.53 (1H, s), 6.74 (1H, s), 7.01 (2H, d), 7.08 (1H, s), 7.47 - 7.56 (3H, m), 7.67  
(1H, d), 7.79 (1H, d), 7.90 (1H, m) and 7.99 (m1H, m).;

10 <sup>m/z</sup> (AP<sup>+</sup>): 332 (MH<sup>+</sup>; 95%)

**Example 41****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-methyl-3-nitrophenyl) urea**

15

The title compound was prepared in 87% yield from amine D5 and 2-methyl-3-nitrophenyl  
isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.27 (3H, s), 2.44 (3H, s), 2.69 (2H, t, J = 6 Hz), 2.89 (2H,  
20 t, J = 6 Hz), 3.53 (2H, s), 6.80 (1H, br. s), 6.86 (1H, br. s), 7.06 (3H, s), 7.30 (1H, t, J = 8  
Hz), 7.57 (1H, d, J = 7 Hz) and 7.95 (1H, d, J = 8 Hz);

<sup>m/z</sup> (AP<sup>+</sup>): 339 (MH<sup>+</sup>; 95%)

**Example 42**

25

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-cyanophenyl) urea**

The title compound was prepared in 13% yield from amine D5 and 2-cyanophenyl  
isocyanate using a method similar to that of Example 1(a).

30

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.47(3H, s) 2.70(2H, br. s.) 3.02(2H, br, s), 3.62(2H, br. s)  
other aliphatics poorly resolved 6.89(1H, d), 6.97(1H, s), 7.05(1H, d), 7.16(1H, t), 7.32(1H,  
d), 7.47(1H, s), 8.19(1H, d) and 9.14(1H, br. s.);

<sup>m/z</sup> (AP<sup>+</sup>): 307 (MH<sup>+</sup>; 95%)

35

**Example 43****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-cyano-3-methylphenyl) urea**

The isocyanate D10 (160mg) was dissolved in dimethylformamide (10ml), 6-methyl-2-aminobenzonitrile (0.13g) added and the mixture heated at 100°C for 3h.

Dimethylformamide was removed at reduced pressure and the residue partitioned between  
5 dichloromethane and water. The organic phase was washed with water, dried MgSO<sub>4</sub>) and solvent removed at reduced pressure. The residue was column chromatographed using a gradient of 0 → 10 % [9:1 EtOH – ammonia] in MDC (silica gel ethanol/dichloromethane 1:9 → ammonia/ethanol/dichloromethane 1:9:90) to give the title compound (0.01g 3%).  
10 <sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.27(3H, s), 2.40 (3H, s), 2.51 (2H, t, J = 6 Hz), 2.69 (2H, t, J = 6 Hz), 3.38 (2H, s), 6.96(1H, d, J = 9 Hz), 7.02(1H, d, J = 8Hz), 7.11(1H, s), 7.14(1H, d), 7.45(1H, t, J = 8 Hz), 7.84(1H, d, 8 Hz), 8.56(1H, s) and 9.25 (1H, s);  
<sup>m/z</sup> (API<sup>+</sup>): 326 (MH<sup>+</sup>; 95%)

#### Example 44

15

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(1-acetyldolin-7-yl) urea

The title compound was prepared in 14% yield from 7-amino-1-acetyldoline and the isocyanate D10 using the method of Example 43

20 <sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.41(3H, s), 2.46 (2H, t, J = 5.5 Hz), 2.63(2H, t, J = 5.4 Hz), 2.96(2H, t, J = 7.5 Hz), 3.31(2H, s), 4.03(2H, t, 7.6 Hz), 6.85(2H, m), 7.00(1H, t, J = 7.7 Hz), 7.1(2H, m), 7.45(1H, d, J = 8.0 Hz), 8.65(1H, br. s.) and 9.15(1H, br. s.);  
<sup>m/z</sup> (API<sup>+</sup>): 365 (MH<sup>+</sup>; 95%)

#### 25 Example 45

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-cyanophenyl) urea

The title compound was prepared in 12% yield from 3-aminobenzonitrile and the isocyanate  
30 D10 using the method of Example 43

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.44 (3H, s), 2.68 (2H, t, J = 5.8Hz), 2.89 (2H, t, J = 5.8Hz), 3.52 (2H, s), 6.88 (1H, br.s), 6.98 - 7.09 (3H, m), 7.19 - 7.39 (3H, m), 7.62 (2H, m).  
<sup>m/z</sup> (API<sup>+</sup>): 307 (MH<sup>+</sup>)

#### 35 Example 46

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-ethylphenyl) urea

The title compound was prepared in 12% yield from 3-ethylaniline and the isocyanate D10 using the method of Example 43

$^1\text{H}$  NMR (250MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.19 (3H, t,  $J = 7.5\text{Hz}$ ), 2.42 (3H, s), 2.54 - 2.66 (4H, m), 2.85 (2H, m), 3.48 (2H, s) and 6.90 - 7.26 (7H, m).

5  $m/z$  ( $\text{API}^+$ ): 310( $\text{MH}^+$ )

#### Example 47

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3, 5-dinitrophenyl) urea**

10

The title compound was prepared in 12% yield from 3,5-dinitroaniline and the isocyanate D10 using the method of Example 43.

$^1\text{H}$  NMR (250MHz,  $d^6$ -DMSO)  $\delta$ : 2.18 (3H, s), 2.42 (2H, t,  $J = 5.5\text{Hz}$ ), 2.60 (2H, t,  $J = 5.5\text{Hz}$ ), 3.29 (2H, s), 6.88 (1H, d,  $J = 8.8\text{Hz}$ ), 7.06 (2H, br. s), 8.24 (1H, s), 8.59 (2H, d),  
15 8.80 (1H, s) and 9.52 (1H, s).

$m/z$  ( $\text{API}^+$ ): 372 ( $\text{MH}^+$ )

#### Example 48

20 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2,3-dichlorophenyl) urea**

The title compound was prepared in 66% yield from amine D5 and 2, 3-dichlorophenyl isocyanate using a method similar to that of Example 1(a).

$^1\text{H}$  NMR (250MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.46 (3H, s), 2.70 (2H, t,  $J = 5.8\text{Hz}$ ), 2.91 (2H, t,  $J = 5.8\text{Hz}$ ),  
25 3.55 (2H, s), 6.93 (1H, br. s), 7.06 - 7.21 (5H, m), 7.37 (1H, s) and 8.18 (1H, dd,  $J = 2.1$ , 7.8Hz).

$m/z$  ( $\text{API}^+$ ): 350, 352 ( $\text{MH}^+$ )

#### Example 49

30

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-chloro-4-fluorophenyl) urea**

The title compound was prepared in 95% yield from amine D5 and 3-chloro-4-fluorophenyl isocyanate using a method similar to that of Example 1(a).

35  $^1\text{H}$  NMR (250MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.40 (3H, s), 2.61 (2H, t,  $J = 5.2\text{Hz}$ ), 2.82 (2H, t,  $J = 5.2\text{Hz}$ ), 3.41 (2H, s), 6.76 - 7.07 (5H, m), 7.26 - 7.35 (2H, m) and 7.42 (1H, s).

$m/z$  ( $\text{API}^+$ ): 334, 336 ( $\text{MH}^+$ )

**Example 50**

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-chloro-5-trifluoromethylphenyl) urea**

5

The title compound was prepared in 24% yield from amine D5 and 2-chloro-5-trifluoromethylphenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.44 (3H, s), 2.70 (2H, t, J = 5.2Hz), 2.88 (2H, t, J = 5.2Hz), 3.51 (2H, s), 7.02 - 7.20 (4H, m), 7.38 - 7.49 (2H, m), 8.50 (1H, s) and 8.61 (1H, s).

10 <sup>m/z</sup> (AP<sup>+</sup>): 384, 386 (MH<sup>+</sup>)**Example 51**

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-isopropoxyphenyl) urea**

15

The title compound was prepared in 42% yield from 3-isopropoxyaniline and the isocyanate D10 using the method of Example 43.

20 <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 1.27 (6H, d, J = 6.0Hz), 2.40 (3H, s), 2.62 (2H, t, J = 5.7Hz), 2.83 (2H, t, J = 5.7Hz), 3.44 (2H, s), 4.48 (1H, m), 6.58 (1H, dd, J = 2.0, 8.2Hz), 6.76 (1H, d, J = 8.0Hz), 6.97 - 7.15 (6H, m) and 7.21 (1H, s).<sup>m/z</sup> (AP<sup>+</sup>): 340 (MH<sup>+</sup>)**Example 52**

25

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-ethoxyphenyl) urea**

The title compound was prepared in 45% yield from 3-ethoxyaniline and the isocyanate D10 using the method of Example 43.

30

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 1.34 (3H, t, J = 6.8Hz), 2.39 (3H, s), 2.62 (2H, t, J = 5.7Hz), 2.81 (2H, m), 3.41 (2H, s), 6.57 (1H, d, 7.7Hz), 6.76 (1H, d, J = 8.0Hz), 6.92 - 6.98 (3H, m) 7.11 (1H, t, J = 8Hz), 7.26 (1H, s) and 7.49 (1H, s).

<sup>m/z</sup> (AP<sup>+</sup>): 326 (MH<sup>+</sup>)

35

**Example 53**

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-*tert*butylphenyl) urea**

The title compound was prepared in 39% yield from 3-*tert*butylaniline and the isocyanate D10 using the method of Example 43.

- 5 <sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 1.27 (9H, s), 2.32 (3H, s), 2.56 (2H, m), 2.72 (2H, m), 3.43 (2H, s), 7.00 (3H, m), 7.16 - 7.25 (4H, m), 7.45 (1H, s), 8.45 (1H, s) and 8.58 (1H, s).  
<sup>m/z</sup> (AP<sup>+</sup>): 338 (MH<sup>+</sup>)

#### Example 54

10

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-(1,3-oxazol-5-yl)phenyl) urea**

The title compound was prepared in 72% yield from 3-(1,3-oxazol-5-yl)aniline and the isocyanate D10 using the method of Example 43.

15

- <sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.33 (3H, s), 2.57 (2H, t, J = 5.6Hz), 2.75 (2H, m), 3.45 (2H, s), 7.01 (1H, d, J = 8.3Hz), 7.17 - 7.20 (2H, m), 7.35 (3H, m), 7.65 (1H, s), 7.94 (1H, s), 8.48 (1H, s), 8.63 (1H, s) and 8.83 (1H, s).  
<sup>m/z</sup> (AP<sup>+</sup>): 349 (MH<sup>+</sup>)

20

#### Example 55

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-benzyloxyphenyl) urea**

- 25 The title compound was prepared in 78% yield from 3-benzyloxyaniline and the isocyanate D10 using the method of Example 43.

- <sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.32 (3H, s), 2.55 (2H, t, J = 5.5Hz), 2.73 (2H, m), 3.43 (2H, s), 5.07 (2H, s), 6.62 (1H, d, J = 8.0Hz), 6.92 (1H, d, J = 7.8Hz), 7.00 (1H, d, J =  
30 8.8Hz), 7.17 (3H, m), 7.33 (1H, s), 7.33 - 7.47 (5H, m), 8.58 (1H, s) and 8.68 (1H, s).  
<sup>m/z</sup> (AP<sup>+</sup>): 388 (MH<sup>+</sup>)

#### Example 56

- 35 **N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-phenoxyphenyl) urea**

The title compound was prepared in 75% yield from 3-phenoxyaniline and the isocyanate D10 using the method of Example 43.

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.31 (3H, s), 2.55 (2H, t, J = 5.5Hz), 2.73 (2H, m), 3.42 (2H, s), 6.60 (1H, d, J = 7.1Hz), 6.95 - 7.29 (9H, m), 7.40 (2H, m), 8.48 (1H, s) and 8.74 (1H, s).

5 <sup>m/z</sup> (API<sup>+</sup>): 374 (MH<sup>+</sup>)

#### Example 57

##### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-fluorophenyl) urea

10

The title compound was prepared in 37% yield from amine D5 and 3-fluorophenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.33 (3H, s), 2.58 (2H, m), 2.72 (2H, m), 3.45 (2H, s), 6.76 (1H, t, J = 6.7Hz), 6.99 - 7.33 (5H, m), 7.48 (1H, d, J = 12Hz), 8.58 (1H, s) and 8.85

15 (1H, s).

<sup>m/z</sup> (API<sup>+</sup>): 300 (MH<sup>+</sup>)

#### Example 57

##### 20 N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-fluorophenyl) urea

The title compound was prepared in 45% yield from amine D5 and 2-fluorophenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.32 (3H, s), 2.56 (2H, t, J = 5.6Hz), 2.74 (2H, m), 3.44 (2H, s), 6.95 - 7.31 (6H, m), 8.15 (1H, t), 8.50 (1H, s) and 8.96 (1H, s).

25

<sup>m/z</sup> (API<sup>+</sup>): 300 (MH<sup>+</sup>)

#### Example 58

##### 30 N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-methylthiophenyl) urea

The title compound was prepared in 58% yield from amine D5 and 3-methylthiophenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.33 (3H, s), 2.45 (3H, s), 2.56 (2H, t, J = 5.6Hz), 2.74 (2H, m), 3.44 (2H, s), 6.85 (1H, d, J = 7.5Hz), 6.99 (1H, d, J = 8.8Hz), 7.10 - 7.24 (4H, m), 7.47 (1H, s), 8.53 (1H, s) and 8.65 (1H, s).

35

<sup>m/z</sup> (API<sup>+</sup>): 328 (MH<sup>+</sup>)

**Example 59****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-carboethoxyphenyl) urea**

5 The title compound was prepared in 91% yield from amine D5 and 3-carboethoxyphenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 1.33 (3H, t, J = 7.0Hz), 2.37 (3H, s), 2.60 (2H, m), 2.78 (2H, m), 3.37 (2H, s), 4.30 (2H, q, J = 7.0Hz), 6.91 - 7.05 (3H, m), 7.26 (1H, t, J = 7.8Hz), 7.66 (3H, m) and 7.82 - 7.90 (2H, m).

10 <sup>m/z</sup> (AP<sup>+</sup>): 354 (MH<sup>+</sup>)

**Example 60****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-fluorophenyl) urea**

15

The title compound was prepared in 98% yield from amine D5 and 4-fluorophenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.32 (3H, s), 2.55 (2H, m), 2.74 (2H, m), 3.43 (2H, s), 6.97 - 7.15 (5H, m), 7.45 (2H, m), 7.52 (1H, s) and 7.67 (1H, s).

20 <sup>m/z</sup> (AP<sup>+</sup>): 300 (MH<sup>+</sup>)

**Example 61****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3, 4-difluorophenyl) urea**

25

The title compound was prepared in 72% yield from amine D5 and 3, 4-difluorophenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.32 (3H, s), 2.56 (2H, t, J = 5.5Hz), 2.74 (2H, m), 3.43 (2H, s), 7.0 (1H, d, J = 8.7Hz), 7.08 - 7.15 (2H, m), 7.27 - 7.37 (2H, m), 7.61 - 7.73 (1H, m), 8.60 (1H, s) and 8.84 (1H, s).

30

<sup>m/z</sup> (AP<sup>+</sup>): 318 (MH<sup>+</sup>)

**Example 62****35 N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-benzoylphenyl) urea**

The title compound was prepared in 67% yield from 3-benzoylaniline and the isocyanate D10 using the method of Example 43.

$^1\text{H}$  NMR (250MHz,  $\text{d}^6$ -DMSO)  $\delta$ : 2.32 (3H, s), 2.56 (2H, m), 2.73 (2H, m), 3.42 (2H, s), 6.99 (1H, d), 7.16 (2H, m), 7.32 (1H, d), 7.39 - 7.80 (7H, m), 7.87 (1H, s), 8.55 (1H, s) and 8.92 (1H, s).

$m/z$  (AP $^+$ ): 386 (MH $^+$ )

5

### Example 63

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-methoxyphenyl) urea

- 10 The title compound was prepared in 96% yield from 4-methoxyaniline and the isocyanate D10 using the method of Example 43.

$^1\text{H}$  NMR (250MHz,  $\text{d}^6$ -DMSO)  $\delta$ : 2.32 (3H, s), 2.56 (2H, m), 2.73 (2H, m), 3.43 (2H, s), 3.71 (3H, s), 6.85 (2H, d,  $J = 8.7\text{Hz}$ ), 6.98 (1H, d,  $J = 9.0\text{Hz}$ ), 7.14 (2H, m), 7.33 (2H, d,  $J = 8.7\text{Hz}$ ), 8.45 (1H, s) and 8.48 (1H, s).

- 15  $m/z$  (AP $^+$ ): 312 (MH $^+$ )

### Example 64

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-bromo-4-methoxyphenyl) urea

20

A solution of 3-bromo-4-methoxybenzoic acid (0.924g) in dioxan (10ml) was treated with 1,8-bis(dimethylamino)naphthalene (0.857g). After stirring for 30min diphenylphosphoryl azide was added and the mixture boiled for 6h. After cooling to room temperature the amine D5 (0.245g) in dichloromethane (10ml) was added and the mixture stirred for 16h.

- 25 Solvent was removed at reduced pressure, the residue column chromatographed (methanol/dichloromethane mixtures) to give the title compound (0.34g).

$^1\text{H}$  NMR (250MHz,  $\text{d}^6$ -DMSO)  $\delta$ : 2.82 (3H, s), 2.96 (2H, m), 3.38 (4H, m), 3.79 (3H, s), 4.20 (2H, s), 6.95 - 7.35 (5H, m), 7.79 (1H, m), 9.10 (1H, s), 9.13 (1H, s) and 10.30 (1H, br. s).

- 30  $m/z$  (AP $^+$ ): 390, 392 (MH $^+$ )

### Example 65

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-bromo-4-methoxyphenyl) urea

35

The title compound was prepared in 24% yield from amine D9 and 3-bromo-4-methoxybenzoic acid using the method of Example 64.

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.38 (3H, s), 2.76 (2H, m), 2.83 (2H, m), 3.66 (2H, s), 3.81 (3H, s), 6.60 (1H, d, J = 7.5Hz), 6.67 (1H, d, J = 8.9Hz), 7.17 (1H, m), 7.60 (1H, d, J = 2.4Hz), 7.69 (1H, d), 8.02 (1H, s), 8.70 (1H, s).

<sup>m/z</sup> (AP<sup>+</sup>): 390, 392 (MH<sup>+</sup>)

5

#### Example 66

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(2,3-dichlorophenyl) urea

10 The title compound was prepared in 95% yield from amine D9 and 2,3-dichlorophenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.47 (3H, s), 2.71 (2H, m), 2.85 (2H, m), 3.62 (2H, s), 6.51 (1H, br. s), 7.00 (1H, d, J = 7.7Hz), 7.09 – 7.35 (5H, m) and 8.17 (1H, d, J = 7.7Hz).

<sup>m/z</sup> (AP<sup>+</sup>): 350, 352 (MH<sup>+</sup>)

15

#### Example 67

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(2-chloro-5-trifluoromethylphenyl) urea

20

The title compound was prepared in 36% yield from amine D9 and 2-chloro-5-trifluoromethylphenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.45 (3H, s), 2.67 (2H, m), 2.83 (2H, m), 3.58 (2H, s), 6.91 (1H, br. s), 6.98 (1H, d, J = 7.5Hz), 7.17 – 7.46 (5H, m) and 8.60 (1H, s).

25 <sup>m/z</sup> (AP<sup>+</sup>): 384, 386 (MH<sup>+</sup>)

#### Example 68

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-chloro-4-fluorophenyl) urea

30

The title compound was prepared in 90% yield from amine D9 and 3-chloro-4-fluorophenyl isocyanate using a method similar to that of Example 1(a).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.44 (3H, s), 2.64 (2H, m), 2.75 (2H, m), 3.56 (2H, s), 6.44 (1H, br. s), 6.82 (1H, br. s), 6.94 – 7.29 (5H, m) and 7.44 (1H, m).

35 <sup>m/z</sup> (AP<sup>+</sup>): 334, 336 (MH<sup>+</sup>)

#### Example 69

**N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(4-methoxyphenyl) urea**

A mixture of the amine D9 (0.245g) and carbonyl diimidazole (0.245g) in dichloromethane (10ml) was stirred for 45 min at room temperature. Solvent was removed at reduced pressure and a solution of 4-methoxyaniline (0.185g) in dimethylformamide (10ml) added. The mixture was heated at 100°C for 1 h. solvent removed at reduced pressure and the residue column chromatographed (silica gel, ether/methanol and dichloromethane/methanol mixtures) to give the title compound (0.25g).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) 2.33 (3H, s), 2.65 (4H, m), 3.46 (2H, s), 3.71 (3H, s), 6.72 (1H, d, J = 7.5Hz), 6.86 (2H, d, J = 8.9Hz), 7.06 (1H, t, J = 7.8Hz), 7.35 (2H, d, J = 8.9Hz), 7.70 (1H, d, J = 8.0Hz), 7.77 (1H, s) and 8.88 (1H, s).

<sup>m/z</sup> (AP<sup>+</sup>): 311 (MH<sup>+</sup>)

**Example 70****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-ethylphenyl) urea**

The title compound was prepared in 55% yield from amine D9 and 3-ethylaniline using a method similar to that of Example 69.

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 1.19 (3H, t, J = 7.6Hz), 2.43 (3H, s), 2.55 – 2.96 (6H, m), 3.56 (2H, s), 6.43 (1H, s), 6.77 (1H, s), 6.91 (2H, d, J = 7.5Hz), 7.11 – 7.23 (4H, m) and 7.40 (1H, d, J = 7.8Hz).

<sup>m/z</sup> (AP<sup>+</sup>): 310 (MH<sup>+</sup>)

**Example 71****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3, 5-dinitrophenyl) urea**

The title compound was prepared in 24% yield from amine D9 and 3, 5-dinitroaniline using a method similar to that of Example 69.

<sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.35 (3H, s), 2.64 – 2.76 (4H, m), 3.63 (2H, s), 6.85 (1H, d, J = 7.5Hz), 7.13 (1H, t, J = 7.7Hz), 7.56 (1H, d, J = 8.0Hz), 8.21 (1H, s), 8.39 (1H, t), 8.73 (2H, d) and 10.04 (1H, s).

<sup>m/z</sup> (AP<sup>+</sup>): 372 (MH<sup>+</sup>)

**Example 72****N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-cyanophenyl) urea**

The title compound was prepared in 56% yield from amine D9 and 3-aminobenzonitrile using a method similar to that of Example 69.

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.44 (3H, s), 2.64 (2H, m), 2.74 (2H, m), 3.57 (2H, s), 6.23 (1H, s), 6.82 (1H, d, J = 7.3Hz), 7.14 – 7.36 (5H, m), 7.55 (1H, d, J = 8.0Hz), 7.64 (1H, s).  
5 <sup>m/z</sup> (AP<sup>+</sup>): 307 (MH<sup>+</sup>)

### Example 73

#### 10 N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-bromo-4-methoxyphenyl) urea

The title compound was prepared in 20% yield from amine D9 and 3-bromo-4-methoxyaniline using a method similar to that of Example 69.

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.46 (3H, s), 2.72 – 2.77 (4H, m), 3.57 (2H, s), 3.89 (3H, s),  
15 6.61 (1H, dd, J = 2.5, 8.5Hz), 7.13 (1H, t, J = 7.7Hz), 7.35 (1H, d, J = 8.4Hz), 7.54 (1H, s),  
7.65 (1H, d, J = 2.5Hz), 7.70 (1H, d, J = 8.0Hz) and 8.67 91H, s).  
<sup>m/z</sup> (AP<sup>+</sup>): 389, 391 (MH<sup>+</sup>)

#### 20 Example 74

#### N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-aminophenyl) urea

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-nitrophenyl) urea E2 (1.2g) was  
25 dissolved in ethanol (50ml), purged with argon and treated with 10% palladium/charcoal  
(0.1g, paste) and ammonium formate (1.16g). The mixture was stirred at room temperature  
for 16h, filtered (celite pad) and the filtrate evaporated under reduced pressure. The  
obtained residue was dissolved in water, basified with sodium carbonate and the  
precipitated title compound (0.98g) collected by filtration.

30 <sup>1</sup>H NMR (250MHz, d<sup>6</sup>-DMSO) δ: 2.71 (3H, s), 2.76 (2H, m), 2.93 (2H, m), 3.63 (2H, s),  
5.22 (2H, br. s), 6.08 91H, d, J = 7.8Hz), 6.45 (1H, d, J = 7.9Hz), 6.67 (1H, s), 6.78 (1H, t,  
J = 8.0Hz), 6.88 (1H, m), 7.06(2H, m), 8.26 (1H, s) and 8.36 (1H, s). <sup>m/z</sup> (AP<sup>+</sup>): 297  
(MH<sup>+</sup>)

#### 35 Example 75

#### N-{3-[3-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)ureido]phenyl}acetamide hydrochloride

A solution of N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-aminophenyl) urea E74 (0.296g) and triethylamine (0.151g) in dichloromethane was treated with acetyl chloride (0.078g) and stirred for 6h. Aqueous sodium hydrogen carbonate was added with vigorous stirring and the precipitated solid collected by filtration. The material was dissolved in methanol and treated with an excess of ethereal HCl. The precipitated title compound (0.145g) was collected by filtration and dried in vacuo.

<sup>1</sup>H NMR (400MHz, d<sup>6</sup>-DMSO) δ: 2.03 (3H, s), 2.86 (3H, s), 2.94 (1H, m), 3.17 (1H, m), 1 resonance under HOD, 3.58 (1H, m), 4.21 (1H, m), 4.40 (1H, m), 7.12 – 7.15 (3H, m), 7.26 – 7.32 (2H, m), 7.35 91H, s), 7.68 91H, s), 9.44 91H, s), 9.62 (1H, s) and 10.00 (1H, s).

<sup>m/z</sup> (AP<sup>+</sup>): 339 (MH<sup>+</sup>)

### Example 76

N-{3-[3-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)ureido]phenyl}bis methanesulphonimide hydrochloride

A solution of N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-aminophenyl) urea E74 (0.150g) and triethylamine (0.21ul) in dichloroethane was treated with methanesulphonyl chloride (0.085ul) and stirred for 16h. The organic phase was washed with water, aqueous sodium hydrogen carbonate and brine. Solvent was removed at reduced pressure and the residue converted to the HCl salt (see Example 75) of the title compound (0.082g).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.44 (3H, s), 2.690 (2H, m), 2.85 (2H, m), 3.40 (6H, s), 3.50 (2H, s), 6.97 – 7.02 (4H, m), 7.19 (1H, s), 7.20 – 7.29 (2H, m), 7.49 (1H, s) and 7.68 (1H, m).

<sup>m/z</sup> (AP<sup>+</sup>): 453 (MH<sup>+</sup>)

### Example 77

N-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(1-methylindol-5-yl) urea

The title compound was prepared in 68% yield from amine D9 and 1-methyl-5-aminoindole using a method similar to that of Example 69.

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ: 2.33 (3H, s), 2.65 (4H, m), 3.45 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J = 2.8Hz), 6.72 (1H, d, J = 7.5Hz), 6.03 – 7.16 (2H, m), 7.26 (1H, d, J = 3.0Hz), 7.33 (1H, d, J = 8.7Hz), 7.51 – 7.58 (3H, m) and 8.63 (1H, s).

$m/z$  (AP<sup>+</sup>): 335 (MH<sup>+</sup>)

## PHARMACOLOGICAL DATA

### 5 1. Binding Assay Method

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 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.

- 20 To carry out the radioligand binding assay, aliquots of tissue prepared as above (usually at a concentration of 1-2mg protein/ml) are mixed with aliquots of [3H]-Compound A dissolved in buffer. The final concentration of [3H]-Compound A in the mixture is usually 20nM. The mixture is incubated at room temperature for 1 hour. [3H]-Compound A bound to the tissue is then separated from unbound [3H]-Compound A by filtration through
- 25 Whatman GF/B glass fibre filters. The filters are then washed rapidly with ice-cold buffer. The amount of radioactivity bound to the tissue trapped on the filters is measured by addition of liquid scintillation cocktail to the filters followed by counting in a liquid scintillation counter.
- 30 In order to determine the amount of "specific" binding of [3H]-Compound A, parallel assays are carried out as above in which [3H]-Compound A and tissue are incubated together in the presence of unlabelled Compound A (usually 3 µM). The amount of binding of [3H]-Compound A remaining in the presence of this unlabelled compound is defined as "non-specific" binding. This amount is subtracted from the total amount of [3H]-
- 35 Compound A binding (i.e. that present in the absence of unlabelled compound) to obtain the amount of "specific" binding of [3H]-Compound A to the novel site.

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

### Results

Compounds of this invention were active in this test with pKi values greater than 6. For example, compounds of Examples 1, 2, 6, 7, 8, 16 and 23 gave pKi values greater than 8.

### 2. MEST Test

The maximal electroshock seizure (MEST) threshold test in rodents is particularly sensitive for detecting potential anticonvulsant properties<sup>1</sup>. In this model, anticonvulsant agents elevate the threshold to electrically-induced seizures whilst proconvulsants lower the seizure threshold.

### Method

20

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% (CC<sub>50</sub>) of the mice in a particular treatment group is determined by the 'up and down' method of Dixon and Mood (1948)<sup>2</sup>. Statistical comparisons between vehicle- and drug-treated groups are made using the method of Litchfield and Wilcoxon (1949)<sup>3</sup>.

30 In control animals the CC<sub>50</sub> 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.

35 The percentage increase or decrease in CC<sub>50</sub> 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.

- 5 Drugs are suspended in 1% methyl cellulose.

### References

1. Loscher, W. and Schmidt, D. (1988). Epilepsy Res., 2, 145-181
- 10 2. Dixon, W.J. and Mood, A.M. (1948). J. Amer. Stat. Assn., 43, 109-126
3. Litchfield, J.T. and Wilcoxon, F.(1949). J. Pharmacol. exp. Ther., 96, 99-113

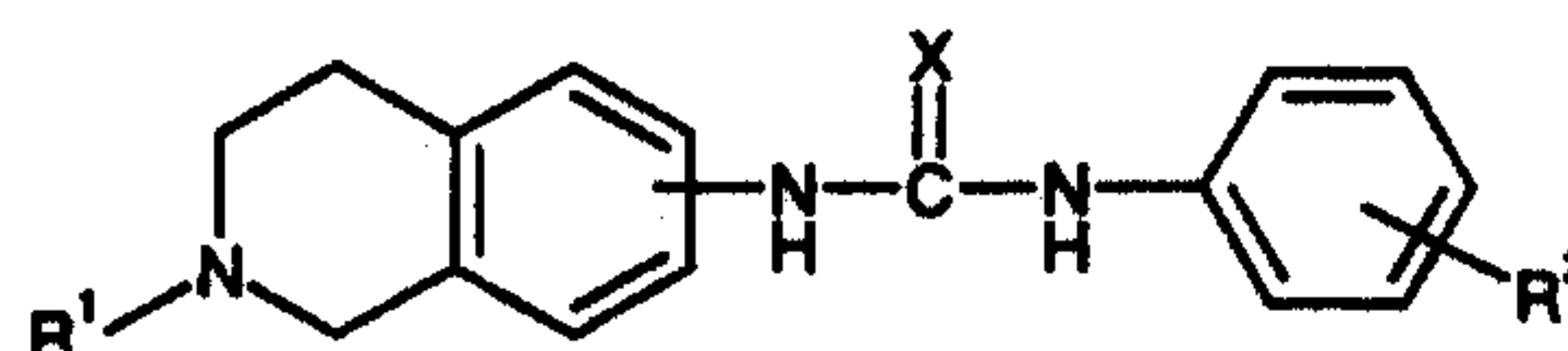
### Results

- 15 Compounds of this invention dosed by the oral route as a suspension in methyl cellulose and tested one hour post dosing show an increase in seizure threshold. For example, the product of Example 1 showed a statistically significant increase (35%) when examined at a dose of 10 mg/kg p.o.

## CLAIMS

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

5



(I)

where X is O or S

10  $R^1$  is hydrogen, phenyl- $C_{1-6}$  alkyl or  $C_{1-6}$  alkyl,

$R^2$  is hydrogen or up to three substituents independently selected from halogen,

$NO_2$ , CN,  $N_3$ ,  $C_{1-6}$  alkylO-,  $C_{1-6}$  alkylS-,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,

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

$C_{1-6}$  haloalkylCO-,  $C_{1-6}$  alkylCO-,  $C_{3-6}$  cycloalkylCO-,

15  $C_{3-6}$  cycloalkyl- $C_{1-4}$  alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl,

phenyl- $C_{1-4}$  alkyl-, O- $C_{1-6}$  haloalkyl,  $CO_2C_{1-4}$  alkyl,  $S(O)_2C_{1-6}$  alkyl,

$C_{1-4}$  alkylsulfamoyl or heterocyclyl, or  $-NR^6R^7$  where

$R^6$  is hydrogen,  $C_{1-4}$  alkyl or  $S(O)_2C_{1-6}$  alkyl, and

$R^7$  is hydrogen,  $C_{1-4}$  alkyl, -CHO,  $S(O)_2C_{1-6}$  alkyl - $CO_2C_{1-4}$  alkyl or

20 - $COC_{1-4}$  alkyl,

or an adjacent pair of  $R^2$  groups together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring.

2. A compound of claim 1 which is a (tetrahydroisoquinolin-5-yl) or  
25 (tetrahydroisoquinolin-7-yl) urea or thiourea.

3. A compound of claim 1 in which

$R^1$  is hydrogen, benzyl, methyl, ethyl, *iso*-propyl or *t*-butyl

$R^2$  is hydrogen, methyl, ethyl, *n*-butyl, *iso*-propyl, *t*-butyl, phenyl, benzyl,

30 methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, phenoxy,

benzyloxy, bromo, chloro, iodo, fluoro, nitro, cyano, acetyl,

pivaloyl, *iso*-butyryl, benzoyl, trifluoromethyl, trifluoromethoxy,

trifluoroacetyl, carbomethoxy, carboethoxy, methylthio,

*n*-propylsulfonyl, isopropylsulfonyl, dimethylsulfamoyl or oxazolyl,

35  $R^6$  and  $R^7$  are independently hydrogen, acetyl or methanesulfonyl,

or two R<sup>2</sup> groups linked to form naphthyl, indolyl or idolinyl, optionally substituted by acetyl or methyl.

4. A compound of claim 1 in which
  - 5 R<sup>1</sup> is hydrogen or methyl,
  - R<sup>2</sup> is hydrogen, methyl, ethyl, *t*-butyl, methoxy, ethoxy, *iso*-propoxy, phenoxy, benzyloxy, methylthio, bromo, chloro, fluoro, nitro, cyano, acetyl, benzoyl, trifluoromethyl, trifluoromethoxy, carbomethoxy, carboethoxy, amino, acetylamino, methanesulphonylamino or oxazolyl,
  - 10 or two R<sup>2</sup> groups form methylindolyl or acetylindolinyl or naphthyl.
5. A compound of claim 1 which is
  - N-(1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-nitrophenyl) urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-nitrophenyl) urea
  - 15 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-ethoxyphenyl) urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(4-ethoxyphenyl) urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-trifluoromethylphenyl)thiourea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-trifluoromethylphenyl)urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-methoxyphenyl)urea
  - 20 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-bromophenyl) urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-trifluoromethylphenyl)urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(5-chloro-2,4-dimethoxyphenyl) urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-*tert*-butyl, 2-methoxyphenyl)urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(phenyl) urea
  - 25 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-acetylphenyl)urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-methylphenyl)urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-methoxyphenyl)urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-chlorophenyl)urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-chloro-6-methoxyphenyl)urea
  - 30 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3,5-di-trifluoromethylphenyl)urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-trifluoromethoxyphenyl)urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-chloro-4-methylphenyl)urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-trifluoromethylphenyl)urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(5-chloro-2,4-dimethoxyphenyl)urea
  - 35 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-nitrophenyl)urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-bromophenyl) urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-methoxyphenyl)urea
  - N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(4-trifluoromethoxyphenyl)urea

- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(4-trifluoromethylphenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(phenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-acetylphenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-chloro-4-methylphenyl)urea  
 5 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-chloro-6-methoxyphenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-chlorophenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(2-methoxyphenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(2-methylphenyl)urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3,5-di-trifluoromethylphenyl)urea  
 10 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-trifluoromethylphenyl)thiourea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-carbomethoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2, 3-dimethylphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-methoxy-3-chlorophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(1-naphthyl) urea  
 15 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-methyl-3-nitrophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-cyanophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-cyano-3-methylphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(1-acetylinolin-7-yl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-cyanophenyl) urea  
 20 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-ethylphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3, 5-dinitrophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2, 3-dichlorophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-chloro-4-fluorophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-chloro-5-trifluoromethylphenyl)  
 25 urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-isopropoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-ethoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-*tert*butylphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-[3-(1,3-oxazol-5-yl)phenyl] urea  
 30 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-benzyloxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-phenoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-fluorophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(2-fluorophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-methylthiophenyl) urea  
 35 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-carboethoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-fluorophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3, 4-difluorophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-benzoylphenyl) urea

- N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(4-methoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-bromo-4-methoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-bromo-4-methoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(2,3-dichlorophenyl) urea  
 5 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(2-chloro-5-trifluoromethylphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-chloro-4-fluorophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(4-methoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-ethylphenyl) urea  
 10 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3, 5-dinitrophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-cyanophenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(3-bromo-4-methoxyphenyl) urea  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(3-aminophenyl) urea  
 N-{3-[3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)ureido]phenyl} acetamide  
 15 N-{3-[3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)ureido]phenyl} bis  
 methanesulphonimide or  
 N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(1-methylindol-5-yl) urea.

6. A process for the preparation of compounds of formula (I), which comprises  
 20 reacting a compound of formula (II)

(II)

25

where  $R^{1A}$  is  $R^1$  as defined for formula (I) or a group convertible to  $R^1$ , and  
 P is  $NH_2$  or  $NCX$ , X being as defined for formula (I),

with a compound of formula (III)

30

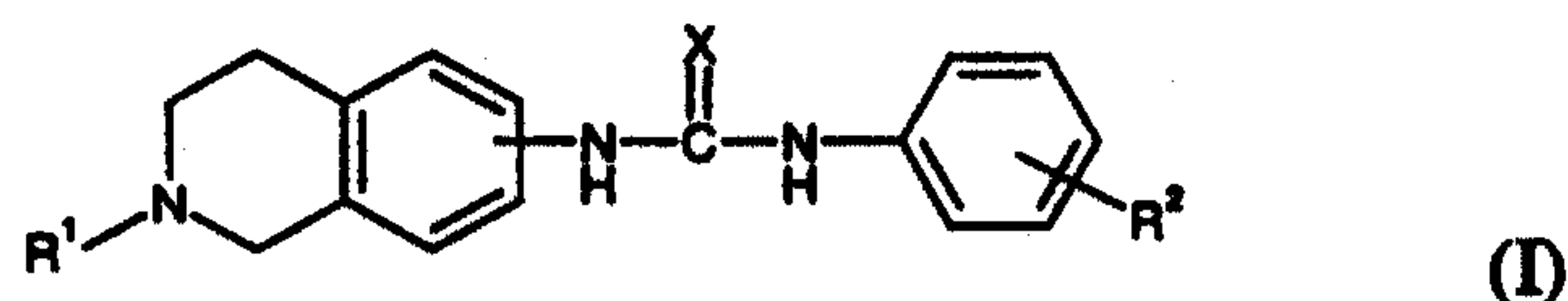
(III)

- where Q is  $NCX$  or  $NH_2$  and different from P, X being as defined for formula (I), and  
 35  $R^{2A}$  is  $R^2$  as defined for formula (I) or a group or groups convertible to  $R^2$ ,  
 and where required converting a  $R^{1A}$  or  $R^{2A}$  group to a  $R^1$  or  $R^2$  group, converting one  
 $R^1$  or  $R^2$  group to another  $R^1$  or  $R^2$  group, converting a salt product to the free base or

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

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

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



20

where X is O or S,

R<sup>1</sup> is hydrogen or C<sub>1-6</sub> alkyl,

R<sup>2</sup> is hydrogen or up to three substituents independently selected from halogen, CF<sub>3</sub>, NO<sub>2</sub>, CN, N<sub>3</sub>, C<sub>1-6</sub> alkylO-, C<sub>1-6</sub> alkylS-, C<sub>1-6</sub> alkyl,

25

C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkyl-C<sub>1-4</sub>alkyl-, C<sub>1-6</sub>alkenyl, C<sub>1-6</sub>alkynyl, CF<sub>3</sub>CO-, CF<sub>3</sub>O, C<sub>1-6</sub>alkylCO-, C<sub>3-6</sub>cycloalkylCO-,

C<sub>3-6</sub>cycloalkyl-C<sub>1-4</sub>alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C<sub>1-4</sub>alkyl-, heterocyclyl, or -NR<sup>6</sup>R<sup>7</sup> where

R<sup>6</sup> is hydrogen or C<sub>1-4</sub> alkyl, and

30

R<sup>7</sup> is hydrogen, C<sub>1-4</sub>alkyl, -CHO, -CO<sub>2</sub>C<sub>1-4</sub>alkyl or -COC<sub>1-4</sub>alkyl.