Title: 1,2,3,4-TETRAHYDRO-1-NAPHTHALENAMINE COMPOUNDS USEFUL IN THERAPY

Abstract:

The invention provides compounds of formula (I), wherein R¹ and R² independently represent H or C₁₋₆ alkyl; R³ represents phenyl substituted by at least one group selected from halo, CF₃, OCF₃, CN, OH, C₁₋₆ alkyl and C₁₋₆ alkoxy; and R⁴, R⁵ and R¹¹ independently represent H or (CH₂)₂–A, wherein n represents 0, 1 or 2, provided that at least one of R⁴, R⁵ and R¹¹ is other than H; A represents CONR³R⁵ or SO₂NR³R⁵, wherein R⁶ and R⁷ independently represent H, C₆–C₁₀ cycloalkyl or C₁₋₆ alkyl, the C¹⁻C₆ alkyl group being optionally substituted, in addition, R⁶ and R⁷ may, together with the N atom to which they are attached, represent a ring which is optionally substituted; CO₂R⁺, wherein R³ represents H or C₁₋₆ alkyl; NR³R¹¹, wherein R⁹ and R¹₀ independently represent H, C₁₋₆ alkyl (optionally substituted), (C₆–C₁₀ alkyl)CO₂–, H₂NSO₂– or H₂NCO₂–; a 5– or 6–membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O, which is optionally substituted; SO₂(C₁₋₆ alkyl), wherein x represents 0, 1 or 2; OH, CN, NO₂ or C₁₋₆ alkoxy which is optionally substituted; provided that when NR³R⁵R⁷ represents N(H) methyl, R⁴ represents H and R³ represents 4–chlorophenyl, then R⁵ does not represent methoxy; and pharmaceutically acceptable salts thereof. The compounds of the invention are useful in the treatment or prevention of a variety of disorders, including those in which the regulation of monoamine transporter function is implicated.
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1,2,3,4-Tetrahydro-1-naphthalenamine compounds useful in therapy

This invention relates to 1,2,3,4-tetrahydro-1-naphthalenamine compounds useful in the treatment or prevention of a variety of disorders, including those in which the regulation of monoamine transporter function is implicated, such as depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders and sexual dysfunction including premature ejaculation, and to pharmaceutical formulations containing such compounds.

European Patent N° 30081 discloses a group of 1,2,3,4-tetrahydro-1-naphthalenamine compounds indicated as antidepressants, including cis-(1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride (see Example 2 therein). This compound is known as sertraline and is available as LUSTRAL™ and ZOLOFT™. European Patent N° 30081 also discloses N-methyl-4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride (see Example 21 therein).

European Patent N° 415613 discloses the use of sertraline in the treatment of premature ejaculation. It also gives a vague indication that some of the other compounds disclosed in the sertraline patent may be effective in the treatment of premature ejaculation.

According to the present invention, there is provided a compound of formula I,

![Chemical Structure](image)

wherein

R¹ and R² independently represent H or C₁₋₆ alkyl;

R³ represents phenyl substituted by at least one group selected from hal₅, CF₃, OCF₂, CN, OH, C₁₋₆ alkyl and C₁₋₆ alkoxy; and

R⁴, R⁵ and R¹¹ independently represent H or -(CH₂)ₙ₋₁₋ₐ-A, wherein n represents 0, 1 or 2, provided that at least one of R⁴, R⁵ and R¹¹ is other than H;
A represents:

\[ \text{CONR}^6\text{R}^7 \text{ or SO}_2\text{NR}^6\text{R}^7, \] wherein \( R^6 \) and \( R^7 \) independently represent H, C\(_{3-6}\) cycloalkyl or C\(_{1-6}\) alkyl,
the C\(_{1-6}\) alkyl group being optionally substituted by one or more groups
selected from OH, CO\(_2\)H, C\(_{3-6}\) cycloalkyl, NH\(_2\), CONH\(_2\), C\(_{1-6}\) alkoxy, C\(_{1-6}\)
alkoxycarbonyl and a 5- or 6-membered heterocyclic ring (containing 1, 2
or 3 heteroatoms selected from N, S and O);
in addition, \( R^6 \) and \( R^7 \) may, together with the N atom to which they are
attached, represent a pyrrolidine or piperidine ring (which rings are
optionally substituted by OH or CONH\(_2\)) or a morpholine ring (which is
optionally substituted by CONH\(_2\));

\[ \text{CO}_2\text{R}^8, \] wherein \( R^8 \) represents H or C\(_{1-6}\) alkyl;
\[ \text{NR}^9\text{R}^{10}, \] wherein \( R^9 \) and \( R^{10} \) independently represent H, C\(_{1-6}\) alkyl (optionally
substituted by OH or C\(_{1-6}\) alkoxy), (C\(_{1-6}\) alkyl)\( \text{SO}_2\)\(^-\), (C\(_{1-6}\) alkyl)\( \text{CO}_2\)\(^-\), H\(_2\)\( \text{NSO}_2\)\(^-\) or
H\(_2\)NCO\(^-\);
a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected
from N, S and O, optionally substituted by one or more groups selected from C\(_{1-6}\)
alkyl, NH\(_2\), OH, =O and CONHCH\(_3\);
\[ \text{S(O)}_x\text{(C}_{1-6}\text{ alkyl)}, \] wherein \( x \) represents 0, 1 or 2;

\[ \text{OH}; \]
\[ \text{CN}; \]
\[ \text{NO}_2; \] or
\[ \text{C}_{1-6}\text{ alkoxy optionally substituted by one or more groups selected from SO}_2\text{NH}_2\]
and CONH\(_2\);

provided that when NR\(^1\)R\(^2\) represents N(H)methyl, R\(^4\) represents H and R\(^5\) represents 4-
chlorophenyl, then R\(^5\) does not represent methoxy;
and pharmaceutically acceptable salts thereof.

The pharmaceutically acceptable salts of the compounds of formula I which contain a
basic centre are, for example, non-toxic acid addition salts formed with inorganic acids
such as hydrochloric, hydrobromic, sulphuric and phosphoric acid, with carboxylic acids,
ammonia or with organo-sulphonic acids. Examples include the hydrochloride,
hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, camyslate, ammonium, methanesulphonate, benzenesulphonate, and p-toluenesulphonate salts. Compounds of formula I containing an acidic centre may also form pharmaceutically acceptable metal salts, in particular non-toxic alkali or alkaline earth metal salts, with bases. Examples include the calcium, sodium and potassium salts. For a review of suitable pharmaceutical salts see J. Pharm, Sci., 1977, 66, 1.

"Halo" includes fluorine, chlorine, bromine and iodine.

Alkyl groups which \( R^{1-5} \) and \( R^{11} \) may represent or comprise may be straight chain or branched.

Heterocyclic rings that \( A \) may represent or comprise may be saturated or unsaturated. A specific heterocyclic ring that \( R^4 \) or \( R^7 \) may comprise is furanyl. Specific heterocyclic rings that \( A \) may represent include oxadiazolyl, triazolyl, pyrazolyl, pyridinyl and pyrimidinyl.

Because \( R^4 \) and \( R^5 \) are defined independently, when both represent \(-\text{CH}_2\)\(_n\)-\( A \), the nature of these two groups is not necessarily the same. The same applies to other substituents that are defined independently.

The compounds of formula I may possess one or more chiral centres and so exist in a number of stereoisomeric forms. All stereoisomers and mixtures thereof are included in the scope of the present invention. Racemic compounds may either be separated using preparative HPLC and a column with a chiral stationary phase or resolved to yield individual enantiomers utilising methods known to those skilled in the art. In addition, chiral intermediate compounds may be resolved and used to prepare chiral compounds of formula I.
The compounds of formula I may exist in one or more tautomeric forms. All tautomers and mixtures thereof are included in the scope of the present invention. For example, a claim to 2-hydroxypyridinyl would also cover its tautomeric form, α-pyridonyl.

The invention also includes radiolabelled compounds of formula I.

Preferred groups of compounds include those in which:
(a) $\text{NR}^1\text{R}^2$ represents NH(C$_{1-6}$ alkyl), more preferably N(H)methyl;
(b) $\text{R}^3$ represents phenyl disubstituted with halo, more preferably 3,4-dichlorophenyl;
(c) $\text{R}^4$ represents H;
(d) $\text{R}^5$ represents -(CH$_2$)$_n$-A;
(e) $\text{R}^{11}$ represents H;
(f) $\text{A}$ represents CONR$^6$R$^7$, SO$_2$NR$^6$R$^7$ or NO$_2$;
(g) one of $\text{R}^6$ and $\text{R}^7$ represents H, and the other represents H or C$_{1-6}$ alkyl optionally substituted by OH;
(h) $n$ represents 0; and
(i) the stereochemistry is as shown in formula Ia,

![Chemical Structure Ia](image)

wherein $\text{R}^{1-5}$ and $\text{R}^{11}$ are as defined above.

Another group of compounds that may be mentioned is compounds of formula $\text{I}'$,

![Chemical Structure I'](image)

wherein
$\text{R}^1$ and $\text{R}^2$ independently represent H or C$_{1-6}$ alkyl;
R³ represents phenyl substituted by at least one group selected from halo, CF₃, OCF₃, CN, OH, C₁₋₆ alkyl and C₁₋₆ alkoxy; and

R⁴ and R⁵ independently represent H or -(CH₂)ₙ-A, wherein n represents 0, 1 or 2, provided that at least one of R⁴ and R⁵ is other than H;

A represents:

CONR⁶R⁷ or SO₂NR⁶R⁷, wherein R⁶ and R⁷ independently represent H, C₁₋₆
cycloalkyl or C₁₋₆ alkyl,

the C₁₋₆ alkyl group being optionally substituted by one or more groups
selected from OH, CO₂H, C₁₋₆ cycloalkyl, NH₂, CONH₂, C₁₋₆ alkoxy, C₁₋₆
alkoxycarbonyl and a 5- or 6-membered heterocyclic ring (containing 1, 2
or 3 heteroatoms selected from N, S and O);

in addition, R⁶ and R⁷ may, together with the N atom to which they are
attached, represent a pyrrolidine or piperidine ring (which rings are
optionally substituted by OH or CONH₂) or a morpholine ring (which is
optionally substituted by CONH₂);

CO₂R⁸, wherein R⁸ represents H or C₁₋₆ alkyl;

NR⁹R¹⁰, wherein R⁹ and R¹⁰ independently represent H, C₁₋₆ alkyl (optionally
substituted by OH or C₁₋₆ alkoxy), (C₁₋₆ alkyl)SO₂⁻, (C₁₋₆ alkyl)CO⁻, H₂NSO₂⁻ or
H₂NCO⁻;

a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected
from N, S and O, optionally substituted by one or more groups selected from C₁₋₆
alkyl, NH₂, OH, =O and CONHCH₃;

S(O)ₓ(C₁₋₆ alkyl), wherein x represents 0, 1 or 2;

OH;

CN;

NO₂; or

C₁₋₆ alkoxy optionally substituted by one or more groups selected from SO₂NH₂
and CONH₂;

provided that when NR¹R² represents N(H)methyl, R⁴ represents H and R⁵ represents 4-
chlorophenyl, then R³ does not represent methoxy;

and pharmaceutically acceptable salts thereof.
The invention also provides a process for the production of a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, which includes:

(a) when $R^4, R^5$ or $R^{11}$ represents CONR$^6$R$^7$, reaction of a compound of formula II,

(b) when $R^4, R^5$ or $R^{11}$ represents SO$_2$NR$^6$R$^7$, reaction of a compound of formula IV,

(c) when $R^4, R^5$ or $R^{11}$ represents CO$_2$(C$_{1-6}$ alkyl), reaction of a compound of formula II, as defined above; with CO and a C$_{1-6}$ alkanol in the presence of a Pd(0) catalyst;

(d) when $R^4, R^5$ or $R^{11}$ represents NO$_2$, reaction of a compound of formula V,

wherein $R^{1-3}$ are as defined above;
(e) when $R^4$, $R^5$ or $R^{11}$ represents a heterocyclic ring attached to the rest of the molecule by a N atom, reaction of a compound of formula II as defined above; with a heterocyclic compound containing an NH group in the ring, in the presence of a copper catalyst;

(f) when $R^4$, $R^5$ or $R^{11}$ represents a heterocyclic ring attached to the rest of the molecule by a C atom, reaction of a compound of formula VI,

\[
\text{VI}
\]

wherein $R^{13}$ are as defined above, the corresponding group $R^{4f}$, $R^{5f}$ or $R^{11f}$ represents a group of formula F,

\[
\text{F}
\]

and the remainder represent H or $-(\text{CH}_2)_n$-$\text{A}$, wherein n and A are as defined above; with a heterocyclic compound containing a C-Br or C-I group in the ring, in the presence of a Pd(0) catalyst;

(g) when $R^4$, $R^5$ or $R^{11}$ represents a heterocyclic ring attached to the rest of the molecule by a C atom, reaction of a compound of formula II, as defined above; with a heterocyclic compound which is optionally substituted with iodo on the C atom by which the heterocyclic ring will be attached to the rest of the molecule, in the presence of butyl lithium and a Pd(0) catalyst;

(h) when $R^4$, $R^5$ or $R^{11}$ represents $\text{S(O)}_x(\text{C}_{1-6}\text{ alkyl})$, reaction of a compound of formula II, as defined above; with a compound of formula VII,

\[
\text{VII}
\]

in the presence of a copper or palladium catalyst, followed by oxidation if desired to give compounds in which x is 1 or 2;

(i) when $R^4$, $R^5$ or $R^{11}$ represents CN, reaction of a compound of formula II, as defined above; with zinc cyanide, in the presence of a Pd(0) catalyst;
(j) when \( R^4, R^5 \) or \( R^{11} \) represents \( CH_2CH_2SO_2NR^6R^7 \) or \( CH_2CH_2SO_2(C_{1-6} \text{ alkyl}) \), reaction of a compound of formula II, as defined above; with a compound of formula IX,

\[
CH_2=CHA^k
\]

IX

wherein \( A^k \) represents \( SO_2NR^6R^7 \) or \( SO_2(C_{1-6} \text{ alkyl}) \) as appropriate, in which \( R^6 \) and \( R^7 \) are as defined above, in the presence of a Pd(II) catalyst, followed by reduction of the resulting alkene;

(k) when \( R^4, R^5 \) or \( R^{11} \) represents \( CH_2CH_2CO_2(C_{1-6} \text{ alkyl}) \), reaction of a compound of formula II, as defined above; with a compound of formula X,

\[
CH_2=CHCO_2(C_{1-6} \text{ alkyl})
\]

X

in the presence of a Pd(II) catalyst, followed by reduction of the resulting alkene; or

(l) when one of \( R^1 \) and \( R^2 \) represents \( C_{1-6} \text{ alkyl} \) and the other represents \( H \), removing a protecting group from a compound of formula XI,

![Diagram of XI](image)

wherein \( R^{3-5} \) and \( R^{11} \) are as defined above, and \( Pg \) is a protecting group;

and where desired or necessary, converting the resulting compound into a pharmaceutically acceptable salt, or vice versa.

In process (a), the reaction is preferably carried out in a solvent that does not adversely affect the reaction (for example dimethylformamide), at an elevated temperature. Suitable Pd(0) catalysts include tetrakis(triphenylphosphine)palladium.

In process (b), the reaction is preferably carried out in a solvent that does not adversely affect the reaction (for example dichloromethane or acetonitrile), at or around room temperature.

In process (c), the reaction is preferably carried out in a solvent that does not adversely affect the reaction (for example dimethylformamide), at an elevated temperature. The
solvent may be the reacting C_{1,6} alkanol (for example methanol). Suitable Pd(0) catalysts include tetrakis(triphenylphosphine)palladium.

In process (d), the reaction is preferably carried out in a solvent that does not adversely affect the reaction (for example trifluoroacetic acid), below room temperature. The alkali metal nitrate may be potassium nitrate and the sulphonic acid may be triflic acid.

In process (e), the reaction is preferably carried out without a solvent, at an elevated temperature (for example 160°C) in the presence of a base such as potassium carbonate.

In process (f), the reaction is preferably carried out in a solvent that does not adversely affect the reaction (for example dioxan/water), at an elevated temperature. Suitable Pd(0) catalysts include tetrakis(triphenylphosphine)palladium. Preferably, caesium carbonate is also present.

In process (g), the reaction is preferably carried out in a solvent that does not adversely affect the reaction (for example diethyl ether or tetrahydrofuran), at an elevated temperature. Suitable Pd(0) catalysts include tetrakis(triphenylphosphine)palladium. Preferably, zinc chloride is also present.

In process (h), the reaction is preferably carried out in a solvent that does not adversely affect the reaction (for example ethylene glycol), at an elevated temperature in the presence of a base such as potassium carbonate. Suitable palladium catalysts include tetrakis(triphenylphosphine)palladium and palladium acetate. Suitable oxidizing agents include hydrogen peroxide in trifluoroacetic acid.

In process (i), suitable palladium catalysts include tetrakis(triphenylphosphine)palladium. The reaction is preferably carried out in a solvent that does not adversely affect the reaction (for example dimethylformamide), at an elevated temperature.

In processes (j) and (k), the reaction is preferably carried out in a solvent that does not adversely affect the reaction (for example acetonitrile), at an elevated temperature.
Suitable Pd(II) catalysts include palladium acetate. Preferably, tri(o-tolyl)phosphine and triethylamine are also present. The resulting alkene may be reduced using tosylhydrazine in toluene at an elevated temperature.

In process (I), suitable protecting groups include tert-butyloxycarbonyl. In this case, the protecting group is preferably removed by the action of HCl, for example by bubbling HCl gas through a solution of the compound of formula XI, or by adding a saturated solution of HCl in a solvent such as dichloromethane to a compound of formula XI. Preferably, the reaction is carried out below room temperature, for example 0°C.

The invention also provides compounds of formulae II, IV, VI and XI as defined above. When R' represents H, compounds of formulae II, IV and VI may be obtained from compounds of formula V as shown in the following scheme (in which R' is as defined above) and as illustrated by the accompanying Examples:

Compounds of formula V are disclosed in European Patent No 30081. The following general method is given on page 5 of European Patent No 30081, and is used to produce sertraline (the compound in which W represents H, and X and Y each represent Cl):
Compounds of formula I may be converted into other compounds of formula I using known techniques, as illustrated by the examples. For example when A represents:

(1) NH₂, it may be converted to OH by reaction with formic acid and acetic anhydride and then reacting the resulting formamide with sodium nitrite and concentrated sulphuric acid;

(2) NH₂, it may be converted to NH(C₁₆ alkyl) by reductive amination with a C₁₆ aldehyde and sodium triacetoxyborohydride;

(3) CO₂(C₁₆ alkyl), it may be reduced to CH₂OH, which may in turn be converted to CH₂Cl, both of which groups may undergo a wide variety of reactions;

(4) CO₂(C₁₆ alkyl), it may be converted to CONR²R⁷ by reaction with HNR⁶R³;
(5) NO₂, it may be converted to NH₂ by reaction with iron powder and calcium chloride;
(6) OH, it may be converted to optionally substituted C₃₋₄ alkoxy by reaction with Cl-(optionally substituted C₃₋₄ alkyl);
(7) CN, it may be converted to CH₂NH₂ by reduction using lithium aluminium hydride;
(8) CN, it may be converted to CONH₂ by reaction with concentrated sulphuric acid; and
(9) CONH₂, it may be converted to CH₂NH₂ by reaction with B₂H₆ in tetrahydrofuran
(see Kruijtzer et al, Tetrahedron Lett, vol 38(30), 1997, pp 5335-5338), which may then be reacted with MeSO₂Cl in pyridine (see Ito et al, Chem Pharm Bull, vol 25(7), 1977, pp 1732-1739) to give a group of formula CH₂NH₂SO₃Me.

When R⁴, R⁵ or R¹¹ represents CH₂OH, it may be converted to CH₂Cl by reaction with hydrogen chloride and thionyl chloride, which group may undergo displacement of the chlorine atom by, for example a heterocyclic compound containing an NH group, to give compounds of formula I in which n is 1. The CH₂Cl group may also be reacted with thiourea and sodium hydroxide (see Yamada et al, J Med Chem, vol 39(2), 1996, pp 594-604) to give a group of formula CH₂SH, which may then be reacted with KNO₃ and SO₂Cl₂ in CH₂CN (see Park et al, Chem Lett, vol 8, 1992, pp 1483-1486) to give a group of formula CH₂SO₂NH₂.

In the above processes (a)-(k), preferably the reaction is carried out to produce a compound of formula I in which one of R⁴ and R⁵ is -(CH₂)ᵦ-A and the other is H and R¹¹ is H.

As illustrated in Example 88 below, an iodine atom may be introduced into the 6-position of the 1,2,3,4-tetrahydro-1-naphthalenamine ring using benzyltrimethylammonium dichloroiodiate, giving access to compounds of formula I in which R⁴ and R⁵ both independently represent -(CH₂)ᵦ-A. In compounds of this type, when R⁵ represents NH₂, this group can be replaced by hydrogen by reaction with tert-butyl nitrite to give
compounds in which $R^4$ represents $-(\text{CH}_2)_n-\text{A}$ and $R^5$ represents H (see Example 90 below).

As illustrated in Example 112 below, a bromine atom may be introduced into the 8-position of the 1,2,3,4-tetrahydro-1-naphthalenamine system using N-bromosuccinimide, giving access to compounds of formula I in which $R^{11}$ represents $-(\text{CH}_2)_n-\text{A}$.

Compounds of formulae III, V, VII, IX and X are either known or are available using known techniques.

It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of formula I. This may be achieved by conventional techniques, for example as described in ‘Protective Groups in Organic Synthesis’, 3rd edition, by T W Greene and P G M Wuts, John Wiley and Sons Inc, 1999. Compounds of formula XI in which the amine group at position 1 of the 1,2,3,4-tetrahydro-1-naphthalenamine system is protected are illustrated by the accompanying examples.

The compounds of formula I, and their pharmaceutically acceptable salts, are useful because they have pharmacological activity in animals, including humans. More particularly, they are useful in the treatment or prevention of a disorder in which the regulation of monoamine transporter function is implicated. Disease states that may be mentioned include hypertension, depression (e.g. depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, paediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, and post partum depression), generalized anxiety disorder, phobias (e.g. agoraphobia, social phobia and simple phobias), posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, eating disorders (e.g. anorexia nervosa and bulimia nervosa), obesity, chemical dependencies (e.g. addictions to alcohol, cocaine, heroin, phenobarbital, nicotine and benzodiazepines), cluster headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder, panic disorder, memory disorders (e.g. dementia, amnestic
disorders, and age-related cognitive decline (ARCD), Parkinson's diseases (e.g. dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias), endocrine disorders (e.g. hyperprolactinaemia), vasospasm (particularly in the cerebral vasculature), cerebellar ataxia, gastrointestinal tract disorders (involving changes in motility and secretion), negative symptoms of schizophrenia, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male impotence, attention deficit hyperactivity disorder (ADHD), chronic paroxysmal hemicrania, headache (associated with vascular disorders), emotional lability, pathological crying and sleeping disorder (cataplexy).

Disorders of particular interest include depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders and sexual dysfunction including (in particular) premature ejaculation. The compounds of formula I, and their pharmaceutically acceptable salts, may be administered alone or as part of a combination therapy.

Premature ejaculation may be defined as persistent or recurrent ejaculation before, upon or shortly after penile penetration of a sexual partner. It may also be defined as ejaculation occurring before the individual wishes [see 'The Merck Manual', 16th edition, p 1576, published by Merck Research Laboratories, 1992].

Thus, according to a further aspect of the invention, there is provided a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

There is further provided a pharmaceutical formulation containing a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention also provides the use of a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of a disorder in which the regulation of monoamine transporter
function is implicated, for example depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders or sexual dysfunction including premature ejaculation. The invention also provides a method of treatment or prevention of these diseases, which comprises administering a therapeutically effective amount of a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, to a patient in need of such treatment or prevention.

The invention also provides the use of N-methyl-4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of premature ejaculation, and also provides a method of treatment or prevention of premature ejaculation comprising the administration of this compound to a patient in need of such treatment or prevention.

The invention also provides a method of increasing ejaculatory latency which comprises the administration of an effective amount of a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, or N-methyl-4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine, or a pharmaceutically acceptable salt thereof, to a male desiring increased ejaculatory latency.

For human use the compounds of formula I, and their pharmaceutically acceptable salts, can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of formula I, and their pharmaceutically acceptable salts, can be administered orally, buccally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications.
Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of formula I, and their pharmaceutically acceptable salts, may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The compounds of formula I, and their pharmaceutically acceptable salts, can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intrarethraly, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

The compounds of formula I, and their pharmaceutically acceptable salts, can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebulizer with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-
tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray or nebulizer may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of formula I, and their pharmaceutically acceptable salts, and a suitable powder base such as lactose or starch.

Alternatively, the compounds of formula I, and their pharmaceutically acceptable salts, can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of formula I, and their pharmaceutically acceptable salts, may also be dermally or transdermally administered, for example, by the use of a skin patch. They may also be administered by the pulmonary or rectal routes.

They may also be administered by the ocular route, particularly for treatment of the eye. For ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

For application topically to the skin, the compounds of formula I, and their pharmaceutically acceptable salts, can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.
For oral or parenteral administration to human patients the daily dosage levels of compounds of formula I, and their pharmaceutically acceptable salts, will be from 0.01 to 30 mg/kg (in single or divided doses) and preferably will be in the range 0.01 to 5 mg/kg. Thus tablets will contain 1mg to 0.4g of compound for administration singly or two or more at a time, as appropriate. The above dosages are, of course only exemplary of the average case and there may be instances where higher or lower doses are merited, and such are within the scope of the invention.

Oral administration is preferred. Preferably, administration takes place shortly before an effect is required.

Without being limited by theory, the compounds of formula I are believed to be serotonin re-uptake inhibitors (SRIs). Compounds that selectively inhibit the re-uptake of serotonin, but not noradrenaline or dopamine, are preferred.

The compounds of formula I, and their pharmaceutically acceptable salts, have the advantage that they are selective inhibitors of the re-uptake of serotonin (and so are likely to have reduced side effects), they have a rapid onset of action (making them suitable for administration shortly before an effect is required), they are more potent, or have other more desirable properties than the compounds of the prior art.

The present invention may be defined in an alternative manner as a compound of formula B,

\[
\begin{align*}
R^5 & \quad R^{11} \\
R^4 & \quad NR^1R^2 \\
R^3 & \quad \text{B}
\end{align*}
\]

wherein
R\(^1\) and R\(^2\) independently represent H or C\(_{1-6}\) alkyl;
R\(^3\) represents phenyl substituted by at least one group selected from halo, CF\(_3\), OCF\(_3\), CN, OH, C\(_{1-6}\) alkyl and C\(_{1-6}\) alkoxy; and
R\(^4\), R\(^5\) and R\(^{11}\) independently represent H or -(CH\(_2\))\(_n\)-A', wherein A' is a polar group and n represents 0, 1 or 2, provided that at least one of R\(^4\), R\(^5\) and R\(^{11}\) is other than H; provided that when NR\(^1\)R\(^2\) represents N(H)methyl, R\(^4\) represents H and R\(^5\) represents 4-chlorophenyl, then R\(^5\) does not represent methoxy; and pharmaceutically acceptable salts thereof.

In this alternative definition, polar groups may be defined as those having a negative π-value (see C Hansch and A Leo, 'Substituent Constants for Correlation Analysis in Chemistry and Biology', Wiley, New York, 1979). In this system, H has a π-value of 0.00, -OCH\(_3\) has a π-value of -0.02, and -SO\(_2\)NH\(_2\) has a π-value of -1.82, for example [see Table VI-I, 'Well-Characterized Aromatic Substituents', p 49, ibid]. More preferred polar groups have a more negative π-value: thus, preferred groups have π-values of a greater negative value than -0.1, more preferably a greater negative value than -0.5, and most preferably a greater negative value than -1.0. Even when n is other than zero in the above definition, the definition of A' is based on the above reference as if n was zero.

The present invention also provides use of a serotonin re-uptake inhibitor comprising both a basic amine group [for example NHCH\(_3\), N(CH\(_3\))\(_2\), NH\(_2\), -NH- or -N(CH\(_3\))-] and a polar group in the manufacture of a medicament for the treatment of premature ejaculation. In this aspect of the invention, it is preferred that:

(a) the serotonin re-uptake inhibitor is more than 10-fold (more preferably more than 100-fold) as potent in the inhibition of serotonin transporters than in the inhibition of both dopamine transporters and noradrenaline transporters – relative potency for inhibition of serotonin, dopamine and noradrenaline transporters may be determined in Test A below;

(b) the polar group is attached directly to an aromatic ring (see the definition and preferences in the preceding paragraph);

(c) the polar group has a π-value more negative than -0.1; and/or

(d) the serotonin re-uptake inhibitor is a derivative or analogue of sertraline, paroxetine, fluoxetine, citalopram, fluvoxamine, norfluoxetine, femoxetine, tomoxetine or venlafaxine (whose structures are given below).
The biological activity of the compounds of formula I, and their pharmaceutically acceptable salts, may be demonstrated in the following test:

Test A
Uptake of $^3$H-biogenic amines into human embryonic kidney cells expressing the human serotonin (5-HT), noradrenaline or dopamine transporter

Cell Culture

Human embryonic kidney cells (HEK-293) stably transfected with either the human serotonin transporter (hSERT), noradrenaline transporter (hNET) or dopamine transporter (hDAT) were cultured under standard cell culture techniques (cells were grown at 37°C and 5% CO$_2$ in DMEM-culture media (supplemented with 10% dialysed foetal calf serum (FCS), 2mM l-glutamine and 250μg/ml geneticin)). Cells were harvested for the assay to yield a cell suspension of 750,000 cells/ml.

Determination of inhibitor potency

All test compounds were dissolved in 100% DMSO and diluted down in assay buffer to give appropriate test concentrations. Assays were carried out in 96-well filter bottom plates. Cells (7500 cells/assay well) were pre-incubated in standard assay buffer containing either test compound, standard inhibitor or compound vehicle (1% DMSO) for 5 minutes. Reactions were started by addition of either $^3$H-Serotonin, $^3$H-Noradrenaline or $^3$H-Dopamine substrates. All reactions were carried out at room temperature in a shaking incubator. Incubation times were 5 minutes for the hSERT and hDAT assays and 15 minutes for the hNET assay. Reactions were terminated by removal of the reaction mixture using a vacuum manifold followed by rapid washing with ice cold assay buffer. The quantity of $^3$H-substrate incorporated into the cells was then quantified.

Assay plates were dried in a microwave oven, scintillation fluid added, and radioactivity measured. Potency of test compounds was quantified as IC$_{50}$ values (concentration of test compound required to inhibit the specific uptake of radiolabelled substrate into the cells by 50%).

Standard Assay Buffer Composition:

30 Trizma hydrochloride (26mM)
NaCl (124mM)
KCl (4.5mM)
KH₂PO₄ (1.2mM)
MgCl₂·6H₂O (1.3mM)
Ascorbic acid (1.136mM)
Glucose (5.55mM)

pH 7.40
CaCl₂ (2.8mM)
Pargyline (100µM)

Note: The pH of the buffer was adjusted to 7.40 with 1M NaOH before addition of CaCl₂ and pargyline.

Summary of Assay Parameters

<table>
<thead>
<tr>
<th></th>
<th>hSERT Assay</th>
<th>hDAT Assay</th>
<th>hNET Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell concentration per</td>
<td>75,000</td>
<td>75,000</td>
<td>75,000</td>
</tr>
<tr>
<td>assay well.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substrate Concentration.</td>
<td>³H-5HT (50nM)</td>
<td>³H-Dopamine (200nM)</td>
<td>³H-Noradrenaline (200nM)</td>
</tr>
<tr>
<td>Incubation time (minutes)</td>
<td>5</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>
The invention is illustrated by the following Examples, in which the following abbreviations are used:

- 0.88 ammonia
- concentrated ammonium hydroxide solution, 0.88 SG
- BOC
- tert-butyloxycarbonyl
- DMAP
- 4-N,N-dimethylaminopyridine
- EDC
- 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
- Et₂O
- diethylether
- h
- hour
- 10
- HOBT
- 1-hydroxybenzotriazole hydrate
- min
- minute
- DMSO
- dimethylsulphoxide
- EtOAc
- ethyl acetate
- MS
- mass spectrum
- 15
- NMR
- nuclear magnetic resonance
- TBTU
- O-benzothiazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoro-
  borate

**Example 1**

20 Cis-(1S)-N-methyl-7-carboxamido-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-
  naphthalenamine

(a) Cis-(1S)-N-methyl-7-iodo-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-
  naphthalenamine

N-Iodosuccinimide (19.7g, 0.088mol) was added to a stirred solution of cis-(1S)-N-
  methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine (Sertraline, see
  European Patent 0030081, Example 2) (30g, 0.098mol) and trifluoromethanesulphonic
  acid (29ml) in dichloromethane (150ml) at 0°C. The reaction was stirred for 16h and a
  further portion of N-iodosuccinimide (4.41g, 0.0196mol) added. After 7 hours, 2N
aqueous sodium hydroxide solution (200ml) was added and the mixture extracted with
diethyl ether (3x200ml). The combined organic extracts were washed with saturated
aqueous sodium thiosulphate solution (200ml), dried (MgSO₄), filtered and evaporated
under reduced pressure to give a brown oil. The crude compound was purified on silica
gel eluting with 50:50:1 ethyl acetate:pentane:diethylamine to give the subtitle compound
as a yellow oil (29.5g, 79%). MS m/z 431 (M)+. ¹H-NMR (CDCl₃): δ = 1.79 (1H, m),
1.99 (3H, m), 2.53 (3H, m), 3.66 (1H, t), 3.92 (1H, dd), 6.54 (1H, d), 6.94 (1H, d), 7.22
(1H, s), 7.35 (1H, d), 7.42 (1H, d), 7.73 (1H, s).

(b) Cis-(1S)-N-methyl-7-carboxamido-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-
naphthalenamine

![Chemical Structure](image)

The product iodide from step (a) (0.25g, 0.00058mol),
tetrakis(triphenylphosphine)palladium (0.033g, 0.00003mol) and triethylamine (0.12ml)
in ammoniacal ethanol (15ml) were heated at 80°C at 690 kPa (100 p.s.i.) pressure under
an atmosphere of carbon monoxide for 3 hours. The reaction was cooled, the solvent
removed under reduced pressure and the crude product purified on silica gel eluting with a
gradient of 97:3:0.5 to 90:10:2 dichloromethane:methanol: 0.88 ammonia to give the
subtitle compound as a white foam (0.03g, 13%). MS m/z 348 (M)+. ¹H-NMR (CDCl₃): δ
= 1.90 (1H, m), 2.06 (3H, m), 2.57 (3H, s), 3.81 (1H, t), 4.02 (1H, dd), 6.90 (1H, d), 6.97
(1H, d), 7.25 (1H, s), 7.38 (1H, d), 7.55 (1H, d), 7.93 (1H, s).

An alternative route to the title compound of Example 1 is given in steps (c) and (d)
below:

(c) Cis-(1S)-N-methyl-7-cyano-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-
naphthalenamine hydrochloride
Zinc cyanide (0.07g, 0.0006mol) and tetrakis(triphenylphosphine)palladium (0.08g, 0.00007mol) were added to a stirred solution of the iodide produced in step (a) (0.37g, 0.0085mol) in N,N-dimethylformamide (10ml) and the mixture heated at 100°C for 3 hours. The mixture was cooled, poured into water (30ml) and extracted with diethyl ether (50ml). The organic phase was washed with water (3x50ml), dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 97.5:2.5:0.25 dichloromethane:methanol:0.88 ammonia. The solvent was removed under reduced pressure and the residue treated with a saturated solution of hydrogen chloride in diethyl ether (15ml). The solvent was removed under reduced pressure, the residue dissolved in methanol (15ml) and the solvent removed in vacuo to give the subtitle compound (0.173g, 62%). MS m/z 330 (M⁺). ¹H-NMR (CDCl₃): δ = 2.13 (2H, m), 2.36 (2H, m), 2.70 (3H, s), 4.00 (1H, dd), 4.40 (1H, t), 7.02 (1H, d), 7.22 (1H, d), 7.37 (1H, d), 7.49 (2H, m), 8.17 (1H, s).

(d) Cis-(1S)-N-methyl-7-carboxamido-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

A solution of the nitrile produced in step (c) (1.3g, 0.0039mol) in concentrated sulphuric acid (40ml) was heated at 100°C for 70 minutes. The mixture was cooled and poured into water (300ml). The mixture was extracted with ethyl acetate (2x100ml), the organic extracts combined, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with a gradient of 90:10:2
to 80:20:3 dichloromethane:methanol:0.88 ammonia to give the title compound (0.34g, 25%), identical with the material obtained in step (b).

Using the general procedure described in Example 1(b), the following amides were prepared by reaction of the iodide produced in Example 1(a) and the appropriate amine:

![Chemical Structure](attachment:chemical_structure.png)

<table>
<thead>
<tr>
<th>Example No.</th>
<th>R</th>
<th>(^1\text{H}-\text{NMR and mass spectral data} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>N(CH(_3))(_2)</td>
<td>(\delta = 1.85 \text{ (1H, m), 2.06 (3H, m), 2.53 (3H, s), 3.06 (2 x 3H, s), 3.77 (1H, t), 3.98 (1H, dd), 6.83 (1H, d), 6.97 (1H, d), 7.17 (1H, d), 7.25 (1H, s), 7.35 (1H, d), 7.52 (1H, s) (NH missing). MS (m/z) 376 (M(^+)).} )</td>
</tr>
<tr>
<td>3</td>
<td>[\text{N-structure}]</td>
<td>(\delta = 1.74-2.11 \text{ (8H, m), 2.50 (3H, s), 3.46 (2H, m), 3.61 (2H, t), 3.70 (1H, t), 3.95 (1H, dd), 6.80 (1H, d), 6.94 (1H, d), 7.22 (2H, m), 7.32, (1H, d), 7.53 (1H, s) (NH missing). MS (m/z) 402 (M(^+)).} )</td>
</tr>
<tr>
<td>4</td>
<td>HO – NH</td>
<td>(\delta = 1.85 \text{ (1H, m), 2.03 (3H, m), 2.57 (3H, s), 3.63 (2H, m), 3.77 (1H, t), 3.84 (2H, m), 4.01 (1H, dd), 6.61 (1H, m), 6.90 (1H, d), 6.96 (1H, d), 7.22 (1H, s), 7.36 (1H, d), 7.52 (1H, d), 7.86 (1H, s). MS (m/z) 392 (M(^+)).} )</td>
</tr>
<tr>
<td>5</td>
<td>[\text{NH-structure}]</td>
<td>(\delta = 0.28 \text{ (2H, dd), 0.54 (2H, dd), 1.62-1.90 (4H, m), 2.05 (1H, m), 2.55 (3H, s), 3.32 (2H, t), 3.78 (1H, t), 4.00 (1H, dd), 6.30 (1H, br.), 6.86 (1H, d), 6.96 (1H, d), 7.23 (1H, s), 7.36 (1H, d), 7.85 (1H, s). MS (m/z) 402 (M(^+)).} )</td>
</tr>
</tbody>
</table>
Example 6

Cis-(1S)-N-methyl-7-(N-methylamido)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

(a) Cis-(1S)-N-methyl-7-(methoxycarbonyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

The iodide product of Example 1(a) (0.5g, 0.0012mol), tetrakis(triphenylphosphine)palladium (0.067g, 0.00006mol) and triethylamine (0.27ml) in methanol (12ml) were heated at 80°C at 690 kPa (100 p.s.i.) pressure under an atmosphere of carbon monoxide for 2 hours. The reaction was cooled, the solvent removed under reduced pressure and the crude reaction mixture partitioned between saturated aqueous potassium carbonate (50ml) and ethyl acetate (50ml). The organic layer was dried (MgSO₄), filtered, the solvent removed under reduced pressure and the product purified on silica gel eluting with a gradient of 100:0 to 97:3 dichloromethane:methanol to give the subtitle compound (0.424g, 100%). MS m/z 364 (MH)⁺. ¹H-NMR (CDCl₃): δ = 1.83 (1H, m), 2.05 (3H, m), 2.55 (3H, s), 3.77 (1H, t), 3.92 (3H, s), 4.21 (1H, dd), 6.89 (1H, d), 6.96 (1H, d), 7.25 (1H, s), 7.37 (1H, d), 7.77 (1H, d), 8.05 (1H, s).

(b) Cis-(1S)-N-methyl-7-(N-methylamido)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

A solution of the ester product of step (a) (0.15g, 0.0004mol) in ethanolic methylamine (5ml) was heated at 100°C for 16 hours. The reaction was cooled, the solvent removed under reduced pressure and the residue purified on silica gel eluting with a gradient of 100:0:0 to 95:5:0.5 dichloromethane:methanol:0.88 ammonia. The solvent was removed under reduced pressure, the product azeotroped in toluene (3x5ml) and then stirred with diethyl ether (10ml) to give the title compound. (0.07g, 47%). ¹H-NMR (CDCl₃): δ =
1.83 (1H, m), 2.03 (3H, m), 2.55 (3H, s), 3.02 (3H, d), 3.75 (1H, t), 4.00 (1H, dd), 6.17 (1H, br.), 6.85 (1H, d), 6.94 (1H, d), 7.21 (1H, s), 7.35 (1H, d), 7.47 (1H, d), 7.82 (1H, s). MS m/z 363 (MH⁺).

Example 7

Cis-(1S)-N-methyl-7-(N-(carboxymethyl)amido)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

(a) Cis-(1S)-N-methyl-7-(N-(methoxycarbonylmethyl)amido)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

The iodide product of step (a) (0.4g, 0.0009mol), tetrakis(triphenylphosphine)palladium (0.054g, 0.00005mol), glycine methyl ester hydrochloride (1.16g, 10 equivs) and triethylamine (0.32ml) in N,N-dimethylformamide (10ml) were heated at 100°C under an atmosphere of carbon monoxide for 14 hours. The reaction was cooled, the solvent removed under reduced pressure and the crude reaction mixture purified on silica gel eluting with a gradient of 97:3:0.25 to 90:10:2 dichloromethane:methanol:0.88 ammonia to give the subtitle compound (0.28g, 72%). ¹H-NMR (CDCl₃): δ = 1.96 (1H, m), 2.11 (3H, m), 2.58 (3H, s), 3.76 (3H, s), 4.05 (3H, m), 4.20 (1H, t), 6.89 (1H, d), 7.02 (1H, d), 7.27 (1H, s), 7.36 (1H, d), 7.62 (1H, d), 8.12 (1H, s). MS m/z 421 (MH⁺).

(b) Cis-(1S)-N-methyl-7-(N-(carboxymethyl)amido)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

A solution of the ester product of step (a) (0.274g, 0.00065mol) and 2N aqueous hydrochloric acid (4ml) in dioxan (10ml) was heated at reflux for 16 hours. The mixture was cooled to room temperature, the solvent removed under reduced pressure and the
crude product purified on silica gel eluting with a gradient of 90:10:2 to 80:20:3
dichloromethane:methanol:0.88 ammonia to give the title compound as a white powder
(0.148g, 56%).  $^1$H-NMR (d$_6$-DMSO): $\delta$ = 1.79-2.15 (4H, m), 2.50 (3H, d), 3.67 (2H, s),
4.09 (1H, m), 4.15 (1H, m), 6.71 (5/8H, d), 6.80 (3/8H, d), 7.23 (1H, m), 7.50 (1H, s),
7.55 (1H, d), 7.59-7.72 (1H, m), 8.12 (3/8H, s), 8.38 (5/8H, s).

Example 8

Cis-(1S)-N-methyl-7-sulphonamido-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-
naphthalenamine

(a) Cis-(1S)-N-methyl-7-chlorosulphonyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-
naphthalenamine hydrogen sulphate

To a vigorously stirred solution of trifluoroacetic acid (60ml) was added cis-(1S)-N-
methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride
(sertraline, 20g, 0.0584mol) in portions. To this colourless solution was carefully added
chlorosulphonic acid (20ml, 0.292mol) and the mixture stirred at room temperature under
nitrogen for 16 hours. A further portion of chlorosulphonic acid was then added (20ml)
and the reaction stirred for 24 hours. The mixture was poured onto ice-water (1L), the
solid filtered off and dried under suction. The white precipitate was dissolved in
dichloromethane (700ml), dried (MgSO$_4$), filtered and the solvent removed under reduced
pressure to give the subtitle compound (21.1g, 72%) as a white foam.

(b) Cis-(1S)-N-methyl-7-sulphonamido-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-
naphthalenamine

A solution of the sulphonyl chloride product of step (a) (0.38g) in dichloromethane (10ml) was added to a saturated ammoniacal ethanol solution (10ml) and the reaction allowed to stand at room temperature for 16 hours. The reaction was diluted with diethyl ether (20ml) and washed with water (3x20ml) and brine (20ml). The solution was dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product purified on silica gel eluting with 95:5:0.5 dichloromethane:methanol:0.88 ammonia, the solvent removed under reduced pressure and the product then azeotroped with dichloromethane and diethyl ether to give the title compound (0.117g). MS m/z 385 (MH)+. ¹H-NMR (d₄-MeOH): δ = 1.93 (1H, m), 2.08 (3H, m), 2.50 (3H, s), 3.30 (1H, s), 3.82 (1H, m), 4.13 (1H, t), 6.96 (1H, d), 7.15 (1H, d), 7.38 (1H, s), 7.43 (1H, d), 7.65 (1H, d), 7.95 (1H, s).

Example 8A

Alternative preparation of cis-(1S)-N-methyl-7-sulphonamido-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of cis-(1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride (375g, 1.09 mole) in dichloromethane (2875 ml) was added chlorosulphonic acid (728 ml, 10.9 mole) over about 30 minutes, maintaining the temperature below 20°C. Thionyl chloride (158 ml, 2.19 mole) was then added over about 5 minutes and the reaction allowed to stir at room temperature for 16 hours. The reaction mixture was slowly quenched into a solution of water (3125ml) and trifluoroacetic acid (232ml) over about 2 hours, maintaining the temperature below 20°C. The organic phase was then separated and concentrated to about 750 ml, under reduced pressure.

The above solution was added to a mixture of 0.88 ammonia (750 ml) in acetonitrile (2.5 l), maintaining the temperature below 10°C (ice-water bath cooling), and the resulting suspension allowed to warm to room temperature and stir for 16 hours. The solid was filtered off, washed with acetonitrile (375 ml) and dried under vacuum at 60°C for 16 hours to yield crude title compound (387g, 85%w/w, 78%). This product was added to methanol (1875 ml) and the suspension stirred at reflux for 16 hours, then cooled to
ambient. The white precipitate was filtered off, washed with methanol (375 ml) and dried at 60°C under vacuum for 4 hours to give the title compound (246g, 58% from sertraline·HCl).

Using the procedure described in Example 8(b), the following sulphonamides were prepared by reaction of the sulphonyl chloride product of Example 8(a) and the appropriate amine:

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Example No.</th>
<th>R</th>
<th>$^1$H-NMR and mass spectral data</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>NHCH$_3$</td>
<td>(CDCl$_3$): $\delta$ = 1.87 (1H, m), 2.06 (3H, m), 2.55 (3H, s), 2.70 (3H, s), 3.78 (1H, t), 4.00 (1H, dd), 4.45 (1H, s), 6.93 (2H, t), 7.02 (1H, s), 7.38 (1H, d), 7.58 (1H, d), 7.92 (1H, s). MS m/z 399 (MH)$^+$.</td>
</tr>
<tr>
<td>10</td>
<td>N(CH$_3$)$_2$</td>
<td>(CDCl$_3$): $\delta$ = 1.86 (1H, m), 2.04 (2H, m), 2.15 (1H, m), 2.54 (3H, s), 2.75 (6H, s), 3.78 (1H, m), 4.02 (1H, dd), 6.96 (2H, t), 7.23 (1H, s), 7.38 (1H, d), 7.50 (1H, d), 7.80 (1H, s). MS m/z 413 (MH)$^+$.</td>
</tr>
<tr>
<td>11</td>
<td>[Chemical Structure]</td>
<td>(CDCl$_3$): $\delta$ = 1.80 (4H, m), 1.86 (1H, m), 2.04 (2H, m), 2.12 (1H, m), 2.55 (3H, m), 3.28 (4H, t), 3.78 (1H, m), 4.02 (1H, dd), 6.94 (2H, dd), 7.24 (1H, s), 7.38 (1H, d), 7.56 (1H, d), 7.86 (1H, s). MS m/z 439 (MH)$^+$.</td>
</tr>
<tr>
<td>12</td>
<td>HO-NH$_2$</td>
<td>(CDCl$_3$): $\delta$ = 1.88 (1H, m), 2.04 (3H, m), 2.56 (3H, s), 3.12 (2H, m), 3.64 (2H, m), 3.79 (1H, t), 4.00 (1H, t), 6.94 (2H, d), 7.22 (1H, s), 7.36 (1H, d), 7.58 (1H, d), 7.95 (1H, s). MS m/z 429 (MH)$^+$.</td>
</tr>
</tbody>
</table>
| 13 | \[
\begin{array}{c}
\text{(CDCl}_{3}\text{): } \delta = 0.13 \text{ (2H, m), 0.46 (2H, m), 0.88 (1H, m), 1.83 (1H, m), 2.05 (3H, m), 2.56 (3H, s), 2.88 (2H, t), 3.77 (1H, t), 4.02 (1H, t), 4.48 (1H, t), 6.94 (2H, m), 7.20 (1H, s), 7.38 (1H, d), 7.59 (1H, d), 7.92 (1H, s). MS m/z 439 (MH)^{+}.}
\end{array}
\] |
| 14 | \[
\begin{array}{c}
\text{(CDCl}_{3}\text{): } \delta = 1.88 \text{ (1H, m), 2.07 (3H, m), 2.56 (3H, m), 2.88 (3H, s), 3.22 (2H, t), 3.78 (3H, m), 4.01 (1H, dd), 6.96 (2H, m), 7.22 (1H, s), 7.38 (1H, d), 7.52 (1H, d), 7.84 (1H, s). MS m/z 443 (MH)^{+}.}
\end{array}
\] |
| 15 | \[
\begin{array}{c}
\text{(CDCl}_{3}\text{): } \delta = 1.66 \text{ (2H, m), 1.80-2.20 (7H, m), 2.58 (3H, s), 3.16 (2H, m), 3.68 (2H, m), 3.82 (1H, m), 4.02 (1H, t), 6.94 (2H, dd), 7.22 (1H, s), 7.38 (1H, d), 7.59 (1H, d), 7.96 (1H, s). MS m/z 443 (MH)^{+}.}
\end{array}
\] |
| 16 | \[
\begin{array}{c}
\text{(CDCl}_{3}\text{): } \delta = 1.80-2.20 (4H, m), 2.57 (3H, s), 3.04 (4H, m), 3.78 (4H, m), 3.85 (1H, m), 4.04 (1H, t), 7.00 (2H, dd), 7.27 (1H, s), 7.39 (1H, d), 7.48 (1H, d), 7.86 (1H, s). MS m/z 454 (M)^{+}.}
\end{array}
\] |
| 17 | \[
\begin{array}{c}
\text{(CDCl}_{3}\text{): } \delta = 1.4-2.20 (10H, m), 2.57 (3H, s), 2.93 (2H, m), 3.35 (2H, m), 3.81 (2H, m), 4.01 (1H, dd), 6.98 (2H, d), 7.26 (1H, s), 7.38 (1H, d), 7.50 (1H, d), 7.82 (1H, s). MS m/z 469 (MH)^{+}.}
\end{array}
\] |
| 18 | \[
\begin{array}{c}
\text{(CDCl}_{3}\text{): } \delta = 1.84 (1H, m), 2.07 (3H, m), 2.55 (3H, s), 3.78 (1H, t), 4.00 (1H, dd), 4.23 (2H, s), 6.09 (1H, d), 6.23 (1H, dd), 6.92 (1H, d), 6.97 (1H, d), 7.21 (1H, s), 7.26 (1H, s), 7.39 (1H, d), 7.54 (1H, d), 7.87 (1H, s). MS m/z 465 (MH)^{+}.}
\end{array}
\] |
| 19 | \[
\begin{array}{c}
\text{(HOCH}_{2}\text{)}_{2}\text{CHNH}_{-}\text{ (CDCl}_{3}\text{): } \delta = 1.90 (1H, m), 2.04 (3H, m), 2.56 (3H, m), 3.35 (1H, m), 3.50 (1H, m), 3.68 (3H, m), 3.82 (1H, m), 4.04 (1H, t), 6.94 (2H, d), 7.22 (1H, s), 7.38 (1H, d), 7.60 (1H, d), 8.04 (1H, s). MS m/z 459 (MH)^{+}.}
\end{array}
\] |
<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>Chemical Shifts</th>
<th>MS m/z</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>H₂NCH₂CH₂NH-</td>
<td>δ = 1.92 (1H, m), 2.08 (3H, m), 2.49 (3H, s), 2.68 (2H, t), 2.92 (2H, t), 3.82 (1H, m), 4.16 (1H, t), 7.00 (1H, d), 7.16 (1H, d), 7.40 (1H, s), 7.45 (1H, d), 7.61 (1H, d), 7.92 (1H, s). MS m/z 428 (MH)⁺.</td>
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</tr>
<tr>
<td>21</td>
<td>H₂NC(O)CH₂NH-</td>
<td>(CDCl₃): δ = 1.86 (1H, m), 2.04 (3H, m), 2.54 (3H, s), 3.62 (2H, s), 3.80 (1H, m), 4.03 (1H, t), 5.77 (1H, s), 6.33 (1H, s), 6.95 (2H, m), 7.22 (1H, s), 7.38 (1H, d), 7.58 (1H, d), 7.95 (1H, s). MS m/z 442 (MH)⁺.</td>
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</tr>
<tr>
<td>22</td>
<td>(R)-CH₃CHOHCH₂NH-</td>
<td>(CDCl₃): δ = 1.18 (3H, d), 1.86 (1H, m), 2.05 (3H, m), 2.57 (3H, s), 2.80 (1H, dd), 3.12 (1H, dd), 3.78 (1H, m), 3.93 (1H, m), 4.01 (1H, m), 6.93 (2H, m), 7.22 (1H, s), 7.38 (1H, d), 7.58 (1H, d), 7.92 (1H, s). MS m/z 443 (MH)⁺.</td>
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</tr>
<tr>
<td>23</td>
<td>(R)-HOCH₂CH(CH₃)NH-</td>
<td>(CDCl₃): δ = 1.12 (3H, d), 1.90 (1H, m), 2.05 (3H, m), 2.57 (3H, s), 3.43 (3H, m), 3.78 (1H, m), 4.02 (1H, t), 6.93 (2H, m), 7.22 (1H, s), 7.38 (1H, d), 7.62 (1H, d), 7.97 (1H, s). MS m/z 443 (MH)⁺.</td>
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</tr>
<tr>
<td>24</td>
<td>(S)-HOCH₂CH(CH₃)NH-</td>
<td>(CDCl₃): δ = 1.08 (3H, d), 1.87 (1H, m), 2.06 (3H, m), 2.56 (3H, s), 3.42 (2H, m), 3.60 (1H, m), 3.78 (1H, m), 4.02 (1H, t), 6.93 (2H, t), 7.19 (s, 1H), 7.38 (1H, d), 7.60 (1H, d), 7.94 (1H, s). MS m/z 443 (MH)⁺.</td>
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</tr>
<tr>
<td>25</td>
<td>CH₃CH₂CH₂NH-</td>
<td>(CDCl₃): δ = 0.90 (3H, t), 1.52 (2H, m), 1.85 (1H, m), 2.06 (3H, m), 2.56 (3H, m), 2.96 (2H, q), 3.77 (1H, m) 4.02 (1H, dd), 4.35 (1H, t), 6.94 (2H, m), 7.22 (1H, s), 7.38 (1H, d), 7.56 (1H, d), 7.90 (1H, s). MS m/z 427 (MH)⁺.</td>
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</tr>
<tr>
<td>26</td>
<td>(S)-CH₃CH(OH)CH₂NH⁻</td>
<td>(CDCl₃): δ = 1.16 (3H, d), 1.87 (1H, m), 2.07 (3H, m), 2.56 (3H, m), 2.83 (1H, dd), 3.10 (1H, dd), 3.77 (1H, m), 3.84 (1H, m), 4.01 (1H, t), 6.96 (2H, m), 7.22 (1H, s), 7.38 (1H, d), 7.58 (1H, d), 7.93 (1H, s). MS m/z 443 (MH⁺).</td>
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</tr>
<tr>
<td>27⁴</td>
<td>CH₃CH₂NH⁻</td>
<td>(CDCl₃): δ = 1.13 (3H, t), 1.87 (1H, m), 2.08 (3H, m), 2.57 (3H, m), 3.05 (2H, q), 3.75 (1H, t), 4.00 (1H, dd), 4.30 (1H, t), 6.93 (2H, m), 7.22 (1H, s), 7.37 (1H, d), 7.58 (1H, d), 7.90 (1H, s). MS m/z 413 (MH⁺).</td>
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</tr>
<tr>
<td>28</td>
<td>CH₃OCH₂CH₂NH⁻</td>
<td>(CDCl₃): δ = 1.86 (1H, m), 2.04 (3H, m), 2.57 (3H, m), 3.15 (2H, t), 3.28 (3H, s), 3.42 (2H, t), 3.78 (1H, t), 4.00 (1H, dd), 6.96 (2H, m), 7.22 (1H, s), 7.37 (1H, d), 7.57 (1H, d), 7.92 (1H, s). MS m/z 443 (MH⁺).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29¹</td>
<td>(HOCH₂CH₂)₂N⁻</td>
<td>(CDCl₃): δ = 1.95 (1H, m), 2.04 (3H, m), 2.48 (3H, s), 3.30 (4H, m), 3.72 (4H, m), 3.82 (1H, m), 4.17 (1H, t), 7.02 (1H, d), 7.14 (1H, d), 7.42 (1H, s), 7.46 (1H, d), 7.60 (1H, d), 7.92 (1H, s). MS m/z 473 (MH⁺).</td>
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<tr>
<td>30⁵</td>
<td></td>
<td>(CDCl₃): δ = 1.70-2.20 (9H, m), 2.50 (5H, m), 3.78 (3H, m), 4.00 (1H, t), 5.40 (2H, s), 6.96 (2H, m), 7.23 (1H, s), 7.38 (1H, d), 7.48 (1H, d), 7.80 (1H, s). MS m/z 496 (MH⁺).</td>
<td></td>
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</tr>
<tr>
<td>31⁶</td>
<td></td>
<td>(CDCl₃): δ = 1.24 (3H, t), 2.13 (2H, m), 2.36 (2H, m), 2.59 (2H, m), 2.64 (3H, s), 3.19 (2H, m), 4.02 (1H, m), 4.12 (2H, q), 4.50 (1H, m), 6.98 (1H, d), 7.18 (1H, d), 7.40 (1H, d), 7.44 (1H, s), 7.68 (1H, d), 8.44 (1H, s). MS m/z 485 (MH⁺).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Dioxan/dichloromethane mixture used as solvent.

2. Ethanol/dichloromethane used as solvent. Triethylamine (5 equivalents) added to reaction.
3. Amine used as solution in water. Triethylamine (5 equivalents) added to reaction.
4. Dioxan used as solvent.
5. Ethanol used as solvent.
6. Ethanol/dichloromethane used as solvent. Triethylamine (10 equivalents) added to reaction. Amine used as solution in water.

**Example 32**

**Cis-(1S)-N-methyl-7-(2-carboxyethyl(sulphonamido))-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride**

![Chemical Structure]

To a solution of the product of Example 31 (1.3g, 0.0027mol) in dioxan (20ml) was added 2N aqueous hydrochloric acid solution (5ml) and the reaction heated at 90°C for 2 hours. The reaction was cooled to room temperature, the solvent removed under reduced pressure and the residue azeotroped with toluene (x1) and dichloromethane (x5). Diethyl ether was added and the solution filtered. The solid was collected and dried to give the title compound (1.07g, 81%), as a white powder. MS m/z 457 (MH+). 1H-NMR (d4-MeOH): δ = 2.08 (1H, m), 2.16-2.44 (3H, m), 2.52 (2H, t), 2.88 (3H, s), 3.17 (2H, t), 4.26 (1H, m), 4.63 (1H, s), 4.84 (4H, s), 7.14 (1H, d), 7.24 (1H, d), 7.48 (1H, s), 7.52 (1H, d), 7.79 (1H, d), 8.12 (1H, s).

**Example 33**

**Cis-(1S)-N-methyl-7-carboxy-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine**

(a) **Cis-(1S)-N-methyl-7-(ethyoxycarbonyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine**
The subtitle compound was prepared by an analogous procedure to that described in Example 6(a), but substituting ethanol for methanol.

(b) Cis-(1S)-N-methyl-7-carboxy-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

A solution of the ethyl ester from step (a) (0.14g, 0.00037mol) in dioxan (10ml) and 2N aqueous hydrochloric acid (3ml) was heated at reflux for 16 hours. The reaction was cooled to room temperature and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with a gradient of 80:20:3 to 80:20:5 dichloromethane:methanol:0.88 ammonia to give the title compound (0.121g, 93%). MS m/z 350 (MH⁺). ¹H-NMR (d₆-DMSO): δ = 1.78-2.10 (4H, m), 2.53 (3H, s), 3.98 (1H, br), 4.13 (1H, m), 6.72 (1H, d), 7.20 (1H, d), 7.46 (1H, s), 7.55 (1H, d), 7.65 (1H, d), 8.38 (1H, s).

Example 34

Cis-(1S)-N-methyl-7-(methanesulphonamidomethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

(a) Cis-(1S)-N-methyl-7-(aminomethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

A solution of the nitrile product of Example 1(c) (1.22g, 0.0037mol) in tetrahydrofuran (50ml) was added to a stirred suspension of lithium aluminium hydride (0.42g, 0.011mol) in tetrahydrofuran (50ml) at 0°C. After 1 hour, the reaction was heated to 50°C for 3 hours, cooled in an ice-bath and quenched with 2N aqueous sodium hydroxide solution (5ml). The reaction was dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 93:7:1
dichloromethane:methanol:0.88 ammonia and the solvent removed under reduced pressure to give a gum which was azeotroped with dichloromethane (3x10ml). The product was treated with a saturated solution of hydrogen chloride gas in diethyl ether (5ml) and the solvent removed under reduced pressure to give the subtitle compound as a white solid (0.96g). MS m/z 335 (MH)⁺. ¹H-NMR (d₄-MeOH): δ = 1.94-2.38 (4H, m), 2.85 (3H, s), 4.16 (2H, s), 4.19 (1H, dd), 4.47 (1H, t), 7.00 (1H, d), 7.22 (1H, d), 7.41 (2H, m), 7.50 (1H, d), 7.72 (1H, s).

(b) Cis-(1S)-N-methyl-7-(methanesulphonamidomethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

A solution of the amine product of step (a) (0.27g, 0.00066mol) in dichloromethane (20ml) was cooled in an ice-water bath and to this was added a solution of triethylamine (0.234g, 0.0023mol) in dichloromethane (10ml) followed by a solution of methanesulphonyl chloride (0.076g, 0.00066mol) in dichloromethane (20ml), added over 20 minutes. After 2 hours, the solvent was removed under reduced pressure and the crude product purified on silica gel eluting with 93:7:1 dichloromethane:methanol:0.88 ammonia to give the title compound as a white foam (0.155g, 57%). MS m/z 413 (MH)⁺. ¹H-NMR (CDCl₃): δ = 1.82 (1H, m), 2.02 (3H, m), 2.53 (3H, m), 2.93 (3H, s), 3.63 (1H, t), 3.97 (1H, t), 4.30 (2H, s), 6.80 (1H, d), 6.96 (1H, d), 7.09 (1H, d), 7.22 (1H, s), 7.36 (2H, m).

Example 35
Cis-(1S)-N-methyl-7-((N-acetyl)aminomethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine
A solution of the amine product of Example 34(a) (0.15g, 0.00037mol) in dichloromethane (15ml) was cooled in an ice-water bath and to this was added triethylamine (0.123g, 0.0012mol). After 5 minutes, acetyl chloride (0.031g, 0.00039mol) was added. The reaction was allowed to warm to room temperature and stirred for 68 hours. Dichloromethane (20ml) was added and the reaction washed with water (20ml), dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 95:5:0.5 dichloromethane:methanol:0.88 ammonia to give the title compound as a white foam (0.042g, 30%). MS m/z 377 (MH)⁺. ¹H-NMR (d₄-MeOH): δ = 1.97 (1H, m), 1.99 (3H, s), 2.22 (3H, m), 2.84 (3H, s), 4.15 (1H, dd), 4.36 (2H, s), 4.45 (1H, br), 6.86 (1H, d), 7.18 (1H, dd), 7.24 (1H, d), 7.41 (1H, d), 7.46 (1h, d), 7.49 (1H, s).

Example 36

Cis-(1S)-N-methyl-7-((N-aminosulphonyl)aminomethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the amine product of Example 34(a) (0.155g, 0.00046mol) in tetrahydrofuran (10ml) was added sulphamoyl chloride (Chem. Abstract., 1958, 52, 19655f) (0.051g, 0.00044mol) and the mixture heated at reflux for 7 hours. The reaction was cooled, poured into 10% aqueous potassium carbonate solution (30ml) and extracted with ethyl acetate (30ml). The organic phase was washed with brine (30ml), dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 93:7:1 dichloromethane:methanol:0.88 ammonia to give the title compound as a white foam (0.055g, 29%). MS m/z 414 (MH)⁺. ¹H-NMR
(d$_1$-MeOH): δ = 1.83 (1H, m), 1.92 (1H, m), 2.03 (1H, m), 2.25 (1H, m), 2.63 (3H, s),
4.22 (3H, s), 5.10 (1H, dd), 6.95 (2H, m), 7.10 (1H, s), 7.25 (1H, d), 7.41 (1H, d), 7.59
(1H, s).

Example 37

Cis-(1S)-N-methyl-7-((N-aminocarboxy)aminomethyl)-4-(3,4-dichlorophenyl)-
1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

To a suspension of the amine product of Example 34(a) (0.251g, 0.00061mol) in
tetrahydrofuran (10ml) was added triethylamine (175μl). After 5 minutes, the reaction
was cooled in an ice-bath, trimethylsilyl isocyanate (80μl) added and the reaction allowed
to stir for 15 minutes. The reaction was then stirred at room temperature for 16 hours.
Water (1ml) was added, the reaction stirred for 5 minutes and then partitioned between
ethyl acetate (25ml) and 10% aqueous potassium carbonate solution (25ml). The aqueous
layer was extracted with ethyl acetate and the combined organic layers washed with brine
(50ml), dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. The
residue was then dissolved in hot ethyl acetate, filtered and the solvent removed under
reduced pressure. The crude product was purified on silica gel eluting with 93:7:1
dichloromethane:methanol:0.88 ammonia and the solvent removed under reduced
pressure. The material obtained was then purified on silica gel eluting with a gradient of
96:4 to 94:6 ethyl acetate:diethylamine and the solvent removed under reduced pressure.
This material was then purified on silica gel eluting with 93:7:1
dichloromethane:methanol:0.88 ammonia. The solvent was removed under reduced
pressure and the residue treated with a saturated solution of hydrogen chloride in diethyl
ether (5ml). The solvent was removed under reduced pressure, the residue dissolved in
methanol (5ml) and the solvent removed in vacuo to give the title compound (0.055g,
24%). MS m/z 378 (MH$^+$). $^1$H-NMR (d$_1$-MeOH): δ = 1.97 (1H, m), 2.19 (3H, m), 2.80
(3H, s), 4.14 (1H, dd), 4.28 (2H, s), 4.37 (1H, br), 6.86 (1H, d), 7.19 (1H, d), 7.22 (1H, d), 7.40 (2H, m), 7.47 (1H, d).

Example 38

5 Cis-(1S)-N-methyl-7-(3-(5-methyl-1,2,4-oxadiazolyl))-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

(a) Cis-(1S)-N-methyl-7-(aminoioximyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of hydroxylamine hydrochloride (1.67g, 0.024mol) in water (30ml) was added sodium carbonate (2.54g, 0.024mol). This solution was then added to a solution of the nitrile product of Example 1(c) (1.06g, 0.0032mol) in methanol (60ml) and the reaction heated under reflux under an atmosphere of nitrogen for 16 hours. The reaction was cooled, partitioned between dichloromethane (50ml) and water (50ml) and the aqueous phase extracted with dichloromethane (2x50ml). The combined organics were dried (MgSO₄), filtered, the solvent removed under reduced pressure and the residue triturated with diethyl ether and dried to give the subtitle compound (1.1g) which was used without further purification. MS m/z 366 (MH⁺). ¹H-NMR (CDCl₃): δ = 1.85 (1H, m), 2.05 (3H, m), 2.54 (3H, m), 3.76 (1H, m), 3.99 (1H, m), 4.91 (1H, s), 6.79-6.90 (1H, m), 6.95 (1H, d), 7.22 (1H, d), 7.35 (1H, d), 7.40-7.57 (1H, m), 7.66 (0.5H, s), 7.93 (0.5H, s).

(b) Cis-(1S)-N-methyl-7-(3-(5-methyl-1,2,4-oxadiazolyl))-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine
The amidoxime product of step (a) (0.4g, 0.0011mol) and N,N-dimethylacetamide dimethylacetal (2ml) were heated at reflux for 4 hours. The reaction was cooled and the excess N,N-dimethylacetamide dimethylacetal removed in vacuo. This material was then purified on silica gel eluting with a gradient of 97:3:0 dichloromethane:methanol:0.88 ammonia to 97:3:1 dichloromethane: methanol: 0.88 ammonia. The product was collected and the solvent removed under reduced pressure. This was purified further on silica gel eluting with 95:5:0.5 ethyl acetate: methanol: 0.88 ammonia to give the title compound, after trituration with diethyl ether, as a colourless foam (0.05g, 12%). MS m/z 388 (MH+) +. 1H-NMR (CDCl3): δ = 1.78 (2H, m), 2.00 (1H, m), 2.40 (1H, m), 2.53 (3H, s), 2.66 (3H, s), 3.94 (1H, t), 4.18 (1H, t), 6.86 (1H, d), 6.96 (1H, d), 7.13 (1H, s), 7.33 (1H, d), 8.01 (1H, d), 8.17 (1H, s).

Example 39
Cis-(1S)-N-methyl-7-(5-(3-methyl-1,2,4-oxadiazolyl))-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

(a) N-Hydroxyethanimidamide

To a solution of hydroxylamine hydrochloride (35g, 0.5mol) in ethanol (200ml) was added phenolphthalein (0.05g). Sodium ethoxide solution (324ml, 21% w/v) was added over 1 hour. After 3 hours, acetonitrile (13.8g) was added, the reaction stirred at room temperature for 2 hours and then heated at 40°C for 48 hours. The reaction was cooled to room temperature, filtered and the solvent removed under reduced pressure. The residue was allowed to stand at room temperature for 48 hours, methanol (1 litre) added and the crude product absorbed on silica. The product was purified on a silica column eluting with 9:1 dichloromethane: methanol to give the subtitle compound, (20.33g, 81%). 1H NMR (d6-DMSO): δ = 1.60 (3H, s), 5.33 (2H, br), 8.65 (1H, s).
(b) Cis-(1S)-N-methyl-7-(5-(3-methyl-1,2,4-oxadiazolyl))-4-(3,4-dichlorophenyl)-
1,2,3,4-tetrahydro-1-naphthalenamine

A solution of the iodide from Example 1(a) (0.3g, 0.00069mol), the compound of step (a)
(0.205g, 5equiv), tetrakis(triphenylphosphine)palladium (0.40g) and triethylamine
(0.24ml) in toluene (5ml) was heated at reflux under an atmosphere of carbon monoxide
for 16 hours. The reaction was cooled to room temperature, concentrated under reduced
pressure and partitioned between ethyl acetate (15ml) and water (15ml). The aqueous
phase was extracted with ethyl acetate (15ml) and the combined organics dried (MgSO₄),
filtered and the solvent removed under reduced pressure. The crude product was purified
on silica gel eluting with 95:5:0.5 dichloromethane : methanol : 0.88 ammonia. The
solvent was removed under reduced pressure and the compound purified further by
chromatography on silica gel, eluting with a solvent gradient of 98:2 dichloromethane :
methanol to 95:5 dichloromethane : methanol. The solvent was removed under reduced
pressure and the compound finally purified on silica gel eluting with 95:5:0.5 ethyl
acetate : methanol : 0.88 ammonia to give the title compound as a colourless solid after
trituration with diethyl ether (0.083g, 31%). MS m/z 388 (MH)+. ¹H-NMR (CDCl₃): δ =
1.87 (1H, m), 2.09 (3H, m), 2.47 (3H, m), 2.57 (3H, m), 3.80 (1H, t), 4.03 (1H, dd), 6.98
(2H, m), 7.26 (1H, s), 7.37 (1H, d), 7.83 (1H, d), 8.14 (1H, s).

Examples 40 and 41
Cis-(1S)-N-methyl-7-(N(2)-1,2,3-triazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-
1-naphthalenamine hydrochloride
and
Cis-(1S)-N-methyl-7-(N(1)-1,2,3-triazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-
1-naphthalenamine hydrochloride
A mixture of the iodide from Example 1(a) (0.432g, 0.001mol), 1,2,3-triazole (1.6g), copper powder (0.064g) and potassium carbonate (0.138g) was heated at 160°C for 7.5 hours. The reaction was cooled to room temperature and partitioned between saturated aqueous ethyldiamine tetra-acetic acid disodium salt solution and ethyl acetate (60ml). The organic phase was washed with brine (3x60ml), dried (MgSO₄) and the solvent removed under reduced pressure to give a gum. This material was then purified on silica gel eluting with a gradient of 100:0 dichloromethane : methanol to 95:5 dichloromethane : methanol then 95:5:0.5 dichloromethane : methanol : 0.88 ammonia. The appropriate fractions containing the N-2 linked triazole were concentrated to dryness under reduced pressure, the residue taken up in dichloromethane (5ml) and a saturated solution of hydrogen chloride in diethyl ether (2ml) added. The solvent was removed under reduced pressure and the residue triturated with diethyl ether (2x5ml). The solid was filtered and dried at 75°C for 4h to give the first title compound, cis-(1S)-N-methyl-7-(N(2)-1,2,3-triazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride (Example 40) as a white solid (35mg). MS m/z 373 (MH)+. ¹H-NMR (d₆-DMSO): δ = 2.05 (3H, m), 3.30 (1H, m), 3.70 (1H, s), 4.20 (1H, m), 4.55 (1H, s), 6.95 (1H, d), 7.40 (1H, d), 7.65 (2H, dd), 7.95 (1H, d), 8.15 (2H, s), 8.3 (1H, s), 9.30 (2H, br. s). This product was followed off the column by the N-1 linked isomer. The solvent was removed under reduced pressure and the residue taken up in dichloromethane (5ml) and a saturated solution of hydrogen chloride in diethyl ether (2ml) added. The solvent was removed under reduced pressure and the residue triturated with diethyl ether (2x5ml). The solid was filtered and dried at 75°C for 4h to give the second title compound, cis-(1S)-N-methyl-7-(N(1)-1,2,3-triazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride (Example 41) as a white powder (57mg). MS m/z 373 (MH)+. ¹H-NMR (d₆-DMSO): δ = 2.05 (3H, m), 2.21 (1H, m), 2.7 (3H, m), 4.25 (1H, m), 4.55 (1H, s), 7.0 (1H, d), 7.32 (1H, d), 7.60 (2H, m), 7.8 (1H, dd), 8.00 (1H, s), 8.18 (1H, s), 8.85 (1H, s), 9.30 (1H, br), 9.55 (1H, br).
Using the general procedure described in the preparation of Examples 40 and 41, the following N-linked heterocycles were prepared by reaction of the iodide of Example 1(a) and the appropriate heterocycle:

<table>
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<tr>
<th>Example No.</th>
<th>R</th>
<th>(^1)H-NMR and mass spectral data</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>(N\equiv N)</td>
<td>(CDCl(_3))(free base): (\delta = 2.0) (4H, m), 2.55 (3H, s), 3.8 (1H, dd), 4.05 (1H, m), 6.95 (2H, m), 7.2 (1H, d), 7.40 (2H, m), 7.80 (1H, d), 8.1 (1H, s), 8.58 (1H, s). MS m/z 373 (MH(^+)).</td>
</tr>
<tr>
<td>43</td>
<td>(H-N\equiv N)</td>
<td>(d(_6)-DMSO): (\delta = 2.0) (3H, m), 2.2 (1H, m), 4.2 (1H, m), 4.5 (1H, s), 6.2 (1H, s), 6.85 (1H, d), 7.40 (1H, dd), 7.60 (3H, m), 8.20 (1H, s), 8.45 (1H, s), 9.35 (2H, br), 9.75 (2H, br). MS m/z 387 (MH(^+)).</td>
</tr>
<tr>
<td>44</td>
<td>(\text{N} \equiv \text{O})</td>
<td>(d(_6)-DMSO): (\delta = 2.10) (3H, m), 2.30 (1H, m), 3.70 (3H, d), 4.20 (1H, m), 4.45 (1H, s), 6.35 (1H, m), 6.50 (1H, d), 6.85 (1H, d), 7.4 (2H, m), 7.50 (1H, m), 7.65 (4H, m), 9.30 (2H, s). MS m/z 399 (MH(^+)).</td>
</tr>
</tbody>
</table>

**Example 45**

Cis-(1S)-N-methyl-7-(5-(2-amino)pyridyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

(a) Cis-(1S)-N-methyl-7-(boronato)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine
A solution of the iodide product from Example 1(a) (4.64g, 0.0107mol), bis(pinacolato) diboron (3g), DPPF [1,1'-bis(diphenylphosphino)ferrocene, available from Lancaster Synthesis Limited] (0.52g) and potassium acetate (3.16g) in dimethylsulphoxide (70ml) was heated at 70°C for 55 minutes. The reaction was cooled, ethyl acetate added and the mixture washed with water. The organic phase was dried (MgSO₄), filtered and the solvent removed under reduced pressure to give the subtitle compound which was used without further purification.

(b) Cis-(1S)-N-methyl-7-(5-(2-amino)pyridyl)-4-(3,4-dichlorophenyl)-1,2,3,4-
tetrahydronaphthalenamine hydrochloride

A solution of the boronate ester from step (a) (0.432g, 0.001mol), 2-amino-5-
bromopyridine (0.173g), tetrakis(triphenylnphosphine)palladium (0.115g) and caesium carbonate (0.65g) in dioxan (12ml) and water (4ml) was heated at 80°C for 4.5 hours. The reaction was cooled and the solvent removed under reduced pressure. Water (30ml) was added and the aqueous phase extracted with ethyl acetate (3x20ml). The combined organics were washed with brine (50ml), dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 93:7:1 dichloromethane : methanol : 0.88 ammonia. The solvent was removed under reduced pressure, dissolved in ethyl acetate (5ml) and a saturated solution of hydrogen chloride in diethyl ether (2ml) added. The solvent was removed under reduced pressure to give the title compound (0.04g). MS m/z 398 (MH⁺). ¹H-NMR (CDCl₃): δ = 1.82 (1H, m), 2.02 (3H, m), 2.55 (3H, s), 3.66 (1H, t), 4.00 (1H, t), 4.48 (1H, s), 6.58 (1H, d), 6.82 (1H, d), 7.00 (1H, d), 7.25 (2H, m), 7.50 (1H, s), 7.65 (1H, dd), 8.30 (1H, s).
Using the general procedure described in the preparation of Example 45, the following compounds were prepared by reaction of the boronate ester from step (a) and the appropriate bromo- or iodo-heterocycle:

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Example No.</th>
<th>R</th>
<th>(^1\text{H}-\text{NMR and mass spectral data} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td><a href="image">Chemical Structure</a></td>
<td>(CDCl(_3)/D(_2)O): ( \delta = 1.78 ) (3H, m), 2.04 (1H, m), 2.55 (3H, s), 3.80 (1H, t), 4.00 (1H, t), 6.82 (1H, m), 6.98 (1H, m), 7.20 (1H, m), 7.25 (1H, s), 7.35 (1H, d), 7.57 (1H, s). MS m/z 416 (MH(^+)).</td>
</tr>
<tr>
<td>47</td>
<td><a href="image">Chemical Structure</a></td>
<td>(CDCl(_3)): ( \delta = 1.85 ) (1H, m), 2.05 (3H, m), 2.55 (3H, s), 3.75 (1H, t), 4.00 (1H, t), 4.80 (2H, d), 6.87 (1H, d), 7.02 (1H, m), 7.14 (1H, s), 7.28 (1H, m), 7.38 (2H, dd), 7.8 (1H, s). MS m/z 414 (MH(^+)).</td>
</tr>
<tr>
<td>48</td>
<td><a href="image">Chemical Structure</a></td>
<td>(CDCl(_3)): ( \delta = 1.85 ) (1H, m), 2.08 (1H, m), 2.56 (3H, s), 3.00 (3H, s), 3.75 (1H, s), 4.02 (1H, m), 4.90 (2H, s), 5.30 (1H, t), 6.00 (1H, s), 6.89 (1H, m), 7.01 (1H, m), 7.21 (1H, m), 7.40 (1H, m), 7.51 (1H, s), 7.81 (1H, s), 8.45 (1H, s). MS m/z 455 (MH(^+)).</td>
</tr>
<tr>
<td>49</td>
<td><a href="image">Chemical Structure</a></td>
<td>(CDCl(_3)): ( \delta = 1.84 ) (1H, m), 2.06 (3H, m), 2.58 (3H, s), 3.77 (1H, t), 4.00 (1H, t), 5.09 (2H, s), 6.86 (1H, m), 7.00 (1H, m), 7.22 (1H, m), 7.27 (1H, m), 7.38 (1H, m), 7.52 (1H, s), 8.52 (2H, s). MS m/z 399 (MH(^+)).</td>
</tr>
</tbody>
</table>
Example 52

Cis-(1S)-N-methyl-7-(4-pyrazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

(a) N-1-Ethoxymethyl-4-iodo-pyrazole

To a solution of 4-iodopyrazole (5g, 0.026mol) in acetone (40ml) was added potassium carbonate (3.92g, 0.0284mol) and the mixture cooled in an ice-water bath. Chloromethylethylether (2.66ml, 0.0284mol) was added and the reaction stirred for 16 hours. Water (100ml) was added, the mixture extracted with dichloromethane (100ml), the organics dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 9:1 pentane : ethyl acetate to give the subtitle compound (5.77g, 85%). MS m/z 253 (MH)⁺. ¹H-NMR (CDCl₃): δ = 1.18 (3H, t), 3.50 (2H, q), 5.42 (2H, s), 7.54 (1H, s), 7.65 (1H, s).

(b) Cis-(1S)-N-methyl-7-(4-(N(1)-ethoxymethyl)pyrazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine
To a solution of the iodopyrazole product of step (a) (0.635g, 0.00276mol) in diethyl ether (10ml) at -95°C under nitrogen was added n-butyllithium (2.5M solution in hexane) (0.00276mol) and after 10 minutes, zinc chloride (0.00276mol) (0.5M solution in tetrahydrofuran). After 40 minutes, tetrakis(triphenylphosphine)palladium (0.106g) and a solution of the iodide product of Example 1(a) (0.4g, 0.00092mol) in diethyl ether (5ml) were added and the reaction heated at reflux for 16 hours. The reaction was cooled to room temperature, washed with saturated aqueous ethyldiamine tetra-acetic acid di-sodium salt solution and filtered. The aqueous phase was extracted with dichloromethane (50ml) and the combined organics washed with brine (100ml), dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 10:10:0.5 pentane:ethyl acetate:diethylamine to give the subtitle compound (0.184 g, 47%). MS m/z 430 (MH⁺). ¹H-NMR (CDCl₃): δ = 1.18 (3H, t), 1.85 (1H, m), 2.04 (3H, m), 2.58 (3H, s), 3.58 (2H, q), 3.75 (1H, t), 3.99 (1H, q), 5.46 (2H, s), 6.80 (1H, d), 7.00 (1H, dd), 7.20 (1H, s), 7.36 (1H, d), 7.48 (2H, m), 7.68 (1H, dd), 7.84 (1H, s).

(c) Cis-(1S)-N-methyl-7-(4-pyrazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the pyrazole product from step (b) (0.184g, 0.00043mol) in ethanol (8ml) was added aqueous 2N HCl solution (5ml) and the reaction heated at reflux for 16 hours. The reaction was cooled to room temperature and partitioned between saturated aqueous sodium carbonate and ethyl acetate. The organic layer was dried (MgSO₄), filtered and the solvent removed under reduced pressure to give the crude product which was purified
on silica gel to give the title compound (0.074g, 46%). MS m/z 372 (MH)+. ¹H-NMR (CDCl₃): δ = 1.83 (1H, m), 2.02 (3H, m), 2.58 (3H, s), 3.54 (1H, t), 3.99 (1H, q), 6.80 (1H, d), 7.00 (1H, d), 7.24 (2H, m), 7.34 (1H, d), 7.52 (1H, s), 7.83 (2H, s).

Example 53

Cis-(1S)-N-methyl-7-(3-pyrazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

(a) Cis-(1S)-N-methyl-7-(5-(N(1)-ethoxymethyl)pyrazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of N-ethoxymethylpyrazole (prepared using the method described in Example 52(a), but starting with pyrazole) (0.175g, 0.00139mol) in tetrahydrofuran (10ml) at -78°C under nitrogen was added n-butyllithium (2.5M solution in hexane) (0.00139mol) and after 10 minutes, zinc chloride (0.00139mol) (0.5M solution in tetrahydrofuran). After 20 minutes, the reaction was warmed to room temperature and tetrakis(triphenylphosphine) palladium (0.053g) and the iodide from Example 1(a) (0.2g, 0.00046mol) added and the reaction heated at reflux for 16 hours. The reaction was cooled to room temperature, washed with saturated aqueous ethyldiamine tetra-acetic acid di-sodium salt solution and filtered. The aqueous phase was extracted with dichloromethane (50ml) and the organic phase washed with brine (100ml), dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 80:20:5 pentane:ethyl acetate:diethylyamine to give the subtitle compound (0.154 g, 78%). ¹H-NMR (CDCl₃): δ = 0.90 (3H, t), 1.29 (3H, m), 1.88 (1H, m), 2.04 (3H, m), 3.74 (3H, m), 4.01 (1H, m), 5.44 (2H, s), 6.40 (1H, s), 6.98 (1H, d), 7.02 (1H, d), 7.36 (1H, d), 7.40 (1H, d), 7.54 (1H, d), 7.62 (1H, d).

(b) Cis-(1S)-N-methyl-7-(3-pyrazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride
To a solution of the pyrazole from step (a) (0.15g, 0.00038mol) in ethanol (10ml) was added 2N aqueous hydrochloric acid (2ml) and the reaction heated at reflux for 48 hours. The reaction was cooled, the aqueous layer decanted off and the remaining material dissolved in ethanol and filtered. The solvent was removed under reduced pressure and the crude product purified on silica gel eluting with 80 : 20 : 5 pentane : ethyl acetate : diethylamine to give the title compound (0.045 g, 32%). The product was dissolved in dichloromethane (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo to yield the hydrochloride salt. MS m/z 372 (MH⁺). ¹H-NMR (d₄-MeOH): δ = 1.30 (1H, s), 2.01 (1H, m), 2.28 (3H, m), 2.90 (3H, s), 3.30 (1H, s), 4.22 (1H, m), 4.59 (1H, br), 6.98 (1H, br), 7.04 (1H, dd), 7.24 (1H, dd), 7.49 (1H, d), 7.52 (1H, d), 7.76 (1H, d), 8.00 (1H, s), 8.04 (1H, s).

Example 54

Cis-(1S)-N-methyl-7-(3-(N(2)-methyl)pyrazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of N-methylpyrazole (0.114g, 0.00139mol) in tetrahydrofuran (5ml) at -78°C under nitrogen was added n-butyllithium (2.5M solution in hexane) (0.00139mol) and after 10 minutes, zinc chloride (0.00139mol) (0.5M solution in tetrahydrofuran). After 45 minutes, the reaction was warmed to 0°C and tetrakis(triphenylphosphine)palladium (0.053g) and a solution of the iodide product of Example 1(a) (0.2g, 0.00046mol) in tetrahydrofuran (5ml) added and the reaction heated at reflux for 16 hours. The reaction was cooled to room temperature, washed with saturated aqueous ethyldiamine tetra-acetic acid di-sodium salt solution and filtered. The
aqueous phase was extracted with dichloromethane (50ml) and the combined organics was washed with brine (100ml), dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel to give the title compound (0.015g). MS m/z 386 (MH⁺). ¹H-NMR (CDCl₃): δ = 1.88 (1H, m), 2.08 (3H, m), 2.57 (2H, s), 3.78 (1H, t), 3.90 (3H, s), 4.01 (1, m), 6.30 (1H, d), 6.88 (1H, d), 7.00 (1H, d), 7.17 (1H, d), 7.28 (1H, d), 7.3, (1H, d), 7.42 (1H, d), 7.51 (1H, d).

Example 55

Cis-(1S)-N-methyl-7-(3-(1,2,4-triazolyl))-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

(a) Cis-(1S)-N-methyl-7-(3-(((2-ethoxymethyl)-1,2,4-triazolyl))-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of N(2)-ethoxymethyl-1,2,4-triazole (prepared by the method described in Example 52(a), but starting with 1,2,4-triazole) (0.176g, 0.00139mol) in tetrahydrofuran (10ml) at -78°C under nitrogen was added n-butyllithium (2.5M solution in hexane) (0.00139mol) and after 10 minutes, zinc chloride (0.00139mol) (0.5M solution in tetrahydrofuran). After 20 minutes, the reaction was warmed to room temperature and tetrakis(triphenylphosphine)palladium (0.053g) and the iodide product of Example 1(a) (0.2g, 0.00046mol) added and the reaction heated at reflux for 16 hours. The reaction was cooled to room temperature, washed with saturated aqueous ethylidiamine tetra-acetic acid di-sodium salt solution and filtered. The aqueous phase was extracted with dichloromethane (3x30ml) and the combined organics washed with brine (100ml), dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 80 : 20 : 5 pentane : ethyl acetate : diethylamine to give the subtitle compound (0.198 g). MS m/z 431 (MH⁺). ¹H-NMR (CDCl₃): δ = 0.86 (3H, m), 1.22 (3H, m), 1.88 (1H, m), 2.08 (3H, m), 2.58 (3H, s), 3.62 (2H, q), 3.80 (1H, q), 4.03 (1H, m), 5.50, (2H, s), 6.92 (1H, d), 7.00 (1H, d), 7.35 (1H, d), 7.68 (1H, d), 7.96 (1H, d), 8.27 (1H, s).
(b) Cis-(1S)-N-methyl-7-(3-(1,2,4-triazolyl))-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

To a solution of the pyrazole product of step (a) (0.193g, 0.00044mol) in ethanol (8ml) was added 2N aqueous hydrochloric acid (2ml) and the reaction heated at reflux for 16 hours. The reaction was cooled, and concentrated under reduced pressure. The mixture was neutralised with saturated aqueous sodium carbonate and extracted with ethyl acetate. The organic phase was dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 97 : 3 : 1 dichloromethane : methanol : 0.88 ammonia to give the title compound. The product was dissolved in dichloromethane (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo to yield the hydrochloride salt (0.038g). MS m/z 373 (MH⁺). ¹H-NMR (d₄-MeOH): δ: = 2.06 (1H, m), 2.32 (3H, m), 2.92 (3H, s), 4.26 (1H, m), 4.65 (1H, br), 7.12 (1H, d), 7.2 (1H, d), 7.50 (1H, d), 7.54 (1H, d), 7.96 (1H, d), 8.28 (1H, s), 9.24 (1H, s).

Example 56

Cis-(1S)-N-methyl-7-(3-(N(2)methyl-1,2,4-triazolyl))-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

To a solution of N(1)-methyl-1,2,4-triazole (Prepared by the method described in J. Chem. Soc., Perkin Trans. I, 1973, 2506) (0.115g, 0.00139mol) in tetrahydrofuran (5ml)
at -78°C under nitrogen was added n-butyllithium (2.5M solution in hexane) (0.00139mol) and after 10 minutes, zinc chloride (0.00139mol) (0.5M solution in tetrahydrofuran). After 15 minutes, the reaction was warmed to room temperature and tetrakis(triphenylphosphine) palladium (0.053g) and the iodide product of Example 1(a) (0.2g, 0.00046mol) added and the reaction heated at reflux for 16 hours. The reaction was cooled to room temperature, washed with saturated aqueous ethyldiamine tetra-acetic acid di-sodium salt solution and filtered. The aqueous phase was extracted with dichloromethane (3x30ml) and the combined organics washed with brine (100ml), dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 100 : 100 : 5 pentane : ethyl acetate : diethylamine to give the title compound (0.130 g). The product was dissolved in dichloromethane (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo to yield the hydrochloride salt. MS m/z 387 (MH⁺). ¹H-NMR (d₄-MeOH): δ = 2.08 (1H, m), 2.30 (3H, m), 2.9 (3H, s), 3.31 (1H, s), 4.10 (3H, s), 4.30 (1H, m), 4.65 (1H, s), 7.21 (1H, d), 7.28 (1H, d), 7.50 (1H, d), 7.55 (1H, d), 7.65 (1H, m), 7.74 (1H, m), 8.00 (1H, s), 8.39 (1H, s).

Example 57

Cis-(1S)-N-methyl-7-(5-(N(1)methyl-1,2,3-triazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of N(1)-methyl-1,2,3-triazole (Prepared by the general method described in J. Chem. Soc., Perkin Trans. 1, 1973, 2506) (0.115g, 0.00139mol) in tetrahydrofuran (2ml) at -78°C under nitrogen was added n-butyllithium (2.5M solution in hexane) (0.00139mol) and after 15 minutes, zinc chloride (0.00139mol) (0.5M solution in tetrahydrofuran). The reaction was warmed to 0°C and tetrakis(triphenylphosphine)palladium (0.053g) and a solution of the iodide product of Example 1(a) (0.2g, 0.00046mol) in tetrahydrofuran (5ml) added and the reaction heated at reflux for 16 hours. The reaction was cooled to room temperature, saturated aqueous
ethyldiamine tetra-acetic acid di-sodium salt solution was added, the mixture stirred for 30 minutes, water was added and the mixture extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium bicarbonate, brine and dried (MgSO₄). The solution was filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 100 : 2.5 : 1 dichloromethane : methanol : 0.88 ammonia to give the title compound as a pale yellow foam (0.148g, 83%). MS m/z 387 (MH)+. ¹H-NMR (CDCl₃): δ = 1.90 (1H, m), 2.05 (3H, m), 2.55 (3H, s), 3.77 (1H, t), 4.04 (1H, t), 4.10 (3H, s), 6.93 (1H, dd), 7.00 (1H, dd), 7.16 (1H, dd), 7.26 (1H, s), 7.38 (1H, dd), 7.46 (1H, s), 7.70 (1H, s).

Example 58
Cis-(1S)-N-methyl-7-(4-(1,2,3-triazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

(a) N(1)-ethoxymethyl-1,2,3-triazole

To a solution of 1,2,3-triazole (10g, 0.147mol) in acetone (55ml), cooled in an ice-water bath was added potassium carbonate (20.3g, 0.147mol) followed by chloromethylethylether (13.4ml, 0.147mol), dropwise. The reaction was warmed to room temperature and stirred for 60 hours. The acetone was removed in vacuo and the residue suspended in dichloromethane (100ml), filtered, dried (Na₂SO₄), filtered again and the solvent removed under reduced pressure. The crude product was purified on silica eluting with a solvent gradient of 1:1 to 0:100 hexane : dichloromethane to give the subtitle compound.

(b) Cis-(1S)-N-methyl-7-(4-(3-ethoxymethyl)-1,2,3-triazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of N(1)-ethoxymethyl-1,2,3-triazole (0.353g) in tetrahydrofuran (5ml) at -78°C under nitrogen was added n-butyllithium (2.5M solution in hexane) (0.00139mol) and after 15 minutes, zinc chloride (0.00139mol) (0.5M solution in tetrahydrofuran). The reaction was warmed to 0°C and tetrakis(triphenylphosphine)palladium (0.053g) and a
solution of the iodide product of Example 1(a) (0.4g, 0.00093mol) in tetrahydrofuran (5ml) added and the reaction heated at reflux for 16 hours. The reaction was cooled to room temperature, saturated aqueous ethyldiamine tetra-acetic acid di-sodium salt solution was added, the mixture stirred for 1 hour, water added and the mixture extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium bicarbonate, brine and dried (MgSO₄). The solution was filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 100 : 100 : 5 ethyl acetate : pentane : diethylamine to give the subtitle compound as a pale yellow foam (0.5g) which was used without further purification. MS m/z 431 (M⁺). ¹H-NMR (CDCl₃): δ = 1.20 (7H, m), 2.56 (3H, s), 3.56 (2H, q), 3.77 (1H, t), 4.03 (1H, t), 5.67 (2H, s), 6.93 (1H, dd), 7.00 (1H, dd), 7.27 (1H, s), 7.40 (2H, m), 7.65 (1H, d), 7.79 (1H, s).

(c) Cis-(1S)-N-methyl-7-(4-(1,2,3-triazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalenamine hydrochloride

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{Cl} & \quad \text{Cl} \\
\text{N} & \quad \text{N} \\
\text{CH}_3 & \quad \text{NHMe} \\
\end{align*}
\]

To a solution of the triazole from step (b) (0.5g, 0.00093mol) in ethanol (15ml) was added aqueous 2N HCl solution (7ml) and the reaction heated at reflux for 16 hours. The reaction was cooled to room temperature and the ethanol removed in vacuo. The residue was basified with 2M aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic layer was dried (MgSO₄), filtered and the solvent removed under reduced pressure to give the crude product which was purified on silica gel. The product was dissolved in dichloromethane (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo to yield the hydrochloride salt (0.24g). MS m/z 373 (M⁺). ¹H-NMR (d₆-DMSO): δ = 2.05 (3H, t), 2.20 (1H, m), 2.70 (3H, t), 2.90 (1H, m), 4.18 (1H, t), 4.49 (1H, t), 6.85 (1H, dd), 7.33 (1H, dd), 7.60 (2H, m), 7.73 (1H, dd), 8.21 (1H, s), 8.35 (1H, s), 9.25 (1H, d), 9.35 (1H, d).
Example 59

Cis-(1S)-N-methyl-7-(thiomethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

A solution of the iodide product of Example 1(a) (1.3g, 0.02mol), sodium methyl thiolate (0.147g) and copper powder (0.128g) in ethylene glycol (5ml) was warmed to 150°C over 30 minutes. After 1 hour, the reaction was cooled to room temperature and the solvent removed under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous ethyldiamine tetra-acetic acid di-sodium salt solution, the organic phase separated and washed with brine (4x50ml), dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with a gradient of 100:0:0 to 95:5:0.5 dichloromethane:methanol:0.88 ammonia to yield the free base (0.22g, 32%). The product was dissolved in dichloromethane (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo to yield the title compound. MS m/z 352 (MH⁺). ¹H-NMR (d₆-DMSO): δ = 2.00 (3H, m), 2.20 (1H, s), 2.50 (3H, s), 2.65 (3H, d), 4.10 (1H, m), 4.4 (1H, s), 6.65 (1H, d), 7.18 (1H, d), 7.30 (1H, d), 7.60 (3H, m).

Example 60

Cis-(1S)-N-methyl-7-(methylsulphonyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

To a solution of the sulphide product of Example 59 (0.154g) in trifluoroacetic acid (2ml) was added 0.3ml of a solution of 30% H₂O₂ (8.6ml) made up to 25 ml with trifluoroacetic acid, at 0°C. After 24 hours, the solvent was removed under reduced pressure and the
residue partitioned between aqueous 1N sodium hydroxide solution and ethyl acetate. The organic phase was washed with brine, dried (Na₂SO₄) and the solvent removed under reduced pressure. The residue was purified on silica gel with a gradient of 100 : 0 : 0 to 95 : 5 : 0.5 dichloromethane : methanol : 0.88 ammonia, to yield the free base. The product was dissolved in dichloromethane (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo and triturated with diethyl ether to yield the title compound, (0.05g). MS m/z 368 (MH⁺). ¹H-NMR (d₆-DMSO): δ = 2.05 (3H, m), 2.25 (1H, m), 2.70 (3H, d), 2.80 (3H, d), 4.20 (1H, m), 4.50 (1H, s), 6.95 (1H, m), 7.35 (1, d), 7.60 (3H, m), 8.00 (1H, d), 9.40 (2H, d).

Example 61

Cis-(1S)-N-methyl-7-(methylsulphonyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

To a solution of the sulphone product of Example 59 (0.282g) in trifluoroacetic acid (4ml) was added 2.2ml of a solution of 30% H₂O₂ (8.6ml) made up to 25 ml with trifluoroacetic acid, at 0°C. After 24 hours at room temperature, the solvent was removed under reduced pressure and the residue partitioned between aqueous 1N sodium hydroxide solution and ethyl acetate. The organic phase was washed with brine, dried (Na₂SO₄) and the solvent removed under reduced pressure. The residue was purified on silica gel using a solvent gradient of 100 : 0 : 0 to 95 : 5 : 0.5 dichloromethane : methanol : 0.88 ammonia to yield the free base. The product was dissolved in dichloromethane (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo and triturated with diethyl ether to yield the title compound, (0.120g). MS m/z 384 (MH⁺). ¹H-NMR (d₆-DMSO): δ = 2.05 (3H, m), 2.30 (1H, m), 2.7 (3H, s), 3.30 (3H, s), 4.25 (1H, t), 4.60 (1H, s), 7.00 (1H, d), 7.35 (1H, d), 7.60 (2H, dd), 7.80 (1H, d), 8.30 (1H, s).

Example 62
Cis-(1S)-N-methyl-7-(2-(methylsulphonyl)ethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

(a) Cis-(1S)-N-methyl-7-(2-(methylsulphonyl)vinyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

A solution of the iodide product of Example 1(a) (1.3g, 0.003mol), methyl vinyl sulphone (0.478g, 0.0045mol), palladium acetate (0.056g), tri(o-tolyl)phosphine (0.304g, 0.001mol) and triethylamine (1.25ml) in acetonitrile (15ml) was heated under reflux for 4 hours. The reaction was cooled to room temperature, the solvent removed under reduced pressure and the residue partitioned between ethyl acetate and 10% aqueous potassium carbonate solution. The organic phase was washed with brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel using a solvent gradient of 100:0:0 to 95:5:0.5 dichloromethane: methanol: 0.88 ammonia to yield the subtitle compound, (0.9g, 73%). MS m/z 410 (MH⁺). ¹H-NMR (CDCl₃): δ = 1.85 (1H, m), 2.00 (3H, m), 2.55 (3H, s), 3.05 (3H, s), 3.75 (1H, m), 4.00 (1H, t), 6.85 (3H, m), 7.25 (2H, m), 7.35 (1H, d), 7.60 (2H, d).

(b) Cis-(1S)-N-methyl-7-(2-(methylsulphonyl)ethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

A solution of the vinyl sulphone product from Example 62(a) (0.615g, 0.0015mol) and tosylhydrazine (1.4g, 0.0075mol) in dry toluene (20ml) was heated at reflux for 7 hours. The reaction was cooled to room temperature and the residue was purified on silica gel using a solvent gradient of 100:0:0 to 95:5:0.5 dichloromethane: methanol: 0.88
ammonia to yield the free base. The product was dissolved in dichloromethane (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo and tritiated with diethyl ether to yield the title compound (0.390g). MS m/z 412 (MH)⁺. ¹H-NMR (d₆-DMSO): δ = 2.00 (3H, m), 2.20 (1H, m), 2.65 (3H, d), 3.00 (3H, s), 3.05 (3H, m), 3.40 (2H, m), 4.10 (1H, t), 4.40 (1H, s), 6.70 (1H, d), 7.10 (1H, d), 7.20 (1H, d), 7.30 (1H, d), 7.45 (1H, d), 7.60 (1H, d), 9.05 (2H, s).

Using the procedure described in of Example 62, the following ethylsulphonamides were prepared by reaction of the iodide product of Example 1(a) and the appropriate vinylsulphonamide:

<table>
<thead>
<tr>
<th>Example No.</th>
<th>R</th>
<th>¹H-NMR and mass spectral data</th>
</tr>
</thead>
<tbody>
<tr>
<td>63</td>
<td>-SO₂NH₂</td>
<td>(d₆-DMSO): δ = 2.00 (3H, m), 2.25 (1H, m), 2.65 (3H, s), 3.00 (2H, m), 3.30 (2H, m), 4.10 (1H, t), 4.40 (1H, s), 6.65 (1H, d), 6.90 (2H, s), 7.10 (1H, d), 7.35 (1H, d), 7.60 (3H, m), 9.25 (2H, s). MS m/z 413 (MH)⁺.</td>
</tr>
<tr>
<td>64</td>
<td>-SO₂NCH₃</td>
<td>(d₆-DMSO): δ = 2.00 (3H, m), 2.20 (1H, m), 2.60 (3H, d), 2.65 (3H, s), 2.95 (2H, m), 3.30 (2H, m), 4.10 (1H, t), 4.40 (1H, s), 6.70 (1H, d), 7.00 (1H, d), 7.20 (1H, d), 7.30 (1H, d), 7.60 (2H, d), 9.30 (2H, d). MS m/z 427 (MH)⁺.</td>
</tr>
<tr>
<td>65</td>
<td>-SO₂N(CH₃)₂</td>
<td>(d₆-DMSO): δ = 2.00 (3H, m), 2.20 (1H, m), 2.65 (3H, d), 2.80 (6H, s), 3.00 (2H, m), 3.35 (2H, m), 4.10 (1H, t), 4.40 (1H, s), 6.65 (1H, d), 7.20 (1H, d), 7.30 (1H, d), 7.60 (3H, m), 9.20 (1H, s), 9.40 (1H, s). MS m/z 441 (MH)⁺.</td>
</tr>
</tbody>
</table>
Example 66

Cis-(1S)-N-methyl-7-(2-methylcarbamoylethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

(a) Cis-(1S)-N-methyl-7-(2-ethoxycarbonylvinyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

The subtitle compound was prepared using the method described in Example 62(a), using the iodide product of Example 1(a) and ethyl acrylate (yield = 84%). $^1$H NMR (CDCl$_3$): $\delta$ = 1.33 (3H, t), 1.83 (1H, m), 2.02 (3H, m), 2.57 (3H, s), 3.71 (1H, t), 3.98 (1H, dd), 4.28 (2H, q), 6.42 (1H, d), 6.82 (1H, d), 6.97 (1H, dd), 7.23 (1H, d), 7.28 (1H, dd), 7.37 (1H, d), 7.52 (1H, d), 7.68 (1H, d). MS m/z 404 (MH)$^+$. 

(b) Cis-(1S)-N-methyl-7-(2-ethoxycarbonylethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

The subtitle compound was prepared using the method described in Example 62(b), using the product of step (a) and tosyl hydrazine (yield = 70.4%). $^1$H NMR (CDCl$_3$): $\delta$ = 1.26 (3H, t), 1.82 (1H, m), 2.00 (3H, m), 2.53 (3H, s), 2.61 (2H, t), 2.92 (2H, t), 3.69 (1H, t), 3.94 (1H, dd), 4.14 (2H, q), 6.70 (1H, dd), 6.95 (2H, dt), 7.20 (1H, d), 7.25 (1H, d), 7.34 (1H, d). MS m/z 406 (MH)$^+$. 

(c) Cis-(1S)-N-methyl-7-(2-methylcarbamoylethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride
The ester product of step (b) (0.19g) and methylamine (5ml) (33% solution in ethanol) were heated at 100°C for 16 hours. The reaction was cooled and the solvent removed under reduced pressure. The residue was purified on silica gel using a solvent of 87 : 12 : 1 to 95 : 5 : 1 dichloromethane : methanol : 0.88 ammonia to yield the free base. The product was dissolved in ethyl acetate (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo and triturated with diethyl ether to yield the title compound, (0.142g, 68%). 1H NMR (d6-DMSO): δ = 2.00 (3H, m), 2.21 (1H, m), 2.40 (2H, t), 2.54 (3H, d), 2.67 (3H, s), 2.80 (2H, t), 4.08 (1H, t), 4.35 (1H, br), 6.65 (1H, d), 7.10 (1H, d), 7.30 (1H, d), 7.48 (1H, s), 7.58 (1H, s), 7.60 (1H, d), 7.80 (1H, d), 9.15 (2H, br). MS m/z 391 (MH+)°.

Using the procedure described in Example 66(c), the following amides were prepared by reaction of the ester product of Example 66(b) and the appropriate amine:

<table>
<thead>
<tr>
<th>Example No.</th>
<th>R</th>
<th>1H-NMR and mass spectral data</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>-NH(CH2)2OH</td>
<td>(d6-DMSO): δ = 2.00 (3H, m), 2.22 (1H, m), 2.40 (2H, m), 2.67 (3H, s), 2.80 (2H, m), 3.09 (2H, m), 3.32 (2H, m), 4.09 (1H, t), 4.36 (1H, br), 4.65 (1H, br), 6.66 (1H, d), 7.11 (1H, dd), 7.30 (1H, dd), 7.48 (1H, s), 7.58 (1H, s), 7.60 (1H, d), 7.89 (1H, m), 9.13 (2H, br). MS m/z 421 (MH+)°.</td>
</tr>
</tbody>
</table>
Example 69
Cis-(1S)-N-methyl-7-(2-carboxyethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the ester product of Example 66(b) (1.0g, 0.0025mmol) in water (15ml) and methanol (60ml) was added lithium hydroxide (0.419g) and the reaction heated at reflux for 1.25 hours. The reaction was cooled to room temperature and the solvent removed in vacuo. Water (30ml) was added and the pH adjusted to 5-6 by the addition of 2N aqueous hydrochloric acid. The slurry was extracted with a mixture of ethyl acetate and methanol (9:1, x3). The combined organics were washed with water (x3), dried (Na₂SO₄) and the solvent removed under reduced pressure. The solid was triturated with pentane:ether (19:1), to give the title compound, (0.80g) as a cream-white solid. MS m/z 400 (MNa)⁺. ¹H NMR (Selected data) (CDCl₃): δ = 2.44 (3H, s), 2.50 (1H, m), 2.65-3.03 (3H, m), 3.94 (1H, m), 4.29 (1H, m), 6.78 (1H, d).

Example 70
Cis-(1S)-N-methyl-7-(2-propanamido)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride
The acid product of Example 69 (0.57g, 0.0015mol) was converted to the hydrochloride salt using ethereal HCl solution and the solvent removed under reduced pressure. This was dissolved in dichloromethane (10ml) and cooled in an ice-water bath, then oxalyl chloride (0.2ml) and N,N-dimethylformamide (cat), added. The reaction was warmed to room temperature and stirred for 1 hour. The solvent was removed and the solid triturated with dichloromethane. The acid chloride was dissolved in dichloromethane (10ml) and added to a solution of saturated methanolic ammonia (5ml), cooled in an ice-water bath. After 21 hours, the solvent was removed under reduced pressure and the crude product purified on silica gel using of 93 : 7 : 1 dichloromethane : methanol : 0.88 ammonia to yield the free base, (18%). 0.1g of this product was dissolved in ethyl acetate (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo and triturated with diethyl ether to yield the title compound. (CDCl₃): δ = 1.80 (1H, m), 1.98 (3H, m), 2.52 (5H, m), 2.92 (2H, t), 3.66 (1H, t), 3.96 (1H, q), 5.32 (1H, s), 6.71 (1H, d), 6.95 (2H, dd), 7.21 (2H, dd), 7.34 (1H, d).

Example 71
Cis-(1S)-N-methyl-7-(hydroxymethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the ester product of Example 6(a) (3.53g, 0.096mol) in tetrahydrofuran (100ml) at room temperature was added a solution of di-isobutylaluminium hydride in tetrahydrofuran (29ml, 1M solution) over 15 minutes and the reaction stirred at room temperature. A further 4ml of a solution of di-isobutylaluminium hydride in
tetrahydrofuran was added and the reaction stirred at room temperature for 16 hours. Methanol (5ml) was added followed, cautiously, by saturated aqueous ammonium chloride solution, with water-cooling. Ethyl acetate (200ml) was added and the aqueous phase was washed with ethyl acetate. The combined organics were washed with water, brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The solid was triturated with diethyl ether to give the title compound (2.15g). The mother liquors were purified on silica gel using of 93 : 7 : 1 dichloromethane : methanol : 0.88 ammonia as solvent to yield a second crop of the title compound, (0.34g, total yield = 76%). MS m/z 336 (M+). ¹H NMR (CDCl₃): δ = 1.85 (1H, m), 2.02 (3H, m), 2.53 (3H, s), 3.73 (1H, t), 3.95 (1H, dd), 4.67 (2H, s), 6.79 (1H, d), 6.98 (1H, dd), 7.11 (1H, dd), 7.25 (1H, d), 7.34 (1H, d), 7.40 (1H, s).

Example 72

Cis-(1S)-N-methyl-7-(N(1)-1,2,3-triazolylmethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

(a) Cis-(1S)-N-methyl-7-(chloromethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

To a solution of the alcohol product of Example 71 (0.34g) in tetrahydrofuran (10ml) at room temperature was added a saturated solution of hydrogen chloride in diethyl ether (2ml) followed by thionyl chloride (0.5ml) and the reaction stirred at room temperature for 2 hours. The solvent was removed under reduced pressure to give the subtitle compound, (0.42g, 100%). MS m/z 354 (M+). ¹H NMR (d₆-DMSO): δ = 2.05 (3H, m), 2.27 (1H, m), 2.69 (3H, t), 4.14 (1H, t), 4.43 (1H, br), 4.74 (2H, s), 6.78 (1H, dd), 7.33 (2H, dd), 7.60 (1H, d), 7.62 (1H, s), 7.71 (1H, d), 9.2 (1H, br), 9.3 (1H, br).

(b) Cis-(1S)-N-methyl-7-(N(1)-1,2,3-triazolylmethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride
To 1,2,3-triazole (1g) at 120°C was added (72a) (0.2g) over 10 minutes and the reaction heated at 120°C for 1 hour. The reaction was cooled, water added and the mixture extracted with ethyl acetate (x3). The combined organics were washed with brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel using of 93 : 7 : 1 dichloromethane : methanol : 0.88 ammonia as solvent to yield the free base, (0.049g). The product was dissolved in ethyl acetate (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo and triturated with diethyl ether to yield the title compound (51 mg, 23%). MS m/z 387 (MH)+. ¹H NMR (d₆-DMSO): δ = 2.00 (3H, m), 2.25 (1H, m), 2.65 (3H, s), 4.11 (1H, t), 4.39 (1H, br), 5.60 (2H, s), 6.75 (1H, d), 7.22 (1H, d), 7.32 (1H, d), 7.60 (3H, m), 7.74 (1H, s), 8.25 (1H, s), 9.20 (2H, br).

Example 73

Cis-(1S)-N-methyl-7-((methylthio)methyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of chloride product of Example 72(a) (0.1g) in N,N-dimethylformamide (5ml) was added sodium methylthiolate (0.55g) and the reaction heated at 75°C for 3 hours. The reaction was cooled, water added and the mixture extracted with ethyl acetate (x3). The combined organics were washed with water, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure to yield the title compound, (0.08g). MS m/z 366 (MH)+.

Example 74
Cis-(1S)-N-methyl-7-((methylsulphonyl)methyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the sulphide product of Example 73 (0.073g, 0.0002mol) in isopropyl alcohol (2ml), tetrahydrofuran (0.4ml) and water (0.2ml) cooled in an ice-water bath was added OXONE® (2KHSO₅, KHSO₄, K₂SO₄, 0.061g) and the reaction stirred at room temperature for 3 hours. A further portion of OXONE® (0.061g) was added. After 20 minutes, a few drops of 0.88 ammonia were added and the mixture extracted with ethyl acetate (x3). The combined organics were washed with water, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel using 93 : 7 : 1 dichloromethane : methanol : 0.88 ammonia (diluted 1 : 1 with dichloromethane) as solvent to yield the title compound (0.06g, 75%). MS m/z 398 (MH)⁺. ¹H NMR (CDCl₃): δ = 1.82 (1H, m), 2.0 (3H, m), 2.54 (3H, m), 2.80 (3H, s), 3.73 (1H, t), 3.98 (1H, t), 4.2 (2H, t), 6.82-7.42 (6H, m, Ar).

Example 75
Cis-(1S)-N-methyl-7-((methylsulphinyl)methyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

To a solution of the sulphide product of Example 73 (0.290g, 0.00079mol) in isopropyl alcohol (8ml), tetrahydrofuran (1.6ml) and water (0.8ml) cooled in an ice-water bath, was added OXONE® (0.27g) and the reaction stirred at room temperature for 6 hours. Water was added and the mixture extracted with ethyl acetate (x3). The combined organics were washed with water, brine, dried (Na₂SO₄), filtered and the solvent removed under reduced
pressure. The residue was purified on silica gel using 93:7:1 dichloromethane : methanol : 0.88 ammonia (diluted 1:1 with dichloromethane). The product was dissolved in ethyl acetate and diethyl ether (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo and triturated with diethyl ether to yield the title compound, (0.128g). MS m/z 382 (MH+). 1H NMR (CDCl3): δ = 1.82 (1H, m), 2.01 (3H, m), 2.5 (3H, s), 2.55 (3H, s), 3.70 (1H, t), 3.95 (1H, m), 6.8-7.38 (6H, m, Ar).

Example 76
Cis-(1S)-N-methyl-7-((N-methylsulphonamido)methyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

Steps (i)-(v): Preparation of N-[(benzyloxy)methyl](cyano)-N-methyl-methanesulphonamide

(i) Methyl 2-(chlorosulphonyl)acetate

To a solution of methylthioglycolate (1.3kg, 12.25mol) in dichloromethane (9 litres) was added ice (4.5 litres). Chlorine gas was bubbled gently through the solution, maintaining the temperature below 5°C until the solution maintained a slight green colouration. The solution was degassed with nitrogen to remove excess chlorine, the organic phase collected and the solvent removed under reduced pressure to give the subtitle compound
(1.758 kg, 83%) which was used without further purification. $^1$H NMR (CDCl$_3$): 3.91 (3H, s), 4.63 (2H, s).

(ii) Methyl 2-[(methylamino)sulphonyl]acetate

To a solution of the product of step (i) (75g) in tetrahydrofuran (150ml) at 5°C was added a solution of methylamine in tetrahydrofuran (2M solution, 435ml) over one hour. The yellow slurry was allowed to warm to room temperature and after one hour water (750ml) added. Ethyl acetate (750ml) was added and the aqueous phase extracted with ethyl acetate (500ml). The organics were combined and the solvent removed under reduced pressure to give the subtitle compound (40.2g) which was used without further purification. $^1$H NMR (CDCl$_3$): 2.90 (3H, m), 3.75 (3H, s), 4.05 (2H, s), 4.77 (1H, br)

(iii) Methyl 2-{[[benzyloxy)methyl]methylamino)sulphonyl]acetate

To a solution of potassium-t-butoxide (14.76g) in tetrahydrofuran (100ml) at 5°C was added a solution of the product of step (ii) (20g) in tetrahydrofuran (50ml) over two hours. After a further hour, a solution of benzychloromethyl ether (34.35g) in tetrahydrofuran (50ml) was added over 20 minutes, maintaining the temperature below 10°C. After one hour, water (200ml) was added and the mixture extracted with ethyl acetate (200ml). The organic phase was extracted with ethyl acetate (100ml) and the organics were combined. The solvent was removed under reduced pressure to give the crude product which was used without further purification.

(iv) 2-{[[benzyloxy)methyl]methylamino)sulphonyl]acetamide

To a solution of the product of step (iii) (60g) in tetrahydrofuran (60ml) was added 0.880 ammonia solution (180ml). After 18 hours, the reaction was diluted with water and extracted with ethyl acetate. The organic phase was concentrated under reduced pressure, toluene added and the solution concentrated then heated under reflux and allowed to cool to room temperature. The slurry was filtered, washed with toluene and dried under vacuum at 40°C to give the title compound (30%) which was used without further
purification. \(^1\)H NMR (d\(_6\)-DMSO): 2.94 (3H, s), 4.00 (2H, s), 4.50 (2H, s), 4.65 (2H, s), 7.22-7.42 (6H, m), 7.69 (1H, br).

(v) N-[(benzyloxy)methyl](cyano)-N-methylmethanesulphonamide

To a solution of N,N-dimethylformamide (4.96ml) in tetrahydrofuran (100ml) at 5°C was added oxalyl chloride (5.28ml). After 30 minutes, a solution of the product of step (iv) (15g, 0.055mol) in tetrahydrofuran (50ml) was added, maintaining the temperature at 5°C. After 30 minutes, pyridine (9.36ml) was added, the reaction warmed to room temperature and water added. The mixture was extracted with ethyl acetate, the organics combined and the solvent removed under reduced pressure to yield the title compound (13.11g), which was used without further purification. \(^1\)H NMR (CDCl\(_3\)): 3.80 (3H, s), 4.02 (2H, s), 4.60 (2H, s), 4.80 (2H, s), 7.30-7.41 (5H, m).

15 (a) Cis-(1S)-N-methyl-7-(((N-methyl-N-benzyloxyethyl)sulphonamido)cyanomethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of sodium hydride (0.24g) in toluene (12ml) and DME (2ml) under an atmosphere of nitrogen was added a solution of the product of step (v) (0.726g) in toluene (3ml), maintaining the temperature below 5°C. Tetrakis(triphenylphosphine) palladium (0.231g) was added and the reaction allowed to warm to room temperature. A solution of the iodide product of Example 1(a) (0.864g) in toluene (3ml) was added and the reaction heated at reflux for 96 hours. The reaction was cooled, water (20ml) added and the mixture extracted with ethyl acetate (x3). The combined organics were washed with brine, dried (Na\(_2\)SO\(_4\)), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel using 100 : 0 to 95 : 5 dichloromethane : methanol as the solvent, to give the subtitle compound, (1.1g). MS m/z 558 (MH\(^+\)). \(^1\)H NMR (CDCl\(_3\)): \(\delta = 1.80\) (1H, m), 2.00 (3H, m), 2.50 (3H, s), 3.10 (3H, s), 3.15 (1H, m), 3.75 (1H, m), 4.00 (1H, t), 4.60 (4H, m), 6.90-7.70 (11H, m, Ar).

(b) Cis-(1S)-N-methyl-7-(((N-methyl-N-benzyloxyethyl)sulphonamido)methyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine
To a solution of potassium hydroxide (0.605g) in water (15ml) was added a solution of the nitrile product of step (a) (1.0g) in ethanol (15ml) and the reaction heated under reflux for 68 hours. The reaction was cooled, the solvent removed under reduced pressure and the residue partitioned between water and ethyl acetate. The organic phase was dried (Na$_2$SO$_4$), filtered and the solvent removed under reduced pressure to give the subtitle compound, (0.8g), which was used without further purification. MS $m/z$ 533 (MH)$^+$. $^1$H NMR (CDCl$_3$): $\delta$ = 1.60 (3H, m), 1.80 (1H, m), 2.50 (3H, s), 3.85 (3H, s), 3.70 (1H, m), 3.95 (1H, m), 4.20 (2H, s), 4.50 (4H, s), 6.80-7.70 (11H, m).

(c) **Cis-(1S)-N-methyl-7-((N-methylsulphonamido)methyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride**

To a solution of the product of step (b) (0.28g) in methanol (20ml) and water (10ml) was added palladium hydroxide (0.05g) and methane sulphonic acid (0.2ml) and the reaction heated at 60°C under an atmosphere of hydrogen at 414 kPa (60 p.s.i.) for 20 hours. The reaction was cooled to room temperature and filtered through ArbaceI™ filter aid. Water was added to the filtrate, the solution made basic with 1N aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic phase was dried (Na$_2$SO$_4$), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel using a solvent gradient of 100 : 0 : 0 to 95 : 5 : 0.5 dichloromethane : methanol : ammonia to yield the free base. The product was dissolved in dichloromethane (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo, triturated with diethyl ether and dried to yield the title compound, (0.080g). MS $m/z$ 413 (MH)$^+$. $^1$H NMR (d$_6$-DMSO): $\delta$ = 2.00 (3H, m), 2.30 (1H, m), 2.55 (2H, d), 3.30 (3H, s), 4.10 (1H, m), 4.25 (2H, q), 4.40 (1H, s), 6.75 (1H, d), 7.00 (1H, d), 7.25 (1H, d), 7.35 (1H, d), 7.60 (2H, m), 9.20 (1H, s), 9.30 (1H, s).

**Example 77**

**Cis-(1S)-N-methyl-7-((carboxamido)methyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride**
(a) Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-7-(methoxycarbonyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the ester produced in Example 6(a) (4.3g) in tetrahydrofuran (50ml) and di-isopropylethylamine (1.68g) was added di-tert-butyl dicarbonate (2.84g) and the reaction stirred at room temperature for 16 hours. The solvent was removed under reduced pressure, toluene added and the solution washed with water (x2), brine, dried (MgSO4), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel using 9:1 pentane:ethyl acetate as solvent, to yield the subtitle compound, (4.4g, 80%). MS m/z 504 (MNH4)+. 1H NMR (CDCl3) δ = 1.54 (9H, s), 1.79 (2H, m), 2.02 (1H, m), 2.29 (1H, m), 2.66 (3H, s), 3.91 (3H, s), 4.22 (1H, br), 5.30 (0.45H, br), 5.49 (0.55H, br), 6.79 (1H, d), 7.05 (1H, d), 7.07 (1H, d), 7.34 (1H, d), 7.82 (1H, d), 7.91 (1H, s).

(b) Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-7-(carboxy)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine
A solution of the carbamate produced in step (a) (2.0g) in methanol (120ml) and water (30ml), together with lithium hydroxide monohydrate (0.724g) was heated under reflux for 1.5 hours. The reaction was cooled to room temperature, the residue dissolved in water (60ml) and the pH adjusted to 3-4 using 2N aqueous hydrochloric acid solution. The solution was extracted with dichloromethane (x5), the combined organics dried (MgSO₄), filtered and the solvent removed under reduced pressure to give the subtitle compound, (1.81g), which was used without further purification. MS m/z 467 (MNH₄)⁺. ¹H NMR (CDCl₃): δ = 1.55 (9H, s), 1.80 (2H, m), 2.05 (1H, m), 2.30 (1H, m), 2.66 (3H, s), 4.22 (1H, br), 5.32 (0.45H, br), 5.50 (0.55H, br), 6.80 (1H, dd), 7.05 (1H, dd), 7.10 (1H, s), 7.34 (1H, d), 7.90 (1H, dd), 8.00 (1H, br).

(c) **Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-7-(diazomethylcarbonyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine**

To a solution of the sodium salt of (77b) (8.0g) in tetrahydrofuran (100ml) at 0°C was added N,N-dimethylformamide (cat.) followed by oxalyl chloride (3.2g, 1.5 equiv.) over 30 minutes. The reaction was warmed to room temperature and stirred for 2 hours. The solution was cooled to 0°C, a solution of diazomethane (2 equivalents) in diethyl ether (100ml) added and the reaction stirred at room temperature for 16 hours. The reaction was cooled again to 0°C, a solution of diazomethane (2 equivalents) in diethyl ether (100ml) added and the reaction stirred at room temperature for a further 16 hours. Nitrogen was bubbled through the solution for 1 hour to remove excess diazomethane and the solvent removed under reduced pressure. The residue was partitioned between diethyl ether and 10% aqueous citric acid, the organic phase separated and washed with saturated aqueous sodium bicarbonate solution and brine. The organic phase was dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel using 3:1 pentane:ethyl acetate as solvent, to yield the subtitle compound, (3.7g, 46%). ¹H NMR (CDCl₃): δ = 1.52 (9H, s), 1.79 (2H, m), 2.02 (1H, m), 2.28 (1H, m), 2.65 (3H, t), 4.21 (1H, br), 5.30 (0.45H, br), 5.48 (0.55H, br), 5.87 (1H, s), 6.79 (1H, d), 7.04 (1H, d), 7.08 (1H, s), 7.34 (1H, d), 7.58 (1H, d), 7.61 (1H, s).
(d) **Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-7-(methoxycarbonylmethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine**

To a solution of the compound produced in step (c) (0.173g) in methanol (4ml) was added triethylamine (1ml) and silver (I) oxide (0.024g) and the mixture sonicated in an ultrasound bath for 35 minutes. The solvent was removed under reduced pressure and the residue purified on silica gel using 4:1 pentane:ethyl acetate as solvent, to yield the subtitle compound, (57%). MS m/z 495 (MNH$_2$)$^+$. $^1$H NMR (CDCl$_3$): $\delta$ = 1.53 (9H, s), 1.75 (2H, m), 2.00 (1H, m), 2.25 (1H, m), 2.62 (3H, s), 3.62 (2H, s), 3.73 (3H, s), 4.15 (1H, br), 5.30 (0.45H, br), 5.47 (0.55H, br), 6.80 (1H, br), 6.91 (1H, d), 7.09 (3H, m), 7.33 (1H, d).

(e) **Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-7-(carboxymethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine**

To a solution of the ester produced in step (d) (0.1g) in methanol (4ml) and water (1ml) was added lithium hydroxide monohydrate (0.042g) and the mixture heated under reflux for 1.25 hours. The reaction was cooled to room temperature and the solvent removed under reduced pressure. Water was added and the pH adjusted to 2 using 2N aqueous hydrochloric acid. The solution was extracted with ethyl acetate and the combined organics were washed with brine, dried (MgSO$_4$), filtered and the solvent removed under reduced pressure to give the subtitle compound (96%), which was used without further purification. MS m/z 481 (MNH$_2$)$^+$. $^1$H NMR (CDCl$_3$): $\delta$ = 1.52 (9H, s), 1.75 (2H, m), 2.00 (1H, m), 2.27 (1H, m), 2.63 (3H, s), 3.65 (2H, s), 4.15 (1H, br), 5.29 (0.45H, br), 5.46 (0.55H, br), 6.80 (1H, br), 6.93 (1H, d), 7.12 (3H, m), 7.32 (1H, d).

(f) **Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-7-((carboxamido)methyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine**

To a solution of the acid produced in step (e) (0.092g), hydroxybenzotriazole (0.041g), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (0.046g) and ammonium carbonate (0.038g) in dioxan (4ml) was added diisopropylethylamine (0.087ml) and the
reaction stirred at room temperature for 18 hours. The solvent was removed under reduced pressure, water added and extracted with ethyl acetate (x2). The combined organics were dried (MgSO₄), filtered and the solvent removed under reduced pressure to give the subtitle compound (98%), which was used without further purification. MS m/z 480 (MNH)_n.

1H NMR (CDCl₃): δ = 1.52 (9H, m), 1.75 (2H, m), 2.00 (1H, m), 2.25 (1H, m), 2.62 (3H, s), 3.56 (2H, s), 4.15 (1H, t), 5.29 (0.45H, br), 5.41 (0.55H, br), 5.50 (1H, br), 5.69 (1H, br), 6.81 (1H, d), 6.94 (1H, d), 7.10 (3H, m), 7.32 (1H, d).

(g) Cis-(1S)-N-methyl-7-((carboxamidomethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

A solution of the compound produced in step (f) (0.091g) in dichloromethane (5ml) was cooled in an ice-water bath and the solution saturated with hydrogen chloride gas. The reaction was stirred for 1 hour, the solvent removed under reduced pressure, the residue azeotroped with dichloromethane (x3) and then triturated with diethyl ether to give the title compound, (0.065g, 91%). MS m/z 363 (MH)_n. 1H NMR (d₄-MeOH): δ = 1.98 (1H, m), 2.22 (3H, m), 2.88 (3H, s), 3.58 (2H, s), 4.15 (1H, dd), 4.48 (1H, t), 6.88 (1H, d), 7.24 (2H, dt), 7.45 (2H, s), 7.50 (1H, d).

Example 78
Cis-(1S)-N-methyl-7-((N-methylcarboxamidomethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

A solution of the ester product of Example 77(d) (0.043g) in ethanol (0.5ml) and methylamine in ethanol (33% solution) (0.5ml) was heated at 90°C for 3 hours. The reaction was cooled, the solvent removed under reduced pressure and the residue purified
on silica gel using 98:2:0.25 dichloromethane:methanol:0.88 ammonia as solvent to give the subtitle compound (0.033g, 77%). MS m/z = 495 (MNH₂)⁺. ¹H NMR (CDCl₃): δ = 1.52 (9H, s), 1.25 (2H, m), 2.00 (1H, m), 2.25 (1H, m), 2.63 (3H, s), 2.80 (3H, d), 3.54 (2H, s), 4.15 (1H, br), 4.29 (0.45H, br), 5.42 (0.55H, br), 6.82 (1H, d), 6.94 (1H, d), 7.08 (3H, m), 7.32 (1H, d).

(b) Cis-(1S)-N-methyl-7-((N-methylcarboxamido)methyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

A solution of the product of step (a) (0.033g) in dichloromethane (5ml) was cooled in an ice-water bath and the solution saturated with hydrogen chloride gas. The reaction was stirred for 1 hour, the solvent removed under reduced pressure, the residue azeotroped with dichloromethane (x3) and then triturated with diethyl ether to give the title compound, (0.023g, 85%). MS m/z 377 (MH)⁺. ¹H NMR (CDCl₃): δ = 2.06 (2H, m), 2.21 (1H, m), 2.38 (1H, m), 2.55 (3H, s), 2.72 (3H, d), 3.32 (1H, d), 3.47 (1H, d), 3.95 (1H, br), 4.12 (1H, br), 6.66 (1H, br), 6.83 (1H, d), 7.18 (2H, m), 7.21 (1H, d), 7.38 (1H, d), 7.43 (1H, s), 7.70 (1H, s).

Example 79

Cis-(1S)-N-methyl-7-(nitro)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a stirred solution of cis-(1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride (7.8g, 0.0228mol) in trifluoroacetic acid (70ml) in an ice-water bath was added triflic acid (7ml) followed by potassium nitrate (2.32g, 0.0228mol). After 1.5 hours, the reaction was poured into a mixture of ice and 0.88 ammonia and extracted with ethyl acetate (2x100ml). The combined organics were washed with brine (200ml), dried (MgSO₄), filtered and the solvent removed under reduced pressure. The
crude product was purified on silica gel eluting with a gradient of 99.8:0.2 to 99.2:0.8 dichloromethane:methanol to give the title compound (3.8g, 44%). [containing ca., 5% of the 5-nitro isomer]. MS m/z 351 (MH)+. 1H-NMR (CDCl3): δ = 1.8-2.1 (4H, m), 2.5 (3H, s), 3.8 (1H, t), 4.1 (1H, m), 6.9 (1H, dd), 7.0 (1H, d), 7.2 (1H, s), 7.4 (1H, d), 7.9 (1H, dd), 8.3 (1H, s).

Example 80

Cis-(1S)-N-methyl-7-(amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

![Chemical structure]

To a solution of the product of Example 79 (14.7g, 0.0419mol) in 85% aqueous ethanol (300ml) was added iron powder (21.1g, 0.376mol) and calcium chloride (2.1g, 0.019mol) and the reaction heated under reflux for 16 hours. The reaction was cooled and filtered through Arbacefl™, eluting with ethyl acetate. The collected filtrate was concentrated under reduced pressure, dried (MgSO4), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with a gradient of 98:2 dichloromethane:methanol to 90:10:1 dichloromethane:methanol:ammonia to give the title compound (9 g, 67%). MS m/z 321 (MH)+. 1H-NMR (CDCl3): δ = 1.8-2.1 (4H, m), 2.6 (3H, s), 3.7 (2H, br), 3.8 (1H, m), 3.9 (1H, m), 6.5 (1H, d), 6.5 (1H, d), 6.6 (1H, d), 6.9 (1H, s), 7.0 (1H, d), 7.2 (1H, s), 7.3 (1H, d), which was preceded on the column by the 5-amino isomer which was isolated pure following further chromatography, eluting with 99.8:0.2 dichloromethane:methanol (390mg, 3%). MS m/z 321 (MH)+. 1H-NMR (CDCl3, partial data): δ = 1.8-2.2 (4H, m), 3.8 (1H, m), 4.0 (1H, m), 6.6 (1H, d), 6.9 (1H, d), 7.0 (1H, d), 7.1 (1H, t), 7.3 (1H, d).

Example 81

Cis-(1S)-N-methyl-7-((methylsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine
(a) Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-7-(amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the amine product of Example 80 (0.65g, 0.00202mol) in a mixture of dioxan (8ml), water (2ml) and 1N aqueous sodium hydroxide (2ml), cooled in an ice-water bath, was added a solution of di-tert-butyl dicarbonate (0.442g, 0.00202mol). After 1 hour, the reaction was adjusted to pH 4 using 5% aqueous citric acid solution and extracted with ethyl acetate (2x20ml). The combined organics were washed with brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 99.8:0.2 dichloromethane:methanol to give the subtitle compound, (0.33 g, 39%). MS m/z 421 (MH⁺). ¹H-NMR (CDCl₃) (selected data): δ = 1.5 (9H, s), 1.7 (2H, m), 2.0 (1H, m), 2.26 (1H, m), 2.6 (2H, s), 4.1 (1H, t).

(b) Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-7-(methylsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the amine prepared in step (a) (0.32g) and triethylamine (0.328ml) in tetrahydrofuran at room temperature was added methane sulphonic anhydride (0.273g) and the mixture stirred for 1 hour. Water and triethylamine (0.328ml) were added and the mixture extracted with ethyl acetate (x2). The combined organics were dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was stirred in a
solution of 1N aqueous sodium hydroxide : dioxan (1:1) for 0.5 hours, extracted into ethyl acetate (x2), the combined organics were dried (MgSO₄), filtered and the solvent removed under reduced pressure to give the subtitle compound, (0.337g, 89%). MS m/z 518 (MNH₄)⁺. ¹H-NMR (CDCl₃): δ = 1.56 (9H, s), 1.75 (2H, m), 2.00 (1H, m), 2.24 (1H, m), 2.63 (3H, s), 3.04 (3H, s), 4.17 (1H, m), 5.41 (1H, m), 6.36 (1H, m), 6.78-7.36 (6H, m, Ar).

(c) Cis-(1S)-N-methyl-7-((methylsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the product of step (b) (0.12g) in dichloromethane, cooled in an ice-water bath was added trifluoroacetic acid (0.275ml) and the mixture stirred at room temperature for 0.5 hours. Dichloromethane (10ml) was added and the reaction stirred at room temperature for 16 hours. The reaction was poured into a cooled solution of 0.880 ammonia : water (1:3) and extracted with ethyl acetate (x2). The combined organics were dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 95:5:0.5 dichloromethane:methanol:ammonia to give the title compound (0.06 g, 63%). MS m/z 416 (MNH₄)⁺. ¹H-NMR (CDCl₃): δ = 1.8-2.0 (4H, m), 2.6 (3H, s), 3.0 (3H, s), 3.8 (1H, m), 4.0 (1H, m), 6.78-7.38 (6H, m, Ar)

Example 82

Cis-(1S)-N-methyl-7-(N-methyl(methylsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

(a) Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-7-(N-methyl(methylsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine
To a solution of the compound of Example 81(b) (0.23g) in acetone (2ml) was added potassium carbonate (0.067g) and methyl iodide (0.09ml) and the reaction heated at reflux for 16 hours. The reaction was cooled to room temperature, the solvent removed under reduced pressure and the residue partitioned between 10% aqueous potassium carbonate and ethyl acetate. The aqueous phase was extracted with ethyl acetate and the combined organics dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 99.5:0.5 dichloromethane:methanol to give the subtitle compound, (0.15 g, 63%). MS m/z 530 (MNH₄)⁺. ¹H-NMR (CDCl₃): δ = 1.5 (9H, s), 1.8 (2H, m), 2.0 (1H, m), 2.3 (1H, m), 2.6 (3H, s), 2.9 (3H, s), 3.3 (3H, s), 4.2 (1H, s), 5.5 (1H, m), 6.8-7.3 (6H, m, Ar).

(b) Cis-(1S)-N-methyl-7-(N-methyl(methylsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the product of step (a) (0.15g) in dichloromethane, cooled in an ice-water bath was added trifluoroacetic acid (0.23ml) and the mixture stirred at room temperature for 0.5 hours. Dichloromethane (10ml) was added and the reaction stirred at room temperature for 16 hours. The reaction was poured into a cooled solution of 0.88 ammonia : water (1:1) and extracted with ethyl acetate (x2). The combined organics were dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 98:2 dichloromethane:methanol to give the title compound, (0.082 g, 67%). ¹H-NMR (CDCl₃): δ = 1.8-2.0 (4H, m), 2.7 (3H, s), 2.9 (3H, s), 3.2 (3H, s), 3.3 (1H, m), 4.0 (1H, m), 6.8-7.4 (6H, m).

Using the method of Example 82, the following sulphonamides were prepared using the sulphonamide product of Example 81(b) and the appropriate alkylating agent:
Example 85

Cis-(1S)-N-methyl-7-(N(4)-1,2,4-triazolyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the product of Example 80 (0.4g, 0.00125mol) in toluene (10ml) was added N’-[(E)-(dimethylamino)methylidene]-N,N-dimethylhydrazonoformamide (J.Chem. Soc. (C), 1967, 1664) (0.212g) and p-toluene sulphonic acid (0.284g) and the reaction heated at reflux for 16 hours. The reaction was cooled, diluted with ethyl acetate and made basic with saturated aqueous sodium bicarbonate solution. The organic layer was dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude
product was purified on silica gel, eluting with a solvent gradient of 100:100:5 ethyl acetate:pentane:diethylamine to 100:5:5 ethyl acetate:methanol:diethylamine to yield the title compound, (0.194g, 42%). MS m/z 373 (MH)+. 1H-NMR (CDCl3): δ = 1.93 (1H, m), 2.07 (3H, m), 2.57 (3H, s), 3.78 (1H, t), 4.06 (1H, t), 6.97 (1H, dd), 6.99 (1H, dd), 7.13 (1H, dd), 7.22 (1H, d), 7.39 (1H, dd), 7.50 (1H, d), 8.46 (2H, s).

Example 86

Cis-(1S)-N-methyl-7-hydroxy-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

Formic acid (2.45ml) was added to a stirred solution of acetic anhydride (4.9ml), cooled in an ice-water bath. This was heated to 50°C for 0.25h, cooled to 5°C and added to a solution of the product of Example 80 (1.37g) in formic acid (2.6ml). The reaction was stirred at room temperature for 2 hours, ice-water added and the mixture extracted with dichloromethane (x2). The combined organics were washed with 1N aqueous sodium hydroxide solution, brine, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel, eluting with a solvent gradient of 100:0 to 95:5 dichloromethane:methanol to yield the subtitle compound, (1.1g, 74%). MS m/z 377 (MH)+. 1H-NMR (CDCl3): δ = 1.95 (3H, m), 2.30 (1H, m), 2.75 (2H, d), 2.80 (1H, d), 4.20 (1H, m), [4.70 (m), 5.70 (t), 1H], 6.80-8.70 (6H, Ar).

(b) Cis-(1S)-N-methyl-N-formyl-7-(hydroxy)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the product of step (a) (0.995g) in acetone (28.5ml) was added a mixture of concentrated sulphuric acid (5.7ml) and water (28.5ml), in an ice-water bath. Sodium
nitrite (0.217g) was added, stirred in the ice-water bath for 0.5 hours and then allowed to warm to room temperature. The reaction was heated at 75°C for 2 hours, cooled in an ice-water bath and made basic with concentrated aqueous ammonium hydroxide solution. The reaction was extracted with ethyl acetate (x3), the combined organics washed with water, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel, eluting with a solvent gradient of 100 : 0 dichloromethane : methanol to 95 : 5 dichloromethane : methanol to yield the subtitle compound, (0.66g, 66%). MS m/z 350 (MH)⁺. ¹H-NMR (CDCl₃): δ = 2.00 (4H, m), 2.8 (3H, m), 4.15 (1H, m), [4.70 (m), 5.70 (m), 1H], 6.60-8.3 (6H, Ar).

(c) Cis-(1S)-N-methyl-7-hydroxy-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the product of step (b) (0.64g) in dioxan (10ml) was added 6M aqueous hydrochloric acid (15ml) and the reaction heated at reflux for 3.5 hours. The reaction was cooled to room temperature, the solvent removed under reduced pressure and water added. The solution was made basic using concentrated aqueous ammonium hydroxide solution, extracted with ethyl acetate (x3) and the combined organics washed with brine, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel, eluting with a solvent gradient of 100 : 0 : 0 to 95 : 5 : 0.5 dichloromethane : methanol : 0.88 ammonia to yield the title compound. MS m/z 322 (MH)⁺. ¹H-NMR (CDCl₃): δ = 1.80 (1H, m), 2.00 (3H, m), 2.50 (3H, s), 3.70 (1H, t), 3.95 (1H, m), 6.60 (1H, m), 6.65 (1H, d), 6.85 (1H, d), 6.95 (1H, dd), 7.15 (1H, d), 7.30 (1H, d).

Example 87

Cis-(1S)-N-methyl-7-(carboxamidomethoxy)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride
To a solution of the product of Example 86 (0.4g, 0.00124mol) in dichloromethane (15ml) and di-isopropylethylamine (0.23ml), was added di-tert-buty1 dicarbonate (0.297g, 0.00136mol). After 22 hours, the reaction was washed aqueous citric acid solution (x3) and water (x3). The organic phase was dried (Na$_2$SO$_4$), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 9 : 1 pentane : ethyl acetate to 5 : 1 pentane : ethyl acetate to give the subtitle compound (0.41 g). MS m/z 422 (MH$^+$). $^1$H-NMR (CDCl$_3$): δ = 1.53 (9H, s), 1.7 (2H, m), 1.96 (1H, m), 2.21 (1H, m), 2.6 (3H, d), 4.08 (1H, s), 5.38 (1H, m), 6.51 (1H, s), 6.70 (2H, dd), 6.82 (2H, m), 7.04 (1H, d), 7.30 (1H, d).

To a solution of the product of step (a) (0.03g) in tetrahydrofuran (2ml) at room temperature was added sodium hydride (0.0025g, 80% dispersion in oil) and stirred for 10 minutes. Chloroacetamide (0.0072g) was added and the reaction heated at 50-60°C for 2 hours and then stirred at room temperature for 21 hours. Water (15ml) was added and the mixture extracted with ethyl acetate (x3). The combined organics were washed with
water, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure to give the subtitle compound, which was used without further purification. MS m/z 496 (MNH₄)⁺.

¹H-NMR (partial data) (CDCl₃): δ = 1.50 (9H, s), 1.74 (2H, m), 2.0 (1H, m), 2.25 (1H, m), 2.62 (3H, s), 4.14 (1H, m), 5.50 (1H, d), 6.78 (2H, m), 6.90 (1H, d), 7.07 (1H, s), 7.23 (1H, s), 7.35 (1H, d).

(c) Cis-(1S)-N-methyl-7-(carboxamidomethyloxy)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

To a solution of the product of step (b) (0.034g) in dichloromethane (0.4ml) was added trifluoroacetic acid (0.054ml). After 1.5 hours, saturated aqueous sodium bicarbonate solution was added. The aqueous layer was made basic (pH 10) with ammonia solution and extracted with dichloromethane (x2). The combined organics were washed with water, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel eluting with 93:7:1 dichloromethane:methanol:0.88 ammonia to give the free base, (0.01g). The product was dissolved in ethyl acetate (2ml) and a saturated solution of hydrogen chloride in diethyl ether added. The solvent was removed in vacuo, triturated with diethyl ether and dried to yield the title compound (16 mg). MS m/z 379 (MH)⁺. ¹H-NMR (CDCl₃): δ = 1.82 (1H, m), 1.9 (1H, m), 2.00 (2H, t), 2.52 (3H, s), 3.67 (1H, t), 3.95 (1H, t), 4.51 (2H, s), 5.59 (1H, s), 6.53 (1H, s), 6.74 (3H, m), 6.95 (2H, dt), 7.20 (1H, s), 7.35 (1H, d).

Example 88

Cis-(1S)-N-methyl-6-(carboxymethyl)-7-((methylsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride
(a) **Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-6-iodo-7-amino-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine**

To a solution of the product of Example 81(a) (1.55g, 0.00368mol) in dichloromethane (35ml) and methanol (14ml) was added calcium carbonate (0.52g, 0.00519mol) and benzyltrimethylammonium dichloroiodate (1.4g, 0.00402mol) and the reaction stirred for 4 hours. The mixture was poured into saturated aqueous sodium thiosulphate solution (50ml) and extracted with dichloromethane (x2). The organic phases were combined, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica eluting with 95 : 5 to 9 : 1 pentane : ethyl acetate to give the subtitle compound, (0.867g, 43%). MS m/z 564 (MNH₄)⁺. ¹H-NMR (CDCl₃); δ = 1.50 (9H, s), 1.65 (2H, m), 1.93 (1H, m), 2.19 (1H, m), 2.62 (1.8H, s), 2.64 (1.2H, s), 4.06 (3H, m), 5.16 (0.4H, br), 5.36 (0.6H, br), 6.57 (1H, s), 6.83 (1H, m), 7.09 (1H, s), 7.12 (1H, s), 7.34 (1H, d).

(b) **Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-6-(iodo)-7-((bis-methylsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine**

To a solution of the compound of step (a) (0.627g, 0.00115mol) in dichloromethane (10ml), cooled in an ice-water bath was added triethylamine (0.4ml, 0.00287mol) and methane sulphonyl chloride (0.195ml, 0.00252mol) and the reaction stirred for 17 hours.
The mixture was partitioned between dichloromethane (25ml) and water (25ml), the aqueous phase extracted with dichloromethane (15ml) and the combined organics dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica eluting with 85 : 15 to 4 : 1 pentane : ethyl acetate to give the subtitle compound, (0.705g, 87%). MS m/z 720 (MNH₄)⁺. ¹H-NMR (CDCl₃): δ = 1.50 (9H, s), 1.77 (2H, br), 1.99 (1H, m), 2.24 (1H, m), 2.64 (3H, s), 3.42 (2.1H, s), 3.49 (0.9H, br), 3.58 (0.9H, br), 3.63 (2.1H, s), 4.15 (1H, m), 5.23 (0.3H, br), 5.39 (0.7H, br), 6.73 (1H, br), 7.16 (1H, s), 7.37 (1H, d), 7.55 (1H, s).

(c) Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-6-(iodo)-7-((methyIsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the compound of step (b) (0.705g, 0.001mol) in dioxan (9ml) was added 2M aqueous sodium hydroxide (5ml) and the reaction stirred at room temperature for 3 hours. The dioxan was removed under reduced pressure and the residue was partitioned between water (40ml) and ethyl acetate (30ml). The aqueous phase was made acid (pH4) by the addition of 10% aqueous citric acid and extracted with ethyl acetate. The organics were washed with brine, dried (MgSO₄) and the solvent removed under reduced pressure to give the subtitle compound (0.62g, 99%). MS m/z 642 (MNH₄)⁺. ¹H-NMR (CDCl₃): δ = 1.53 (9H, s), 1.75 (2H, m), 1.96 (1H, m), 2.23 (1H, m), 2.66 (3H, s), 3.04 (3H, s), 4.12 (1H, m), 5.25 (0.35H, br), 5.36 (0.65H, br), 6.60 (1H, s), 6.80 (1H, d), 7.09 (1H, s), 7.40 (3H, m).

(d) Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-6-(methoxycarbonyl)-7-((methyIsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the product of step (c) (0.283g, 0.00045mol) in methanol (10ml) was added triethylamine (0.095ml), and tetrakis(triphenylphosphine) palladium (0.026g) and the reaction heated at 80°C under an atmosphere of carbon monoxide at 690 kPa (100p.s.i.) for 4 hours. The reaction was cooled to room temperature, the solvent removed in vacuo and the residue purified on silica using 3 : 1 pentane : ethyl acetate to give the subtitle compound, (0.235g, 93%). MS m/z 574 (MNH₄)⁺. ¹H-NMR (CDCl₃): δ
= 1.54 (9H, s), 1.77 (2H, m), 2.01 (1H, m), 2.26 (1H, m), 2.66 (3H, s), 3.06 (3H, s), 3.84 (3H, s), 4.19 (1H, m), 5.27 (0.25H, br), 5.39 (0.75H, br), 6.79 (1H, d), 7.09 (1H, s), 7.36 (1H, d), 7.55 (1H, s), 7.63 (1H, s), 10.3 (1H, s).

(e) **Cis-(1S)-N-methyl-6-(methoxycarbonyl)-7-((methylsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride**

Hydrogen chloride gas was bubbled through a solution of the product of step (d) (0.037g) in dichloromethane (5ml), cooled in an ice-water bath, for 10 minutes. The reaction was stirred for 40 minutes and the solvent removed under reduced pressure to yield the title compound (0.032g). **MS m/z 455 (MH)+.** 1H-NMR (d6-MeOH): δ = 1.99 (1H, m), 2.17 (3H, m), 2.88 (3H, s), 3.18 (3H, s), 3.83 (3H, s), 4.19 (1H, dd), 4.56 (1H, t), 7.24 (1H, dd), 7.47 (1H, d), 7.53 (1H, d), 7.61 (1H, s), 7.80 (1H, s).

**Example 89**

**Cis-(1S)-N-methyl-6-(carboxy)-7-((methylsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride**

(a) **Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-6-(carboxy)-7-((methylsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine**

To a solution of the product of Example 88(d) (0.185g, 0.00033mol) in tetrahydrofuran (5ml) was added water (5ml) and lithium hydroxide monohydrate (0.03g) and the reaction stirred at room temperature for 16 hours, heated at 50°C for 7 hours and then stirred at room temperature for a further 16 hours. The tetrahydrofuran was removed under reduced pressure, the residue partitioned between dichloromethane (30ml) and water (30ml) and acidified with 10% aqueous citric acid solution. The aqueous layer was washed with dichloromethane and the combined organics dried (MgSO4), filtered and the solvent removed under reduced pressure to give the subtitle compound, (0.177g, 98%). **MS m/z**
560 (MNH₃)⁺. ¹H-NMR (CDCl₃): δ = 1.55 (9H, s), 1.77 (2H, m), 2.01 (1H, m), 2.26 (1H, m), 2.67 (0.6H, br), 2.72 (2.4H, s), 3.07 (3H, s), 4.18 (1H, m), 5.34 (1H, br), 6.81 (1H, d), 7.08 (1H, s), 7.36 (1H, d), 7.53 (1H, br), 7.70 (1H, br), 10.15 (0.2H, br), 10.18 (0.8H, s).

(b) Cis-(1S)-N-methyl-6-(carboxy)-7-((methylsulphonyl)amino)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

Hydrogen chloride gas was bubbled through a solution of the compound of step (a) (0.021g) in dichloromethane (5ml), cooled in an ice-water bath, for 20 minutes. The reaction was stirred for 17 hours and the solvent removed under reduced pressure to yield the title compound (0.017g, 92%). MS m/z 443 (MH)⁺. ¹H-NMR (d₆-MeOH): δ = 1.99 (1H, m), 2.26 (3H, m), 2.89 (3H, s), 3.17 (3H, s), 4.18 (1H, m), 4.55 (1H, br), 7.22 (1H, d), 7.50 (2H, m), 7.64 (1H, s), 7.79 (1H, s).

Example 90
Cis-(1S)-N-methyl-6-(2-(sulphonamido)ethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride
(a) **Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-6-ido-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine**

To N,N-dimethylformamide (1ml) at 60°C was added tert-butylnitrite (0.07ml), followed by a solution of the product of Example 88(a) (0.24g, 0.00044mol) in N,N-dimethylformamide (1ml). After 10 minutes, the reaction was cooled to room temperature, and the reaction mixture partitioned between ethyl acetate (50ml) and water (50ml). The organic phase was washed with brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica eluting with a solvent gradient of 95 : 5 to 9: 1 pentane : ethyl acetate to yield the subtitle compound (0.134g, 57%). MS m/z 549 (MNH₄)⁺. ¹H-NMR (CDCl₃): δ = 1.51 (9H, s), 1.74 (2H, br), 1.96 (1H, m), 2.23 (1H, m), 2.62 (3H, s), 4.13 (1H, m), 5.21 (0.35H, br), 5.40 (0.65H, br), 6.79 (1H, br), 6.95 (1H, br), 7.10 (1H, s), 7.30 (1H, s), 7.36 (1H, d), 7.58 (1H, d).

(b) **Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-6-(2-(sulphonamido)vinyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine**

The subtitle compound was prepared by the general method described in Example 62(a), using the product of step (a) and vinylsulphonamide. MS m/z 528 (MNH₄)⁺. ¹H-NMR (CDCl₃): δ = 1.53 (9H, s), 1.75 (2H, br), 2.01 (1H, m), 2.27 (1H, m), 2.63 (3H, s), 4.19 (1H, m), 4.72 (2H, s), 5.28 (0.4H, br), 5.45 (0.6H, br), 6.83 (2H, m), 7.11 (3H, m), 7.35 (3H, m).

(c) **Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-6-(2-(sulphonamido)ethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine**

The subtitle compound was prepared by the general method described in Example 62(b), using the compound of step (b). MS m/z 530 (MNH₄)⁺. ¹H-NMR (CDCl₃): δ = 1.51 (9H, s), 1.73 (2H, m), 1.98 (1H, m), 2.25 (1H, m), 2.62 (3H, s), 3.07 (2H, m), 3.34 (2H, m), 4.16 (1H, br), 4.54 (2H, br), 5.27 (0.3H, br), 5.42 (0.7H, br), 6.80 (2H, br), 7.11 (3H, m), 7.36 (1H, m).
(d) Cis-(1S)-N-methyl-6-(2-(sulphonamido)ethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

The title compound was prepared by the method of Example 89(b), starting with the compound of step (c). MS m/z 413 (MH)^+. \(^1\)H-NMR (d_6-MeOH): δ = 1.99 (1H, m), 2.23 (3H, m), 2.83 (3H, s), 3.01 (2H, m), 3.22 (2H, m), 4.17 (1H, dd), 4.46 (1H, br), 6.83 (1H, s), 7.18 (1H, d), 7.30 (1H, d), 7.43 (1H, s), 7.53 (2H, m).

Example 91

Cis-(1S)-N-methyl-6-(carboxy)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

(a) Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-6-(methoxycarbonyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

The subtitle compound was prepared by the method of Example 6(a), starting with the product of Example 90(a). MS m/z 481 (MNH_4)^+. \(^1\)H-NMR (CDCl_3): δ = 1.50 (9H, s), 1.74 (2H, br), 2.01 (1H, m), 2.27 (1H, m), 2.62 (3H, s), 3.85 (3H, s), 4.24 (1H, m), 5.29 (0.4H, br), 5.46 (0.6H, br), 6.78 (1H, br), 7.05 (1H, s), 7.30 (2H, m), 7.62 (1H, s), 7.92 (1H, d).

(b) Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-6-(carboxy)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine
The subtitle compound was prepared by the method of Example 89(a), starting with the compound of step (a). MS m/z 467 (MNH₄)⁺. ¹H-NMR (CDCl₃): δ = 1.54 (9H, s), 1.76 (2H, m), 2.02 (1H, m), 2.28 (1H, m), 2.64 (3H, s), 4.24 (1H, m), 5.31 (0.4H, br), 5.50 (0.6H, br), 6.79 (1H, m), 7.04 (1H, s), 7.33 (2H, m), 7.67 (1H, s), 7.97 (1H, d).

(c) Cis-(1S)-N-methyl-6-(carboxy)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

The title compound was prepared by the method of Example 89(b), starting with the product of Example 91(b). MS m/z 350 (MH)⁺. ¹H-NMR (d₆-MeOH): δ = 1.99 (1H, m), 2.25 (3H, m), 2.86 (3H, s), 4.24 (1H, dd), 4.56 (1H, t), 7.20 (1H, d), 7.44 (1H, s), 7.52 (1H, d), 7.59 (1H, s), 7.62 (1H, d), 7.99 (1H, d).

Example 92

Cis-(1S)-N-methyl-6-(methoxycarbonyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride

The title compound was prepared by the method of Example 89(b), starting with the product of Example 91(a). MS m/z 364 (MH)⁺. ¹H-NMR (d₆-MeOH): δ = 2.01 (1H, m), 2.24 (3H, m), 2.86 (3H, s), 3.82 (3H, s), 4.23 (1H, dd), 4.57 (1H, br), 7.20 (1H, d), 7.43 (1H, s), 7.50 (1H, d), 7.57 (1H, s), 7.66 (1H, d), 7.98 (1H, d).

Example 93

Cis-(1S)-N-methyl-6-sulphonamido-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine
(a) Cis-(1S)-N-methyl-N-tert-butoxycarbonyl-6-(sulphonamido)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine

To a solution of the product of Example 90(a) (0.522g, 0.001mol) and thiourea (0.114g, 0.0015mol) in N,N-dimethylformamide (2ml) was added bis(triethylphosphine)nickel-dichloride (0.0366g) and sodium cyanoborohydride (1M solution in tetrahydrofuran) (0.15ml). The reaction was heated at 60°C for 4 hours and then stirred at room temperature for 16 hours. A solution of aqueous sodium hydroxide (1N, 5ml) was added, the reaction stirred for 1 hour and made acid using 10% aqueous citric acid solution. The reaction was extracted with ethyl acetate, the organic phase washed with brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure to give a crude thiol (0.49g), which was used without further purification. A solution of the crude thiol (0.1g) in acetonitrile (2ml) was cooled in an ice-water bath and sulphuryl chloride (0.08g) and powdered potassium nitrate (0.06g) added. After 1 hour, saturated aqueous sodium bicarbonate solution was added and the mixture extracted with diethyl ether. The organic layer was dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was dissolved in saturated ammoniacal methanol solution and allowed to stand for 16 hours. The solvent was removed under reduced pressure and the residue purified on silica eluting with 97.5 : 2.5 dichloromethane : methanol to give the subtitle compound, (0.031g). MS m/z 501 (MNH₄)+. ¹H-NMR (CDCl₃): δ = 1.54 (9H, s), 1.80 (2H, m), 2.06 (1H, m), 2.29 (1H, m), 2.65 (3H, s), 4.25 (1H, br), 4.80 (2H, br), 5.30 (0.45H, br), 5.47 (0.55H, br), 6.79 (1H, d), 7.08 (1H, s), 7.35 (1H, d), 7.39 (1H, d), 7.54 (1H, s), 7.80 (1H, d).

(b) Cis-(1S)-N-methyl-6-sulphonamido-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine
To a solution of the product of step (a) (9.031g) in dichloromethane (5ml) cooled in an ice-water bath, hydrogen chloride gas was added until the solution was saturated. After stirring for 1 hour, the solvent was removed in vacuo and the residue azeotroped with dichloromethane (x2) and triturated with diethyl ether. The solvent was removed under reduced pressure and the residue purified on silica eluting with 93:7:1 dichloromethane: methanol:0.88 ammonia, to give the title compound (0.15g). MS m/z 385 (MH)+. 1H-NMR (CDCl3); δ = 1.86 (1H, m), 2.00 (1H, m), 2.07 (2H, m), 2.54 (3H, s), 3.75 (1H, t), 4.04 (1H, t), 4.70 (2H, br), 6.94 (1H, dd), 7.21 (1H, d), 7.39 (1H, d), 7.40 (1H, s), 7.55 (1H, d), 7.74 (1H, dd).

Example 94

(5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenecarboxamide hydrochloride

(a) tert-Butyl (1S,4S)-6-[(1H-1,2,3-benzotriazol-1-yl)oxy]carbonyl]-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

To a solution of the compound of Example 91(b) (0.155g, 0.00034mol) in N,N-dimethylformamide (2.5ml) at 0°C was added triethylamine (0.055ml, 0.00039mol) and TBTU (0.12g, 0.00037mol) and the reaction stirred for 1 hour.

(b) tert-Butyl (1S,4S)-6-(aminocarbonyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

A portion of the solution prepared in step (a) (0.6 ml) was added to a stirred solution of 0.88 ammonia (1ml) and the reaction stirred for 16 hours. The reaction mixture was diluted with ethyl acetate (20ml) and washed with 10% aqueous citric acid solution (20ml) and brine, dried (MgSO4), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel, eluting with ethyl acetate : pentane (1:1) to give the subtitle compound, (0.037g). MS m/z 466 (MNH+)+. 1H NMR (CDCl3); δ = 1.50 (9H, s), 1.77 (2H, m), 2.02 (1H, m), 2.29 (1H, m), 2.64 (3H, s), 4.24 (1H, m), 5.30-
5.47 (1H, br), 5.63 (1H, br), 5.87 (1H, br), 6.79 (1H, m), 7.06 (1H, s), 7.33 (2H, m), 7.43 (1H, s), 7.67 (1H, d).

(c) (5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenecarboxamide hydrochloride

To the product of step (b) (0.037g) was added a saturated solution of HCl in dichloromethane at 0°C. After 70 minutes, the solvent was removed in vacuo to yield the title compound (0.028g). MS m/z 349 (MH⁺). ¹H NMR (CD₂OD); δ = 2.02 (1H, m), 2.24 (3H, m), 2.87 (3H, s), 4.24 (1H, m), 4.55 (1H, m), 7.19 (1H, d), 7.43 (1H, s), 7.50 (2H, m), 7.64 (1H, d), 7.83 (1H, d).

Example 95

(5S,8S)-8-(3,4-Dichlorophenyl)-N-(2-hydroxyethyl)-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenecarboxamide hydrochloride

(a) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-6-{{(2-hydroxyethyl)amino}carbonyl}-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

The subtitle compound was prepared from a portion of the solution produced in Example 94(a), using the method of Example 94(b), but using ethanolamine as the amine in place of ammonia. MS m/z 514 (MNa⁺). ¹H NMR (CDCl₃); δ = 1.52 (9H, s), 1.76 (1H, m), 2.10 (1H, m), 2.27 (2H, m), 2.62 (3H, s), 3.58 (2H, m), 3.80 (2H, t), 4.23 (1H, m), 5.30-5.46 (1H, br), 6.58 (1H, br, t), 6.79 (1H, d), 7.04 (1H, s), 7.33 (3H, m), 7.65 (1H, d).

(b) (5S,8S)-8-(3,4-dichlorophenyl)-N-(2-hydroxyethyl)-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenecarboxamide hydrochloride
The title compound was prepared from the product of step (a), using the method of Example 94(c). MS m/z 393 (MH)^+. ^1H NMR (CD_3OD); δ = 2.01 (1H, m), 2.25 (3H, m), 2.87 (3H, s), 3.43 (2H, m), 3.64 (2H, t), 4.25 (1H, dd), 4.55 (1H, m), 7.19 (1H, dd), 7.41 (1H, d), 7.46 (1H, s), 7.50 (1H, d), 7.63 (1H, d), 7.82 (1H, d).

Example 96

3-[(5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]propanoic acid hydrochloride

(a) Ethyl (E)-3-[(5S,8S)-5-[(tert-butoxycarbonyl)(methyl)amino]-8-(3,4-dichlorophenyl)-5,6,7,8-tetrahydro-2-naphthalenyl]-2-propenoate

To a solution of the compound of Example 90(a) (0.217g, 0.00041mol) in acetonitrile (10ml) was added triethylamine (0.17ml, 0.00122mol), tri-o-tolylphosphine (0.05g, 0.00016mol), palladium acetate (0.0018g, 0.00008mol) and ethyl acrylate (0.05ml) and the mixture heated under reflux for 75 minutes. The reaction was allowed to cool to room temperature and poured into a mixture of ethyl acetate (30ml) and water (30ml). The organic layer was washed with brine, dried (MgSO_4), filtered and the solvent removed under reduced pressure. The residue was purified on silica eluting with a solvent gradient of ethyl acetate/pentane [5:95] to ethyl acetate/pentane [7.5:92.5] to give the subtitle compound (0.163g). MS m/z 522 (MNH_4)^+. ^1H NMR (CDCl_3); δ = 1.32 (3H, t), 1.54 (9H, s), 1.76 (2H, m), 2.10 (1H, m), 2.26 (1H, m), 2.63 (3H, s), 4.12 (3H, m), 5.28-5.46 (1H, br), 6.34 (1H, d), 6.79 (1H, br), 7.10 (2H, s), 7.23 (1H, d), 7.78 (1H, d).

(b) Ethyl 3-[(5S,8S)-5-[(tert-butoxycarbonyl)(methyl)amino]-8-(3,4-dichlorophenyl)-5,6,7,8-tetrahydro-2-naphthalenyl]propanoate
To a solution of the product of step (a) (0.163g, 0.00032mol) in toluene (10ml) was added tosyl hydrazine (0.3g, 0.00161mol) and the reaction heated at reflux for 5 hours. The reaction was cooled, the solution decanted and concentrated in vacuo to give a residue which was purified on silica eluting with ethyl acetate/pentane [7.5:92.5] solution to give the subtitle compound (0.125g). MS m/z 523 (MNH₄⁺). ¹H NMR (CDCl₃); δ = 1.20 (3H, t), 1.50 (9H, s), 1.71 (2H, m), 1.95 (1H, m), 2.24 (1H, m), 2.55 (2H, t), 2.60 (3H, s), 2.85 (2H, t), 4.08 (2H, q), 4.15 (1H, m), 5.27-5.43 (1H, m), 6.78 (2H, m), 7.08 (3H, m), 7.33 (1H, d).

(c) 3-[(5S,8S)-5-[tert-Butoxycarbonyl][(methyl)amino]-8-(3,4-dichlorophenyl)-5,6,7,8-tetrahydro-2-naphthalenyl]propanoic acid

To a solution of the product of step (b) (0.125g, 0.00025mol) in tetrahydrofuran (5ml) was added water (5ml) and lithium hydroxide (0.025g, 0.0006mol) and the reaction stirred at room temperature for 2.5 hours and then at 50°C for 2 hours. The reaction was cooled to room temperature, acidified with 10% aqueous citric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure to give the subtitle compound (0.118g). MS m/z 495 (MNH₄⁺). ¹H NMR (CDCl₃); δ = 1.51 (9H, s), 1.72 (2H, m), 2.00 (1H, m), 2.27 (1H, m), 2.62 (5H, m), 2.87 (2H, t), 4.16 (1H, m), 5.28-5.43 (1H, m), 6.80 (2H, m), 7.10 (2H, m), 7.33 (1H, d).

(d) 3-[(5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]propanoic acid hydrochloride

HCl gas was bubbled through a solution of the product of step (c) (0.02g) in ethyl acetate (5ml) at 0°C for 15 minutes. After 45 minutes, the reaction was concentrated in vacuo to give the title compound. MS m/z 378 (MH⁺). ¹H NMR (CD₃OD); δ = 1.96 (1H, m), 2.20
(3H, m), 2.48 (2H, t), 2.81 (5H, m), 4.16 (1H, m), 4.44 (1H, m), 6.80 (1H, s), 7.17 (1H, d), 7.24 (1H, s), 7.41 (2H, m), 7.48 (1H, d).

Example 97

(5S,8S)-8-(3,4-Dichlorophenyl)-N-methyl-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenecarboxamide hydrochloride

(a) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-6-[(methylamino)carbonyl]-1,2,3,4-tetrahydronaphthalenyl(methyl)carbamate

The subtitle compound was prepared from a portion of the solution prepared in Example 94(a) (0.6ml, 0.000083mol), using the method of Example 94(b), but using methyamine (1ml, 2M solution in tetrahydrofuran) as the amine in place of ammonia. Yield = 0.035g. MS m/z 480 (MNH₄)⁺. ¹H NMR (CDCl₃); δ = 1.51 (9H, s), 1.76 (2H, m), 2.01 (1H, m), 2.28 (1H, m), 2.61 (3H, s), 2.96 (3H, d), 4.22 (1H, m), 5.30-5.48 (1H, m), 6.03 (1H, s), 6.79 (1H, m), 7.04 (1H, s), 7.27 (1H, m), 7.36 (2H, m), 7.64 (1H, d).

(b) (5S,8S)-8-(3,4-Dichlorophenyl)-N-methyl-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenecarboxamide hydrochloride

The title compound was prepared from the product of step (a), using the method of Example 94(c). MS m/z 363 (MH)⁺. ¹H NMR (CD₃OD); δ = 2.02 (1H, m), 2.24 (3H, m), 2.83 (3H, s), 2.87 (3H, s), 4.24 (1H, m), 4.56 (1H, m), 7.20 (1H, d), 7.41 (1H, s), 7.43 (1H, s), 7.50 (1H, d), 7.65 (1H, d), 7.79 (1H, d).

Example 98

(5S,8S)-8-(3,4-Dichlorophenyl)-N,N-dimethyl-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenecarboxamide hydrochloride
(a) tert-Butyl (1S,4S)-4-(3,4-dichloro-phenyl)-6-[(dimethylamino)carbonyl]-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

The subtitle compound was prepared from a portion of the solution produced in Example 94(a) (0.6ml, 0.000083mol), using the method of Example 94(b), but using dimethyamine (1ml, 2M solution in tetrahydrofuran) as the amine in place of ammonia. Yield = 0.033g. MS m/z 494 (MNH₂)⁺. ¹H NMR (CDCl₃); δ = 1.50 (9H, m), 2.01 (1H, m), 2.27 (1H, m), 2.63 (3H, s), 2.93 (3H, s), 3.05 (3H, s), 4.19 (1H, m), 5.28-5.47 (1H, m), 6.79 (1H, d), 7.00 (1H, s), 7.08 (1H, s), 7.23 (1H, m), 7.33 (2H, m).

(b) (5S,8S)-8-(3,4-Dichlorophenyl)-N,N-dimethyl-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenecarboxamide hydrochloride

The title compound was prepared from the product of step (a), using the method of Example 94(c). MS m/z 377 (MH)⁺. ¹H NMR (CD₃OD); δ = 2.02 (1H, m), 2.26 (3H, m), 2.86 (6H, s), 3.00 (3H, s), 4.22 (1H, m), 4.54 (1H, m), 6.92 (1H, s), 7.22 (1H, d), 7.40 (1H, d), 7.45 (1H, s), 7.65 (1H, d).

Example 99

2-[(5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)-3-[(methylsulphonyl)amino]-5,6,7,8-tetrahydro-2-naphthalenyl]-1-ethanesulphonamide

(a) tert-Butyl (1S,4S)-6-[(E)-2-(aminosulphonyl)ethenyl]-4-(3,4-dichlorophenyl)-7-[(methylsulphonyl)amino]-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

To a solution of the product of Example 88(c) (0.112g, 0.00018mol) in acetonitrile (5ml) was added triethylamine (0.075ml, 0.00054mol), tri-o-tolylphosphine (0.022g, 0.000072mol), palladium acetate (0.0008g, 0.0000036mol) and vinylsulphonamide (0.024g, 0.00022mol) and the mixture heated under reflux for 3.5 hours. The reaction
was allowed to cool to room temperature and poured into a mixture of ethyl acetate (30ml) and water (30ml). The organic layer was washed with brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica eluting with ethyl acetate/pentane (1:1) to give the subtitle compound (0.057g). MS m/z 626 (MNa)⁺. ¹H NMR (CDCl₃); δ = 1.52 (9H, s), 1.77 (2H, m), 2.10 (1H, m), 2.25 (1H, m), 2.66 (3H, s), 3.07 (3H, s), 4.18 (1H, m), 5.25 (2H, br), 5.40 (1H, m), 6.79 (2H, m), 7.10 (1H, s), 7.14 (1H, s), 7.30 (1H, s), 7.37 (1H, d), 7.76 (1H, d).

(b) tert-Butyl (1S,4S)-6-[2-(aminosulphonyl)ethyl]-4-(3,4-dichlorophenyl)-7-[(methylsulphonyl)amino]-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

To a solution of the product of step (a) (0.051g, 0.000084mol) in toluene (5ml) was added tosyl hydrazine (0.078g, 0.00042mol) and the reaction heated at reflux for 17 hours. The reaction was cooled, the solution decanted and concentrated in vacuo to give a residue which was purified on silica eluting with ethyl acetate/dichloromethane [40:60] solution to give the title compound (0.01g). MS m/z 628 (MNa)⁺. ¹H NMR (CDCl₃); δ = 1.51 (9H, s), 1.73 (2H, m), 1.99 (1H, m), 2.24 (1H, m), 2.64 (3H, s), 3.08 (3H, s), 3.18 (2H, m), 3.36 (2H, t), 4.15 (1H, m), 4.94 (2H, br), 5.26-5.38 (1H, m), 6.76 (1H, m), 6.87 (1H, s), 6.93 (1H, br), 7.08 (1H, s), 7.17 (1H, s), 7.36 (1H, d).

(c) 2-[(5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)-3-[(methylsulphonyl)amino]-5,6,7,8-tetrahydro-2-naphthalenyl]-1-ethanesulphonamide

The title compound was prepared from the product of step (b), using the method described in Example 94(c). MS m/z 506 (MH)⁺. ¹H NMR (CD₃OD); δ = 1.98 (1H, m), 2.22 (3H, m), 2.84 (3H, s), 3.13 (5H, s), 3.22 (2H, m), 4.19 (1H, m), 4.48 (1H, m), 6.93 (1H, s), 7.20 (1H, d), 7.45 (1H, s), 7.50 (1H, d), 7.57 (1H, s).

Example 100
(5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)-3-[(methylsulphonyl)amino]-5,6,7,8-tetrahydro-2-naphthalenecarboxamide hydrochloride

(a) tert-Butyl (1S,4S)-6-(aminocarbonyl)-4-(3,4-dichlorophenyl)-7-[(methylsulphonyl)amino]-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

To a solution of the compound of Example 89(a) (0.065g, 0.00012mol) in dioxan (5ml) at room temperature was added triethylamine (0.025ml, 0.00018mol), HOBT (0.022g, 0.00014mol), EDC hydrochloride (0.034g, 0.00018mol) and ammonium carbonate (0.023g, 0.00024mol). After 16 hours, the solvent was removed in vacuo and the residue partitioned between ethyl acetate (30ml) and water (15ml). The organic phase was washed with water, brine, dried (MgSO₄), filtered and the solvent removed in vacuo to yield a residue which was purified on silica using a solvent gradient of ethyl acetate/pentane [1:1 to ethyl acetate/pentane [3:2] to yield the subtitle compound (0.05g). MS m/z 559 (MNH₄)⁺. ¹H NMR (CDCl₃); δ = 1.53 (9H, s), 1.74 (2H, m), 1.99 (1H, m), 2.17 (1H, m), 2.68 (3H, s), 3.05 (3H, s), 4.08 (1H, m), 5.30 (1H, m), 5.77 (1H, m), 6.19 (1H, br), 6.78 (1H, d), 7.09 (1H, s), 7.15 (1H, s), 7.35 (1H, d), 7.48 (1H, s), 10.63 (1H, s).

(b) (5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)-3-[(methylsulphonyl)amino]-5,6,7,8-tetrahydro-2-naphthalenecarboxamide hydrochloride

The title compound was prepared from the product of step (a), using the method of Example 94(c). MS m/z 422 (MH⁺). ¹H NMR (CD₃OD); δ = 1.97 (1H, m), 2.21 (3H, m), 2.87 (3H, s), 3.09 (3H, s), 4.21 (1H, dd), 4.53 (1H, m), 7.18 (1H, dd), 7.40 (1H, s), 7.44 (1H, d), 7.50 (1H, d), 7.77 (1H, s).

Example 101
(5S,8S)-8-(3,4-Dichlorophenyl)-N-(2-hydroxyethyl)-5-(methylamino)-3-[(methylsulphonyl)amino]-5,6,7,8-tetrahydro-2-naphthalenecarboxamide
(a) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-6-[(2-hydroxyethyl)amino][carbonyl]-7-[(methyl)sulphonyl]amino]-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

The subtitle compound was prepared from the product of Example 89(a), using the method of Example 100(a), but using ethanolamine in place of ammonium carbonate. MS m/z 603 (MNH₄)⁺. ¹H NMR (CDCl₃); δ = 1.52 (9H, s), 1.74 (2H, m), 2.00 (1H, m), 2.10 (1H, br), 2.15 (1H, m), 2.66 (3H, s), 3.04 (3H, s), 3.53 (2H, m), 3.77 (2H, m), 4.18 (1H, m), 5.27–5.37 (1H, m), 6.58 (1H, t), 6.79 (1H, d), 7.10 (2H, m), 7.36 (1H, d), 7.49 (1H, s), 10.42 (0.3H, br), 10.53 (0.7H, br).

(b) (SS,8S)-8-(3,4-dichlorophenyl)-N-(2-hydroxyethyl)-5-(methylamino)-3-[(methyl)sulphonyl]amino]-5,6,7,8-tetrahydro-2-naphthalenecarboxamide

The title compound was prepared from the product of step (a), using the method of Example 94(c). MS m/z 486 (MH⁺). ¹H NMR (CD₂OD); δ = 1.98 (1H, m), 2.20 (3H, m), 2.87 (3H, s), 3.40 (2H, m), 3.61 (2H, t), 4.21 (1H, m), 4.52 (1H, m), 7.16 (1H, d), 7.33 (1H, s), 7.42 (1H, s), 7.50 (1H, d), 7.75 (1H, s).

Example 102
(5S,8S)-8-(3,4-dichlorophenyl)-N,N-dimethyl-5-(methylamino)-3-[(methylsulphonyl)amino]-5,6,7,8-tetrahydro-2-naphthalenecarboxamide

(a) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-6-[(dimethylamino)carbonyl]-7-[(methyl)sulphonyl]amino]-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

The subtitle compound was prepared from the product of Example 89(a), using the method of Example 100(a), but using a solution of dimethylamine in ethanol in place of ammonium carbonate. MS m/z 587 (MNH₄)⁺. ¹H NMR (CDCl₃); δ = 1.53 (9H, s), 1.75
(2H, m), 2.00 (1H, m), 2.28 (1H, m), 2.67 (3H, s), 2.98 (6H, br), 3.07 (3H, s), 4.14 (1H, m), 5.28-5.41 (1H, m), 6.78 (1H, d), 6.85 (1H, s), 7.08 (1H, s), 7.32 (1H, d), 7.40 (1H, s), 8.04 (1H, br).

(b) (5S,8S)-8-(3,4-Dichlorophenyl)-N,N-dimethyl-5-(methylamino)-3-
[(methylsulphonyl)amino]-5,6,7,8-tetrahydro-2-naphthalenecarboxamide

The title compound was prepared from the product of step (a), using the method of Example 94(c). MS m/z 470 (MH)+. 1H NMR (CD3OD); δ = 1.96 (1H, m), 2.26 (3H, m), 2.79 (3H, s), 2.88 (3H, s), 3.01 (3H, s), 3.08 (3H, s), 4.19 (1H, dd), 4.50 (1H, dd), 6.82 (1H, s), 7.20 (1H, dd), 7.44 (1H, d), 7.51 (1H, d), 7.67 (1H, s).

Example 103
3-[(5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)-5,6,7,8-tetrahydro-2-
naphthalenyl]propanamide hydrochloride

(a) tert-Butyl (1S,4S)-6-[3(1H-1,2,3-benzotriazol-1-yloxy)-3-oxopropyl]-4-(3,4-
dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

To a solution of the compound of Example 96(c) (0.098g, 0.0002mol) in acetonitrile (3ml) in an ice-water bath was added EDC hydrochloride (0.045g, 0.00023mol) and HOBT (0.035g, 0.00023mol). After 5 minutes, the reaction was warmed to room temperature and stirred for 0.5 hours.

(b) tert-Butyl (1S,4S)-6-(3-amino-3-oxopropyl)-4-(3,4-dichlorophenyl)-1,2,3,4-
tetrahydro-1-naphthalenyl(methyl)carbamate

To a portion of the solution produced in step (a) (1ml) was added a solution of 0.88 ammonia (1ml) and EDC hydrochloride (0.02g, 0.0001mol) and the reaction stirred for 3
hours. The reaction mixture was diluted with ethyl acetate (20ml) and washed with 10% aqueous citric acid solution (20ml) and brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel, eluting with a gradient of ethyl acetate/pentane [3:1] to neat ethyl acetate to give the title compound, (0.03g). MS m/z 494 (MNH₄)+. ¹H NMR (CDCl₃); δ = 1.50 (9H, s), 1.70 (2H, m), 1.98 (1H, m), 2.23 (1H, m), 2.45 (2H, t), 2.60 (3H, s), 2.87 (2H, t), 4.13 (1H, m), 5.27-5.40 (2H, m), 5.55 (1H, br), 6.80 (2H, m), 7.02 (1H, s), 7.10 (2H, m), 7.32 (1H, d).

(c) 3-[(5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]propanamide hydrochloride

The title compound was prepared from the product of step (b), using the method of Example 94(c). MS m/z 377 (MH)+. ¹H NMR (CD2OD); δ = 1.95 (1H, m), 2.20 (3H, m), 2.40 (2H, t), 2.81 (5H, m), 4.16 (1H, dd), 4.44 (1H, m), 6.80 (1H, s), 7.16 (1H, dd), 7.25 (1H, d), 7.43 (2H, m), 7.50 (1H, d).

Example 104
3-[(5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]-N-methylpropanamide hydrochloride

(a) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-6-[3-(methylamino)-3-oxopropyl]-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

To a solution of the compound of Example 103(a) (1ml) was added a 2M solution of methylamine in tetrahydrofuran (1ml) and the reaction stirred for 3 hours. The reaction mixture was diluted with ethyl acetate (20ml) and washed with 10% aqueous citric acid solution (20ml) and brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel, eluting with gradient of ethyl acetate : pentane (1:1) to (3:1) ethyl acetate : pentane to give the title compound, (0.017g). MS
m/z 509 (MNH₄)⁺. ¹H NMR (CDCl₃); δ = 1.50 (9H, s), 1.70 (2H, m), 1.97 (1H, m), 2.24 (1H, m), 2.39 (2H, m), 2.61 (3H, s), 2.71 (3H, d), 2.87 (2H, m), 4.13 (1H, m), 5.27-5.42 (2H, m), 6.78 (2H, m), 7.02 (1H, s), 7.11 (2H, m), 7.33 (1H, d).

(b) 3-[[5S,8S]-8-(3,4-Dichlorophenyl)-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]-N-methylpropanamide hydrochloride

The title compound was prepared from the product of step (a), using the method of Example 94(c). MS m/z 391 (MH⁺). ¹H NMR (CD₂OD); δ = 1.97 (1H, m), 2.20 (3H, m), 2.35 (2H, m), 2.60 (3H, s), 2.80 (5H, m), 4.16 (1H, m), 4.43 (1H, m), 6.75 (1H, s), 7.18 (1H, d), 7.22 (1H, d), 7.47 (3H, m).

Example 105

3-[[5S,8S]-8-(3,4-Dichlorophenyl)-5-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]-N-(2-hydroxyethyl)propanamide

(a) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-60(3-[(2-hydroxyethyl)amino]-3-oxopropyl]-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

To a solution of the compound of Example 103(a) (1ml) was added tetrahydrofuran (1ml) and ethanolamine (0.1ml, 0.00166mol) and the reaction stirred for 3 hours. The reaction mixture was diluted with ethyl acetate (20ml) and washed with 10% aqueous citric acid solution (20ml) and brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel, eluting with a gradient of ethyl acetate : pentane (9:1) to 100% ethyl acetate to give the subtitle compound, (0.022g). MS m/z 521 (MNH₄)⁺. ¹H NMR (CDCl₃); δ = 1.49 (9H, s), 1.70 (2H, m), 1.96 (1H, m), 2.23 (2H, m), 2.41 (2H, m), 2.61 (3H, s), 2.87 (2H, m), 3.32 (2H, m), 3.61 (2H, m), 4.12 (1H, m), 5.25-5.38 (1H, m), 5.78 (1H, br), 6.78 (2H, m), 7.07 (3H, m), 7.32 (1H, d).
(h) 3-[(5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)5,6,7,8-tetrahydro-2-naphthalenyl]-N-(2-hydroxyethyl)propanamide

The title compound was prepared from the product of step (a), using the method of Example 94(c). MS m/z 421 (MH$^+$). $^1$H NMR (CD$_3$OD); $\delta$ = 1.93 (1H, m), 2.20 (3H, m), 2.36 (2H, t), 2.80 (5H, m), 3.18 (2H, t), 3.50 (2H, t), 4.13 (1H, dd), 4.44 (1H, m), 6.79 (1H, s), 7.17 (1H, dd), 7.24 (1H, d), 7.41 (2H, m), 7.49 (1H, d).

Example 106

3-[(5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)-3-[(methylsulphonyl)amino]-5,6,7,8-tetrahydro-2-naphthalenyl]propanamide hydrochloride

(a) Ethyl (E)-3-[(5S,8S)-5-[(tert-butoxycarbonyl)(methyl)amino]-8-(3,4-dichlorophenyl)-3-[(methylsulphonyl)amino]-5,6,7,8-tetrahydro-2-naphthalenyl]-2-propenoate
To a solution of the product of Example 88(c) (0.2g, 0.32 mmol) in acetonitrile (10ml) was added triethylamine (135µl), tri-o-tolyl phosphine (38mg), palladium acetate (14mg) and ethyl acrylate (40µl, 0.37 mmol) and the reaction heated under reflux for 2.5 hours. The reaction was cooled to room temperature and poured into ethyl acetate (50ml) washed with 10% aqueous citric acid solution, water and brine. The organic phase was dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel, eluting with a solvent gradient of ethyl acetate/pentane [25:75] to [35:65] to yield the subtitle compound (172mg, 90%). MS m/z 614 (MNH₄)⁺. ¹H NMR (CDCl₃); δ = 1.25 (3H, t), 1.51 (9H, s), 1.77 (2H, m), 2.00 (1H, m), 2.25 (1H, m), 2.65 (3H, s), 3.03 (3H, s), 4.21 (3H, m), 5.27-5.40 (1H, m), 6.26 (1H, d), 6.80 (2H, m), 7.10 (2H, m), 7.20 (1H, s), 7.33 (1H, m), 7.84 (1H, m).

(b) Ethyl 3-{(5S,8S)-5-[(tert-butoxycarbonyl)(methyl)amino]-8-(3,4-dichlorophenyl)-3-[(methylsulphonyl)amino]-5,6,7,8-tetrahydro-2-naphthalenyl}propanoate

To a solution of the product of step (a) (172mg, 0.29mmol) in toluene (10ml) was added tosylhydrazine (300mg) and the reaction heated under reflux for 5 hours. The reaction was cooled to room temperature and then placed in a freezer for 16 hours. The solution was decanted from the precipitate and concentrated under reduced pressure. The crude product was purified on silica gel, eluting with a solvent gradient of ethyl acetate/dichloromethane [5:95] to [7.5:92.5]. MS m/z 616 (MNH₄)⁺. ¹H NMR (CDCl₃); δ = 1.20 (3H, t), 1.72 (2H, m), 1.96 (1H, m), 2.23 (1H, m), 2.61 (2H, m), 2.63 (3H, s), 2.84 (2H, m), 3.05 (3H, s), 4.10 (3H, m), 5.23-5.40 (1H, m), 6.78 (2H, m), 7.06 (1H, s), 7.24 (1H, m), 7.34 (1H, m), 7.85 (1H, m).

(c) 3-{(5S,8S)-5-[(tert-Butoxycarbonyl)(methyl)amino]-8-(3,4-dichlorophenyl)-3-[(methylsulphonyl)amino]-6,7,8-tetrahydro-2-naphthalenyl}propanoic acid

To a solution of the product of step (b) (124mg, 0.21 mmol) in tetrahydrofuran (5ml) was added aqueous lithium hydroxide solution (1M solution, 2ml) and the reaction stirred at 45°C for 22 hours. The reaction was cooled to room temperature, the tetrahydrofuran removed under reduced pressure and the residue partitioned between dichloromethane and
water and acidified with 10% aqueous citric acid solution. The organic layer was dried (MgSO₄), filtered and the solvent removed under reduced pressure to give the subtitle compound (105mg, 89%). ¹H NMR (CDCl₃); δ = 1.48 (9H, s), 1.97 (1H, m), 2.23 (1H, m), 2.62 (5H, m), 2.76-3.03 (5H, m), 4.12 (1H, m), 5.14-5.40 (1H, m), 6.78 (2H, m), 7.08 (1H, s), 7.22 (1H, s), 7.34 (1H, d), 7.83 (1H, br).

(d) tert-Butyl (1S,4S)-6-(3-amino-3-oxopropyl)-4-(3,4-dichlorophenyl)-7-[(methylsulphonyl)amino]-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

To a solution of the product of step (c) (37mg, 0.065mmol) in dioxan (3ml) was added hydroxybenzotriazole (11mg), EDC hydrochloride (19mg) and ammonium carbonate 19mg) and the reaction stirred for 3 hours. The reaction mixture was diluted with ethyl acetate, washed with 10% aqueous citric acid solution and brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel, eluting with a solvent gradient of ethyl acetate/pentane [1:1] to neat ethyl acetate to give the subtitle compound (62%). MS m/z 592 (MNa)*. ¹H NMR (CDCl₃); δ = 1.50 (9H, s), 1.71 (2H, m), 1.97 (1H, m), 2.22 (1H, m), 2.54 (2H, m), 2.64 (3H, s), 2.76-3.95 (2H, m), 3.04 (3H, s), 4.10 (1H, m), 5.23-5.40 (1H, m), 5.56 (1H, br), 5.63 (1H, br), 6.75 (1H, s), 6.80 (1H, dd), 7.06 (1H, s), 7.25 (1H, m), 7.35 (1H, d), 8.79 (1H, br).

(e) (5S,8S)-8-(3,4-Dichlorophenyl)-5-(methylamino)-3-[[methylsulphonyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]propanamide hydrochloride

The title compound was prepared from the product of step (d), using the method of Example 94(c). MS m/z 470. ¹H NMR (CD₃OD); δ = 1.94 (1H, m), 2.22 (3H, m), 2.43 (2H, t), 2.85 (5H, m), 3.07 (3H, s), 4.16 (1H, dd), 4.44 (1H,m), 6.85 (1H, s), 7.19 (1H, dd), 7.43 (1H, d), 7.50 (1H, d), 7.55 (1H, s).

Example 107

3-[(5S,8S)-5-(3,4-Dichlorophenyl)-8-(methylamino)-2-[[methylsulphonyl]amino]-5,6,7,8-tetrahydro-1-naphthalenyl]-propanamide hydrochloride
(a) tert-Butyl (1S,4S)-7-amino-4-(3,4-dichlorophenyl)-8-iodo-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

To a solution of the product of Example 81(a) (24.85g, 59mmol) in dichloromethane (500ml) and methanol (200ml), cooled in an ice-water bath, was added calcium carbonate (11.4g, 114 mmol) and benzytrimethylammonium dichloroiodate (30.8g, 88.5mmol). After 6h, the reaction was poured into 5% aqueous sodium thiosulphate solution (800ml). The organic phase was washed with 5% aqueous thiosulphate solution, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel, eluting with diethyl ether:pentane to give the subtitle compound. MS m/z 547 (MH⁺). ¹H NMR (CDCl₃): δ = 1.50-1.57 (9H, m), 1.77 (1H, m), 1.88 (1H, m), 1.98 (1H, m), 2.61 (3H, m), 3.90 (1H, m), 4.24 (2H, s), 5.00-5.14 (1H, m), 6.62 (2H, m), 6.95 (1H, m), 7.21 (1H, d), 7.38 (1H, dd).
(b) Ethyl (E)-3-[(5S,8S)-2-amino-8-[(tert-butoxycarbonyl)(methyl)amino]-5-(3,4-dichlorophenyl)-5,6,7,8-tetrahydro-1-naphthalenyl]-2-propenoate

The subtitle compound was prepared by the method of Example 106(a), starting with the product of step (a) above. Yield = 69%. MS m/z 519 (MH)^+. 1H NMR (CDCl3); δ = 1.32 (3H, m), 1.43-1.51 (9H, m), 1.84 (2H, m), 1.97 (1H, m), 2.03 (1H, m), 2.53-2.56 (3H, m), 3.94 (3H, m), 4.22 (2H, m), 5.19-5.37 (1H, m), 6.23 (1H, m), 6.60 (1H, m), 6.67 (1H, m), 6.94 (1H, m), 7.20 (1H, m), 7.35 (1H, m), 7.62 (1H, m).

(c) Ethyl (E)-3-[(5S,8S)-2-[(bis(methylsulphonyl)amino]-8-[(tert-butoxycarbonyl)(methyl)amino]-5-(3,4-dichlorophenyl)-5,6,7,8-tetrahydro-1-naphthalenyl]-2-propenoate

The subtitle compound was prepared from the product of step (b) above, using the method of Example 88(b). MS m/z 692 (MH)^+.

(d) Ethyl 3-[(5S,8S)-2-[(bis(methylsulphonyl)amino]-8-[(tert-butoxycarbonyl)(methyl)amino]-5-(3,4-dichlorophenyl)-5,6,7,8-tetrahydro-1-naphthalenyl]propanoate

The subtitle compound was prepared from the product of step (c) above, using the method of Example 106(b) using above compound (c). Yield = 40%. MS m/z 699 (MNa)^+. 1H NMR (CDCl3); δ = 1.25 (3H, m), 1.52 (9H, m), 1.95 (2H, m), 2.05 (1H, m), 2.19 (1H, m), 2.43 (1H, m), 2.58 (3H, s), 2.62-2.77 (1H, m), 2.93 (1H, m), 3.23 (1H, m), 3.40 (3H, s), 3.61 (3H, s), 4.01 (1H, m), 4.17 (2H, m), 5.30-5.47 (1H, m), 6.84 (1H, d), 6.96 (1H, d), 7.17 (1H, d), 7.23 (1H, m), 7.41 (1H, d).

(e) 3-[(5S,8S)-8-[(tert-Butoxycarbonyl)(methyl)amino]-5-(3,4-dichlorophenyl)-2-[(methylsulphonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenyl]propanoic acid

The subtitle compound was prepared from the product of step (d) above, using the method of Example 106(c). Yield = 61%. MS m/z 593 (MNa)^+. 1H NMR (CDCl3); δ = 1.49-1.55
(9H, m), 1.90 (2H, m), 2.03 (1H, m), 2.13 (1H, m), 2.62 (5H, m), 2.87 (1H, m), 3.03 (4H, m), 3.97 (1H, m), 5.17-5.43 (1H, m), 6.79 (1H, d), 6.96 (1H, m), 7.23 (1H, m), 7.37 (2H, m).

(f) tert-Butyl (1S,4S)-8-(3-amino-3-oxopropyl)-4-(3,4-dichlorophenyl)-7-[(methylsulphonyl)amino]-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

The subtitle compound was prepared from the product of step (e) above, using the method of Example 106(d). Yield = 22%. MS m/z 592 (MNa)^+. 1H NMR (CDCl$_3$); δ = 1.49-1.56 (9H, m), 1.92 (2H, m), 2.03 (1H, m), 2.13 (1H, m), 2.37-3.14 (10H, m), 3.97 (1H, m), 5.28-5.41 (1H, m), 5.49-5.72 (2H, m), 6.79 (1H, m), 6.97 (1H, d), 7.23 (1H, m), 7.38 (2H, m), 9.50-9.66 (1H, m).

(g) 3-[(5S,8S)-5-(3,4-Dichlorophenyl)-8-(methylamino)-2-[(methylsulphonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenyl]-propanamide hydrochloride

The title compound was prepared from the product of step (f), using the method of Example 94(c). Yield = 100%. MS m/z 470 (MH)^+. 1H NMR (CD$_2$OD); δ = 1.93 (1H, m), 2.14 (2H, m), 2.53 (1H, m), 2.70 (1H, m), 2.94 (3H, s), 3.04 (3H, s), 3.17 (3H, m), 4.17 (1H, dd), 4.78 (1H, m), 6.81 (1H, d), 7.22 (1H, dd), 7.30 (1H, d), 7.46 (1H, d), 7.52 (1H, d).

**Example 108**

(1S,4S)-4-(3,4-Dichlorophenyl)-N-methyl-6-(methylsulphonyl)-1,2,3,4-tetrahydro-1-naphthalenamine
(a) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-6-(methylsulphonyl)-1,2,3,4-tetrahydro-1-naphtalenyl(methyl)carbamate

To a solution of the product of Example 90(a) (532mg, 1mmol) in N,N-dimethylformamide (2ml) was added thiourea (114mg), (Et$_3$P)$_2$NiCl$_2$ (37mg) followed by sodium cyanoborohydride (0.15ml, 1M solution in tetrahydrofuran) and the reaction heated at 60°C for 4h. The reaction was allowed to cool to room temperature and 1N aqueous sodium hydroxide solution (5ml) added. After 1h, 10% aqueous citric acid solution was added and the mixture extracted with ethyl acetate, the organic phase washed with brine, dried (MgSO$_4$), filtered and the solvent removed under reduced pressure to give the crude thiol (490mg).

To a solution of the above thiol (343mg) in acetone (15ml) was added caesium carbonate (325mg) followed by methyl iodide (142 mg). After 1h, water was added and the mixture extracted with ethyl acetate. The organic phase was washed with water, dried (MgSO$_4$), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel, eluting with ethyl acetate:petroleum, to give the subtitle compound (181mg, 51%). MS m/z 453 (MH$^+$). $^1$H NMR (CDCl$_3$); δ = 1.50 (9H, s), 1.70 (2H, m), 1.98 (1H, m), 2.23 (1H, m), 2.40 (3H, s), 2.62 (3H, s), 4.12 (1H, s), 5.26-5.41 (1H, m), 6.80 (2H, s), 7.13 (3H, m), 7.33 (1H, d).

(b) (1S,4S)-4-(3,4-Dichlorophenyl)-N-methyl-6-(methylsulphonyl)-1,2,3,4-tetrahydro-1-naphthalenamine

The subtitle compound was prepared from the product of step (a), using the method of Example 94(c). MS m/z 351 (MH$^+$). $^1$H NMR (CDCl$_3$); δ = 1.81 (1H, m), 2.00 (3H, m), 2.35 (3H, s), 2.53 (3H, s), 3.70 (1H, s), 3.96 (1H, t), 6.70 (1H, s), 6.96 (1H, d), 7.11 (1H, d), 7.28 (1H, m), 7.32 (1H, d), 7.37 (1H, d).

Example 109
(1S,4S)-4-(3,4-Dichlorophenyl)-N-methyl-6-(methylsulphinyl)-1,2,3,4-tetrahydro-1-naphthalenamine
(a) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-6-(methylsulphonyl)-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

To a solution of the product of Example 108(a) (60mg, 0.13mmol) in isopropanol : tetrahydrofuran : water (10:2:1) (3ml), cooled in an ice-water bath, was added OXONE™ (potassium peroxymonosulphate, 50mg) in portions. After 2 hours, water was added and the solution made basic with 2N NaOH. The mixture was extracted with ethyl acetate, the organic phase washed with brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The crude product was purified on silica gel, eluting with ethyl acetate to give the subtitle compound (55mg, 89%). MS m/z 485 (MNH₄)⁺. ¹H NMR (CDCl₃); δ = 1.51 (9H, s), 1.79 (2H, m), 2.02 (1H, m), 2.30 (1H, m), 2.63 (3H, s), 2.68 (3H, s), 4.26 (1H, m), 5.30-5.50 (1H, m), 6.79 (1H, d), 7.05 (1H, d), 7.2-7.6 (4H, m).

(b) (1S,4S)-4-(3,4-Dichlorophenyl)-N-methyl-6-(methylsulphonyl)-1,2,3,4-tetrahydro-1-naphthalenamine

The title compound was prepared from the product of step (a), using the method of Example 94(c). MS m/z 368 (MH)⁺. ¹H NMR (CDCl₃); δ = 1.87 (1H, m), 2.06 (3H, m), 2.54 (3H, s), 2.63 (3H, s), 3.78 (1H, d), 4.05 (1H, q), 6.95 (1H, m), 7.09 (1H, d), 7.23 (1H, s), 7.37 (1H, dd), 7.50 (1H, d), 7.59 (1H, m).

Example 110

(1S,4S)-4-(3,4-Dichlorophenyl)-N-methyl-6-(methylsulphonyl)-1,2,3,4-tetrahydro-1-naphthalenamine
(a) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-6-(methylsulphonyl)-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

The subtitle compound was prepared from the product of Example 108(a), using the method of Example 109(a), but using 2 equivalents of OXONE™, and allowing the reaction to warm to room temperature. MS m/z 501 (MNH₄)⁺. ¹H NMR (CDCl₃); δ = 1.53 (9H, s), 1.80 (2H, m), 2.06 (1H, m), 2.31 (1H, m), 2.67 (3H, s), 3.03 (3H, s), 4.29 (1H, s), 5.32-5.49 (1H, br), 6.78 (1H, d), 7.07 (1H, s), 7.37 (1H, d), 7.43 (1H, d), 7.58 (1H, s), 7.82 (1H, d).

(b) (1S,4S)-4-(3,4-Dichlorophenyl)-N-methyl-6-(methylsulphonyl)-1,2,3,4-tetrahydro-1-naphthalenamine

The title compound was prepared from the product of step (a), using the method of Example 94(c). MS m/z 384 (MH⁺). ¹H NMR (CDCl₃); δ = 1.89 (1H, m), 2.08 (3H, m), 2.56 (3H, s), 2.96 (3H, s), 3.80 (1H, t), 4.08 (1H, t), 6.94 (1H, d), 7.22 (1H, s), 7.39 (1H, d), 7.43 (1H, s), 7.65 (1H, d), 7.77 (1H, d).

Example 111

2-[(5S,8S)-5-(3,4-Dichlorophenyl)-8-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]acetic acid

![Chemical structure diagram]

(a) Methyl 2-[(5S,8S)-5-(3,4-dichlorophenyl)-8-(methylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]acetate

The subtitle compound was prepared from the product of Example 77(d), using the method of Example 94(c). MS m/z 379 (MH⁺). ¹H NMR (CDCl₃); δ = 1.81 (1H, m), 2.00
(3H, m), 2.53 (3H, s), 3.60 (2H, s), 3.70 (4H, s), 3.94 (1H, dd), 6.75 (1H, d), 6.95 (1H, d), 7.05 (1H, d), 7.26 (2H, m), 7.34 (1H, d).

(b) 2-[(5S,8S)-5-(3,4-Dichlorophenyl)-8-(methylamino)-5,6,7,8-tetrahydro-2-
5 naphthalenyl]acetic acid

The title compound was prepared from the product of step (a), using the method of Example 77(e). MS m/z 365 (MH)^+. ^1H NMR (d_6-DMSO); δ = 1.73 (1H, m), 1.92 (3H, m), 2.39 (3H, s), 3.43 (2H, s), 3.68 (1H, d), 4.03 (1H, dd), 6.60 (1H, d), 6.99 (1H, d), 7.14 (1H, d), 7.29 (1H, s), 7.42 (1H, s), 7.52 (1H, d).

Example 112

3-[(5S,8S)-5-(3,4-Dichlorophenyl)-8-(methylamino)-5,6,7,8-tetrahydro-1-
naphthalenyl]-N-methyl propanamide
(a) tert-Butyl (1S,4S)-7-amino-8-bromo-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalenyl(methyl)carbamate

To a solution of the product of Example 81(a) (632 mg, 1.5 mmol) in N,N-dimethylformamide (3 ml) cooled in an ice-water bath was added a solution of N-bromosuccinimide (280 mg, 1.05 equiv) in N,N-dimethylformamide (3 ml) and the reaction stirred at room temperature for 2 hours. The mixture was diluted with Et₂O (10 ml) and EtOAc (10 ml), washed with H₂O and the organic phase dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel, eluting with hexane:EtOAc to give the subtitle compound (300 mg, 40%). MS m/z 500 (MH⁺), ¹H-NMR (CDCl₃): δ = 1.53, (9H, s), 1.75-2.02 (3H, m), 2.18 (1H, br), 2.62 (3H, d), 3.91 (1H, m), 4.19 (2H, s), 5.19-5.30 (1H, br), 6.61 (2H, m), 6.98 (1H, t), 7.22 (1H, d), 7.37 (1H, d).

(b) tert-Butyl (1S,4S)-8-bromo-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalenyl(methyl)carbamate

To a solution of t-butyl nitrite (35μl) in N,N-dimethylformamide (0.5 ml) at 60°C was added a solution of the compound of step (a) (100 mg, 0.2 mmol) and the mixture stirred for 10 min. The reaction was cooled and partitioned between ethyl acetate and water. The organic phase was dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel eluting with ethyl acetate:hexane to give the subtitle compound. This material, contaminated with about 30% of the 3,4-dehydro elimination product, could be used without further purification.

To obtain a pure sample, HCl gas was bubbled through a solution of the above crude bromide (269 mg) in dichloromethane, cooled in an ice-water bath, until the solution was saturated. The reaction was stirred for 30 min, the solvent removed under reduced pressure and the residue azeotroped with dichloromethane. This product was purified on silica gel, eluting with dichloromethane:methanol:ammonia to give 8-bromosertraline (107 mg, 50%). MS m/z 383 (MH⁺), ¹H-NMR (d₆-DMSO): δ = 1.55 (1H, t), 1.72 (1H,
br), 1.84 (1H, br), 2.11 (2H, br), 2.41 (3H, s), 3.70 (1H, s), 4.08 (1H, m), 6.66 (1H, d),
7.01 (1H, t), 7.18 (1H, d), 7.45 (2H, m), 7.57 (1H, d).

The above amine was then converted to 112(b) using (BOC)₂O (1.5 equiv), DMAP (0.1
equiv) and di-isopropylethylamine(1.5 equiv), in tetrahydrofuran (75%). ¹H-NMR
(CDCl₃): δ = 1.54 (9H, s), 1.90 (2H, m), 2.04 (1H, br), 2.19 (1H, br) 2.60 (3H, s), 3.99
(1H, br), 5.25-5.35 (1H, br), 6.83 (1H, d), 6.96 (1H, m), 7.02 (1H, t), 7.23 (1H, m), 7.39
(1H, d), 7.44 (1H, d).

(c) Ethyl (E)-3-[(5S,8S)-8-[(tert-butoxycarbonyl)(methyl)amino]-5-(3,4-dichlorophenyl)-
5,6,7,8-tetrahydro-1-naphthalenyl]-2-propenoate and Ethyl (Z)-3-[(5S,8S)-8-[(tert-
butoxycarbonyl)(methyl)amino]-5-(3,4-dichlorophenyl)-5,6,7,8-tetrahydro-1-
naphthalenyl]-2-propenoate

The subtitle compounds were prepared from the product of step (b), using the method of
Example 106(a). MS m/z 503 (MH⁺).

(d) Ethyl 3-[(5S,8S)-8-[(tert-butoxycarbonyl)(methyl)amino]-5-(3,4-dichlorophenyl)-
5,6,7,8-tetrahydro-1-naphthalenyl]propanoate

The subtitle compound was prepared from the products of step (c), using the method of
Example 106(b). ¹H-NMR (CDCl₃): δ = 1.26 (3H, t), 1.55 (9H, s), 1.92 (2H, m), 2.08
(2H, br), 2.55 (2H, m), 2.60 (3H, s), 2.84-3.00 (2H, m), 4.01 (1H, br), 4.13 (2H, q), 5.32-
5.46 (1H, m), 6.75 (1H, d), 6.96 (1H, t), 7.11 (2H, m), 7.23 (1H, m), 7.37 (1H, d).

(e) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-8-[(3-(methylamino)-3-oxopropyl]-1,2,3,4-
tetrahydro-1-naphthalenyl(methyl)carbamate

A solution of the compound of Example 112(d) (110mg) in 33% methylamine in ethanol
solution (2.5ml) was heated at 110°C for 4h. The reaction was cooled to room
temperature, the solvent removed under reduced pressure and the crude product purified
on silica gel, eluting with ethyl acetate:hexane to give the subtitle compound (73mg). MS
m/z 490 (MH⁺).
(f) 3-[(5S,8S)-5-(3,4-Dichlorophenyl)-8-(methylamino)-5,6,7,8-tetrahydro-1-naphthalenyl]-N-methyl propanamide

The title compound was prepared from the product of step (e), using the method of Example 94(c) using above compound (e). "H-NMR (CDCl₃): δ = 1.66 (1H, t), 1.95 (1H, m), 2.01 (1H, m), 2.28 (1H, d), 2.56 (3H, s), 2.62 (2H, q), 2.77 (3H, s), 3.04 (2H, t), 3.86 (1H, s), 3.95 (1H, m), 6.20 (1H, br), 7.00 (1H, d), 7.07 (2H, m), 7.27 (1H, s), 7.35 (12H, d).
Example 113

(5S,8S)-5-(3,4-Dichlorophenyl)-8-(methylamino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic acid

(a) Ethyl 3-[(5S,8S)-8-[(tert-butoxycarbonyl)(methyl)amino]-5-(3,4-dichlorophenyl)-5,6,7,8-tetrahydro-1-naphthalenyl]-2,3-dihydroxypropanoate

10 To a solution of the product of Example 112(c) (745 mg, 1.48 mmol) in acetone (21 ml) at room temperature was added a solution of N-methylmorpholine-N-oxide (520 mg, 10%
wt solution) and then osmium tetroxide (15 mg, 4% wt in H2O) and the reaction stirred for 48 hours. The solvent was removed under reduced pressure and partitioned between ethyl acetate and water. The organic phase was dried (MgSO4), filtered and the solvent removed under reduced pressure to give the intermediate diol (774 mg, 97%) which was used without further purification. MS m/z 539 (M+). 1H-NMR (CDCl3): δ = 1.08-1.40 (3H, m), 1.40-1.65 (9H, m), 1.80-2.25 (4H, m), 2.63 (3H, d), 3.22-3.34 (1H, m), 3.95-4.43 (4H, m), 5.05-5.60 (2H, m), 6.87 (1H, t), 6.98 (1H, m), 7.26 (2H, m), 7.37 (1H, d), 7.52-7.68 (1H, m).

(b) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-8-formyl-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

To a solution of the product of step (a) (774 mg, 1.44 mmol) in dioxan (12.7 ml) at room temperature was added a solution of sodium periodate (338 mg, 1.58 mmol) in water (4.3 ml) and the reaction stirred for 16 hours. The reaction was partitioned between ethyl acetate and water and the organic phase dried (MgSO4), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel, eluting with ethyl acetate/pentane to give the subtitle compound (503 mg, 81%). MS m/z 437 (MH+). 1H-NMR (CDCl3): δ = 1.50 (9H, s), 1.80-2.02 (3H, m), 2.18 (1H, br), 2.52 (3H, s), 4.19 (1H, s), 5.78-5.98 (1H, br), 6.90 (1H, d), 7.16 (2H, m), 7.37 (1H, t), 7.38 (1H, d), 7.75 (1H, d), 10.16 (1H, s).

(c) (5S,8S)-8-[(tert-Butoxycarbonyl)(methyl)amino]-5-(3,4-dichlorophenyl)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic acid.

To a solution of the product of step (b) (382 mg, 0.88 mmol) in tert-butanol (22 ml) and 2-methyl-2-butene (6 ml) at room temperature was added a solution of NaClO2 (856 mg, 10.75 equiv) and KH2PO4 (970 mg, 8.1 equiv) in H2O (9 ml), dropwise, over 10 min. The reaction was then stirred for 16 h. The solvent was then removed under reduced pressure, partitioned between EtOAc and H2O and the organic phase dried (MgSO4), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel, eluting with CH2Cl2:MeOH to give the subtitle compound (423 mg, 94%). MS m/z 450.
\( ^1\)H-NMR (CDCl\(_3\)): \( \delta = 1.49 \) (9H, s), 1.78-2.00 (3H, br), 2.14 (1H, br), 2.58 (3H, s), 4.12 (1H, m), 5.50-5.82 (1H, br), 6.94 (1H, br), 7.06 (1H, d), 7.34 (2H, br), 7.35 (1H, d), 7.60 (1H, s).

(d) (5S,8S)-5-(3,4-Dichlorophenyl)-8-(methylamino)-5,6,7,8-tetrahydro-1-naphthalencarboxylic acid

The title compound was prepared from the product of step (c), using the method of Example 94(c). MS m/z 350 (MH\(^+\)). \(^1\)H-NMR (d\(_6\)-DMSO): \( \delta = 1.94 \) (2H, m), 2.25 (1H, q), 2.41 (1H, d), 2.76 (3H, s), 4.20 (1H, m), 4.95 (1H, br), 6.97 (1H, d), 7.37 (1H, d), 7.40 (1H, t), 7.59 (1H, s), 7.65 (1H, d), 7.94 (1H, d), 8.42 (0.5H, br), 8.76 (0.5H, br).

Example 114

(5S,8S)-5-(3,4-Dichlorophenyl)-8-(methylamino)-5,6,7,8-tetrahydro-1-naphthalencarboxamide hydrochloride

(a) tert-Butyl (1S,4S)-8-(aminocarbonyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

To a solution of the product of Example 113(c) (88 mg, 0.2 mmol) in dioxan (1.5 ml) at room temperature was added HOBT (41 mg, 1.5 equiv), N,N-diisopropylethylamine (87 \(\mu l\), 2.5 equiv), EDC hydrochloride (46 mg, 1.2 equiv) and ammonium carbonate (39 mg, 1.2 equiv) and the reaction stirred overnight. The mixture was partitioned between CH\(_2\)Cl\(_2\) and H\(_2\)O, the organic phase dried (MgSO\(_4\)), filtered and the solvent removed under reduced pressure. The residue was purified on silica gel, eluting with CH\(_2\)Cl\(_2\):MeOH to give the subtitle compound (71 mg, 81%). MS m/z 449 (MH\(^+\)). \(^1\)H-NMR (CDCl\(_3\)): \( \delta = 1.42 \) (9H, s), 1.81 (2H, br), 1.96 (1H, br), 2.17 (1H, br), 2.69 (3H, br), 4.13 (1H, m), 5.38-5.80 (3H, br), 6.87-7.02 (2H, m), 7.22 (2H, m), 7.35 (2H, m).

(b) (5S,8S)-5-(3,4-dichlorophenyl)-8-(methylamino)-5,6,7,8-tetrahydro-1-naphthalencarboxamide hydrochloride
HCl gas was bubbled through a solution of the product of step (a) (69 mg) in dichloromethane (5 ml), and cooled in an ice-water bath until the solution was saturated. After 1.5 h, the solvent was removed under reduced pressure to give the title compound (54 mg, 91%). MS m/z 340 (MH)+. 1H-NMR (d6-DMSO): δ = 1.90 (2H, br), 2.12 (1H, q), 2.40 (1H, d), 2.93 (3H, s), 4.16 (1H, m), 4.42 (1H, br), 6.86 (1H, d), 7.38 (2H, m), 7.52 (1H, d), 7.64 (2H, m), 7.38 (2H, m), 7.52 (1H, d), 7.64 (2H, m), 8.08 (1H, s), 8.44 (1H, s), 9.02 (1H, br), 9.32 (1H, br).

Example 115

(5S,8S)-5-(3,4-dichlorophenyl)-N-methyl-8-(methylamino)-5,6,7,8-tetrahydro-1-naphthalene-carboxamide hydrochloride

(a) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-8-[(methylamino)carbonyl]-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

The subtitle compound was prepared from the product of Example 113(c), using the method of Example 114(a), but using methylamine in THF in place of ammonium carbonate and a 1:0.5 CH2Cl2:THF solvent mixture to give the subtitle compound. (52%). MS m/z 463 (MH)+. 1H-NMR (CDCl3): δ = 1.44 (9H, s), 1.83 (3H, br), 1.96 (1H, br), 2.18 (1H, br), 2.70 (3H, br), 2.95 (3H, d), 4.12 (1H, m), 5.73 (2H, m), 6.90 (2H, m), 7.19 (3H, m), 7.35 (1H, m).

(b) (5S,8S)-5-(3,4-Dichlorophenyl)-N-methyl-8-(methylamino)-5,6,7,8-tetrahydro-1-naphthalene-carboxamide hydrochloride

The title compound was prepared from the product of step (a), using the method of Example 94(c) (yield = 100%). MS m/z 353 (MH)+. 1H-NMR (d6-DMSO): δ = 1.93 (2H, m), 2.16 (1H, q), 2.40 (1H, d), 2.70 (3H, s), 2.92 (3H, s), 4.17 (1H, m), 4.39 (1H, br), 6.87 (1H, d), 7.38 (2H, m), 7.49 (1H, d), 7.62 (1H, d), 7.68 (1H, s), 8.96 (1H, m), 9.04 (1H, br), 9.12 (1H, br)

Example 116
(5S,8S)-5-(3,4-Dichlorophenyl)-N,N-dimethyl-8-(methylamino)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide hydrochloride

(a) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-8-[(dimethylamino)carbonyl]-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

The subtitle compound was prepared from the product of Example 113(c), using the method of Example 115(a), but using dimethylamine hydrochloride in place of methylvamine (yield = 80%). MS m/z 477 (MH)⁺. ¹H-NMR (CDCl₃): δ = 1.48 (9H, s), 1.63-2.13 (4H, m), 2.58-2.83 (5H, br), 2.99 (3H, m), 3.10 (1H, m), 4.11 (1H, m), 5.42 (1H, m), 6.90 (2H, m), 7.15 (3H, m), 7.35 (1H, d).

(b) (5S,8S)-5-(3,4-Dichlorophenyl)-N,N-dimethyl-8-(methylamino)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide hydrochloride

The subtitle compound was prepared from the product of step (a), using the method of Example 94(c) (yield = 57%). MS m/z 378 (MH)⁺. ¹H-NMR (d₆-DMSO): δ = 1.96 (2H, m), 2.12 (1H, q), 2.39 (1H, d), 2.70 (3H, s), 2.87 (3H, s), 3.09 (3H, s), 4.16 (1H, m), 4.30 (1H, br), 6.79 (1H, d), 7.33 (2H, m), 7.42 (1H, d), 7.64 (1H, d), 7.72 (1H, s), 8.78 (1H, br), 9.21 (1H, br).

Example 117

(5S,8S)-5-(3,4-dichlorophenyl)-N-(2-hydroxyethyl)-8-(methylamino)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide

(a) tert-Butyl (1S,4S)-4-(3,4-dichlorophenyl)-8-[(2-hydroxyethyl)amino]carbonyl]-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

The subtitle compound was prepared from the product of Example 113(c), using the method of Example 115(a), but using ethanolamine in place of methylvamine (yield = 80%). MS m/z 493 (MH)⁺. ¹H-NMR (d₆-DMSO): δ = 1.37 (9H, m), 1.64 (1H, br), 1.73
(1H, br), 1.87 (1H, br), 2.05 (1H, m), 3.29 (2H, m), 3.47 (2H, m), 4.25 (1H, m), 4.56 (1H, m), 5.55 (1H, br), 6.92 (1H, d), 7.00-7.40 (4H, m), 7.57 (1H, t), 8.06 (1H, d).

(b) (5S,8S)-5-(3,4-Dichlorophenyl)-N-(2-hydroxyethyl)-8-(methylamino)-5,6,7,8-tetrahydro-1-naphthalenecarboxamide

The title compound was prepared from the product of step (a), using the method of Example 94(c) (yield = 100%). MS m/z 393 (MH)+. 1H-NMR (d6-DMSO): δ = 1.92 (2H, m), 2.16 (1H, q), 2.40 (1H, d), 2.71 (3H, s), 3.37 (2H, m), 3.56 (2H, m), 4.15 (1H, m), 4.36 (1H, br), 4.84 (1H, m), 6.88 (1H, d), 7.37 (2H, m), 7.50 (1H, d), 7.62 (1H, d), 7.68 (1H, s), 8.96 (1H, s), 9.10 (1H, br), 9.24 (1H, br).

Example 118

2-[(5S,8S)-5-(3,4-Dichlorophenyl)-8-(methylamino)-5,6,7,8-tetrahydro-1-naphthalenyl]-1-ethanesulphonamide hydrochloride

(a) tert-Butyl (1S,4S)-8-[(E)-2-(aminosulphonyl)ethenyl]-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl(methyl) carbamate
The subtitle compound was prepared from the product of Example 112(b), using the method of Example 106(a), but using vinylsulphonamide in place of ethyl acrylate (yield = 227 mg, 89%). MS m/z 528 (MH)^+. \[\text{H-NMR (CDCl}_3\text{): }\delta = 1.58 (9H, s), 1.73 (1H, m), 1.88 (1H, m), 1.98 (1H, m), 2.19 (1H, m), 2.40 (3H, s), 4.12 (1H, m), 5.14 (2H, s), 5.39 (1H, m), 6.66 (1H, d), 6.85 (1H, d), 7.00 (1H, d), 7.10 (1H, s), 7.25 (1H, m), 7.37 (1H, d), 7.65 (1H, d).\]

(b) tert-Butyl (1S,4S)-8-[2-(aminosulphonyl)ethyl]-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl(methyl)carbamate

The subtitle compound was prepared from the product of step (a), using the method of Example 106(b).

(c) 2-[(5S,8S)-5-(3,4-Dichlorophenyl)-8-(methylamino)-5,6,7,8-tetrahydro-1-naphthalenyl]-1-ethanesulphonamide hydrochloride

The title compound was prepared from the product of step (b), using the method of Example 94(c). MS m/z 413 (MH)^+. \[\text{H-NMR (CDCl}_3\text{): }\delta = 1.73 (1H, m), 1.85 (1H, q), 2.00 (1H, m), 2.32 (1H, d), 2.57 (3H, s), 3.26 (2H, m), 3.48 (1H, m), 3.69 (1H, m), 3.88 (1H, s), 3.95 (1H, m), 6.67 (1H, m), 6.97 (1H, d), 7.10 (2H, m), 7.26 (1H, m), 7.38 (1H, d).\]

Example 119

Biological activity

A number of compounds were assayed for their ability to inhibit the up-take of serotonin by human serotonin transporters as described in Test A. Compounds having an IC\textsubscript{50} value less than or equal to 100 nM included the title compounds of Examples 1-4, 6-31, 33-35, 37, 39-53, 55, 56, 58-68, 70-72, 74, 76-87, 89-91 and 93.
Claims:

1. A compound of formula I,

\[
\text{I}
\]

wherein

R¹ and R² independently represent H or C₅₋₆ alkyl;
R³ represents phenyl substituted by at least one group selected from halo, CF₃, OCF₃, CN, OH, C₅₋₆ alkyl and C₅₋₆ alkoxy; and
R⁴, R⁵ and R¹¹ independently represent H or -(CH₂)ₙ-A, wherein n represents 0, 1 or 2,

provided that at least one of R⁴, R⁵ and R¹¹ is other than H;

A represents:

CONR⁶R⁷ or SO₂NR⁶R⁷, wherein R⁶ and R⁷ independently represent H, C₃₋₆ cycloalkyl or C₅₋₆ alkyl,

the C₅₋₆ alkyl group being optionally substituted by one or more groups selected from OH, CO₂H, C₃₋₆ cycloalkyl, NH₂, CONH₂, C₅₋₆ alkoxy, C₅₋₆ alkoxy carbonyl and a 5- or 6-membered heterocyclic ring (containing 1, 2 or 3 heteroatoms selected from N, S and O);

in addition, R⁶ and R⁷ may, together with the N atom to which they are attached, represent a pyrrolidine or piperidine ring (which rings are optionally substituted by OH or CONH₂) or a morpholine ring (which is optionally substituted by CONH₂);

CO₂R⁸, wherein R⁸ represents H or C₅₋₆ alkyl;

NR⁹R¹₀, wherein R⁹ and R¹₀ independently represent H, C₅₋₆ alkyl (optionally substituted by OH or C₅₋₆ alkoxy), (C₅₋₆ alkyl)SO₂-, (C₅₋₆ alkyl)CO₂-, H₂NSO₂- or H₂NCO₂-;

a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O, optionally substituted by one or more groups selected from C₅₋₆ alkyl, NH₂, OH, =O and CONHCH₃;
S(O)ₙ(C₆H₅ alkyl), wherein n represents 0, 1 or 2;
OH;
CN;
NO₂; or
C₆H₅ alkoxy optionally substituted by one or more groups selected from SO₂NH₂ and CONH₂;

provided that when NR¹R² represents N(H)methyl, R⁴ represents H and R³ represents 4-chlorophenyl, then R² does not represent methoxy;

and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1, wherein NR¹R² represents NH(C₆H₅ alkyl).
3. A compound as claimed in claim 1 or claim 2, wherein R³ represents phenyl disubstituted with halo.
4. A compound as claimed in any one of the preceding claims, wherein R⁴ represents H.
5. A compound as claimed in any one of the preceding claims, wherein R⁵ represents -(CH₃)₆-A.
6. A compound as claimed in any one of the preceding claims, wherein R¹¹ represents H.
7. A compound as claimed in any one of the preceding claims, wherein A represents CONR²R³, SO₂NR⁵R⁶ or NO₂.
8. A compound as claimed in any one of the preceding claims, wherein one of R⁶ and R⁷ represents H, and the other represents H or C₆H₅ alkyl optionally substituted by OH.
9. A compound as claimed in any one of the preceding claims, wherein n represents 0.
10. A compound as claimed in claim 1, having the stereochemistry shown in formula Ia,

wherein R⁴⁻⁵ and R¹¹ are as defined in claim 1.
11. A compound as defined in claim 1, for use as a pharmaceutical.
12. A pharmaceutical formulation containing a compound as defined in claim 1, and a pharmaceutically acceptable adjuvant, diluent or carrier.
13. Use of a compound as defined in claim 1, in the manufacture of a medicament for the treatment or prevention of a disorder in which the regulation of monoamine transporter function is implicated.
14. The use as claimed in claim 13, wherein the disorder is depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders or sexual dysfunction including premature ejaculation.
15. Use of N-methyl-4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of premature ejaculation.
16. A method of treatment or prevention of a disorder in which the regulation of monoamine transporter function is implicated, comprising the administration of an effective amount of a compound as defined in claim 1 to a patient in need of such treatment or prevention.
17. A method of treatment or prevention of premature ejaculation, comprising the administration of an effective amount of N-methyl-4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine, or a pharmaceutically acceptable salt thereof, to a patient in need of such treatment or prevention.
18. A method of increasing ejaculatory latency which comprises the administration of an effective amount of a compound as defined in claim 1, or N-methyl-4-(4-chlorophenyl)-7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine, or a pharmaceutically acceptable salt thereof, to a male desiring increased ejaculatory latency.
19. A process for the production of a compound as defined in claim 1, which includes:
(a) when R⁴, R⁵ or R¹¹ represents CONR⁴R², reaction of a compound of formula II,
wherein R^{1-3} are as defined in claim 1, the corresponding group R^{4-a}, R^{5-a} or R^{11-a} represents iodo and the remainder represent H or -(CH_{2})_{n}-A, wherein n and A are as defined in claim 1; with CO or an amine of formula III,

HNR^{4}R^{7}  ~ III

wherein R^{6} and R^{7} are as defined in claim 1, in the presence of a Pd(0) catalyst;

(b) when R^{4}, R^{5} or R^{11} represents SO_{2}NR^{4}R^{5}, reaction of a compound of formula IV,

![IV](image)

wherein R^{1-3} are as defined in claim 1, the corresponding group R^{4-b}, R^{5-b} or R^{11-b} represents SO_{2}Cl and the remainder represent H or -(CH_{2})_{n}-A, wherein n and A are as defined in claim 1; with an amine of formula III, as defined above;

(c) when R^{4}, R^{5} or R^{11} represents CO_{2}(C_{1-6} alkyl), reaction of a compound of formula II, as defined above; with CO and a C_{1-6} alkanol in the presence of a Pd(0) catalyst;

(d) when R^{4}, R^{5} or R^{11} represents NO_{2}, reaction of a compound of formula V,

![V](image)

wherein R^{1-3} are as defined in claim 1; with an alkali metal nitrate and a sulphonic acid;

(e) when R^{4}, R^{5} or R^{11} represents a heterocyclic ring attached to the rest of the molecule by a N atom, reaction of a compound of formula II as defined above; with a heterocyclic compound containing an NH group in the ring, in the presence of a copper catalyst;

(f) when R^{4}, R^{5} or R^{11} represents a heterocyclic ring attached to the rest of the molecule by a C atom, reaction of a compound of formula VI,
wherein \( R^{1-3} \) are as defined in claim 1, the corresponding group \( R^{4f}, R^{5f} \) or \( R^{11f} \) represents a group of formula F,

![Chemical Structure](image)

and the remainder represent H or \(-(CH_2)_n-A\), wherein \( n \) and A are as defined in claim 1; with a heterocyclic compound containing a C-Br or C-I group in the ring, in the presence of a Pd(0) catalyst;

(g) when \( R^4, R^5 \) or \( R^{11} \) represents a heterocyclic ring attached to the rest of the molecule by a C atom, reaction of a compound of formula II, as defined above; with a heterocyclic compound which is optionally substituted with iodo on the C atom by which the heterocyclic ring will be attached to the rest of the molecule, in the presence of butyl lithium and a Pd(0) catalyst;

(h) when \( R^4, R^5 \) or \( R^{11} \) represents \( S(O)_x(C_{1-6} \text{ alkyl}) \), reaction of a compound of formula II, as defined above; with a compound of formula VII,

\[
\text{NaS(C}_{1-6}\text{ alkyl}) \quad \text{VII}
\]
in the presence of a copper or palladium catalyst, followed by oxidation if desired to give compounds in which \( x \) is 1 or 2;

(i) when \( R^4, R^5 \) or \( R^{11} \) represents CN, reaction of a compound of formula II, as defined above; with zinc cyanide, in the presence of a Pd(0) catalyst;

(j) when \( R^4, R^5 \) or \( R^{11} \) represents \( CH_2CH_2SO_2NR^6R^7 \) or \( CH_2CH_2SO_2(C_{1-6} \text{ alkyl}) \), reaction of a compound of formula II, as defined above; with a compound of formula IX,

\[
CH_3=CH-A^k \quad \text{IX}
\]
wherein \( A^k \) represents \( SO_2NR^6R^7 \) or \( SO_2(C_{1-6} \text{ alkyl}) \) as appropriate, in which \( R^6 \) and \( R^7 \) are as defined in claim 1, in the presence of a Pd(II) catalyst, followed by reduction of the resulting alkene;
(k) when $R^4$, $R^5$ or $R^{11}$ represents $\text{CH}_2\text{CH}_2\text{CO}_2(\text{C}_{1-6}\text{ alkyl})$, reaction of a compound of formula II, as defined above; with a compound of formula X,

$$\text{CH}_2\text{=CHCO}_2(\text{C}_{1-6}\text{ alkyl})$$

in the presence of a Pd(II) catalyst, followed by reduction of the resulting alkene; or

(l) when one of $R^1$ and $R^2$ represents $\text{C}_{1-6}\text{ alkyl}$ and the other represents H, removing a protecting group from a compound of formula XI,

![Image of chemical structure XI]

wherein $R^{3-5}$ and $R^{11}$ are as defined in claim 1, and Pg is a protecting group; and where desired or necessary, converting the resulting compound into a pharmaceutically acceptable salt, or vice versa.

20. Compounds of formulae II, IV, VI and XI as defined in claim 19.

21. A compound of formula B,

![Image of chemical structure B]

wherein

$R^1$ and $R^2$ independently represent H or $\text{C}_{1-6}\text{ alkyl};$

$R^3$ represents phenyl substituted by at least one group selected from halo, $\text{CF}_3$, $\text{OCF}_3$, $\text{CN}$, $\text{OH}$, $\text{C}_{1-6}\text{ alkyl}$ and $\text{C}_{1-6}\text{ alkoxy}$; and

$R^4$, $R^5$ and $R^{11}$ independently represent H or -(CH$_2$)$_n$-$A'$, wherein $A'$ is a polar group and $n$ represents 0, 1 or 2, provided that at least one of $R^4$, $R^5$ and $R^{11}$ is other than H;

provided that when $NR^1R^2$ represents N(H)methyl, $R^4$ represents H and $R^3$ represents 4-chlorophenyl, then $R^5$ does not represent methoxy; and pharmaceutically acceptable salts thereof.
22. Use of a serotonin re-uptake inhibitor comprising both a basic amine group and a polar group in the manufacture of a medicament for the treatment of premature ejaculation.

23. The use as claimed in claim 22, wherein the serotonin re-uptake inhibitor is more than 10-fold as potent in the inhibition of serotonin transporters than in the inhibition of both dopamine transporters and noradrenaline transporters.

24. The use as claimed in claim 22 or 23, wherein the polar group is attached directly to an aromatic ring.

25. The use as claimed in any one of claims 22-24, wherein the polar group has a π value more negative than -0.1.

26. The use as claimed in any one of claims 22-25, wherein the serotonin re-uptake inhibitor is a derivative or analogue of sertraline, paroxetine, fluoxetine, citalopram, fluvoxamine, norfluoxetine, meroxetine, tooxetine or venlafaxine.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7  C07C237/20  C07C237/48  C07C311/37  C07D249/06  C07C229/50  C07C311/08  A61K31/18  A61K31/16  A61K31/33  A61P25/00  C07D295/22  C07D295/18  C07C259/18  C07C229/46  C07C255/58

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7  C07C  C07D  A61K  A61P

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

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
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</table>
| X        | EP 0 415 613 A (PFIZER)  
6 March 1991 (1991-03-06)  
cited in the application claim | 1,22-26 |
| A        | EP 0 030 081 A (PFIZER INC.;USA)  
10 June 1981 (1981-06-10)  
cited in the application | 1 |
| X        | WO 97 13770 A (NEUROSEARCH AS;MOLDT PETER (DK); SCHEEL KRUEGER JOERGEN (DK); OLS)  
17 April 1997 (1997-04-17)  
page 1, paragraph 1  
page 2, paragraph 3  
claims | 22-26 |

Further documents are listed in the continuation of box C.  

**Patient family members are listed in annex.**

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**Date of the actual completion of the international search**

28 April 2000

**Date of mailing of the international search report**

10/05/2000

**Name and mailing address of the ISA**

European Patent Office, P.B. 5018 Patentlaan 2  
NL - 2280 HV Rijswijk  
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Fax: (+31-70) 340-3016

**Authorized officer**

Pauwels, G.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C233/30 C07C251/42 C07C271/24 C07C211/60 C07C211/64
C07C233/43 C07C235/20 A61P15/00 C07C311/38 C07D307/52
C07D211/62 C07C311/05 C07C275/24 C07D271/06 C07D237/20

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<tr>
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<td>US 5 276 042 A (WIESNER MARK G ET AL) 4 January 1994 (1994-01-04) claims</td>
<td>22-26</td>
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<tr>
<td>X</td>
<td>US 4 507 323 A (STERN WARREN C) 26 March 1985 (1985-03-26) column 1, line 6 - line 39</td>
<td>22-26</td>
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<tr>
<td>X</td>
<td>EP 0 714 663 A (LILLY CO ELI) 5 June 1996 (1996-06-05) page 12, line 45 claims</td>
<td>22-26</td>
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Further documents are listed in the continuation of box C.

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Fax. (+31-70) 340-3016

Authorized officer
Pauwels, G
INTERNATIONAL SEARCH REPORT

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Date of the actual completion of the international search

28 April 2000

Date of mailing of the international search report

Authorized officer

Pauwels, G
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C311/35 C07C311/13

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

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  "S" document member of the same patent family

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28 April 2000

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Fax: (+31-70) 340-3016

Authorized officer

Pauwels, G

Form PCT/ISA/210 (second sheet) (July 1992)
**INTERNATIONAL SEARCH REPORT**

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

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

1. **X** Claims Nos.: Because they relate to subject matter not required to be searched by this Authority, namely:
   
   **Remark:** Although claims 16-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **☐** Claims Nos.: Because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. **☐** Claims Nos.: Because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. **☐** As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

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

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