

GLYCINE TRANSPORT INHIBITORS

The present invention relates to glycine transporter inhibiting compounds, their use in the manufacture of medicaments for treating neurological and neuropsychiatric disorders, in particular psychoses, dementia or attention deficit disorder. The invention further comprises processes to make these compounds and pharmaceutical formulations thereof.

Molecular cloning has revealed the existence in mammalian brains of two classes of glycine transporters, termed GlyT1 and GlyT2. GlyT1 is found predominantly in the forebrain and its distribution corresponds to that of glutamatergic pathways and NMDA receptors (Smith, *et al.*, *Neuron*, 8, 1992: 927-935). Molecular cloning has further revealed the existence of three variants of GlyT1, termed GlyT-1a, GlyT-1b and GlyT-1c (Kim *et al.*, *Molecular Pharmacology*, 45, 1994: 608-617), each of which displays a unique distribution in the brain and peripheral tissues. The variants arise by differential splicing and exon usage, and differ in their N-terminal regions. GlyT2, in contrast, is found predominantly in the brain stem and spinal cord, and its distribution corresponds closely to that of strychnine-sensitive glycine receptors (Liu *et al.*, *J. Biological Chemistry*, 268, 1993: 22802-22808; Jursky and Nelson, *J. Neurochemistry*, 64, 1995 : 1026-1033). Another distinguishing feature of glycine transport mediated by GlyT2 is that it is not inhibited by sarcosine as is the case for glycine transport mediated by GlyT1. These data are consistent with the view that, by regulating the synaptic levels of glycine, GlyT1 and GlyT2 selectively influence the activity of NMDA receptors and strychnine-sensitive glycine receptors, respectively.

NMDA receptors are critically involved in memory and learning (Rison and Staunton, *Neurosci. Biobehav. Rev.*, 19 533-552 (1995); Danysz *et al.*, *Behavioral Pharmacol.*, 6 455-474 (1995)); and, furthermore, decreased function of NMDA-mediated neurotransmission appears to underlie, or contribute to, the symptoms of schizophrenia (Olney and Farber, *Archives General Psychiatry*, 52, 998-1007 (1996)). Thus, agents that inhibit GlyT1 and thereby increase glycine activation of NMDA receptors can be used as novel antipsychotics and anti-dementia agents, and to treat other diseases in which cognitive processes are impaired, such as attention deficit disorders and organic brain syndromes. Conversely, over-activation of NMDA receptors has been implicated in a number of disease states, in particular the neuronal death associated with stroke and possibly neurodegenerative diseases, such as Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral

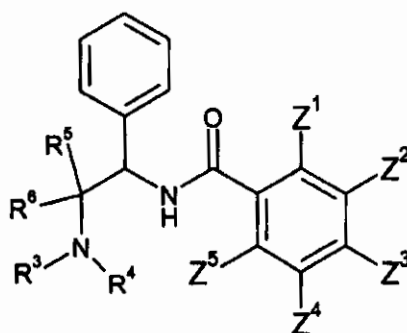
sclerosis or other conditions in which neuronal cell death occurs, such as stroke or head trauma. Coyle & Puttfarcken, Science, 262, 689-695 (1993); Lipton and Rosenberg, New Engl. J. of Medicine, 330, 613-622 (1993); Choi, Neuron, 1, 623-634 (1988). Thus, pharmacological agents that increase the activity of GlyT1 will result in decreased glycine-activation of NMDA receptors, which activity can be used to treat these and related disease states. Similarly, drugs that directly block the glycine site of the NMDA receptors can be used to treat these and related disease states.

Glycine transport inhibitors are already known in the art, for example as disclosed in published international patent application WO03/055478 (SmithKline Beecham).

However, there still remains the need to identify further compounds that can inhibit GlyT1 transporters, including those that inhibit GlyT1 transporters selectively over GlyT2 transporters.

It has now been found that a novel class of compounds inhibit GlyT1 transporters and are thus useful in the treatment of certain neurological and neuropsychiatric disorders, including schizophrenia.

Thus, in a first aspect, there is provided a compound of formula (I) or a salt or solvate thereof:



(I)

wherein

Z¹ is selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, haloC₁₋₄alkyl, phenyl, haloC₁₋₄alkoxy, halophenyl, C₁₋₄alkylsulfoxy, C₁₋₄alkylsulfonyl, bromo and chloro;

Z² is selected from the group consisting of hydrogen, halogen, cyano, C₁₋₄alkyl, phenyl, haloC₁₋₄alkyl, haloC₁₋₄alkoxy, halophenyl, C₁₋₄alkoxyC₁₋₄alkyl and C₃₋₆cycloalkyl;

5 Z³ is selected from the group consisting of hydrogen, halogen, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, haloC₁₋₄alkyl, haloC₁₋₄alkoxy, and C₃₋₆cycloalkyl;

10 Z⁴ is selected from the group consisting of hydrogen, halogen, C₁₋₃alkyl, haloC₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, phenyl, haloC₁₋₄alkoxy, halophenyl, C₁₋₄alkoxyC₁₋₄alkyl and C₃₋₆cycloalkyl;

15 Z⁵ is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo, hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, phenyl, haloC₁₋₄alkyl, haloC₁₋₄alkoxy, halophenyl, C₁₋₄alkoxyC₁₋₄alkyl and C₃₋₆cycloalkyl;

20 whereby if more than one of Z¹ to Z⁵ is methoxy, then only Z¹ and Z⁵ are methoxy

R³ and R⁴ are independently selected from hydrogen and C₁₋₄alkyl, optionally substituted with one or more groups Y; or R³ and R⁴ together with the nitrogen atom to which they are attached form a saturated or partially unsaturated 4-, 5- 6- or 7-membered carbocyclic ring optionally substituted with a group Y';

25 Y is selected from the group consisting of C₁₋₄alkoxy, hydroxy, haloC₁₋₄alkoxy and C₃₋₅cycloalkyl;

30 Y' is selected from the group consisting of C₁₋₄alkyl, C₁₋₄alkoxy, halogen, hydroxy, haloC₁₋₄alkoxy, C₃₋₅cycloalkyl and C₅₋₁₀aryl or Y' forms a -CH₂- or -CH₂-CH₂- bridge between two atoms on the 4-, 5-, 6-, or 7-membered carbocyclic ring;

35 R⁵ and R⁶ are independently C₁₋₄alkyl, optionally substituted with one or more groups X; or R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring optionally substituted with one or more groups X', in the case of R⁵ and R⁶ together with the carbon atom to which they are attached forming a 5-membered saturated carbocyclic ring, that ring may optionally further comprise an additional heteroatom group selected from O, N and S(O)_m; where m = 0, 1 or 2.

X is selected from the group consisting of halogen, hydroxy, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy and C₅₋₁₀aryl; and

X' is selected from the group consisting of halogen, hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy and C₅₋₁₀aryl;

whereby R³, R⁴, R⁵ and R⁶ are not all simultaneously unsubstituted methyl;

with the provisos that

- 10 - when simultaneously Z1 is propyloxy, Z3 is chloro, Z2=Z4=Z5=H, and R5 and R6 are both methyl, then R³ and R⁴ together with the nitrogen atom to which they are attached do not form a 2-methylpyrrolidine group;
- when simultaneously Z1 is methyl, Z3 is methoxy, Z2=Z4=Z5=H, and R5 and R6 are both methyl, then R³ and R⁴ together with the nitrogen atom to which they are attached do not form a pyrrolidine group.

As used herein, the term "alkyl" refers to a straight or branched alkyl group in all isomeric forms. Examples of C₁₋₄alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

As used herein, the term "cycloalkyl" refers to a non-aromatic cyclic saturated hydrocarbon ring. Examples of C₃₋₆cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

As used herein, the term "alkoxy" refers to the group -O-alkyl wherein alkyl is as defined above. The term "methoxy" refers to the group -O-methyl.

As used herein, the term "alkylthio" refers to the group -S-alkyl wherein alkyl is as defined above. The term "methylthio" refers to the group -S-methyl.

As used herein, the term "alkylsulfoxy" refers to the group -S(O)-alkyl wherein alkyl is as defined above.

As used herein, the term "alkysulfonyl" refers to the group -S(O)₂-alkyl wherein alkyl is as defined above.

As used herein, the term "C₅₋₁₀aryl" refers to a 5- or 6- membered monocyclic aromatic group or a 8- to 10- membered bicyclic aromatic group. Examples of C₅₋₁₀aryl include phenyl, indenyl, azulenyl and naphthyl.

- 5 As used herein, the terms "halogen" and its abbreviation "hal" refer to fluorine, chlorine, bromine, or iodine.

As used herein, the term "haloalkyl" refers to an alkyl group as defined above which is substituted with any number of fluorine, chlorine, bromine, or iodine atoms, including with
10 mixtures of those atoms. A haloalkyl group may, for example contain 1, 2 or 3 halogen atoms. For example, a haloalkyl group may have all hydrogen atoms replaced with halogen atoms. Examples of haloalkyl groups include fluoromethyl, difluoromethyl and trifluoromethyl.

- 15 As used herein, the term "salt" refers to any salt of a compound according to the present invention prepared from an inorganic or organic acid or base, quaternary ammonium salts and internally formed salts. Physiologically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compounds. Such salts must clearly have a physiologically acceptable anion or cation.

20 Suitably physiologically acceptable salts of the compounds of the present invention include acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, phosphoric, metaphosphoric, nitric and sulfuric acids, and with organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, formic, propionic, glycolic, gluconic, maleic, succinic, camphorsulfuric, isothionic, mucic, gentisic, isonicotinic, saccharic, glucuronic, furoic, glutamic, ascorbic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, stearic, sulfinilic, alginic, galacturonic and arylsulfonic, for example benzenesulfonic and p-toluenesulfonic, acids; base addition salts formed with alkali metals and alkaline earth metals and organic bases such as N,N-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), lysine and procaine; and internally formed salts. Salts having a non-physiologically acceptable anion or cation are within the scope of the invention as useful intermediates for the preparation of physiologically acceptable salts and/or for use in non-therapeutic, for example, *in vitro*, situations. The salts may have any suitable stoichiometry. For example, a salt may have
35 1:1 or 2:1 stoichiometry. Non-integral stoichiometry ratios are also possible.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water.

In one embodiment, R^3 and R^4 are both simultaneously the same C_{1-4} alkyl, the same C_{1-4} alkyl substituted with one or more groups Y, or R^3 and R^4 together with the nitrogen atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring optionally substituted with a group Y'.

In one embodiment, R^3 and R^4 are both C_{1-4} alkyl, for example methyl or ethyl, for example methyl.

Y may, for example, be selected from the group consisting of C_{1-4} alkoxy, halo C_{1-4} alkoxy and C_{5-10} aryl. In one embodiment, Y is selected from the group consisting of C_{1-4} alkoxy, C_{5-10} aryl.

Y' may, for example, be selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkoxy and C_{5-10} aryl. In one embodiment, Y' is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, C_{5-10} aryl.

In one embodiment, R^3 and R^4 are independently selected from hydrogen, methyl and ethyl, optionally substituted with a group Y, or R^3 and R^4 together with the nitrogen atom to which they are attached form a saturated or partially unsaturated (for example saturated) 4-, 5-, 6- or 7-membered carbocyclic ring optionally substituted with a group Y'.

In a further embodiment, R^3 and R^4 are selected from methyl and ethyl, optionally substituted with a group Y, or R^3 and R^4 together with the nitrogen atom to which they are attached form a saturated 4-, 5- or 6-membered carbocyclic ring optionally substituted with a group Y'. For example, R^3 and R^4 are both unsubstituted methyl, or R^3 and R^4 together with the nitrogen atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring.

Y may, for example, be selected from the group consisting of C₁₋₄alkoxy, hydroxy and C₃₋₅cycloalkyl.

Y' may, for example, be selected from the group consisting of halogen and C₁₋₄alkyl or Y' may form a -CH₂- bridge between two atoms on the 5- or 6- membered carbocyclic ring.

In one embodiment, R⁵ and R⁶ are both simultaneously the same C₁₋₄alkyl, the same C₁₋₄alkyl substituted with one or more groups X, or R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring optionally substituted with a group X', the 5- or 6-membered saturated carbocyclic ring optionally further comprising an additional heteroatom group selected from O, N and S(O)_m (where m is 0, 1, or 2);

In a further embodiment, R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring, for example a 5-membered carbocyclic ring.

X is, for example, selected from the group consisting of halogen, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy and C₅₋₁₀aryl.

In one embodiment, R⁵ and R⁶ are independently selected from methyl and ethyl, optionally substituted with one or more groups X; or R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring and in the case of R⁵ and R⁶ together with the carbon atom to which they are attached forming a 5-membered saturated carbocyclic ring, that ring may optionally further comprise an oxygen heteroatom. In one embodiment one of R⁵ and R⁶ is ethyl and the other is methyl.

For example, in one embodiment R⁵ and R⁶ are independently selected from methyl and ethyl, or R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5-membered carbocyclic ring. For example, in a further embodiment, R⁵ and R⁶ are both methyl, or R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5- membered carbocyclic ring.

X may, for example, be selected from the group consisting of hydroxy and C₁₋₄alkoxy.

X' may, for example, be selected from the group consisting of hydroxy and C₁₋₄alkoxy.

In one embodiment, at least one of the pairs of groups R^3 / R^4 and R^5 / R^8 forms a cyclic group with the Nitrogen or Carbon atom to which they are respectively attached. For example, that cyclic group may be a 5-membered carbocyclic ring.

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In one embodiment of the invention, Z^1 is selected from the group consisting of chloro, C_{1-4} alkyl, halo C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkoxy, C_{1-4} alkylthio, phenyl, and halophenyl;

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Z^2 is selected from the group consisting of hydrogen, iodo, bromo, chloro, fluoro, C_{1-4} alkyl, halo C_{1-4} alkyl, halo C_{1-4} alkoxy, phenyl, and halophenyl;

Z^3 is selected from the group consisting of hydrogen, iodo, bromo, chloro, C_{1-4} alkyl, halo C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkoxy;

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Z^4 is selected from the group consisting of hydrogen, iodo, bromo, chloro, fluoro, C_{1-4} alkoxy, halo C_{1-4} alkoxy, phenyl, and halophenyl; and

Z^5 is selected from the group consisting of hydrogen, iodo, bromo, chloro, C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkoxy, phenyl, and halophenyl;

20

wherein no more than three of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are hydrogen.

In another embodiment, Z^1 is selected from the group consisting of chloro, halo C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkoxy, phenyl, and halophenyl, and Z^2 , Z^3 , Z^4 and Z^5 are hydrogen.

25

In a further embodiment,

Z^1 is selected from the group consisting of, chloro, C_{1-4} alkyl, and C_{1-4} alkoxy;

Z^2 is selected from the group consisting of hydrogen, halo C_{1-4} alkyl, and C_{1-4} alkyl;

30

Z^3 is hydrogen;

Z^4 is hydrogen; and

35

Z^5 is selected from the group consisting of hydrogen, and C_{1-4} alkyl;

wherein no more than three of Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are hydrogen.

In one embodiment, Z^1 is selected from the group consisting of C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{1-2} alkoxy, C_{1-4} alkylthio, halo C_{1-4} alkyl, phenyl, halo C_{1-4} alkoxy, halophenyl, C_{1-4} alkylsulfoxy,
 5 C_{1-4} alkylsulfonyl, bromo and chloro.

In one embodiment, Z^1 is selected from the group consisting of C_{1-4} alkyl, C_{1-2} alkoxy, C_{1-4} alkylthio, halo C_{1-4} alkyl, phenyl, halo C_{1-4} alkoxy, halophenyl and chloro;

10 For example, Z^1 is selected from the group consisting of C_{1-4} alkyl, C_{1-2} alkoxy, C_{1-4} alkylthio, halo C_{1-4} alkyl, and chloro, particularly from the group consisting of C_{1-4} alkyl and C_{1-2} alkoxy. For example, Z^1 may be selected from methyl, methylthio, ethoxy and methoxy.

In one embodiment, Z^2 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, phenyl and halo C_{1-4} alkyl. For example, Z^2 may be selected from the group
 15 consisting of hydrogen, halogen, and C_{1-4} alkyl. For example Z^2 may be selected from hydrogen, bromo and methyl. For example Z^2 may be hydrogen

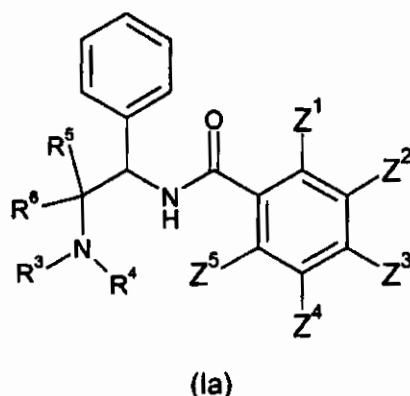
In one embodiment, Z^3 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy and halo C_{1-4} alkyl. For example, Z^3 may be selected from the group
 20 consisting of hydrogen, halogen, C_{1-4} alkyl and halo C_{1-4} alkyl. For example Z^3 may be selected from hydrogen, fluoro, chloro and trifluoromethyl.

In one embodiment, Z^4 is selected from the group consisting of hydrogen, halogen, C_{1-3} alkyl, phenyl, C_{1-4} alkoxy and halo C_{1-4} alkyl. For example Z^4 may be selected from the
 25 group consisting of hydrogen and halogen. For example Z^4 may be hydrogen.

In one embodiment, Z^5 is selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, bromo, C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkyl and halo C_{1-4} alkoxy; Z^5 may be selected
 30 from the group consisting of chloro, bromo, C_{1-4} alkyl, C_{1-4} alkoxy and halo C_{1-4} alkyl. For example, Z^5 may be selected from the group consisting of bromo, methyl, and trifluoromethyl.

In one embodiment, Z^1 and Z^5 are both simultaneously not hydrogen. In a further
 35 embodiment, Z^1 , Z^3 and Z^5 are all simultaneously not hydrogen.

Accordingly, in one embodiment, the present invention provides a compound of formula (Ia) or a salt or solvate thereof:



wherein

Z¹ is selected from the group consisting of C₁₋₄alkyl, C₁₋₂alkoxy, C₁₋₄alkylthio, haloC₁₋₄alkyl, and chloro;

Z² is selected from the group consisting of hydrogen, halogen, haloC₁₋₄alkyl, and C₁₋₄alkyl;

Z³ is selected from the group consisting of hydrogen, halogen, haloC₁₋₄alkyl and C₁₋₄alkyl;

Z⁴ is selected from the group consisting of hydrogen and halogen;

Z⁵ is selected from the group consisting of bromo, C₁₋₄alkyl, C₁₋₄alkoxy and haloC₁₋₄alkyl;

R³ and R⁴ are independently unsubstituted methyl or ethyl, or R³ and R⁴ together with the nitrogen atom to which they are attached form a saturated 5- or 6-membered carbocyclic ring;

R⁵ and R⁶ are independently methyl or ethyl, or R⁵ and R⁶ together with the carbon atom to which they are attached form a saturated 5- membered carbocyclic ring;

and at least one of the pairs of groups R³ / R⁴ and R⁵ / R⁶ forms a cyclic group with the Nitrogen or Carbon atom to which they are respectively attached.

It is to be understood that features of an embodiment of the invention described with reference to one parameter can be combined with the features of another embodiment. The disclosure herein thus includes the combination of the features of any one embodiment with the features of any other embodiment described. All embodiments and
5 features of compounds of formula (I) apply to compounds of formula (Ia).

Examples of compounds of the invention include Examples 1 to 260 shown below, as well as salts and solvates thereof.

10 The compounds of formula (I) may have the ability to crystallise in more than one form. This is a characteristic known as polymorphism, and it is understood that such polymorphic forms ("polymorphs") are within the scope of formula (I). Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallisation process. Polymorphs can be distinguished
15 by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point.

Certain of the compounds described herein may exist in stereoisomeric forms (i.e. they may contain one or more asymmetric carbon atoms or may exhibit *cis-trans* isomerism).
20 The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are included within the scope of the present invention. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

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25 As referred to above, individual enantiomers of compounds of formula (I) may be prepared. In a preferred embodiment, an optically pure enantiomer is desired. The term "optically pure enantiomer" means that the compound contains greater than about 90 % of the desired isomer by weight, preferably greater than about 95 % of the desired isomer by weight, and most preferably greater than about 99 % of the desired isomer by weight, said
30 weight percent based upon the total weight of the isomer(s) of the compound. In some cases, one enantiomer of a particular structure may have a significantly higher activity than the other enantiomer of the same structure. Chirally pure, or chirally enriched compounds may be prepared by chirally selective synthesis or by separation of enantiomers. The separation of enantiomers may be carried out on the final product or,
35 alternatively on a suitable intermediate.

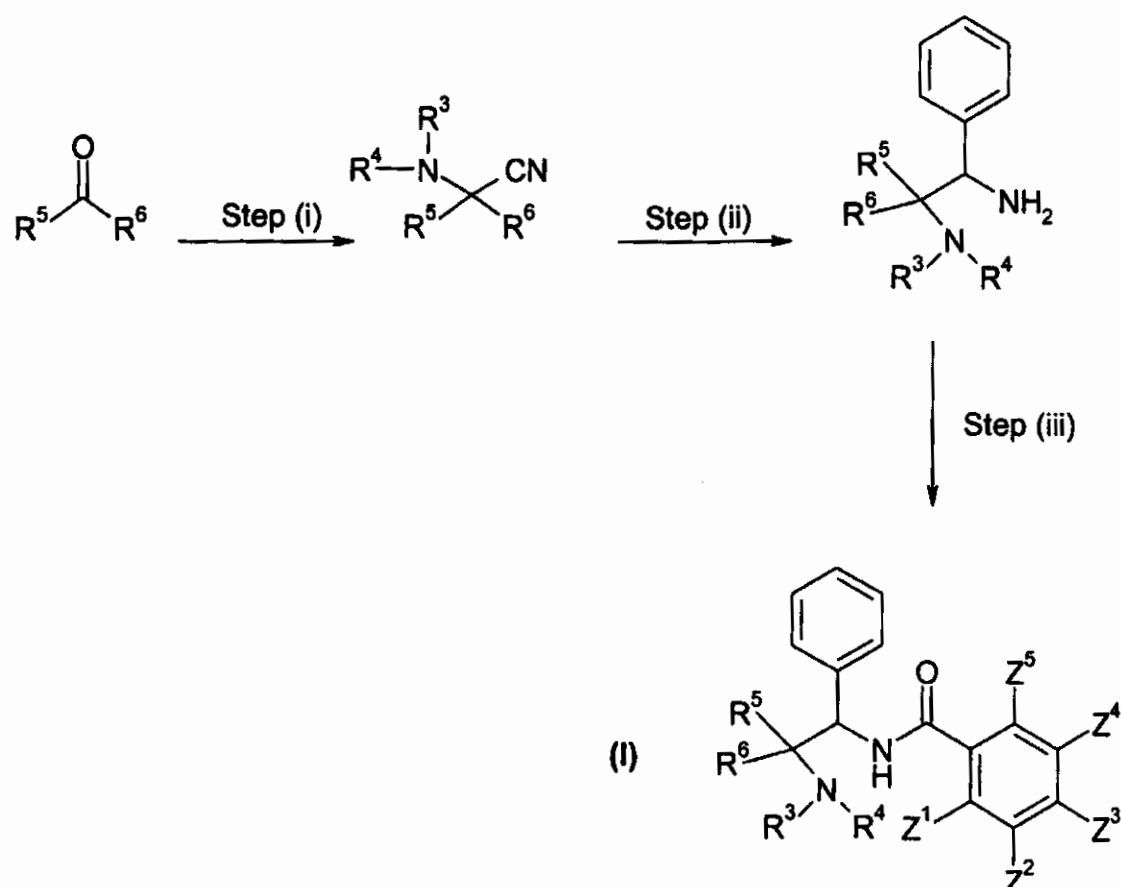
The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working
5 Examples.

Compounds of general formula (I) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthesis schemes. It is also recognised that in all of the schemes described below, it is well understood that protecting
10 groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts (1991) Protecting Groups in Organic Synthesis, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled
15 in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formula (I). Those skilled in the art will recognise if a stereocentre exists in compounds of formula (I). Accordingly, the present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well. Where the
20 stereochemistry is indicated as being variable at certain positions, a mixture of stereoisomers may be obtained, this mixture having been separated where indicated. Stereoisomers may be separated by high-performance liquid chromatography or other appropriate means. When a compound is desired as a single enantiomer, it may be
C obtained by stereospecific synthesis or by resolution of the final product or any convenient
25 intermediate. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Organic Compounds by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

30 Typical reaction routes for the preparation of a compound of formula (I) as hereinbefore defined, are shown in the following schemes. The starting materials and reagents are known to the skilled person in the art and/or can be prepared using methods known in the art.

35 Compounds of formula (I) can be synthesised by known methods; for example by, but not limited to, the synthetic route outlined in the scheme below

Scheme 1

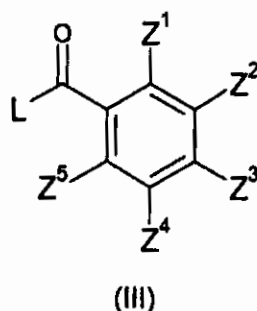


- 5 wherein $R^3, R^4, R^5, R^6, Z^1, Z^2, Z^3, Z^4$ and Z^5 are as defined for the compound of formula (I).

Step (i) is carried out for example by reaction of a ketone with an amine or amine salt in the presence of inorganic cyanide, for example potassium cyanide, in solvent such as water or by reaction of a ketone with an amine and trimethylsilyl cyanide in either the absence of solvent or in a solvent such as acetic acid.

Step (ii) can be achieved by successive reaction with an appropriate organometallic reagent, for example phenyllithium, in a suitable inert solvent for example tetrahydrofuran, followed by reduction with a reducing agent, for example, sodium borohydride in a suitable solvent, for example methanol.

Acylation step (iii) can be achieved by reaction with a compound of formula (III):



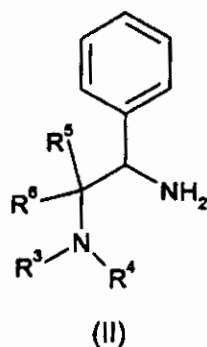
- 5 wherein Z^1 , Z^2 , Z^3 , Z^4 and Z^5 are as defined in formula (I) and L represents a suitable leaving group. Examples of leaving groups include halogen, hydroxy, $OC(=O)alkyl$, $OC(=O)O-alkyl$ and OSO_2Me . L may be halogen and acylation in step (iii) may be carried out in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine. When L represents hydroxy, the reaction preferably takes place in an inert solvent such as dichloromethane in the presence of a coupling reagent, for example a diimide reagent such as N,N dicyclohexylcarbodiimide (DCC), N-(3-(dimethylamino)propyl)-N-ethylcarbodiimide hydrochloride (EDC), polymer-supported EDC, polymer-supported DCC or O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoro phosphate (HATU).

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Within the scheme there is scope to convert a group R^3 into another group R^3 and similarly for groups R^4 , R^5 and R^6 , and Z^1 , Z^2 , Z^3 , Z^4 and Z^5 .

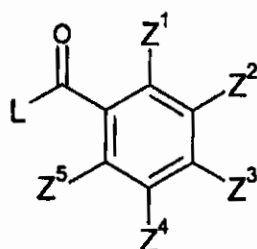
- 20 Accordingly, in a second aspect, the present invention provides a method of preparing a compound of formula (I), comprising the step of:

reacting a compound of formula (II):



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wherein R^3 , R^4 , R^5 and R^6 are as defined in formula (I), with a compound of formula (III):



(III)

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wherein Z^1 , Z^2 , Z^3 , Z^4 and Z^5 are as defined in formula (I) and L represents a suitable leaving group;

and thereafter optionally:

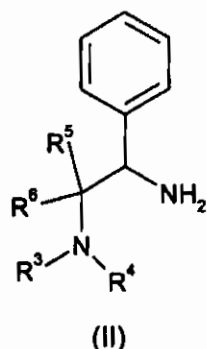
- 10
- removing any protecting groups and/or
 - converting a compound of formula (I) into another compound of formula (I) and/or
 - forming a salt or solvate.

15 Suitable leaving groups L include halogen, hydroxy, $OC(=O)alkyl$, $OC(=O)O-alkyl$ and OSO_2Me .

20 Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. For example, and by way of illustration rather than limitation, possible conversion reactions include acylation with an appropriate acylating agent such as acetyl chloride, alkylation using an appropriate alkylating reagent such as methyl iodide, and sulfonylation using a sulfonylating agent such as methanesulfonic anhydride and N-alkylation by reductive amination using a ketone or an aldehyde in the presence of a reducing agent such as sodiumtriacetoxymethylborohydride.

25 Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

In a further aspect, the present invention provides a compound of formula (II):



wherein R^3 , R^4 , R^5 and R^6 are as defined in formula (I), with the proviso that the compound of formula (II) is not the compound wherein simultaneously R^3 and R^4 together with the nitrogen atom to which they are attached form an unsubstituted piperidine ring and R^5 and R^6 together with the carbon atom to which they are attached form an unsubstituted cyclopentyl ring.

Compounds of formula (II) are useful as intermediates in the synthesis of compounds of the invention.

The compounds of the present invention inhibit the GlyT1 transporter. The compounds may selectively inhibit the GlyT1 transporter over the GlyT2 transporter.

Such compounds would be suitable for the treatment of certain neurological and neuropsychiatric disorders. As used herein, the terms "treatment" and "treating" refer to the alleviation and/or cure of established symptoms as well as prophylaxis.

The affinities of the compounds of this invention for the GlyT1 transporter can be determined by the following assay:

HEK293 cells expressing the Glycine (Type 1) transporter were grown in cell culture medium [DMEM/NUT mix F12 containing 2mM L-Glutamine, 0.8mg/mL G418 and 10% heat inactivated fetal calf serum] at 37°C and 5% CO₂. Cells grown to 70-80% confluency in T175 flasks were harvested and resuspended at 1.32×10^8 cells/mL in assay buffer [140mM NaCl, 5.4mM KCl, 1.8mM CaCl₂, 0.8mM MgSO₄, 20mM HEPES, 5mM glucose and 5mM alanine, pH 7.4]. Compounds were serially diluted 2.5-fold in DMSO from a top concentration of 2.5mM with each compound giving a 11 data point dose-response. 100nL of compound at each concentration was added to the assay plate. An equal

volume of Leadseeker™ WGA SPA beads (12.5mg/ml suspended in assay buffer) was added to the cell suspension (1.32×10^6) and 5 μ L of the cell/bead suspension transferred to each well of a 384-well white solid bottom plate (3300 cells/well) containing 100nL of test compounds. Substrate (5 μ L) was added to each well [1:100 dilution of [3 H]-glycine stock in assay buffer containing 2.5 μ M glycine). Final DMSO concentration was 1% v/v. Data was collected using a Perkin Elmer Viewlux. pIC₅₀ values were determined using ActivityBase.

The following assay may also be used:

HEK293 cells expressing the Glycine (Type 1) transporter are grown in cell medium (DMEM/NUT mix F12) containing 2 mM L-Glutamine, 0.8 mg/mL G418 and 10% heat inactivated fetal calf serum (Gibco BRL) at 37°C in 5% CO₂. Cells grown to 70-80% confluency in T175 flasks are harvested and resuspended at 4×10^5 cells/ml in assay buffer [NaCl (140 mM), KCl (5.4 mM), CaCl₂ (1.8 mM), MgSO₄ (0.8 mM), HEPES (20mM), glucose (5 mM) and alanine (5 mM), pH 7.4]. An equal volume of Leadseeker™ SPA beads (12.5mg/ml suspended in assay buffer) is added to the cell suspension. Compounds are prepared as 10mM stocks in DMSO. 2.5 fold serial dilutions of the compounds are made in DMSO from a top conc of 2.5 mM. 100 nL of compound at each concentration is added to the assay plate (384-well white solid bottom plate) using the hummingbird dispenser. 5 μ L of the cell/bead mix is then added on top of the compound using a multidrop dispenser. Substrate (5 μ L) is then added to each well (1:100 dilution of H³-glycine in assay buffer containing 2.5 μ M glycine) Data is collected using a PerkinElmer Viewlux as 5 minute exposures. pIC₅₀ data values are determined using Activity Base.

25

Compounds may be assayed in their free base form or in the form of a salt, for example the hydrochloride salt or the formate salt. The assays described above are generally considered to provide data that is correct to ± 3 standard deviations = ± 0.5 .

Compounds having a pIC₅₀ at the GlyT1 transporter of greater than or equal to 5.0 are considered to be active at the GlyT1 transporter. The example compounds below were found to have a pIC₅₀ at the GlyT1 transporter of greater than or equal to 5.0.

Accordingly, in a further aspect of the invention, there is provided a compound of formula (I) or a salt or solvate thereof: for use in therapy.

In another aspect of the invention, there is provided a compound of formula (I) as hereinbefore described or a salt or solvate thereof, for use in the treatment of a disorder mediated by GlyT1.

- 5 As used herein, the term "a disorder mediated by GlyT1" refers to a disorder that may be treated by the administration of a medicament that alters the activity of the GlyT1 transporter. As hereinbefore described, the action of GlyT1 transporters affects the local concentration of glycine around NMDA receptors. As a certain amount of glycine is needed for the efficient functioning of NMDA receptors, any change to that local concentration can affect NMDA-mediated neurotransmission. As hereinbefore described, changes in NMDA-mediated neurotransmission have been implicated in certain neuropsychiatric disorders such as dementia, depression and psychoses, for example schizophrenia, and learning and memory disorders, for example attention deficit disorders and autism. Thus, alterations in the activity of the GlyT1 transporter are expected to influence such disorders.

- The disorders mediated by GlyT1 referred to herein include neurological and neuropsychiatric disorders, including psychoses such as schizophrenia, dementia and other forms of impaired cognition such as attention deficit disorders and organic brain syndromes. Other neuropsychiatric disorders include drug-induced (phencyclidine, ketamine and other dissociative anesthetics, amphetamine and other psychostimulants and cocaine) psychosis, psychosis associated with affective disorders, brief reactive psychosis, schizoaffective psychosis, and psychosis NOS, "schizophrenia-spectrum" disorders such as schizoid or schizotypal personality disorders, or illness associated with psychosis (such as major depression, manic depressive (bipolar) disorder, Alzheimer's disease and post-traumatic stress syndrome), and NMDA receptor-related disorders such as autism, depression, benign forgetfulness, childhood learning disorders and closed head injury.

- 30 The compounds of formula (I) are of use as antipsychotic agents for example in the treatment of schizophrenia, schizo-affective disorders, schizophreniform diseases, psychotic depression, mania, acute mania, paranoid and delusional disorders.

- Within the context of the present invention, the terms used herein are classified in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM-IV) and/or the International Classification of

Diseases, 10th Edition (ICD-10). The various subtypes of the disorders mentioned herein are contemplated as part of the present invention. Numbers in brackets after the listed diseases below refer to the classification code in DSM-IV.

- 5 In particular, the compounds of formula (I) are of use in the treatment of schizophrenia including the subtypes Paranoid Type (295.30), Disorganised Type (295.10), Catatonic Type (295.20), Undifferentiated Type (295.90) and Residual Type (295.60); Schizophreniform Disorder (295.40); Schizoaffective Disorder (295.70) including the subtypes Bipolar Type and Depressive Type; Delusional Disorder (297.1) including the
10 subtypes Erotomanic Type, Grandiose Type, Jealous Type, Persecutory Type, Somatic Type, Mixed Type and Unspecified Type; Brief Psychotic Disorder (298.8); Shared Psychotic Disorder (297.3); Psychotic Disorder Due to a General Medical Condition including the subtypes With Delusions and With Hallucinations; Substance-Induced Psychotic Disorder including the subtypes With Delusions (293.81) and With
15 Hallucinations (293.82); and Psychotic Disorder Not Otherwise Specified (298.9).

- The compounds of formula (I) are also of use in the treatment of mood disorders including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode; Depressive Disorders including Major Depressive Disorder, Dysthymic Disorder (300.4),
20 Depressive Disorder Not Otherwise Specified (311); Bipolar Disorders including Bipolar I Disorder, Bipolar II Disorder (Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80); Other Mood Disorders including Mood Disorder Due to a General
C Medical Condition (293.83) which includes the subtypes With Depressive Features, With
25 Major Depressive-like Episode, With Manic Features and With Mixed Features), Substance-Induced Mood Disorder (including the subtypes With Depressive Features, With Manic Features and With Mixed Features) and Mood Disorder Not Otherwise Specified (296.90).

- 30 The compounds of formula (I) are also of use in the treatment of anxiety disorders including Panic Attack, Agoraphobia, Panic Disorder, Agoraphobia Without History of Panic Disorder (300.22), Specific Phobia (300.29) including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type), Social Phobia (300.23), Obsessive-Compulsive Disorder (300.3), Posttraumatic Stress
35 Disorder (309.81), Acute Stress Disorder (308.3), Generalized Anxiety Disorder (300.02),

Anxiety Disorder Due to a General Medical Condition (293.84), Substance-Induced Anxiety Disorder and Anxiety Disorder Not Otherwise Specified (300.00).

The compounds of formula (I) are also of use in the treatment of substance-related disorders including Substance Use Disorders such as Substance Dependence and Substance Abuse; Substance-Induced Disorders such as Substance Intoxication, Substance Withdrawal, Substance-Induced Delirium, Substance-Induced Persisting Dementia, Substance-Induced Persisting Amnesic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Mood Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders such as Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnesic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9); Amphetamine (or Amphetamine-Like)-Related Disorders such as Amphetamine Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication (292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and Amphetamine-Related Disorder Not Otherwise Specified (292.9); Caffeine Related Disorders such as Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9); Cannabis-Related Disorders such as Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9); Cocaine-Related Disorders such as Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9); Hallucinogen-Related Disorders such as Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30), Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (Flashbacks) (292.89),

Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9); Inhalant-Related Disorders such as Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium, Inhalant-Induced Persisting Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9); Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9);

10 Opioid-Related Disorders such as Opioid Dependence (304.00), Opioid Abuse (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9); Phencyclidine (or Phencyclidine-Like)-Related Disorders

15 such as Phencyclidine Dependence (304.60), Phencyclidine Abuse (305.90), Phencyclidine Intoxication (292.89), Phencyclidine Intoxication Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders such as Sedative, Hypnotic,

20 or Anxiolytic Dependence (304.10), Sedative, Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic- Persisting Amnesic Disorder, Sedative-,

C 25 Hypnotic-, or Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder and Sedative-, Hypnotic-, or Anxiolytic-Related Disorder Not Otherwise Specified (292.9); Polysubstance-Related Disorder such as

30 Polysubstance Dependence (304.80); and Other (or Unknown) Substance-Related Disorders such as Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide.

The compounds of formula (I) are also of use in the treatment of sleep disorders including primary sleep disorders such as Dyssomnias such as Primary Insomnia (307.42), Primary

35 Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified

- (307.47); primary sleep disorders such as Parasomnias such as Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47); Sleep Disorders Related to Another Mental Disorder such as Insomnia Related to Another Mental Disorder (307.42) and
- 5 Hypersomnia Related to Another Mental Disorder (307.44); Sleep Disorder Due to a General Medical Condition; and Substance-Induced Sleep Disorder including the subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type.

- The compounds of formula (I) are also of use in the treatment of eating disorders such as
- 10 Anorexia Nervosa (307.1) including the subtypes Restricting Type and Binge-Eating/Purging Type; Bulimia Nervosa (307.51) including the subtypes Purging Type and Nonpurging Type; Obesity; Compulsive Eating Disorder; and Eating Disorder Not Otherwise Specified (307.50).

- 15 The compounds of formula (I) are also of use in the treatment of Autistic Disorder (299.00); Attention-Deficit /Hyperactivity Disorder including the subtypes Attention-Deficit /Hyperactivity Disorder Combined Type (314.01), Attention-Deficit /Hyperactivity Disorder Predominantly Inattentive Type (314.00), Attention-Deficit /Hyperactivity Disorder Hyperactive-Impulse Type (314.01) and Attention-Deficit /Hyperactivity Disorder Not
- 20 Otherwise Specified (314.9); Hyperkinetic Disorder; Disruptive Behaviour Disorders such as Conduct Disorder including the subtypes childhood-onset type (321.81), Adolescent-Onset Type (312.82) and Unspecified Onset (312.89), Oppositional Defiant Disorder (313.81) and Disruptive Behaviour Disorder Not Otherwise Specified; and Tic Disorders such as Tourette's Disorder (307.23).

25

- The compounds of formula (I) are also of use in the treatment of Personality Disorders including the subtypes Paranoid Personality Disorder (301.0), Schizoid Personality Disorder (301.20), Schizotypal Personality Disorder (301.22), Antisocial Personality Disorder (301.7), Borderline Personality Disorder (301.83), Histrionic Personality Disorder
- 30 (301.50), Narcissistic Personality Disorder (301.81), Avoidant Personality Disorder (301.82), Dependent Personality Disorder (301.6), Obsessive-Compulsive Personality Disorder (301.4) and Personality Disorder Not Otherwise Specified (301.9).

- The compounds of Formula (I) are also of use in the enhancement of cognition including
- 35 the treatment of cognition impairment in other diseases such as schizophrenia, bipolar disorder, depression, other psychiatric disorders and psychotic conditions associated with

cognitive impairment. Within the context of the present invention, the term cognitive impairment includes for example the treatment of impairment of cognitive functions including attention, orientation, learning disorders, memory (i.e. memory disorders, amnesia, amnesic disorders, transient global amnesia syndrome and age-associated memory impairment) and language function; cognitive impairment as a result of stroke, Alzheimer's disease, Huntington's disease, Pick disease, Aids-related dementia or other dementia states such as Multiinfarct dementia, alcoholic dementia, hypotiriodism-related dementia, and dementia associated to other degenerative disorders such as cerebellar atrophy and amyotrophic lateral sclerosis; other acute or sub-acute conditions that may cause cognitive decline such as delirium or depression (pseudodementia states) trauma, head trauma, age related cognitive decline, stroke, neurodegeneration, drug-induced states, neurotoxic agents, mild cognitive impairment, age related cognitive impairment, autism related cognitive impairment, Down's syndrome, cognitive deficit related to psychosis, and post-electroconvulsive treatment related cognitive disorders; and dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism, and tardive dyskinesias.

The compounds of formula (I) are also of use in the treatment of sexual dysfunctions including Sexual Desire Disorders such as Hypoactive Sexual Desire Disorder (302.71), and Sexual Aversion Disorder (302.79); sexual arousal disorders such as Female Sexual Arousal Disorder (302.72) and Male Erectile Disorder (302.72); orgasmic disorders such as Female Orgasmic Disorder (302.73), Male Orgasmic Disorder (302.74) and Premature Ejaculation (302.75); sexual pain disorder such as Dyspareunia (302.76) and Vaginismus (306.51); Sexual Dysfunction Not Otherwise Specified (302.70); paraphilias such as Exhibitionism (302.4), Fetishism (302.81), Frotteurism (302.89), Pedophilia (302.2), Sexual Masochism (302.83), Sexual Sadism (302.84), Transvestic Fetishism (302.3), Voyeurism (302.82) and Paraphilia Not Otherwise Specified (302.9); gender identity disorders such as Gender Identity Disorder in Children (302.6) and Gender Identity Disorder in Adolescents or Adults (302.85); and Sexual Disorder Not Otherwise Specified (302.9).

The invention also provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of schizophrenia, mood disorders, anxiety disorders, substance-related disorders, sleep disorders, eating disorders, autistic disorder, attention-deficit/hyperactivity disorder, disruptive behaviour disorder, tic disorders, personality disorders, cognition impairment in

other diseases, sexual dysfunction, Parkinson's disease, dyskinetic disorders, depression, bipolar disorder, cognitive impairment, obesity, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, vertigo, dementia and circadian rhythm disorders.

5

The invention also provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of psychotic disorders, substance abuse, cognitive impairment, obesity, and gastric motility disorders.

10 In another aspect of the invention, there is provided a method of treating a mammal, including a human, suffering from or susceptible to a disorder mediated by GlyT1, which comprises administering an effective amount of a compound of formula (I) as hereinbefore defined or a salt or solvate thereof.

15 The invention also provides a method of treating schizophrenia, mood disorders, anxiety disorders, substance-related disorders, sleep disorders, eating disorders, autistic disorder, attention-deficit/hyperactivity disorder, disruptive behaviour disorder, tic disorders, personality disorders, cognition impairment in other diseases, sexual dysfunction, Parkinson's disease, dyskinetic disorders, depression, bipolar disorder, cognitive
20 impairment, obesity, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, vertigo, dementia and circadian rhythm disorders which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof.

25 The invention also provides a method of treating psychotic disorders, substance abuse, cognitive impairment, obesity and gastric motility disorders which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof.

30 The compounds of formula (I) are also of use as anticonvulsants. The compounds of formula (I) are thus useful in the treatment of convulsions in mammals, and particularly epilepsy in humans. "Epilepsy" is intended to include the following seizures: simple partial seizures, complex partial seizures, secondary generalised seizures, generalised seizures including absence seizures, myoclonic seizures, clonic seizures, tonic seizures, tonic
35 clonic seizures and atonic seizures. The invention also provides a method of treating convulsions, which comprises administering to a mammal in need thereof an effective

amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof. Treatment of epilepsy may be carried out by the administration of a non-toxic anticonvulsant effective amount of a compound of the formula (III) or a pharmaceutically acceptable salt, or a composition as hereinbefore defined.

The compounds of formula (I) also find use in the treatment of neuropathic pain, for example in diabetic neuropathy, sciatica, non-specific lower back pain, multiple sclerosis pain, fibromyalgia, HIV-related neuropathy, neuralgia such as post-herpetic neuralgia and trigeminal neuralgia and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions.

In another aspect of the invention, there is provided use of a compound of formula (I) as hereinbefore defined or a salt or solvate thereof in the preparation of a medicament for the treatment of a disorder mediated by GlyT1.

Preferably, the disorder mediated by GlyT1 to be treated by the use or method as hereinbefore described is a psychosis, including schizophrenia, dementia and attention deficit disorders, particularly schizophrenia.

The invention also provides the use of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of schizophrenia, mood disorders, anxiety disorders, substance-related disorders, sleep disorders, eating disorders, autistic disorder, attention-deficit/hyperactivity disorder, disruptive behaviour disorder, tic disorders, personality disorders, cognition impairment in other diseases, sexual dysfunction, Parkinson's disease, dyskinetic disorders, depression, bipolar disorder, cognitive impairment, obesity, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, vertigo, dementia and circadian rhythm disorders.

The invention also provides the use of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of psychotic disorders, substance abuse, cognitive impairment, obesity and gastric motility disorders.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician.

- 5 Compounds for use according to the invention may be administered as the raw material but the active ingredients are preferably provided in the form of pharmaceutical compositions.

10 Accordingly, in a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) as hereinbefore described or a salt or solvate thereof, and at least one pharmaceutically acceptable carrier, diluent or excipient.

These pharmaceutical compositions may be used in the treatment of clinical conditions for which a GlyT1 inhibitor is indicated such as, for example, schizophrenia. The carrier must
15 be pharmaceutically acceptable to the recipient and must be compatible with, i.e. not have a deleterious effect upon, the other ingredients in the composition. The carrier may be a solid or a liquid and is preferably formulated with at least one compound of formula (I) or a salt or solvate thereof as a unit dose formulation. If desired, other physiologically active ingredients may also be incorporated in the pharmaceutical compositions of the invention.

20

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents such as 5HT3 antagonists, serotonin agonists, NK-1 antagonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline
C re-uptake inhibitors (SNRI), tricyclic antidepressants, dopaminergic antidepressants, H3
25 antagonists, 5HT1A antagonists, 5HT1B antagonists, 5HT1D antagonists, D1 agonists, M1 agonists and/or anticonvulsant agents, as well as atypical antipsychotic drugs and cognitive enhancers.

- 30 Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

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Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

- 5 Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptyline, clomipramine and nortriptyline.

10

○ Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

- 15 Suitable anticonvulsant agents which may be used in combination of the compounds of the invention include for example divalproex, carbamazepine and diazepam.

Suitable atypical antipsychotic drugs which may be used in combination of the compounds of the invention include for example risperidone, olanzapine, ziprasidone, aripiprazole and clozapine.

20

It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

- 25 The compounds of formula (I) and their pharmaceutically acceptable salts and solvates thereof are also suitable for combination with other typical and atypical antipsychotics to provide improved treatment of psychotic disorders. Particular advantages associated with the combinations, uses and methods of treatment of compounds of formula (I) and their pharmaceutically acceptable salts and solvates thereof include equivalent or improved
30 efficacy at doses of administration which are lower than those commonly used for the individual components. Improved treatments of positive symptoms and/or negative symptoms and/or cognitive symptoms of the psychotic disorder may also be observed. The combinations, uses and methods of treatment of the invention may also provide advantages in treatment of patients who fail to respond adequately or who are resistant to
35 treatment with certain neuroleptic agents.

The combination therapies of the invention are preferably administered adjunctively. By adjunctive administration is meant the coterminous or overlapping administration of each of the components in the form of separate pharmaceutical compositions or devices. This regime of therapeutic administration of two or more therapeutic agents is referred to generally by those skilled in the art and herein as adjunctive therapeutic administration; it is also known as add-on therapeutic administration. Any and all treatment regimes in which a patient receives separate but coterminous or overlapping therapeutic administration of the compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one neuroleptic agent are within the scope of the current invention. In one embodiment of adjunctive therapeutic administration as described herein, a patient is typically stabilised on a therapeutic administration of one or more of the components for a period of time and then receives administration of another component. Within the scope of this invention, it is preferred that the compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof is administered as adjunctive therapeutic treatment to patients who are receiving administration of at least one neuroleptic agent, but the scope of the invention also includes the adjunctive therapeutic administration of at least one neuroleptic agent to patients who are receiving administration of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The combination therapies of the invention may also be administered simultaneously. By simultaneous administration is meant a treatment regime wherein the individual components are administered together, either in the form of a single pharmaceutical composition or device comprising or containing both components, or as separate compositions or devices, each comprising one of the components, administered simultaneously. Such combinations of the separate individual components for simultaneous combination may be provided in the form of a kit-of-parts.

In a further aspect therefore, the invention provides a method of treatment of a psychotic disorder by adjunctive therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof to a patient receiving therapeutic administration of at least one neuroleptic agent. In a further aspect, the invention provides the use of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of at least one neuroleptic agent. The invention further provides

compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of at least one neuroleptic agent.

- 5 In a further aspect, the invention provides a method of treatment of a psychotic disorder by adjunctive therapeutic administration of at least one neuroleptic agent to a patient receiving therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof. In a further aspect, the invention provides the use of at least one neuroleptic agent in the manufacture of a medicament for adjunctive
10 therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof. The invention further provides at least one neuroleptic agent for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of compounds of formula (I) or a pharmaceutically
15 acceptable salt or solvate thereof.

- In a further aspect, the invention provides a method of treatment of a psychotic disorder by simultaneous therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof in combination with at least one
20 neuroleptic agent. The invention further provides the use of a combination of compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one neuroleptic agent in the manufacture of a medicament for simultaneous therapeutic administration in the treatment of a psychotic disorder. The invention further provides the use of compounds of formula (I) or a pharmaceutically acceptable salt thereof in the
25 manufacture of a medicament for simultaneous therapeutic administration with at least one neuroleptic agent in the treatment of a psychotic disorder. The invention further provides compounds of formula (I) or a pharmaceutically acceptable salt thereof for use for simultaneous therapeutic administration with at least one neuroleptic agent in the treatment of a psychotic disorder. The invention further provides the use of at least one
30 neuroleptic agent in the manufacture of a medicament for simultaneous therapeutic administration with compounds of formula (I) or a pharmaceutically acceptable salt thereof in the treatment of a psychotic disorder.

- In further aspects, the invention provides a method of treatment of a psychotic disorder
35 by simultaneous therapeutic administration of a pharmaceutical composition comprising compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at

least one mood stabilising or antimanic agent, a pharmaceutical composition comprising compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one mood stabilising or antimanic agent, the use of a pharmaceutical composition comprising compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one mood stabilising or antimanic agent in the manufacture of a medicament for the treatment of a psychotic disorder, and a pharmaceutical composition comprising compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one mood stabilising or antimanic agent for use in the treatment of a psychotic disorder.

10

In a further aspect, the invention provides a kit-of-parts for use in the treatment of a psychotic disorder comprising a first dosage form comprising compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof and one or more further dosage forms each comprising a neuroleptic agent for simultaneous therapeutic administration.

15

Within the context of the present invention, the term psychiatric disorder includes those disorders mentioned above, such as schizophrenia, mood disorders, anxiety disorders, substance-related disorders, sleep disorders, eating disorders, autistic disorder, attention-deficit/hyperactivity disorder, disruptive behaviour disorder, tic disorders, personality disorders, cognition impairment in other diseases, sexual dysfunction, dyskinetic disorders, depression, bipolar disorder, cognitive impairment and obsessive-compulsive disorders and all the various forms of the disorders as mentioned herein. which are contemplated as part of the present invention.

25

Examples of neuroleptic/antipsychotic drugs that are useful in the present invention include, but are not limited to: butyrophenones, such as haloperidol, pimozide, and droperidol; phenothiazines, such as chlorpromazine, thioridazine, mesoridazine, trifluoperazine, perphenazine, fluphenazine, thiflupromazine, prochlorperazine, and acetophenazine; thioxanthenes, such as thiothixene and chlorprothixene ; thienobenzodiazepines; dibenzodiazepines; benzisoxazoles; dibenzothiazepines; imidazolidinones ; benzisothiazolyl-piperazines; triazine such as lamotrigine; dibenzoxazepines, such as loxapine; dihydroindolones, such as molindone; aripiprazole; and derivatives thereof that have antipsychotic activity.

35

Examples of neuroleptic drugs that are preferred for use in the present invention are shown in Table A.

Table A
Neuroleptic drugs

Common Name	Trade Name	Route of Administration	Form	Dosage Range and (Median) ^a
Clozapine	CLOZARIL	oral	tablets	12.5-900 mg/day (300-900 mg/day)
Olanzapine	ZYPREXA	oral	tablets	5-25 mg/day (10-25 mg/day)
Ziprasidone	GEODON	oral	capsules	20-80mg/twice a day (80-160 mg/day)
Risperidone	RISPERDAL	oral	solution tablets	2-16 mg/day tablets (4-12 mg/day)
Quetiapine fumarate	SEROQUEL	oral	tablets	50-900 mg/day (300-900 mg/day)
Sertindole	SERLECT			(4-24 mg/day)
Amisulpride				
Haloperidol	HALDOL	oral	tablets	1-100 mg/day (1-15 mg/day)
Haloperidol Decanoate	HALDOL Decanoate	parenteral	injection	
Haloperidol lactate	HALDOL INTENSOL	oral	solution	

Common Name	Trade Name	Route of Administration	Form	Dosage Range and (Median) ^a
		parenteral	injection	
Chlorpromazine	THORAZINE	rectal	suppositories	30-800 mg/day (200-500 mg/day)
		oral	capsules solution tablets	
		parenteral	injection	
Fluphenazine	PROLIXIN			0.5-40 mg/day (1-5 mg/day)
Fluphenazine decanoate	PROLIXIN Decanoate	parenteral	injection	(about one-half the dosage shown for oral)
Fluphenazine enanthate	PROLIXIN	parenteral	injection	(same as above)
Fluphenazine hydrochloride	PROLIXIN	oral	elixir solution	
		parenteral	injection	
Thiothixene	NAVANE	oral	capsules	6-60 mg/day (8-30 mg/day)
Thiothixene hydrochloride	NAVANE	oral	solution	
		parenteral	injection	
Trifluoperazine	STELAZINE			(2-40 mg/day)
Perphenazine	TRILAFON	oral	solution tablets	12-64 mg/day (16-64 mg/day)
		parenteral	injection	
Perphenazine and Amitriptyline hydrochloride	ETRAFON TRIAVIL	oral	tablets	
Thioridazine	MELLARIL	oral	suspension solution tablets	150-800 mg/day (100-300 mg/day)

Common Name	Trade Name	Route of Administration	Form	Dosage Range and (Median) ^a
Mesoridazine				(30-400 mg/day)
Molindone	MOBAN			50-225 mg/day (15-150 mg/day)
Molindone hydrochloride	MOBAN	oral	solution	
Loxapine	LOXITANE			20-250 mg/day (60-100 mg/day)
Loxapine hydrochloride	LOXITANE	oral	solution	
		parenteral	injection	
Loxapine succinate	LOXITANE	oral	capsules	
Pimozide				(1-10 mg/day)
Flupenthixol				
Promazine	SPARINE			
Triflupromazine	VESPRIN			
Chlorprothixene	TARACTAN			
Droperidol	INAPSINE			
Acetophenazine	TINDAL			
Prochlorperazine	COMPAZINE			
Methotrimeprazine	NOZINAN			
Pipotiazine	PIPOTRIL			

Common Name	Trade Name	Route of Administration	Form	Dosage Range and (Median) ^a
Aripiprazole				
Hoperidone				

Examples of tradenames and suppliers of selected neuroleptic drugs are as follows :

clozapine (available under the tradename CLOZARIL®, from Mylan, Zenith Goldline,

UDL, Novartis); olanzapine (available under the tradename ZYPREX®, from Lilly ;

5 ziprasidone (available under the tradename GEODON®, from Pfizer); risperidone (available under the tradename RISPERDAL®, from Janssen); quetiapine fumarate (available under the tradename SEROQUEL®, from AstraZeneca); haloperidol (available

under the tradename HALDOL®, from Ortho-McNeil); chlorpromazine (available under the

tradename THORAZINE®, from SmithKline Beecham (GSK); fluphenazine (available

10 under the tradename PROLIXIN®, from Apothecon, Copley, Schering, Teva, and American Pharmaceutical Partners, Pasadena); thiothixene (available under the

tradename NAVANE®, from Pfizer); trifluoperazine (10-[3-(4-methyl-1-piperazinyl)propyl]-

2-(trifluoromethyl)phenothiazine dihydrochloride, available under the tradename

STELAZINE®, from Smith Klein Beckman; perphenazine (available under the tradename

15 TRILAFON®, from Schering); thioridazine (available under the tradename MELLARIL®;

from Novartis, Roxane, HiTech, Teva, and Alparma) ; molindone (available under the

tradename MOBAN®, from Endo); and loxapine (available under the tradename

LOXITANE®, from Watson). Furthermore, benperidol (Glianimon®), perazine (Taxilan®)

or melperone (Eunerpan®)) may be used.

20

Other preferred neuroleptic drugs include promazine (available under the tradename

SPARINE®), trifluorpromazine (available under the tradename VESPRIN®),

chlorprothixene (available under the tradename TARACTAN®), droperidol (available

under the tradename INAPSINE®), acetophenazine (available under the tradename

25 TINDAL®), prochlorperazine (available under the tradename COMPAZINE®),

methotrimeprazine (available under the tradename NOZINAN®), pipotiazine (available

under the tradename PIPOTRIL®), ziprasidone, and hoperidone.

Particularly preferred neuroleptic agents for use in the invention are olanzapine, risperidone, quetiapine, aripiprazole, haloperidol, clozapine, ziprasidone and osanetant.

- 5 It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents such as 5HT3 antagonists, serotonin agonists, NK-1 antagonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants, dopaminergic antidepressants, H3
10 antagonists, 5HT1A antagonists, 5HT1B antagonists, 5HT1D antagonists, D1 agonists, M1 agonists and/or anticonvulsant agents, as well as atypical antipsychotic drugs and cognitive enhancers.

- Suitable 5HT3 antagonists which may be used in combination of the compounds of the
15 inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

- Suitable SSRIs which may be used in combination with the compounds of the invention
20 include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

- Suitable SNRIs which may be used in combination with the compounds of the invention
include venlafaxine and reboxetine.

25

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptyline, chlormipramine and nortriptyline.

- Suitable dopaminergic antidepressants which may be used in combination with a
30 compound of the invention include bupropion and amineptine.

Suitable anticonvulsant agents which may be used in combination of the compounds of the invention include for example divalproex, carbamazepine and diazepam.

Suitable atypical antipsychotic drugs which which may be used in combination of the compounds of the invention include for example risperidone, olanzapine, ziprasidone, aripiprazole and clozapine.

- 5 It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

10 For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) as hereinbefore described or a pharmaceutically (i.e. physiologically) acceptable salt thereof and a pharmaceutically (i.e. physiologically) acceptable carrier. The pharmaceutical composition can be for use in the treatment of any of the conditions described herein.

15

Possible formulations include those suitable for oral, sub-lingual, buccal, parenteral (for example, subcutaneous, intramuscular, or intravenous), rectal, topical and intranasal administration and in forms suitable for administration by inhalation or insufflation (either through the mouth or nose). The most suitable means of administration for a particular patient will depend on the nature and severity of the conditions being treated and on the nature of the active compound, but, where possible, oral administration is preferred.

20

Formulations suitable for oral administration may be provided as discrete units, such as tablets, capsules, cachets, or lozenges, each containing a predetermined amount of the active compound; as powders or granules; as solutions or suspensions in aqueous or non-aqueous liquids; or as oil-in-water or water-in-oil emulsions. For example, a compound of the invention may be prepared as a formulation with a controlled release profile. This may be in any of the above mentioned pharmaceutical forms. For example, it may be a gel formulation in a non aqueous oily vehicle, for example Miglyol, with a suitable gelling agent if required, for example methyl cellulose or hydrophobic colloidal silica.

25

30

Formulations suitable for sublingual or buccal administration include lozenges comprising the active compound and, typically, a flavoured base, such as sugar and acacia or tragacanth and pastilles comprising the active compound in an inert base, such as gelatin and glycerin or sucrose and acacia.

35

Formulations suitable for parenteral administration typically comprise sterile aqueous solutions containing a predetermined concentration of the active compound; the solution is preferably isotonic with the blood of the intended recipient. Although such solutions are preferably administered intravenously, they may also be administered by subcutaneous or intramuscular injection.

Formulations suitable for rectal administration are preferably provided as unit-dose suppositories comprising the active ingredient and one or more solid carriers forming the suppository base, for example, cocoa butter.

Formulations suitable for topical or intranasal application include ointments, creams, lotions, pastes, gels, sprays, aerosols and oils. Suitable carriers for such formulations include petroleum jelly, lanolin, polyethylene glycols, alcohols, and combinations thereof.

Formulations of compounds of the invention may, for example, be composed so as to improve the exposure profile of the compound of the invention.

Compositions suitable for transdermal administration include ointments, gels and patches. Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

The formulations of the invention may be prepared by any suitable method, typically by uniformly and intimately admixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions and then, if necessary, shaping the resulting mixture into the desired shape.

For example, a tablet may be prepared by compressing an intimate mixture comprising a powder or granules of the active ingredient and one or more optional ingredients, such as a binder, lubricant, inert diluent, or surface active dispersing agent, or by moulding an intimate mixture of powdered active ingredient and inert liquid diluent.

Aqueous solutions for parenteral administration are typically prepared by dissolving the active compound in sufficient water to give the desired concentration and then rendering the resulting solution sterile and isotonic.

It will be appreciated that the precise dose administered will depend on the age and condition of the patient and the frequency and route of administration and will be at the ultimate discretion of the attendant physician. The compound may be administered in single or divided doses and may be administered one or more times, for example 1 to 4 times per day.

A proposed dose of the active ingredient for use according to the invention for oral, sublingual, parenteral, buccal, rectal, intranasal or topical administration to a human (of approximately 70 kg bodyweight) for the treatment of neurological and neuropsychiatric disorders mediated by a GlyT1 inhibitor, including schizophrenia, may be about 1 to about 1000 mg, preferably about 5 to about 500 mg, more preferably about 10 to about 100 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Compounds of the invention may be used as PET ligands (for example labelled with carbon-11 or fluorine-18) or as SPECT ligands (for example labelled with iodine-123 or meta stable technetium-99) for *in vivo* visualisation and quantification of the GlyT1 transporter. For example, they may be used in PET or SPECT imaging of the brain. In the context of this patent, PET shall mean: positron emission tomography and SPECT (= SPET) shall mean: single photon emission (computed) tomography.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The invention is further illustrated by the following non-limiting examples.

Abbreviations:

THF	tetrahydrofuran
DCM	dichloromethane
DMF	dimethylformamide
HATU	O-(7-azabenzotriazol-1-yl) - N,N,N',N'-tetramethyluroniumhexafluorophosphate
EDC	N-(3-(dimethylamino)propyl)-N-ethylcarbodiimide hydrochloride
HOAt	3H-(1,2,3)-triazolo(4,5-b)pyridine-3-ol

NMP	N-methylpyrrolidinone
DIPEA	N,N-diisopropylethylamine
HOBt	1-hydroxybenzotriazole hydrate

5 Analytical LC/MS chromatography conditions:

Method A

Column: Waters Atlantis 50mm x 4.6mm, 3µm particle size

Mobile phase: A: 0.05% Formic acid + Water

B: Acetonitrile +0.05% Formic acid

10 Gradient: 5-min runtime: 3%B to 97%B over 4min

Flow rate: 3 ml/min

UV wavelength range: 220 -330 nm

Temperature: 30°C

15 Method B *

Column: Waters Atlantis 20mm x 4.6mm, 3µm particle size

Mobile phase: A: 0.1% Formic acid + Water

B: Acetonitrile +0.1% Formic acid

Gradient: 5.5-min runtime: 3%B to 97%B over 5.3min

20 Flow rate: 1 ml/min

UV wavelength range: 210 -350 nm

Temperature: Ambient

Mass Directed Auto-Purification System chromatography conditions:

25 Column: Waters Atlantis 19mm x 100mm or 30mm X 100mm, 5µm particle size

Mobile phase: A: 0.1% Formic acid + Water

B: Acetonitrile +0.1% Formic acid

30 Gradient: 13.5 min runtime with 10min gradient dependant on analytical retention time

Flow rate: 20 or 40 ml/min

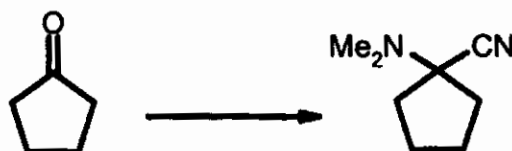
General:

35 Throughout the examples section, the following terminology is adopted with regard to chiral compounds: when a mixture of two enantiomers has been prepared, the compound is described as (±). When a single enantiomer (that is to say mixture chirally enriched in

one of the enantiomers) has been prepared, it is referred to as "chiral". The absolute stereochemistry has not been ascertained at the time of filing. Individual enantiomers of some materials prepared are identified by virtue of optical rotations and such materials are identified as the (+) or (-) enantiomers. Where optical rotation information is not yet available, individual enantiomers of the products are individually identifiable by virtue of the chiral HPLC characteristics of the amine intermediate.

Where reactions are described as having been carried out in a similar manner to earlier, more completely described reactions, the general reaction conditions used were essentially the same. Work up conditions used were of the types standard in the art, but may have been adapted from one reaction to another.

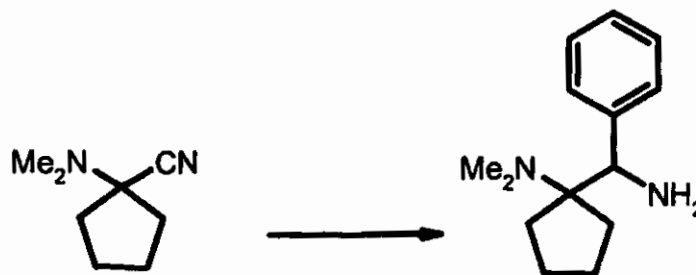
Description 1: 1-(Dimethylamino)cyclopentanecarbonitrile



To a suspension of dimethylamine hydrochloride (8.15g; 0.1mol) in cyclopentanone (8.4g; 0.1mol) cooled (ice bath) was added dropwise a solution of potassium cyanide (6.5g; 0.1mol) in water (50ml) over 10min. After vigorous stirring at room temperature for 18h, the crude reaction mixture was extracted three times with diethyl ether (3 x 200ml) and the combined extracts washed twice with water (2 x 50ml), dried (Na_2SO_4), and evaporated to afford the title product as a pale yellow oil (12.5g) which was used without further purification. ^1H NMR (CDCl_3) δ : 1.7 – 2.0 (6H, m), 2.15 – 2.3 (2H, m), 3.3 (6H, s). Mass Spectrum (Electrospray LC/MS): Found 112 ($\text{MH}^+ - \text{HCN}$). $\text{C}_8\text{H}_{14}\text{N}_2$ requires 138.

Alternative method:

To a stirred, ice cooled mixture of dimethylamine hydrochloride (26.32g; 0.323mol) and cyclopentanone (27.15g; 0.323mol) was added dropwise a solution of potassium cyanide (21.02g; 0.323mol) in water (170ml) over 10min. The mixture was stirred at room temperature overnight. Then, the mixture was extracted into diethylether (2 x 200ml) and the combined organics were washed with brine (200ml), dried (Na_2SO_4), and evaporated *in vacuo* to afford the title product as a colourless liquid (43g, 96.5%)

Description 2: ($\pm$){1-[Amino(phenyl)methyl]cyclopentyl}dimethylamine

To a solution of 1-(dimethylamino)cyclopentanecarbonitrile D1 (4g; 28.9mmol) in THF (30ml) at -70°C under argon was added dropwise a solution of phenyllithium in dibutylether (17.7ml of a 1.8M solution; 32mmol). The reaction mixture was allowed to warm to room temperature over 3h., recooled to 0°C and methanol added (30ml) followed by careful addition of sodium borohydride (3.3g; 87mmol). After stirring at room temperature for 18h, the reaction mixture was cooled to 0°C and saturated aqueous sodium bicarbonate added. The organic phase was evaporated and the resulting slurry extracted three times with DCM (3 x 150ml). The combined extracts were dried (Na_2SO_4), and evaporated to afford the crude product as a yellow oil (6.8g). Half of the crude product was chromatographed on silica gel eluting with DCM-methanol (9/1) and DCM-2M ammonia in methanol mixtures (95/5 to 9/1 to 8/2) to afford the title product as a colourless oil (2.3g). This oil was dissolved in diethyl ether (20ml) and hydrogen chloride in diethylether was added at 0°C . After 20min, the suspension was filtered to give the dihydrochloride salt (2.8g) of the title product as a white solid. ^1H NMR (DMSO) δ : 1.25 (2H, bs), 1.36 (2H, bs), 1.66 – 2.13 (4H, m), 2.64 (3H, s), 2.79 (3H, s), 4.92 (1H, bs), 7.32 (3H, m), 7.54 (2H, m), 8.95 (3H, bs), 10.82 (1H, bs).

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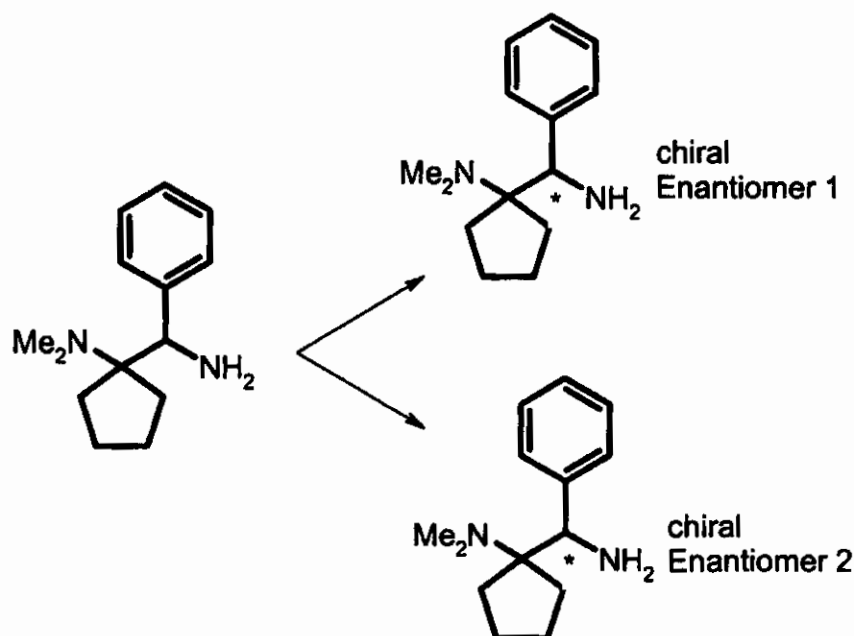
Alternative method:

To a solution of 1-(dimethylamino)cyclopentanecarbonitrile D1 (43g; 311mmol) in THF (1L) at -70°C under argon was added dropwise a solution of phenyllithium in dibutylether (346ml of a 1.8M solution; 622mmol) over 10 minutes. The reaction mixture was stirred at -70°C for 2h, then allowed to warm to room temperature and it was stirred overnight. The reaction mixture was cooled in ice and saturated aqueous sodium bicarbonate solution was added. The mixture was stirred for 30 minutes, separated and the aqueous layer extracted with diethyl ether. The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to give an oil.

25

The oil was dissolved in methanol (1.2L) and cooled in ice. Sodium borohydride (20g) was added in 4 portions over 5 minutes and the mixture was stirred for half an hour with ice cooling. The cooling was then removed and stirring was continued at room temperature for one and a half hours. The reaction mixture was then ice cooled and water was added. The resultant mixture was evaporated *in vacuo* and fractioned between 2N HCl and ethyl acetate. The organics were extracted with 2N HCl. The combined acid extracts were washed with ethyl acetate, basified with NaOH and extracted into DCM. The combined DCM extracts were dried (Na_2SO_4), and evaporated *in vacuo* to afford the product as a pale green liquid (64.66g, 95.4%).

Description 3: {1-[Amino(phenyl)methyl]cyclopentyl}dimethylamine Enantiomer 1 and Enantiomer 2



Method 1.

Racemic {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D2 (0.6g; 2.75mmol) was separated by semi-preparative chiral HPLC using the conditions described below to afford the title products, enantiomer 1, (0.27g); Chiral HPLC: 98% ee; ^1H NMR (CDCl_3) δ : 0.42 (1H, m), 1.32 (3H, m), 1.49 (1H, m), 1.63 (1H, m), 1.76 (1H, m), 1.95 (3H, m), 2.29 (6H, s), 4.39 (1H, s), 7.28 (3H, m), 7.50 (2H, d); Mass spectrum (Electrospray LC/MS): Found 219 (MH^+). $\text{C}_{14}\text{H}_{22}\text{N}_2$ requires 218; and enantiomer 2 (0.28g); Chiral HPLC: 98% ee; ^1H

NMR (CDCl₃) δ : 0.42 (1H, m), 1.32 (3H, m), 1.49 (1H, m), 1.63 (1H, m), 1.76 (1H, m), 1.95 (3H, m), 2.29 (6H, s), 4.39 (1H, s), 7.28 (3H, m), 7.50 (2H, d); Mass spectrum (Electrospray LC/MS): Found 219 (MH⁺). C₁₄H₂₂N₂ requires 218.

5 Semi-preparative HPLC conditions:

Column: Chiralpak AD-H 5 μ m, 250 x 21mm
 Mobile phase: A: n-Hexane; B: Ethanol + 0.1% isopropylamine
 Gradient: isocratic 5%B
 Flow rate: 7ml/min
 10 UV wavelength range: 225nm
 Elution time: 30min

Analytical chromatography conditions:

Column: chiralpak AD-H 5 μ m, 250 x 4.6 mm
 15 Mobile phase: A: n-Hexane; B: Ethanol + 0.1% isopropyl amine
 Gradient: isocratic 5% B
 Flow rate: 1 ml/min
 UV wavelength range: 200-400 nm
 Analysis time: 10 min
 20 Ret. Time: 5.9min (Enantiomer 1); 7.6min (Enantiomer 2)

Method 2.

Salt formation:

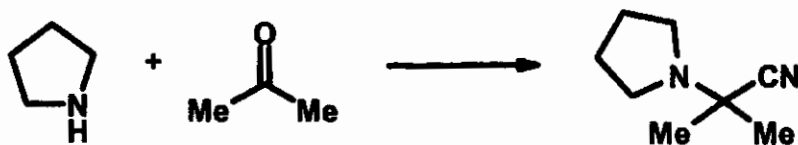
To a solution of racemic {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D2 (16.9g; 77.5mmol) in isopropanol (170ml) at 50 °C, was added dropwise a solution of (R)-methoxy phenylacetic acid (12.84g; 77.5mmol) in isopropanol (75ml). After 20 min the mixture was cooled to room temperature and left stirring for a further 4h. The precipitated solid was collected by filtration (13.42g).

30 Regeneration of chiral free base:

The solid was then treated with 1M NaOH (50ml) and DCM (167ml). The phases were separated and the aqueous phase washed with DCM (4x167ml). The combined organic phases were washed with 1M NaOH (2x35ml), then brine (100ml), dried (Na₂SO₄), and concentrated to yield the title compound, enantiomer 2, as a colourless oil (7.6g). Chiral
 35 HPLC: >96% ee; ¹H NMR (CDCl₃) δ : 0.42 (1H, m), 1.32 (3H, m), 1.49 (1H, m), 1.63 (1H,

m), 1.76 (1H, m), 1.95 (3H, m), 2.29 (6H, s), 4.39 (1H, s), 7.28 (3H, m), 7.50 (2H, d); Mass spectrum (Electrospray LC/MS): Found 219 (MH⁺). C₁₄H₂₂N₂ requires 218.

Description 4: 2-Methyl-2-(1-pyrrolidinyl)propanenitrile

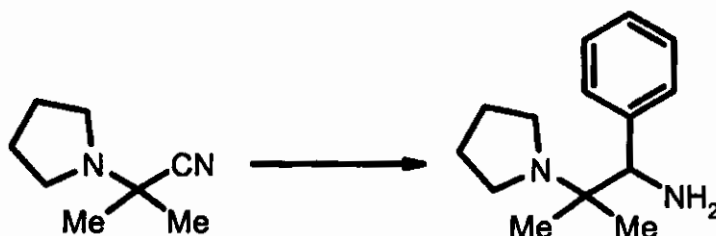


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To a stirred, ice-cooled mixture of pyrrolidine (8.35ml; 0.1mol) and acetone (7.34ml; 0.1mol) was added a solution of potassium cyanide (6.51g; 0.1mol) in water (50ml) dropwise over 10min. After stirring at room temperature overnight, the crude reaction mixture was extracted with diethyl ether (2 x 250ml) and the combined extracts washed with saturated brine (150ml), dried (MgSO₄), and evaporated under reduced pressure to afford the title product as a pale green liquid (10.7g; 78%) which was used without further purification. ¹H NMR (CDCl₃) δ: 1.51 (6H, s), 1.80 – 1.90 (4H, m), 2.70 – 2.80 (4H, m).

Description 5: (±)[2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine



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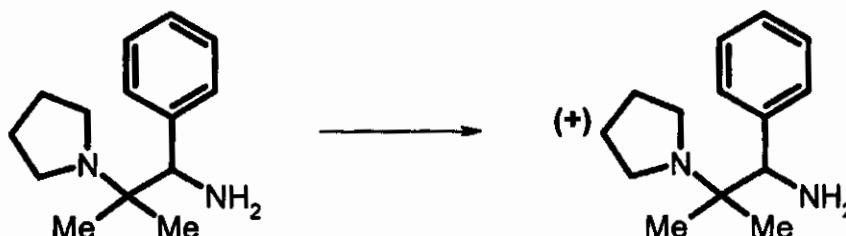
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To a solution of 2-methyl-2-(1-pyrrolidinyl)propanenitrile D4 (10.7g; 77.54mmol) in THF (400ml) at -70°C under argon was added over 10 minutes a solution of phenyllithium in dibutylether (86.3ml of a 1.8M solution; 155mmol). The reaction mixture was stirred at -70°C for 2 hours then allowed to warm to room temperature and stirred overnight. The reaction mixture was cooled in ice as saturated aqueous sodium hydrogen carbonate (400ml) was added. After stirring for a further 30 minutes the layers were separated, and the aqueous layer extracted with ether (200ml). Combined organics were dried (MgSO₄) and evaporated. The residual amber oil was dissolved in methanol (400ml), cooled in ice and sodium borohydride (5.2g; 137mmol) added in four portions over 5 minutes. The reaction mixture was stirred with ice cooling for 30 minutes, the ice removed and stirred at room temperature for 1.5 hours. The mixture was cooled in ice as water (50ml) was added prior to concentration *in vacuo* to approx 70ml. The mixture was partitioned between 2N HCl (100ml) and ethyl acetate (400ml) and the organics extracted with 2N HCl (2 x 100ml). Combined acidic aqueous layers were washed with ethyl acetate (200ml),

basified with 50% NaOH and extracted with DCM (3 x 150ml). Combined DCM organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a colourless solid (15g; 88%) ^1H NMR (CDCl_3), δ : 0.75 (3H, s), 0.99 (3H, s), 1.70 – 1.76 (4H, m), 1.80 (2H, bs), 2.65 – 2.70 (4H, m), 4.08 (1H, s), 7.20 – 7.42 (5H, m).

5

Description 6: (+)- [2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine



A solution of (R)-(-)- α -methoxyphenylacetic acid (8.08g; 49mmol) in 2-propanol (50ml) was added dropwise over 10 minutes to a stirred solution of [2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D5 (10.64g; 49mmol) in 2-propanol (107ml) at 57°C. After complete addition heating was continued for a further 10 minutes. Heating was then removed and stirring continued for one and three quarter hours. Further 2-propanol (100ml) was added and the mixture filtered and the solid washed with 2-propanol (3 x 50ml), ether (100ml) and dried. The solid was recrystallised from boiling 2-propanol (1L) and the crystals filtered, washed with cold 2-propanol, ether and dried. A sample was partitioned between saturated aqueous sodium hydrogen carbonate and DCM and the organic layer passed through a phase separation cartridge and blown down with argon to afford the title compound as a colourless solid. ^1H NMR (CDCl_3), δ : 0.75 (3H, s), 0.99 (3H, s), 1.70 – 1.79 (4H, m), 1.85 (2H, bs), 2.65 – 2.70 (4H, m), 4.08 (1H, s), 7.20 – 7.42 (5H, m). Chiral HPLC: 97.5% ee, corresponding to the slower running enantiomer 2. $[\alpha]_D^{25} = +28.5^\circ$ ($c=1$, CHCl_3 at 27.5°C). The remaining free base was liberated in a similar manner (3.55g, 66%).

20

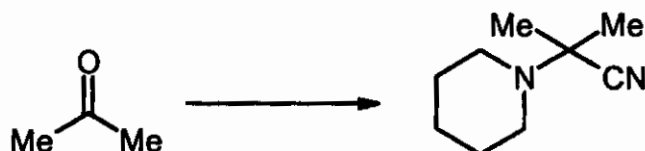
Conditions for resolution of racemate D5 were as follows:-

Analytical chromatography conditions:

25	Column:	chiralcel OD-H 5 μm , 250 x 4.6 mm i.d. 10 micron particle size
	Mobile phase:	Heptane : Ethanol (90:10)
	Gradient:	isocratic
	Flow rate:	1 ml/min
30	UV wavelength range:	254 nm
	Analysis time:	10 min

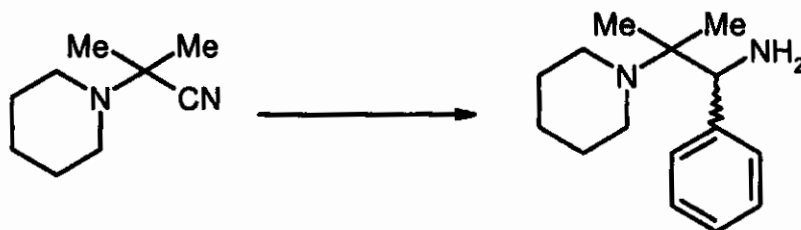
Ret. Time: 5.4min (Enantiomer 1); 7.0min (Enantiomer 2)

Description 7 : 2-Methyl-2-(1-piperidiny)propanenitrile



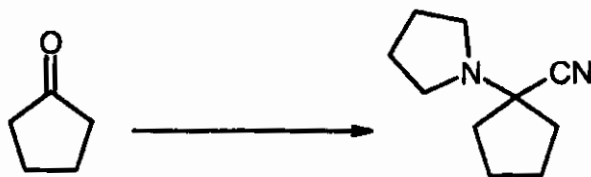
The title compound (2.33g, 77%) was prepared from piperidine hydrochloride (2.43g, 20mmol), acetone (1.16g, 20mmol) and potassium cyanide (1.30g, 20mmol) in water (10ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 1.46 (2H, m), 1.50 (6H, s), 1.63 (4H, m), 2.59 (4H, m).

Description 8 : (±)2-Methyl-1-phenyl-2-(1-piperidiny)-1-propanamine



The title compound (1.16g, 56%) was prepared from 2-methyl-2-(1-piperidiny)propanenitrile D7 (1.30g, 8.6mmol), and phenyllithium in dibutylether (5.2ml of a 1.8M solution; 9.4mmol) in THF (15ml), followed by reaction with sodium borohydride (0.975g, 25.7mmol) in methanol (20ml) in a similar manner to that described in D2. ¹H NMR (CDCl₃) δ: 0.76 (3H, s), 0.91 (3H, s), 1.44 (2H, m), 1.54 - 1.65 (4H, m), 1.95 (2H, m), 2.57 (4H, m), 4.19 (1H, s), 7.20 - 7.31 (3H, m), 7.40 (2H, m).

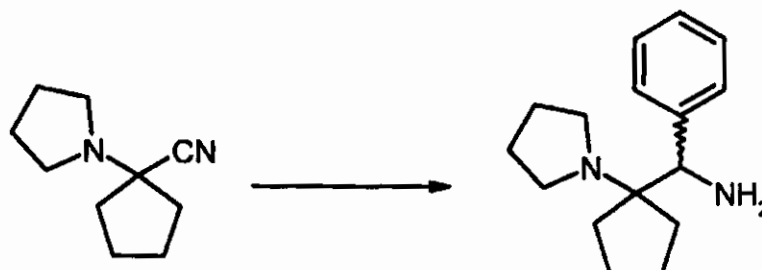
Description 9 : 1-(1-Pyrrolidiny)cyclopentanecarbonitrile



The title compound (2.50g, 76%) was prepared from pyrrolidine (1.42g, 20mmol), cyclopentanone (1.68g, 20mmol) and potassium cyanide (1.30g, 20mmol) in water (10ml)

in a similar manner to that described in D4. ^1H NMR (CDCl_3) δ : 1.80 – 1.90 (10H, m), 2.15 (2H, m), 2.71 (4H, m).

Description 10 : ($\pm$)-1-Phenyl-1-[1-(1-pyrrolidinyl)cyclopentyl]methanamine

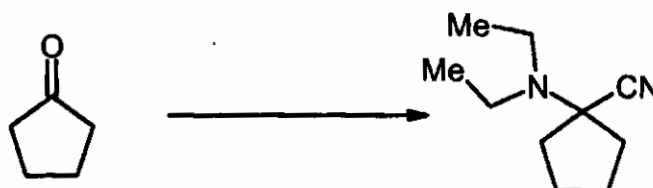


5

The title compound (0.55g, 56%) was prepared from 1-(1-pyrrolidinyl)cyclopentane carbonitrile D9 (0.66g, 4mmol), and phenyllithium in dibutylether (2.4ml of a 1.8M solution; 4.4mmol) in THF (4ml), followed by reaction with sodium borohydride (0.456g, 12mmol) in methanol (4ml) in a similar manner to that described in D2. ^1H NMR (CDCl_3) δ : 0.41 (1H, m), 1.17 (1H, m), 1.35 (2H, m), 1.60 (2H, m), 1.73 (5H, m), 1.84 – 2.02 (3H, m), 2.64 – 2.74 (4H, m), 4.27 (1H, s), 7.21 – 7.31 (3H, m), 7.48 (2H, m).

10

Description 11 : 1-(Diethylamino)cyclopentanecarbonitrile

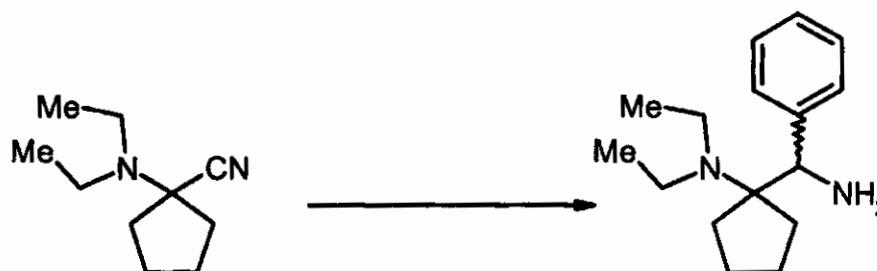


15

The title compound (2.06g, 62%) was prepared from diethylamine hydrochloride (2.14g, 20mmol), cyclopentanone (1.68g, 20mmol) and potassium cyanide (1.30g, 20mmol) in water (10ml) in a similar manner to that described in D1. ^1H NMR (CDCl_3) δ : 1.11 (6H, t, J = 7Hz), 1.78 – 1.88 (6H, m), 2.22 (2H, m), 2.71 (4H, q, J = 7Hz).

20

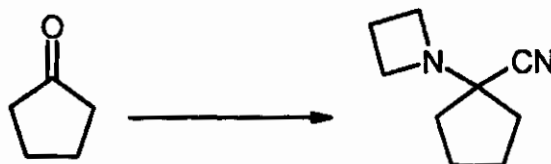
Description 12 : ($\pm$)-1-[Amino(phenyl)methyl]-N,N-diethylcyclopentanamine



The title compound (0.45g, 47%) was prepared from 1-(diethylamino)cyclopentane carbonitrile D11 (0.65g, 3.9mmol), and phenyllithium in dibutylether (2.4ml of a 1.8M solution; 4.3mmol) in THF (4ml), followed by reaction with sodium borohydride (0.445g, 11.7mmol) in methanol (4ml) in a similar manner to that described in D2. ¹H NMR (CDCl₃)

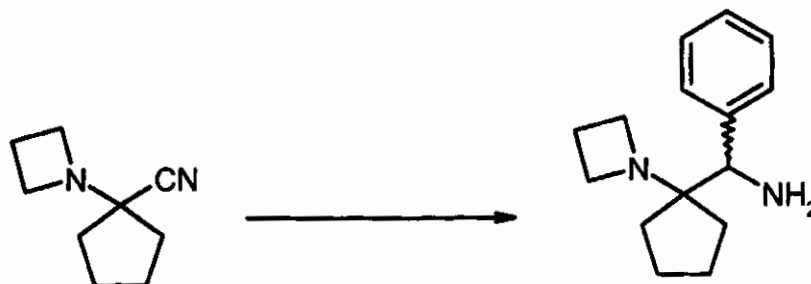
5 δ : 0.42 (1H, m), 1.10 (6H, m), 1.35 (3H, m), 1.55 (1H, m), 1.66 (2H, m), 1.80 – 2.08 (3H, m), 2.53 – 2.70 (4H, m), 4.22 (1H, s), 7.20 – 7.31 (3H, m), 7.47 (2H, m).

Description 13 : 1-(1-Azetidinyl)cyclopentanecarbonitrile



- 10 The title compound (1.29g, 43%) was prepared from azetidine hydrochloride (1.85g, 20mmol), cyclopentanone (1.68g, 20mmol) and potassium cyanide (1.30g, 20mmol) in water (10ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ : 1.70 – 1.82 (6H, m), 1.86 (2H, m), 2.07 (2H, quin, J = 7Hz), 3.32 (4H, t, J = 7Hz).

15 **Description 14 : ($\pm$)-1-[1-(1-Azetidinyl)cyclopentyl]-1-phenylmethanamine**



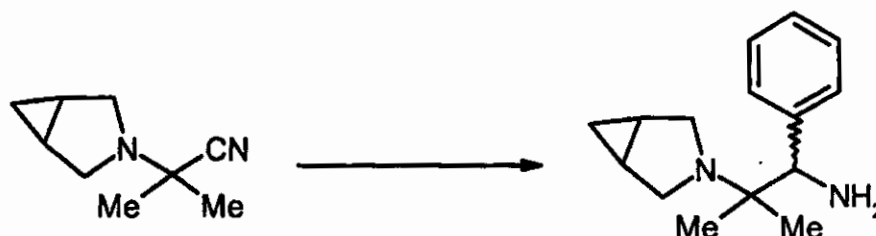
- The title compound (0.45g, 47%) was prepared from 1-(1-azetidiny)cyclopentanecarbonitrile D13 (0.60g, 4.0mmol), and phenyllithium in ethers (2.6ml of a 1.7M solution; 4.4mmol) in THF (5ml), followed by reaction with sodium
- 20 borohydride (0.456g, 12mmol) in methanol (5ml) in a similar manner to that described in D2. ¹H NMR (CDCl₃) δ : 0.67 (1H, m), 1.06 (1H, m), 1.32 (4H, m), 1.48 (2H, m), 1.91 – 2.03 (4H, m), 3.24 (4H, m), 3.83 (1H, s), 7.20 – 7.32 (3H, m), 7.44 (2H, m).

Description 15 : 2-(3-Azabicyclo[3.1.0]hex-3-yl)-2-methylpropanenitrile



The title compound (583mg, 84%) was prepared from 3-azabicyclo[3.1.0]hexane hydrochloride (550mg, 4.6mmol) [Pestic. Chem: Hum. Welfar Environ., Proc. Int. Congr. Pestic. Che., 5th, 1982, 1,159-64, 1983], acetone (267mg, 4.6mmol) and potassium cyanide (300mg, 4.6mmol) in water (2.5ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 0.40 (1H, m), 0.58 (1H, m), 1.43 (8H, m), 2.64 (2H, m), 3.10 (2H, d, J = 8Hz).

Description 16 : (±)2-(3-Azabicyclo[3.1.0]hex-3-yl)-2-methyl-1-phenyl-1-propanamine

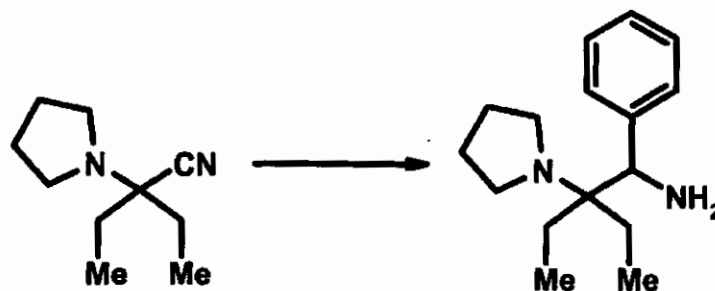


The title compound (393mg, 44%) was prepared from 2-(3-azabicyclo[3.1.0]hex-3-yl)-2-methylpropanenitrile D15 (583mg, 3.9mmol), and phenyllithium in dibutylether (2.15ml of a 2.0M solution; 4.3mmol) in THF (7ml), followed by reaction with sodium borohydride (445mg, 11.7mmol) in methanol (10ml) in a similar manner to that described in D2. ¹H NMR (CDCl₃) δ: 0.38 (1H, m), 0.66 (1H, m), 0.74 (3H, s), 0.93 (3H, s), 1.30 – 1.40 (2H, m), 1.74 (2H, bs), 2.67 (2H, m), 2.91 (2H, t, J = 8Hz), 4.03 (1H, s), 7.20 – 7.30 (3H, m), 7.38 (2H, m).

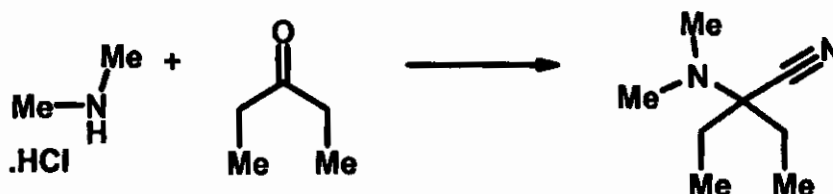
Description 17: 2-Ethyl-2-(1-pyrrolidiny)butanenitrile



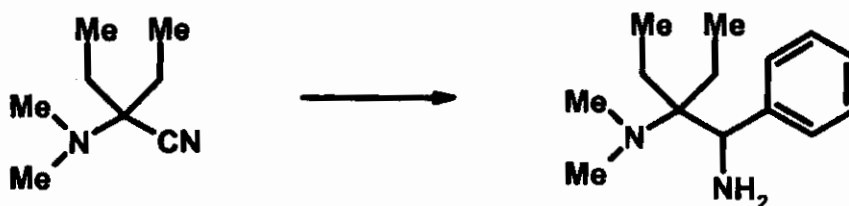
The title compound (8.8g, 100%) was prepared from pyrrolidine (8.96ml, 0.107mol), 3-pentanone (8.61g, 0.1mol) and potassium cyanide (6.51g, 0.1mol) in water (50ml) in a similar manner to that described in D4. ¹H NMR (CDCl₃) δ: 0.95 (6H, t, J = 7.6Hz), 1.67 – 1.90 (8H, m), 2.67 – 2.72 (4H, m).

Description 18: (±)[2-Ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]amine

The title compound (11.5g, 88%) was prepared from 2-ethyl-2-(1-pyrrolidinyl)butanenitrile D17 (8.8g, 0.053mol) and phenyllithium in dibutylether (59ml of a 1.8M solution; 0.106mol) in THF (350ml), followed by reaction with sodium borohydride (3.9g, 0.103mol) in methanol (300ml) in a similar manner to that described in D5. ¹H NMR (CDCl₃) δ: 0.75 (3H, t), 0.95 (3H, t, J = 7.6Hz), 1.50 – 1.90 (10H, m), 2.70 – 2.95 (4H, m), 4.01 (1H, s), 7.19 – 7.41 (5H, m).

10 Description 19: 2-(Dimethylamino)-2-ethylbutanenitrile

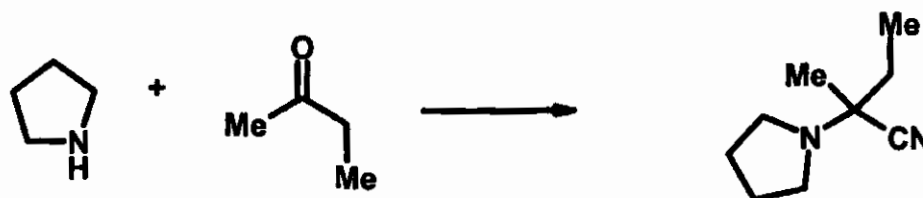
The title compound (8.05g, 57.5%) was prepared from dimethylamine hydrochloride (8.154g, 0.1mol), 3-pentanone (8.61g, 0.1mol) and potassium cyanide (6.51g, 0.1mol) in water (50ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 0.96 (6H, t, J = 7.6Hz), 1.67 – 1.90 (4H, m), 2.33 (6H, s).

Description 20: (±){1-[Amino(phenyl)methyl]-1-ethylpropyl}dimethylamine

20 The title compound (11.12g, 88%) was prepared from 2-(dimethylamino)-2-ethylbutanenitrile D19 (8.05g, 0.0575mol) and phenyllithium in dibutylether (64ml of a 1.8M solution; 0.115mol) in THF (350ml), followed by reaction with sodium borohydride (3.9g, 0.103mol) in methanol (300ml) in a similar manner to that described in D5. ¹H NMR

(CDCl₃) δ : 0.72 (3H, t, J = 7.6Hz), 0.97 (3H, t, J = 7.6Hz), 1.40 – 1.68 (4H, m), 1.70 (2H, br. m), 2.43 (6H, s), 4.09 (1H, s), 7.19 – 7.43 (5H, m).

Description 21: 2-Methyl-2-(1-pyrrolidinyl)butanenitrile



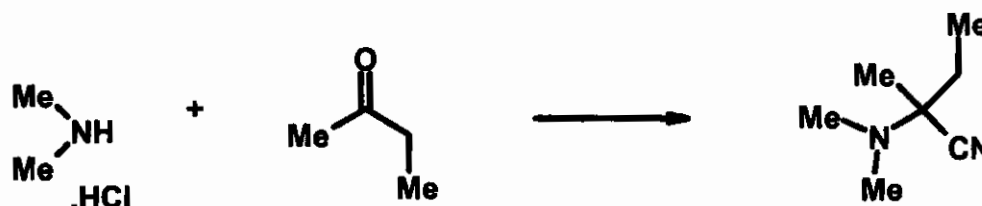
The title compound (9.6g, 63%) was prepared from pyrrolidine (8.35ml, 0.1mol), 2-butanone (8.96g, 0.1mol) and potassium cyanide (6.51g, 0.1mol) in water (50ml) in a similar manner to that described in D4. ¹H NMR (CDCl₃) δ : 1.06 (3H, t, J = 7.2Hz), 1.45 (3H, s), 1.66 – 1.93 (6H, m), 2.70 – 2.75 (4H, m).

Description 22: ($\pm$)[2-Methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]amine



The title compound (13.4g, 94%) was prepared from 2-methyl-2-(1-pyrrolidinyl)butanenitrile D21 (9.6g, 0.063mol) and phenyllithium in dibutylether (63ml of a 2M solution; 0.126mol) in THF (200ml), followed by reaction with sodium borohydride (3.5g, 0.092mol) in methanol (200ml) in a similar manner to that described in D5, except that after addition of the sodium borohydride stirring was continued with ice cooling for 0.5 hours then at room temperature for 66 hours. Mass spectrum (Electrospray LC/MS), ES⁺: Found 233 (MH⁺). C₁₅H₂₄N₂ requires 232. Ret. times 0.78 and 1.06 min.

Description 23: 2-(Dimethylamino)-2-methylbutanenitrile



The title compound (9.95g, 78%) was prepared from dimethylamine hydrochloride (8.15g, 0.1mol), 2-butanone (8.96ml, 0.1mol) and potassium cyanide (6.51g, 0.1mol) in water (50ml) in a similar manner to that described in D1. ^1H NMR (CDCl_3) δ : 1.00 (3H, t, J = 7.2Hz), 1.43 (3H, s), 1.75 – 1.87 (2H, m), 2.33 (6H, s).

5

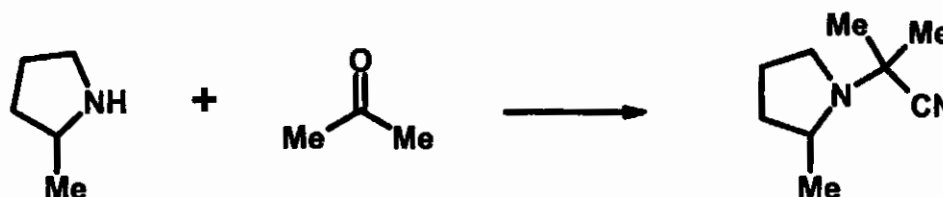
Description 24: ($\pm$){1-[Amino(phenyl)methyl]-1-methylpropyl}dimethylamine



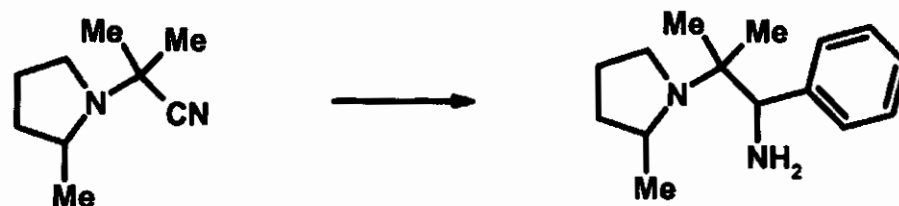
The title compound (15g, 93%) was prepared from 2-(dimethylamino)-2-methylbutanenitrile D23 (9.9g, 0.078mol) and phenyllithium in dibutylether (87.3ml of a 1.8M solution; 0.157mol) in THF (400ml), followed by reaction with sodium borohydride (5.25g, 0.138mol) in methanol (450ml) in a similar manner to that described in D5. Mass spectrum (Electrospray LC/MS), ES^+ : Found 207 (MH^+). $\text{C}_{13}\text{H}_{22}\text{N}_2$ requires 206. Ret. times 0.83 and 1.10 min.

15

Description 25 : 2-Methyl-2-(2-methyl-1-pyrrolidinyl)propanenitrile

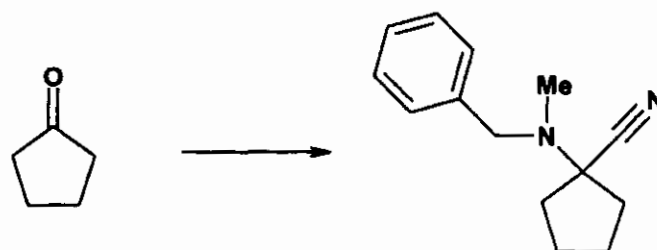


To a stirred, ice-cooled mixture of 2-(RS)-methylpyrrolidine (4.25g; 0.05mol) and acetone (3.67ml; 0.05mol) was added a solution of potassium cyanide (3.25g; 0.05mol) in water (25ml) dropwise over 10min. After stirring at room temperature overnight, the crude reaction mixture was extracted with diethyl ether (2 x 200ml) and the combined extracts washed with brine (200ml), dried (Na_2SO_4) and evaporated under reduced pressure to afford a pale yellow oil. This was dissolved in DCM and PS-Isocyanate (4.5g of resin loading 1.53mmol/g) added. The mixture was stirred for 3 hours, filtered and the filtrate evaporated to afford the title compound as a colourless semi-solid (2.82g; 37.5%). ^1H NMR (CDCl_3) δ (inter alia): 1.10 (3H, d), 1.45 (3H, s), 1.55 (3H, s), 1.75 – 2.00 (4H, m) 2.65 (1H, m) and 3.05 – 3.20 (2H, m).

Description 26: (±)[2-Methyl-2-(2-methyl-1-pyrrolidiny)-1-phenylpropyl]amine

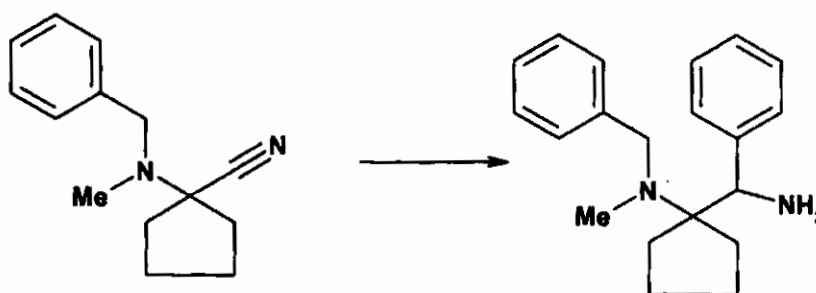
- 5 To a solution of 2-methyl-2-(2-methyl-1-pyrrolidiny)propanenitrile D25 (2.82g; 18.56 mmol) in THF (100ml) at -70°C under argon was added over 15 minutes a solution of phenyllithium in dibutylether (20.6ml of a 1.8M solution; 37.11mmol). The reaction mixture was stirred at -70°C for 2 hours then allowed to warm to room temperature and stirred overnight. Saturated aqueous sodium hydrogen carbonate (100ml) was added and stirring continued for a further 10 minutes. The mixture was extracted with diethyl ether (2 x 150ml). Combined organics were dried (Na₂SO₄) and evaporated *in vacuo*. The residual yellow oil was dissolved in methanol (100ml) and sodium borohydride (2.12g; 0.056mol) added portionwise over 5 minutes. The reaction mixture was stirred at room temperature for 4 hours, further sodium borohydride (1g; 0.026mol) added and the mixture heated at 15 60°C for 1.5 hours. The mixture was cooled and excess sodium borohydride decomposed by dropwise addition of water. The reaction mixture was evaporated *in vacuo* and the residue partitioned between saturated sodium hydrogen carbonate (150ml) and DCM (150ml). Solid potassium carbonate was added and the aqueous layer extracted with DCM (150ml). Combined organic extracts were dried (Na₂SO₄) and evaporated to give a green oil. This was divided into 8 portions and each portion passed down a 10g SCX column. After washing each column with DCM, 50%DCM in methanol and methanol the product was eluted with 1M ammonia in methanol to yield the title compound as a pale yellow oil (3.46g; 80%). Mass spectrum (Electrospray LC/MS), ES⁺: Found 233 (MH⁺). C₁₅H₂₄N₂ requires 232. Ret. times 0.96 and 1.07 min.

25

Description 27: 1-[Methyl(phenylmethyl)amino]cyclopentanecarbonitrile

The title compound (15g; 84%) was prepared from N-methylbenzylamine (10.08g; 83mmol), cyclopentanone (7g; 83mmol) and potassium cyanide (5.41g; 83mmol) in water (45ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 1.90 (6H, m), 2.20 (3H, s), 2.3 (2H, m), 3.62 (2H, s), 7.25 (1H, m), 7.32 (4H, m); Mass Spectrum (Electrospray LC/MS): Found 188 (MH⁺-HCN). C₁₄H₁₈N₂ requires 214. Ret. time 1.21 min.

Description 28: (±)-{1-[Amino(phenyl)methyl]cyclopentyl}methyl (phenylmethyl) amine

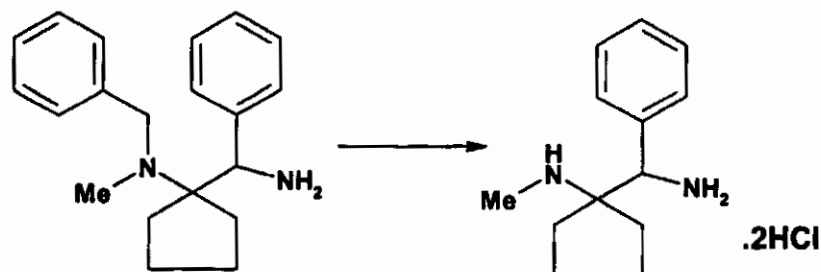


10

The title compound (3.90g; 47%) was prepared from 1-[methyl(phenylmethyl)amino]cyclopentanecarbonitrile D28 (6.0g; 28mmol) and phenyllithium in di-n-butylether (16.21ml of 1.9M solution; 30.8mmol) in THF (60ml), followed by reaction with sodium borohydride (3.2g; 84mmol) in methanol (60ml) in a similar manner to that described in D2. Mass Spectrum (Electrospray LC/MS), API⁺: Found 295 (MH⁺). C₂₀H₂₆N₂ requires 294. Ret. time 2.12 min.

15

Description 29: (±)-{1-[Amino(phenyl)methyl]cyclopentyl}methylamine dihydrochloride

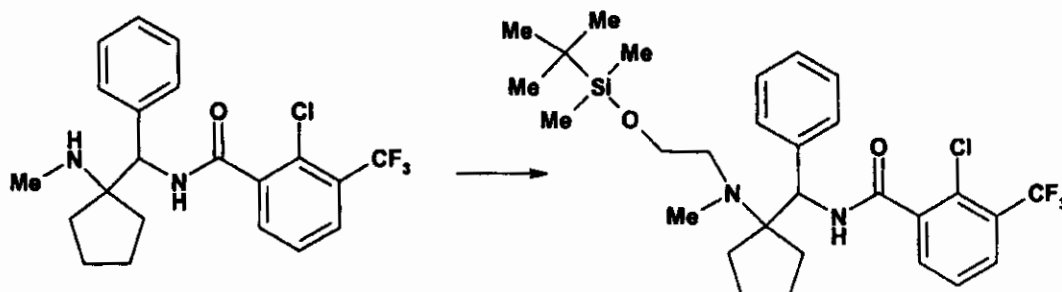


20

To a solution of (±)-{1-[amino(phenyl)methyl]cyclopentyl}methyl(phenylmethyl)amine D28 (0.5g; 1.7mmol) in ethanol was added 3N HCl (1ml) and 10% palladium carbon (0.1g). The catalytic hydrogenation was carried out for 16h at room temperature and atmospheric pressure. The catalyst was filtered off through kieselguhr and the filtrate evaporated under

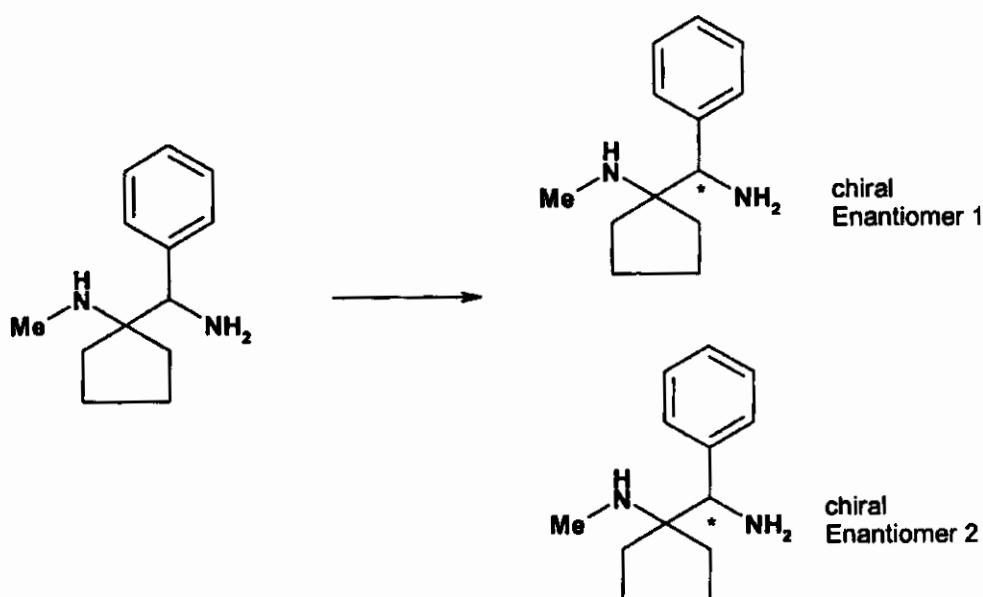
reduced pressure to give the title compound (0.32g; 69%). ^1H NMR (DMSO) δ : 1.3-2.2 (8H, m), 2.5 (3H, s), 4.6 (1H, s), 7.4 (3H, m), 7.6 (2H, m), 8.0 (2H, bs), 9.0 (1H, bs).

Description 30: ($\pm$)-2-Chloro-*N*-[1-[(2-[[[(1,1-dimethylethyl)(dimethyl)silyl]oxy]ethyl)(methyl)amino]cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide



The title compound (0.390g, 99%) was prepared from ($\pm$)-2-chloro-*N*-[1-(methylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide (0.282g; 0.686mmol), (tert-butyldimethylsilyloxy acetaldehyde (90%; 0.265g; 1.52mmol) and sodium triacetoxymethylborohydride (0.290g; 1.52mmol) in DCM (5ml) in a similar manner to that described in E30. Mass Spectrum (Electrospray LC/MS). Found 569(MH⁺). C₂₉H₄₀³⁵ClF₃N₂O₂Si requires 568. Ret. time: 3.04 min.

Description 31: {1-[Amino(phenyl)methyl]cyclopentyl)methylamine
Enantiomer 1 and Enantiomer 2



Racemic ($\pm$)-{1-[amino(phenyl)methyl]cyclopentyl}methylamine D29 (0.342g; 1.67mmol) was separated by preparative chiral HPLC to afford the title products enantiomer 1 (0.134g); Chiral HPLC: 99.8% ee; ^1H NMR (CDCl_3) δ : 1.30-1.78 (11H, m), 2.33 (3H, s), 4.08 (1H, s), 7.22 (1H, m), 7.28 (2H, m), 7.35 (2H, m), and enantiomer 2 (0.127g); Chiral HPLC: 99.8% ee; ^1H NMR (CDCl_3) δ : 1.30-1.78 (11H, m), 2.33 (3H, s), 4.08 (1H, s), 7.22 (1H, m), 7.28 (2H, m), 7.35 (2H, m).

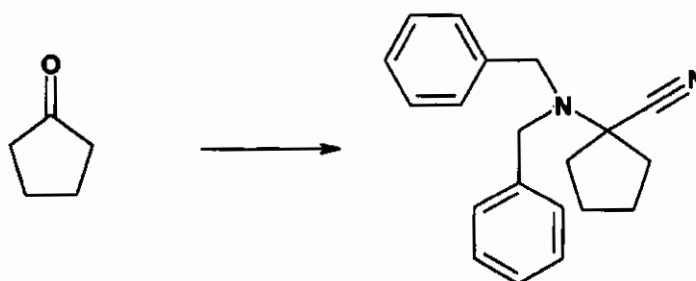
Analytical HPLC conditions:

Column: Chiral OD 10micron particle size 20mm i.d. x 250mm
 10 Mobile phase: Heptane:Absolute Ethanol (90:10 v/v)
 Gradient: Isocratic
 UV Wavelength: 215nm
 Flow rate: 1ml/min
 Ret. Time: 7.5min (Enantiomer 1); 15.6min (Enantiomer 2)

15 Preparative HPLC conditions:

Column: Chiral OD 10micron particle size 20mm i.d. x 250mm
 Mobile phase: Heptane:Absolute Ethanol (90:10 v/v)
 Gradient: Isocratic
 UV Wavelength: 215nm
 20 Flow rate: 17ml/min

Description 32: 1-[Bis(phenylmethyl)amino]cyclopentanecarbonitrile



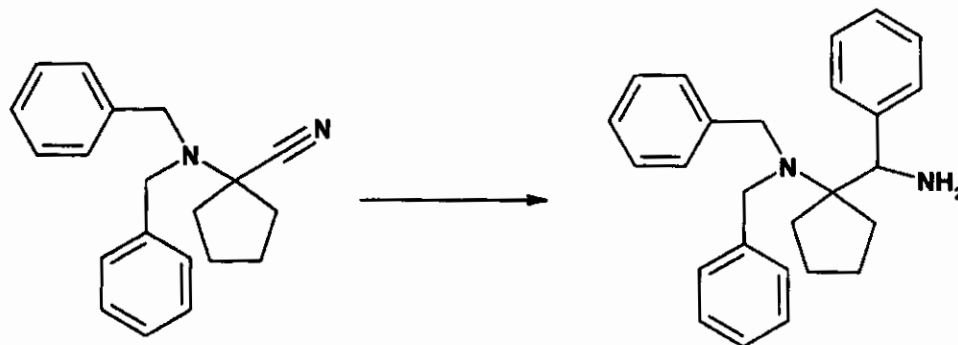
25

To an ice-cooled suspension of dibenzylamine hydrochloride (13.5g; 0.058mol) and cyclopentanone (4.86g; 0.058mol) in 25% ethanol in water (100ml) was added ethanol (60ml) and a solution of potassium cyanide (3.78g; 0.058mol) in water (35ml) dropwise over 20 minutes with stirring. After 6 days the reaction mixture was extracted with ethyl acetate, washed with sodium bicarbonate solution, dried (Na_2SO_4) and evaporated in

30

vacuo to afford the title compound as an off white solid (8.32g, 49%). ¹H NMR (CDCl₃) δ: 1.72 (6H, m), 2.12 (2H, m), 3.78 (4H, m), 7.1-7.3 (10H, m); Mass Spectrum (Electrospray LC/MS): Found 264 (MH⁺-HCN). C₂₀H₂₂N₂ requires 290. Ret. time 1.88min.

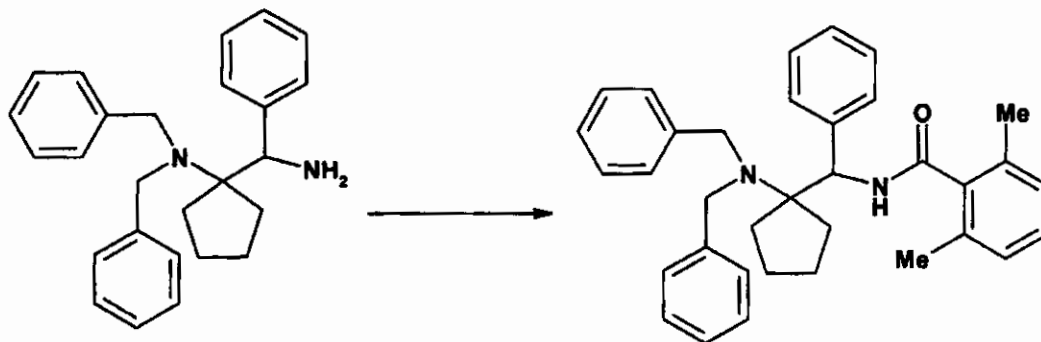
5 **Description 33: (±)-{1-[Amino(phenyl)methyl]cyclopentyl} bis(phenylmethyl)amine**



The title compound (2.31g; 38%) was prepared from 1-[bis(phenylmethyl)amino]cyclopentanecarbonitrile D32 (4.0g; 13.8mmol), and phenyllithium in di-n-butylether (8.4ml of 1.8M solution; 15.2mmol) in THF (80ml), followed by reaction with sodium borohydride (1.57g; 41.4mmol) in methanol (80ml) in a similar manner to that described in D2. Mass Spectrum (Electrospray LC/MS), API⁺: Found 371 (MH⁺). C₂₆H₃₀N₂ requires 370. Ret. time 2.62 min.

15

Description 34: (±)-N-[[1-[bis(phenylmethyl)amino]cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide

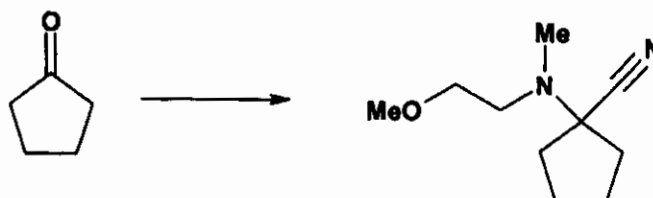


20 The title compound (2.51g; 80%) was prepared from (±)-{1-[amino(phenyl)methyl]cyclopentyl}bis(phenylmethyl)amine D33 (2.31g; 6.23mmol), 2,6-dimethyl benzoyl chloride (1.15g; 6.85mmol), triethylamine (1.73ml; 12.5mmol) in DCM (70ml) in a similar manner to

that described in E13. ^1H NMR (CDCl_3) δ : 1.40-2.05 (8H, m), 2.28 (6H, s), 3.68 (4H, s), 5.37 (1H, d), 6.78 (1H, m), 6.95-7.36 (16H, m), 7.45 (2H, m); Mass Spectrum (Electrospray LC/MS), API^+ : Found 503 (MH^+). $\text{C}_{35}\text{H}_{38}\text{N}_2\text{O}$ requires 502. Ret. time 3.77 min.

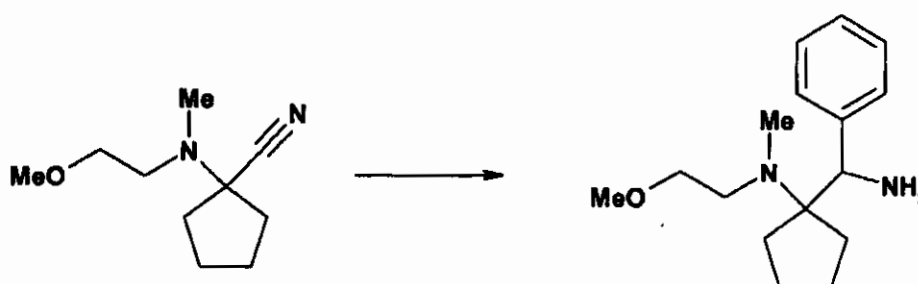
5

Description 35: 1-[Methyl[2-(methyloxy)ethyl]amino]cyclopentanecarbonitrile



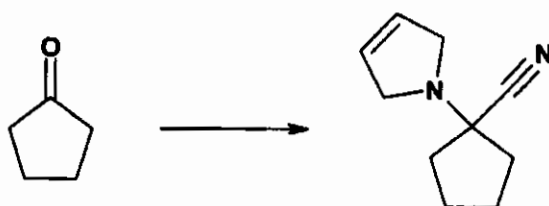
The title compound (3.39g; 82%) was prepared from N-(2-methoxyethyl) methylamine hydrochloride (2.84g; 22.6mmol), cyclopentanone (1.90g, 22.6mmol) and potassium cyanide (1.47g; 22.6mmol) in water (15ml) in a similar manner to that described in D1. ^1H NMR (CDCl_3) δ : 1.83 (6H, m), 2.20 (2H, m), 2.48 (3H, s), 2.68 (2H, t), 3.46 (3H, s), 3.5 (2H, t).

Description 36: ($\pm$)-[1-[Amino(phenyl)methyl]cyclopentyl] methyl[2-(methyloxy)ethyl]amine

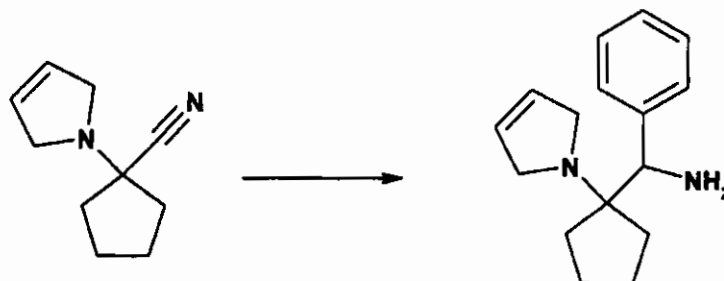


The title compound (1.22g; 42%) was prepared from 1-[methyl[2-(methyloxy)ethyl]amino]cyclopentanecarbonitrile D35 (2.0g; 11mmol), and phenyllithium in di-n-butylether (6.7ml of 1.8M solution; 12mmol) in THF (25ml), followed by reaction with sodium borohydride (1.25g; 33mmol) in methanol (25ml) in a similar manner to that described in D2. Mass Spectrum (Electrospray LC/MS). Found 263 (MH^+). $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}$ requires 262. Ret. time 1.57min.

25

Description 37: 1-(2,5-Dihydro-1H-pyrrol-1-yl)cyclopentanecarbonitrile

The title compound (2.8g; 64%) was prepared from 3-pyrroline (1.86g; 27mmol),
 5 cyclopentanone (2.26g; 27mmol) and potassium cyanide (1.75g; 27mmol) in water (15ml)
 in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 1.85 (6H, m), 2.08 (2H,
 m), 3.61 (4H, s), 5.78 (2H, s).

Description 38: (±)-[[1-(2,5-Dihydro-1H-pyrrol-1-yl)cyclopentyl] (phenyl)methyl] amine

The title compound (1.35g; 45%) was prepared from 1-(2,5-dihydro-1H-pyrrol-1-yl)cyclopentanecarbonitrile D37 (2.0g; 12.3mmol), and phenyllithium in di-n-butylether (7.5ml of 1.8M solution; 13.5mmol) in THF (20ml), followed by reaction with sodium borohydride (1.402g; 36.9mmol) in methanol (20ml) in a similar manner to that described in D2. Mass Spectrum (Electrospray LC/MS): Found 243 (MH⁺). C₁₆H₂₂N₂ requires 242. Ret. time 1.02min.

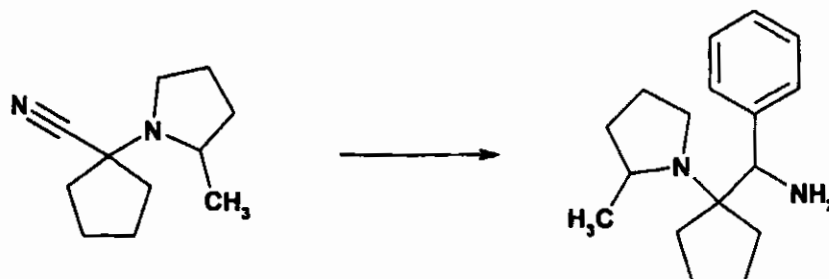
Description 39: (±)-1-(2-Methyl-1-pyrrolidinyl)cyclopentanecarbonitrile

A mixture of cyclopentanone (1.34g, 16mmol) and 2-methylpyrrolidine (1.36g; 16mmol) was cooled to 0°C (ice bath). A solution of potassium cyanide (1.04g, 16mmol) in water (10ml) was added dropwise over 10min and the whole mixture stirred vigorously for 18 h

at 20°C, and then partitioned between ethyl acetate and water. The organic layer was dried (Na₂SO₄) and evaporated in vacuo to afford the title compound (2.24g; 79%). ¹NMR (CDCl₃) δ: 1.1 (3H, d), 1.45 (1H, m), 1.75-2.05 (9H, m), 2.13 (2H, m), 2.65 (1H, m), 3.1 (2H, m).

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Description 40: (±)-[1-(2-methyl-1-pyrrolidiny)cyclopentyl](phenyl) methyl]amine

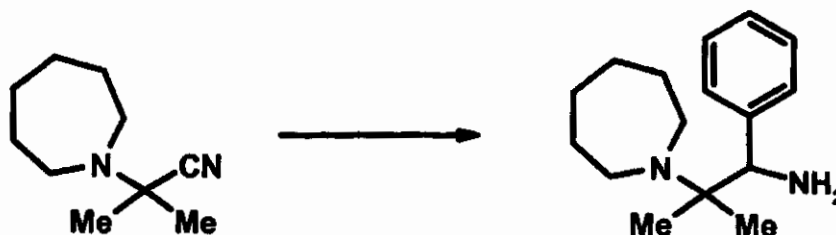


A solution of (±)-1-(2-methyl-1-pyrrolidiny)cyclopentanecarbonitrile D39 (0.997g; 5.6mmol) in dry THF was cooled to -70°C. To this phenyllithium (1.7M in C₆H₁₄/ether, 1.1 equiv) was added slowly. The whole mixture was allowed to warm slowly to room temperature over 3 h with stirring under argon. Reaction cooled to 0°C and methanol added followed by sodium borohydride (portionwise) and allowed to react at 20°C overnight. The reaction was cooled to 0°C and quenched with saturated sodium bicarbonate, extracted with ethyl acetate, dried (Na₂SO₄) and evaporated. The product was purified by chromatography on a 5g SCX column eluting from 0-100% ethyl acetate in pet. ether, 0-10% methanol in ethyl acetate then 2% 0.880 ammonia in ethyl acetate to give the title compound as an oil (0.67g; 46%) was obtained. Mass Spectrum (Electrospray LC/MS): Found 259 (MH⁺). C₁₇H₂₆N₂ requires 258. Ret. time 1.19min.

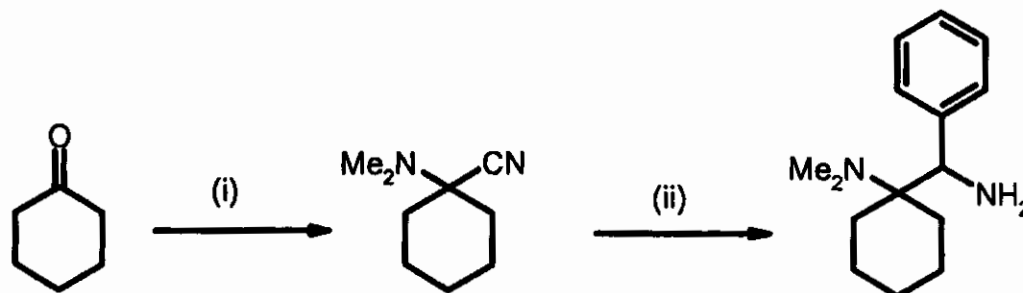
Description 41: 2-(Hexahydro-1H-azepin-1-yl)-2-methylpropanenitrile



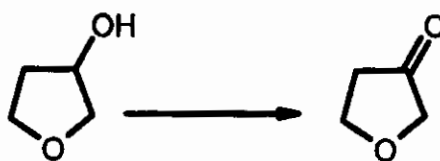
The title compound (6.6g; 80%) was prepared from homopiperidine hydrochloride (6.7g; 49mmol), acetone (3.67ml; 50mmol), and potassium cyanide (3.25g; 50mmol) in water (25ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ 1.43 (6H, s), 1.50 – 1.65 (8H, m), 2.66 (4H, m).

Description 42: (±)[2-(Hexahydro-1H-azepin-1-yl)-2-methyl-1-phenylpropyl]amine

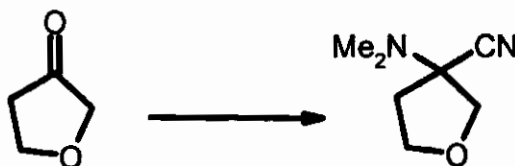
The title compound (3.7g; 83%) was prepared from 2-(hexahydro-1H-azepin-1-yl)-2-methylpropanenitrile D41 (3g; 18mmol) and phenyllithium in dibutylether (18ml of a 2M solution; 36mmol) in THF (100ml), followed by reaction with sodium borohydride (2.13g, 54mmol) in methanol (100ml) in a similar manner to that described in D5. ¹H NMR (CDCl₃) δ 0.78 (3H, s), 0.98 (3H, s), 1.55 – 1.70 (8H, m), 1.83 (2H, br s), 2.67 – 2.79 (4H, m), 4.18 (1H, s), 7.20 – 7.30 (3H, m), 7.40 – 7.42 (2H, m).

Description 43 : (±){1-[Amino(phenyl)methyl]cyclohexyl}dimethylamine

The title compound was prepared in two stages from (i) dimethylamine hydrochloride (3.26 g, 0.04 mol), cyclohexanone (3.9 g, 0.04 mol) and potassium cyanide (2.60 g, 0.04 mol) in water (25 ml) in a similar manner to that described in D1 to make 1-(dimethylamino)cyclohexanecarbonitrile (6.6 g, 100%). This was reacted directly in (ii) with phenyl lithium in dibutyl ether (10.5 ml of a 1.9M solution, 0.02 mol) in THF (30 ml) followed by sodium borohydride (1.51 g, 0.04 mol) in a similar manner to that described in D2 to afford the title compound (2.5 g, 36%). ¹H NMR (CDCl₃) δ: 0.85 (1H, m), 1.00 (1H, m), 1.25 (2H, m), 1.35-1.60 (6H, br m), 1.70 (1H, m), 2.10 (1H, m), 2.46 (6H, s), 4.15 (1H, s), 7.20-7.32 (5H, m).

Description 44 : Dihydro-3(2H)-furanone

- A mixture of 3-hydroxytetrahydrofuran (3.0 g, 0.034 mol) and pyridinium chlorochromate (14.7 g, 0.068 mol) in DCM (100 ml) was stirred at room temperature overnight. The title product was obtained by pouring the crude product through a silica pad using ethyl acetate as the eluent. The title product was obtained from 2 elutions (2.29 g; 79%). ¹H NMR (CDCl₃) δ: 2.50 (2H, t), 3.87 (2H, s), 4.26 (2H, t).

10 Description 45 : (±)3-(Dimethylamino)tetrahydro-3-furancarbonitrile

- The title compound (6.54 g, 88%) was prepared from dihydro-3(2H)-furanone D44 (4.54 g, 0.053 mol), dimethylamine hydrochloride (4.9 g, 0.06 mol) and potassium cyanide (3.5 g, 0.054 mol) in water (100 ml) in a similar manner to that described in D1. ¹H NMR (CDCl₃) δ: 2.15 (1H, m), 2.33 (6H, s), 2.44 (1H, m), 3.69 (1H, d), 4.02-4.13 (2H, m), 4.17 (1H, m).

Description 46: (±){3-[Amino(phenyl)methyl]tetrahydro-3-furanyl}dimethylamine diastereoisomers

- To a solution of 3-(dimethylamino)tetrahydro-3-furancarbonitrile D45 (4.55 g, 0.032 mol) in tetrahydrofuran (30ml) at -70°C under argon was added dropwise a solution of phenyllithium in dibutylether (36.1ml of a 1.8M solution; 0.064 mol). The reaction mixture was stirred and maintained at -50 to -70°C for 16 hours followed by careful addition of saturated aqueous sodium bicarbonate. The resulting slurry was extracted three times with DCM. The combined extracts were dried (Na₂SO₄) and evaporated to afford the

crude product as an orange oil which was chromatographed on silica gel eluting with 0 to 100% ethyl acetate / pentane to afford the imine intermediate as a yellow oil (5.18g). The oil was dissolved in methanol, sodium borohydride (1.8 g, 0.047 mol) added and the mixture stirred at room temperature overnight. The methanol was evaporated and the slurry partitioned between DCM and saturated aqueous sodium bicarbonate. The organics were dried by passage through a Phase-Sep column and evaporated to afford the title compound (3.47 g, 49%). ¹H NMR (CDCl₃) δ: 1.68 and 2.20 (1H, 2 x m), 1.75 (2H, br s), 1.90 and 2.05 (1H, 2 x m), 2.32 and 2.35 (6H, 2 x s), 2.70 and 3.42 (1H, 2 x m), 3.66-3.98 (3H, br m), 4.32 and 4.48 (1H, 2 x s), 7.20-7.51 (5H, m).

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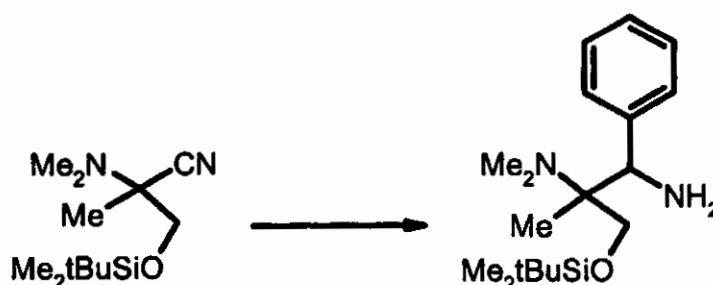
Description 47: (±)2-(Dimethylamino)-3-([(1,1-dimethylethyl)(dimethyl)silyl]oxy)-2-methylpropanenitrile



The title compound (2.16 g, 45%) was prepared from 1-(t-butyldimethylsilyloxy)-2-propanone (3.77 g, 0.02 mol), dimethylamine hydrochloride (1.71 g, 0.02 mol) and potassium cyanide (1.37 g, 0.02 mol) in water (50 ml) in a similar manner to that described in D1. An additional purification step was passage of the compound through SCX resin, elution with DCM to remove the starting material and then elution with 1M ammonia in methanol to elute the title compound. ¹H NMR (CDCl₃) δ: 0.00 (6H, d), 0.81 (9H, s), 1.38 (3H, s), 2.25 (6H, s), 3.36 (1H, d), 3.78 (1H, d).

20

Description 48: (±)[2-Amino-1-([(1,1-dimethylethyl)(dimethyl)silyl]oxy)methyl]-1-methyl-2-phenylethyl]dimethylamine diastereoisomers



The title compound (930 mg, 33%) was prepared from 2-(dimethylamino)-3-([(1,1-dimethylethyl)(dimethyl)silyl]oxy)-2-methylpropanenitrile D47 (2.1 g, 8.67 mmol), phenyl lithium (10.0 ml of a 1.8M solution in dibutyl ether, 18.0 mmol) in THF (30 ml) followed by

sodium borohydride (830 mg, 26.0 mmol) in methanol (50 ml) in a similar manner to that described in D2. Chromatography (Blotage Horizon) to isolate the title compound was carried out using (i) 0 to 100% ethyl acetate/ pentane, (ii) 100% ethyl acetate and (iii) 0 to 20% methanol/ ethyl acetate. The product containing fractions were combined and evaporated. Mass spectrum (Electrospray LC/MS), API⁺: Found 323 (MH⁺), 306 (M-16). C₁₈H₃₄N₂OSi requires 322. Ret. time 2.35-2.39 min. (broad peak).

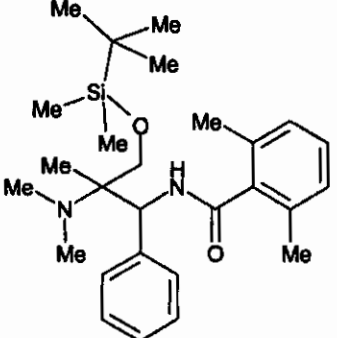
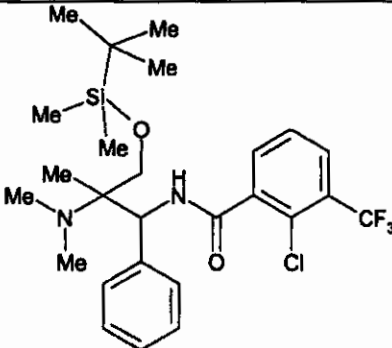
Description 49 : (±)N-(2-(Dimethylamino)-3-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)-2-methyl-1-phenylpropyl)-2,3-dimethylbenzamide diastereoisomers



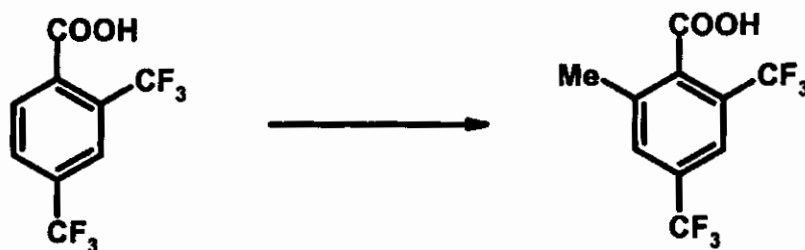
The title compound (64 mg; 30%) was prepared from [2-amino-1-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-1-methyl-2-phenylethyl] dimethylamine D48 (150 mg; 0.46mmol), 2,3-dimethylbenzoic acid (75 mg; 0.5mmol), PL-dicyclohexylcarbodiimide (385 mg; 0.5mmol; Polymer Labs 1.3 mmol/g), 1-hydroxybenzotriazole (77 mg; 0.5mmol) in DCM (5ml) in a similar manner to that described in E1. Mass spectrum (Electrospray LC/MS) : Found 455 (MH⁺), C₂₇H₄₂N₂O₂Si requires 454. Ret. time 2.57 and 2.61 min.

The compounds in Table 1 below were prepared in a manner similar to that described in description D49.

Table 1

Description	Structure	Mass spectrum (Electrospray LC/MS), API ⁺ Ret.time (min)	Name
50		Found 455 (MH ⁺) C ₂₇ H ₄₂ N ₂ O ₂ Si requires 454; 2.60 and 2.62.	(±)-N-(2-(dimethylamino)-3- {[(1,1- dimethylethyl)(dimethyl)silyl] oxy}-2-methyl-1- phenylpropyl)-2,6- dimethylbenzamide diastereoisomers
51		Found 529 (MH ⁺) C ₂₈ H ₃₆ ³⁵ ClF ₃ N ₂ O ₂ Si requires 528; 2.72 and 2.79.	(±)-2-chloro-N-(2- (dimethylamino)-3- {[(1,1- dimethylethyl)(dimethyl)silyl] oxy}-2-methyl-1- phenylpropyl)-3- (trifluoromethyl)benzamide diastereoisomers

5 Description 52: 2-Methyl-4,6-bis(trifluoromethyl)benzoic acid



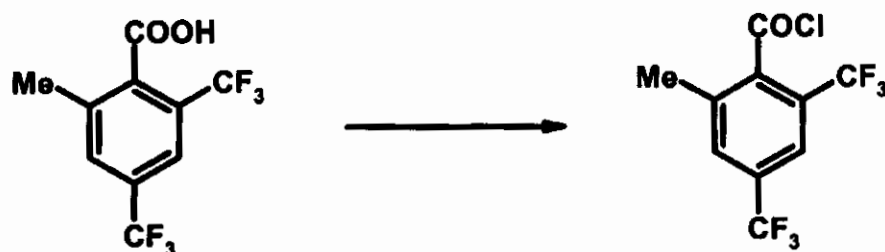
Dry THF (5ml) was stirred under argon at -80°C and treated with sec-butyl lithium (3.05ml of a 1.4M solution in cyclohexane, 4.27mmol) and N,N,N',N'-tetramethylethylenediamine (640ul, 4.27mmol). A solution of 2,4-bis(trifluoromethyl)benzoic acid (0.50g, 1.94mmol) in dry THF (2ml) was added dropwise over 30 minutes and allowed to stir for a further 30

minutes at -80°C. Iodomethane (483ul, 7.76mmol) was added dropwise over 5 minutes and the reaction stirred at -70°C for a further 20 minutes and allowed to warm to room temperature. Water (1ml) was added dropwise and the mixture partitioned between ethyl acetate and water. The water layer was acidified with 2M hydrochloric acid and extracted
 5 twice with ethyl acetate. The combined extracts were dried over magnesium sulphate and evaporated to afford a crude solid (416mg). NMR indicated this to be a mixture of 2-methyl-4,6-bis(trifluoromethyl)benzoic acid and recovered 2,4-bis(trifluoromethyl)benzoic acid. It was used without further purification.

10 **Description 52: 2-Methyl-4,6-bis(trifluoromethyl)benzoic acid - Alternative method.**

Dry THF (5ml) was stirred under argon at -80°C and treated with sec-butyl lithium (4.0ml of a 1.4M solution in cyclohexane, 5.60mmol) and N,N,N',N'-tetramethylethylenediamine (640ul, 4.27mmol). A solution of 2,4-bis(trifluoromethyl)benzoic acid (0.50g, 1.94mmol) in dry THF (2ml) was now added dropwise over 30 minutes and allowed to stir for a further
 15 30 minutes at -80°C. Iodomethane (483ul, 7.76mmol) was now added dropwise over 5 minutes and the reaction stirred at -70°C for a further 20 minutes and allowed to warm to room temperature. Water (1ml) was added dropwise and the mixture partitioned between ethyl acetate and water. The water layer was acidified with 2M hydrochloric acid and extracted twice with ethyl acetate. The combined extracts were dried over magnesium
 20 sulphate and evaporated to afford a crude solid (420mg). NMR indicated this to be a mixture of 2-methyl-4,6-bis(trifluoromethyl)benzoic acid (ca.80%), ¹H NMR (CDCl₃) δ: 2.54 (3H, s), 7.73 (1H, s), 7.81 (1H, s), and recovered 2,4-bis(trifluoromethyl)benzoic acid (ca.20%).

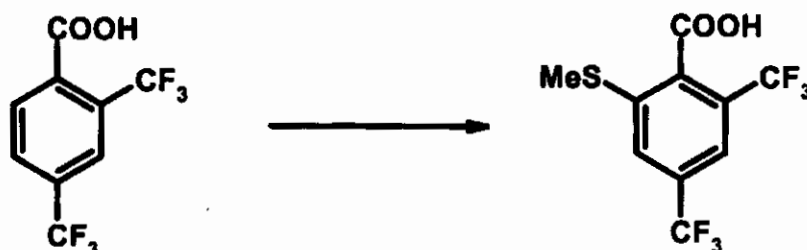
25 **Description: 53: 2-Methyl-4,6-bis(trifluoromethyl)benzoyl chloride**



A solution of 2-methyl-4,6-bis(trifluoromethyl)benzoic acid D52 alternative method (400mg, approximately 1.47mmol) in DCM (5ml), containing DMF (1drop), was treated
 30 with oxalyl chloride (166ul, 1.91mmol) and stirred under argon for 1 hour. The solvent was carefully removed under reduced pressure and the residue re-evaporated from

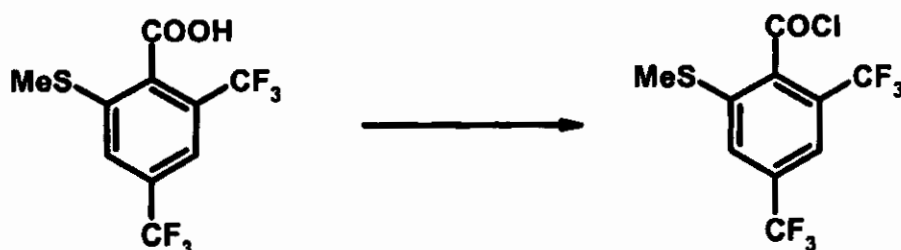
further DCM. The mixture of acid chlorides was then treated with methanol (3ml) and kept at room temperature for 2 hours after which time the solvent was again carefully removed under reduced pressure. NMR data indicated this to be a mixture of the title product 2-methyl-4,6-bis(trifluoromethyl)benzoyl chloride and methyl 2,4-bis(trifluoromethyl)benzoate. The mixture was used without further purification.

Description: 54: 2-(Methylthio)-4,6-bis(trifluoromethyl)benzoic acid



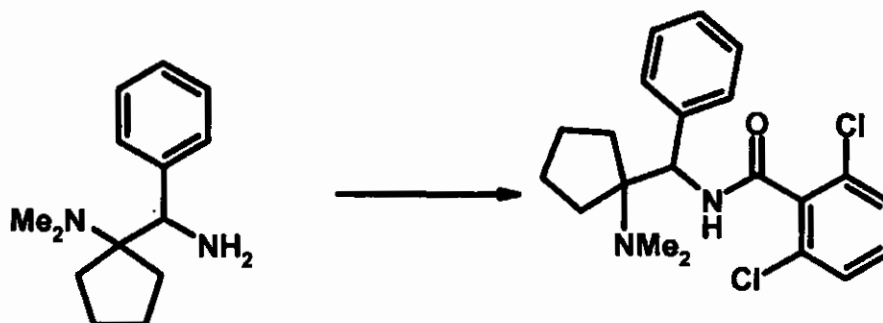
Dry THF (5ml) was stirred under argon at -80°C and treated with N,N,N',N'-tetramethylethylenediamine (640ul, 4.27mmol) followed by sec-butyl lithium (3.05ml of a 1.4M solution in cyclohexane, 4.27mmol). A solution of 2,4-bis(trifluoromethyl)benzoic acid (0.50g, 1.94mmol) in dry THF (2ml) was now added dropwise over 15 minutes and allowed to stir for a further 60 minutes at -80°C . Dimethyldisulphide (687ul, 7.76mmol) was now added dropwise over 2 minutes and the reaction stirred at -80°C for a further 40 minutes and allowed to warm to room temperature by cooling bath removal. Stirred at room temperature overnight. Water (1ml) was added dropwise and the mixture partitioned between ethyl acetate and water. The water layer was acidified with 2M hydrochloric acid and extracted twice with ethyl acetate. The combined extracts were dried over magnesium sulphate and evaporated to afford a crude solid (400mg). NMR indicated this to be a mixture of the title product 2-(methylthio)-4,6-bis(trifluoromethyl)benzoic acid and recovered 2,4-bis(trifluoromethyl)benzoic acid which was used without further purification.

Description: 55: 2-(Methylthio)-4,6-bis(trifluoromethyl)benzoyl chloride



A solution of the mixture containing 2-(methylthio)-4,6-bis(trifluoromethyl)benzoic acid D54 (225mg) in dry DCM (4ml), containing dry DMF (1drop), was treated with oxalyl chloride (87ul, 1.0mmol) and stirred at room temperature for 1 hour. The solvent was removed under reduced pressure to afford a crude product which was treated with dry methanol (2ml) and stirred at room temperature overnight. The solvent was then carefully removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 0-10% ethyl acetate in pentane to afford the title product 2-(methylthio)-4,6-bis(trifluoromethyl)benzoyl chloride (60mg). ¹H NMR (CDCl₃) δ: 2.62 (3H, s), 7.77 (1H, s), 7.82 (1H, s). Further elution gave methyl 2,4-bis(trifluoromethyl)benzoate (100mg).

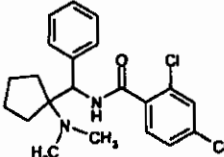
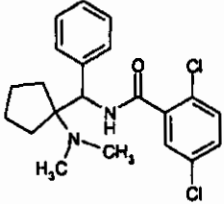
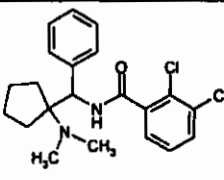
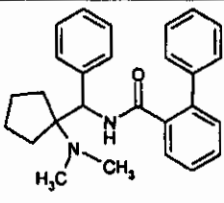
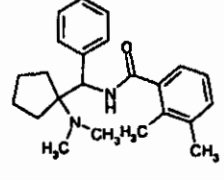
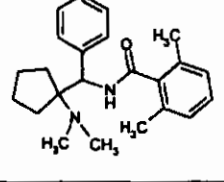
Example 1: (±)-2,6-Dichloro-N-[[1-(dimethylamino)cyclopentyl] (phenyl)methyl] benzamide



To a solution of 2,6-dichlorobenzoic acid (20mg; 0.105mmol) in DCM (2ml) and N-methylpyrrolidinone (0.1-0.5ml) was added 1-hydroxybenzotriazole (18mg; 0.11mmol) and PL-dicyclohexylcarbodiimide (88mg; 0.14mmol; Polymer Labs 1.59mmol/g). The mixture was shaken at room temperature for 1 hour and then 1-[amino(phenyl)methyl]cyclopentyl]dimethylamine dihydrochloride D2 (20mg; 0.07mmol) and PS-diisopropylethylamine (82mg; 0.21mmol; Polymer Labs 2.59mmol/g) were then added and shaking continued overnight at room temperature. An excess of PS-Trisamine was then added and after shaking for a further 4h, the mixture was filtered and the resins washed well with DCM and methanol. The filtrate was reduced in volume by evaporation *in vacuo* and loaded onto an SCX cartridge (500mg). Washing with DCM, then methanol followed by elution with 1M ammonia in methanol afforded the title product (22.8mg). ¹H NMR (CDCl₃) δ: 0.98 (1H, m), 1.26 (1H, m), 1.40 (2H, m), 1.68 (2H, m), 1.85 (2H, m), 2.22 (6H, s), 5.08 (1H, bs), 7.27 (7H, m), and 7.47 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 391 (MH⁺). C₂₁H₂₄³⁵Cl₂N₂O requires 390. Ret. time 1.88 min.

The compounds in Table 2 below were prepared using similar methods to that described for Example 1. Coupling method: P = Polymer-supported DCC

Table 2

Ex	Structure	Method	Mass spectrum (Electrospray LC/MS), API ⁺ Ret.time (min)	Name
2		P	Found 391 (MH ⁺) C ₂₁ H ₂₄ ³⁵ Cl ₂ N ₂ O requires 390; 2.03	(±)-2,4-Dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]benzamide
3		P	Found 391 (MH ⁺) C ₂₁ H ₂₄ ³⁵ Cl ₂ N ₂ O requires 390; 2.01	(±)-2,5-Dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]benzamide
4		P	Found 391 (MH ⁺) C ₂₁ H ₂₄ ³⁵ Cl ₂ N ₂ O requires 390; 2.02	(±)-2,3-Dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]benzamide
5		P	Found 399 (MH ⁺) C ₂₇ H ₃₀ N ₂ O requires 398; 2.13	(±)-N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2-biphenylcarboxamide
6		P	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 1.96	(±)-N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2,3-dimethylbenzamide
7		P	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 1.87	(±)-N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide

8		P	Found 367 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₂ requires 366; 1.80	(±)-N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-6-(methoxy)benzamide
9		P	Found 425 (MH ⁺) C ₂₂ H ₂₄ ³⁵ ClF ₃ N ₂ O requires 424; 2.16 and 2.19.	(±)-2-Chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide

C

Example 10: 2-Chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide enantiomer 2

- 5 Racemic 2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide E9 (250mg; 0.59mmol) was separated by semi-preparative chiral HPLC to afford the title product enantiomer 1 (82mg); Chiral HPLC >99.8% ee; and the title product enantiomer 2 (86mg); Chiral HPLC >99.8% ee.

10 Semi-preparative chromatography conditions

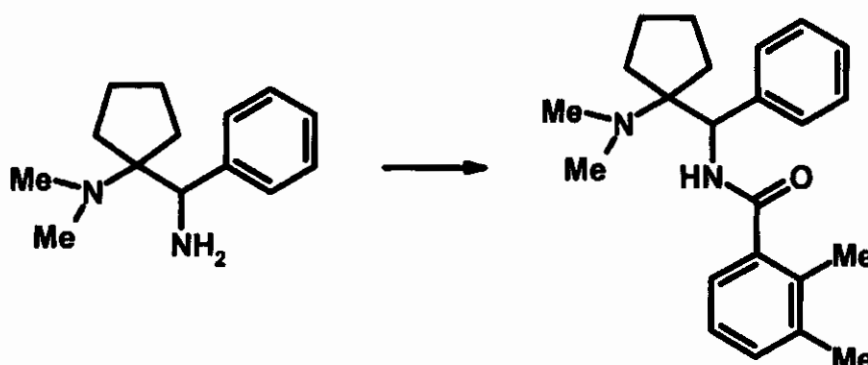
Column: chiralpak AD-H 5 μ m, 250 x 21 mm
 Mobile phase: A: n-Hexane; B: Isopropanol + 0.1% isopropylamine
 Gradient: isocratic 15% B
 Flow rate: 7 ml/min
 UV wavelength range: 225 nm
 Analysis time: 45 min

C

Analytical chromatography conditions

- Column: chiralpak AD-H 5 μ m, 250 x 4.6 mm
 20 Mobile phase: A: n-Hexane; B: Isopropanol
 Gradient: isocratic 15% B
 Flow rate: 1 ml/min
 UV wavelength range: 200-400 nm
 Analysis time: 25 min
 25 Ret. Time: 6.5min (Enantiomer 1); 10.1min (Enantiomer 2)

Example 11: N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2,3-dimethylbenzamide chiral

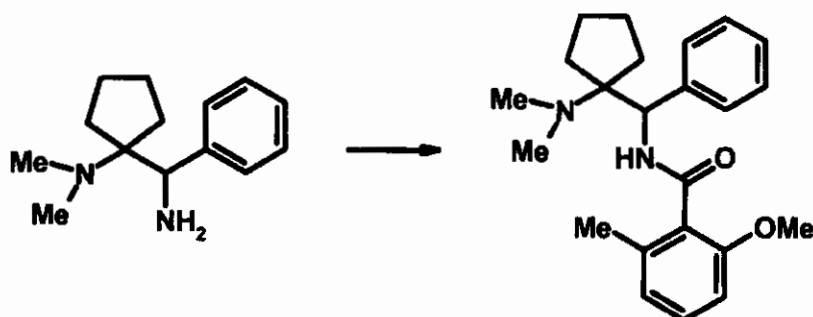


5 A mixture of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (0.102g, 0.47mmol), 2,3-dimethylbenzoic acid (0.100g, 0.67mmol), 1-hydroxybenzotriazole hydrate (0.092g, 0.6mmol) and PS-DCC (0.63g of 1.3mmol/g loading, 0.82mmol) in DCM (7ml) was shaken for 20h. The mixture was filtered and the resin washed with DCM (2 x 4ml). Combined organics were washed with saturated sodium hydrogen carbonate (20ml), the layers separated and the organic layer applied to

10 a 2g SCX cartridge. The cartridge was washed with DCM (2 volumes), 50% methanol in DCM (1 volume) and methanol (2 volumes). Elution with 1M ammonia in methanol (2 volumes) and evaporation of the solvent afforded a colourless gum. Chromatography on silica gel (10g) eluting with 0-100% ethyl acetate in pentane gradient afforded the title compound as a colourless solid (0.14g; 86%). ¹H NMR (CDCl₃) δ: 0.90 – 1.15 (1H, m),

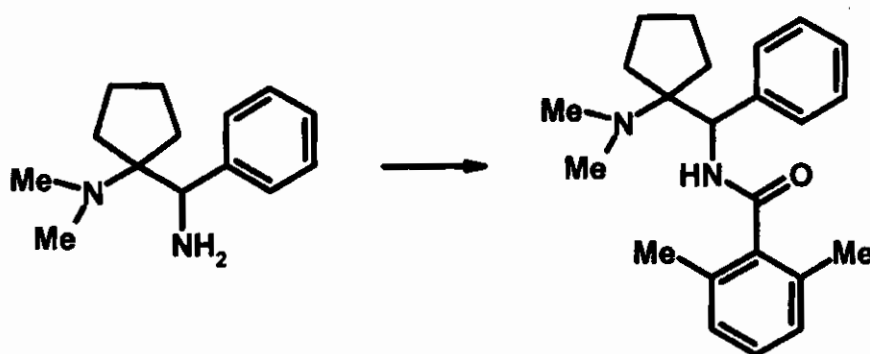
15 1.20 – 1.38 (1H, m), 1.40 – 1.55 (2H, m), 1.60 – 1.75 (2H, m), 1.79 – 1.90 (2H, m), 2.22 (6H, s), 2.28 (6H, s), 5.15 (1H, d, J = 6Hz), 6.98 (1H, d, J = 6Hz), 7.10 – 7.15 (1H, m), 7.19 – 7.27 (3H, m), 7.29 – 7.35 (2H, m), 7.39 – 7.43 (2H, m). Mass spectrum (Electrospray LC/MS), ES⁺: Found 351 (MH⁺). C₂₃H₃₀N₂O requires 350. Ret. time 1.90 min. The title product was converted to the corresponding hydrochloride salt (0.150 g).

Example 12: N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-6-(methoxy)benzamide chiral



A mixture of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (0.220 g, 1 mmol), 2-methoxy-6-methylbenzoic acid (0.200 g, 1.2 mmol), 1-hydroxybenzotriazole hydrate (0.183 g, 1.2 mmol) and PS-DCC (1 g of 1.3 mmol/g loading, 1.3 mmol) in DCM (10ml) was stirred vigorously overnight. The mixture was washed with saturated aqueous sodium hydrogen carbonate, the layers separated through a phase separation cartridge and the organic layer applied to an SCX cartridge. The cartridge was eluted with DCM (x2), and then methanol (x2) followed by 1M ammonia in methanol. Evaporation of the solvent afforded the title compound which was characterised. ¹H NMR (CDCl₃) δ: 1.00 – 1.10 (1H, m), 1.25 – 1.40 (1H, m), 1.40 – 1.60 (2H, m), 1.60 – 1.80 (2H, m), 1.80 – 2.00 (2H, m), 2.24 (6H, s), 2.28 (3H, s), 3.80 (3H, s), 5.17 (1H, d, J = 6Hz), 6.75 (1H, d, J = 8Hz), 6.79 (1H, d, J = 8Hz), 7.10 (1H, br s), 7.15 – 7.30 (4H, m), 7.44 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 367 (MH⁺). C₂₃H₃₀N₂O₂ requires 366. Ret. time 1.92 min. The title product was converted to the corresponding hydrochloride salt (0.34 g, 85%).

Example 13: N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethyl benzamide chiral



A solution of 2,6-dimethylbenzoyl chloride (1.7 g, 10.1 mmol) in DCM (10ml) was added dropwise to a mixture of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (2.0 g, 9.2 mmol), and triethylamine (1.4 ml, 10.0 mmol) in DCM (40ml) and stirred at room temperature for 2 h. The mixture was washed with saturated aqueous sodium hydrogen carbonate, the organic layer was separated through a phase separation cartridge and then evaporated to a white solid. Chromatography with eluent 50-100% ethyl acetate / pentane, then 0-10% methanol / ethyl acetate afforded the title product as a white solid (3.1 g, 97%). ¹H NMR (CDCl₃) δ: 0.85 – 1.00 (1H, m), 1.30 -1.55 (3H, m), 1.60 – 1.75 (2H, m), 1.78 – 1.90 (2H, m), 2.21 (6H, s), 2.31 (6H, s), 5.19 (1H, d, J = 6Hz), 6.79 (1H, br d), 7.02 (2H, d, J = 8Hz), 7.16 (1H, t, J = 8Hz), 7.20 – 7.35 (3H, m), 7.43 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 351 (MH⁺). C₂₃H₃₀N₂O requires 350.

Ret. time 2.0 min. The white solid product was converted to the HCl salt using 1M HCl/diethylether to afford the salt as a white solid on evaporation.

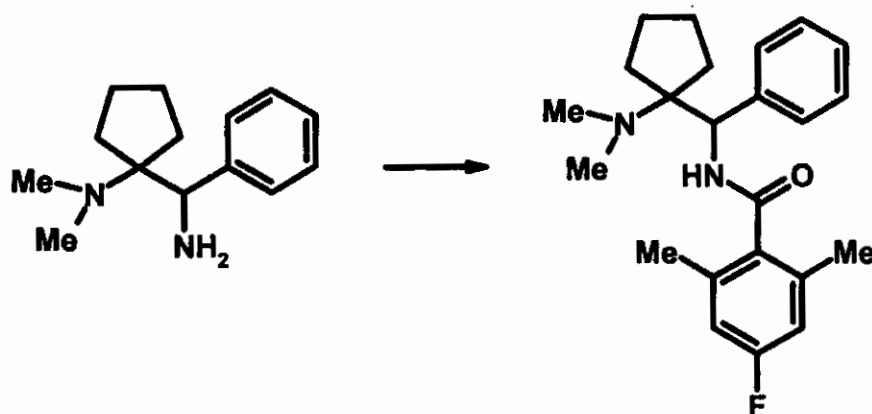
Example 13b: Succinate salt of N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethyl benzamide chiral

To a mixture of 26.25g of the free base of the compound of Example 13 and 9.286g of succinic acid, was added 262ml of IPA (isopropyl alcohol) under nitrogen and the mixture was stirred at room temperature for 12 hours. Then the mixture was heated at 40°C for 1 hour, cooled at room temperature and chilled at 0°C for 1 hour. After further 30min at room temperature the solid is collected by filtration, dried overnight at 45°C under vacuum to get 31.92g of title material as a white solid.

Example 13c: Formulation of N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethyl benzamide chiral

10.6mg of N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethyl benzamide was dissolved in 7ml of Miglyol 812N. 217.1mg of Methocel K4M was added and the suspension was homogenised with a high shear mixer. The resulting concentrations were 1.5mg ml⁻¹ of active ingredient and 30mg ml⁻¹ of Methocel excipient.

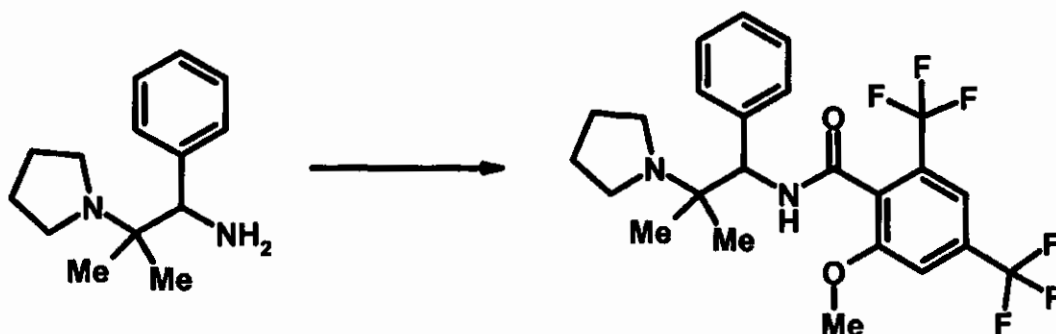
Example 14: N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-4-fluoro-2,6-dimethylbenzamide chiral



To {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (0.904g; 4.147mmol) in DCM (45ml) under argon at room temperature was added triethylamine (0.573ml; 4.15mmol), followed by a solution of 4-fluoro-2,6-dimethylbenzoyl chloride (0.773g; 4.144mmol) in DCM (5ml). After 16h. the reaction was washed with water, dried with MgSO₄ and evaporated. The residue was chromatographed on silica gel eluting with an ethyl acetate – hexane 0 to 100% gradient to give the title compound (1.57g; 100%).

¹H NMR (CDCl₃) δ: 0.85 – 1.00 (1H, m), 1.30 – 1.60 (3H, m), 1.60 – 1.75 (2H, m), 1.75 – 1.90 (2H, m), 2.22 (6H, s), 2.31 (6H, m), 5.18 (1H, d, J = 6Hz), 6.73 (2H, d, J = 9.6Hz overlaps 1H, br s), 7.20 – 7.35 (3H, m), 7.42 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 369 (MH⁺). C₂₃H₂₉FN₂O requires 368. Ret. time 1.99min. The free base was dissolved in methanol. 1M HCl/diethylether was added to the stirred solution and stirring continued at room temperature for 5 minutes. The solution was then evaporated under reduced pressure, redissolved in DCM and evaporated at reduced pressure. The resulting foam was dried for 16 hours at reduced pressure. The hydrochloride salt was obtained as a white foam (1.45g).

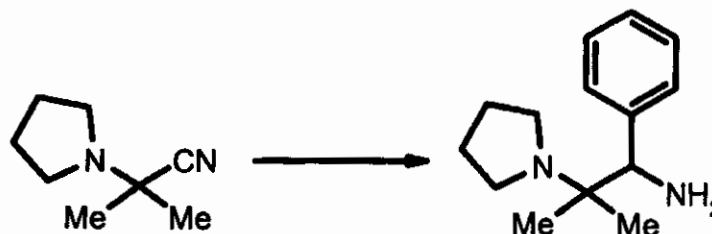
Example 15: 2-(Methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide chiral



To a solution of diisopropylethylamine (0.915ml; 5.37mmol), 2,4-difluoromethyl-6-methoxy-benzoic acid (0.511g; 1.78mmol) and (+)- [2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D6 (0.501g; 1.74mmol) in DMF (50ml) under argon was added HATU (0.676g; 1.78mmol) portionwise. After stirring at room temperature for 3h., followed by standing for ca. 2 days the reaction mixture was purified using an SCX column and the resulting product partitioned between ethyl acetate and water. The solvent was removed in vacuo to afford the title product. ¹H NMR (CDCl₃) δ: 0.94 (6H, s), 1.60 – 1.80 (4H, m), 2.55 – 2.75 (4H, m), 3.89 (3H, s), 4.78 (1H, s), 7.20 – 7.40 (7H, m), 7.52 (1H, s). Mass Spectrum (Electrospray LC/MS): Found 489 (MH⁺). C₂₄H₂₆F₆N₂O₂ requires 488. Ret. time 2.06min. Conversion of the title product to the corresponding hydrochloride salt afforded an off-white solid (0.893g; 96%).

Example 15b: 2-(Methyloxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide hydrochloride chiral alternative method

Step 1: (±)[2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine (D5)



5

To a solution of 2-methyl-2-(1-pyrrolidinyl)propanenitrile D4 (40g; 289.85mmol) in dry THF (0.8L) under nitrogen, cooled at -78°C, was added dropwise a solution of phenyl lithium in dibutyl ether over 40 minutes (305.1mL of a 1.9M solution; 579.70mmol). After 2h the reaction was allowed to reach room temperature and then stirred overnight at this temperature. The mixture was quenched at 0°C with a saturated solution of NaHCO₃ (0.8L) and stirred for 15 minutes and diluted with water (ca.0.6L). The phases were separated and the aqueous back extracted with diethylether (2x1L). The collected organics were dried over Na₂SO₄ and evaporated in vacuo to get 90g of crude material as a yellow oil that was dissolved in methanol (1L) at 0°C and treated portionwise with sodium borohydride (21.93g; 579.70mmol). After 1 hour at 0°C and then overnight at room temperature the mixture was cooled and quenched with water (ca.0.5L). Methanol was evaporated in vacuo and the aqueous phase, diluted with water (200mL), was extracted with DCM (3x800mL). The collected organics were dried over Na₂SO₄ and evaporated in vacuo to get the title product (51g) as a yellow solid, used in step 2 without further purification.

20

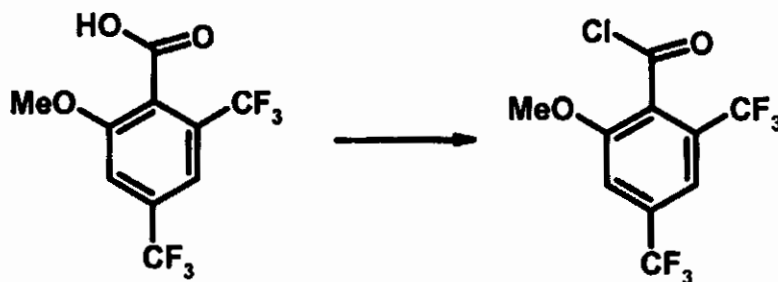
Step 2: [2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine R(-)α methoxy phenyl acetic acid salt

[2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D5 from step 1 (51g; 234mmol) was dissolved in isopropanol (0.765L, 15 volumes, relative volumes being referred to the quantity of [2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine). To this stirred solution, heated at 50°C, was added a solution of R(-)α methoxy phenyl acetic acid (38.83g; 234mmol) in isopropanol (0.255L, 5 volumes, relative volumes being referred to the quantity of [2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine). After 1.5h the mixture was cooled to room temperature and then left stirring at this temperature overnight. The solid was recovered by filtration and washed with cold isopropanol. This solid (40.5g) was

30

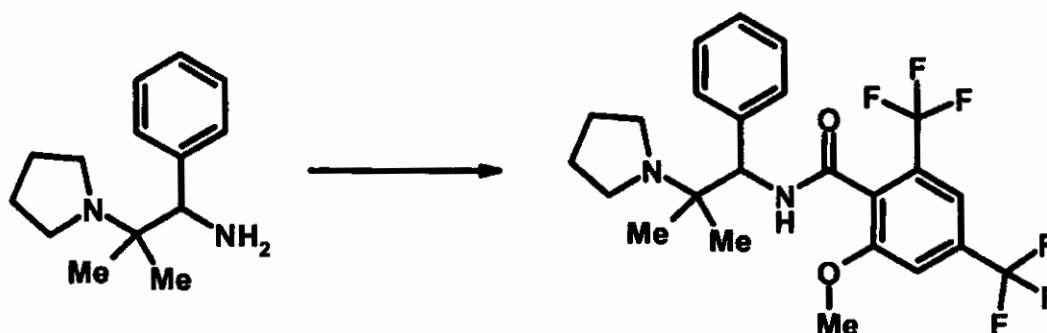
suspended in isopropanol (0.648L, 16 volumes, relative volumes being referred to the quantity of solid obtained in the last filtration step), and heated at 60°C for 2h, at room temperature overnight and recovered by filtration. This solid (38.5g) was suspended in isopropanol (0.616L, 16 volumes, relative volumes being referred to the quantity of solid obtained in the last filtration step), and heated at 60°C for 2h and at room temperature overnight, then recovered by filtration. This solid (37.8g) was suspended in isopropanol (0.756L, 20 volumes, relative volumes being referred to the quantity of solid obtained in the last filtration step), and heated at 60°C for 2h and at room temperature overnight, then recovered by filtration. This solid (36.5g) was suspended in isopropanol (0.912L, 25 volumes, relative volumes being referred to the quantity of solid obtained in the last filtration step), and heated at 60°C for 2h and then filtered at room temperature. This solid (34g) was suspended in isopropanol (0.850L, 25 volumes, relative volumes being referred to the quantity of solid obtained in the last filtration step), and heated at 60°C for 2h and filtered at room temperature. This solid (31.5g) was suspended in isopropanol (0.787L, 25 volumes, relative volumes being referred to the quantity of solid obtained in the last filtration step), and heated at 60°C for 2h, cooled down to 40°C and then filtered to get the title material (27g) as a white solid.

Step 3: 2-(Methoxy)-4,6-bis(trifluoromethyl)benzoyl chloride



To a solution of 2-(methoxy)-4,6-bis(trifluoromethyl)benzoic acid (20.2g; 70.14mmol) in dry DCM (400mL), at 0°C, was added dropwise oxalyl chloride (13.4mL; 154.31mmol) followed by dry DMF (5 drops). The reaction was allowed to reach room temperature. After overnight stirring the solvent was evaporated in vacuo to get the title product (23.5g) as a yellow slurry used without further purification.

Step 4: 2-(Methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide chiral (E15)

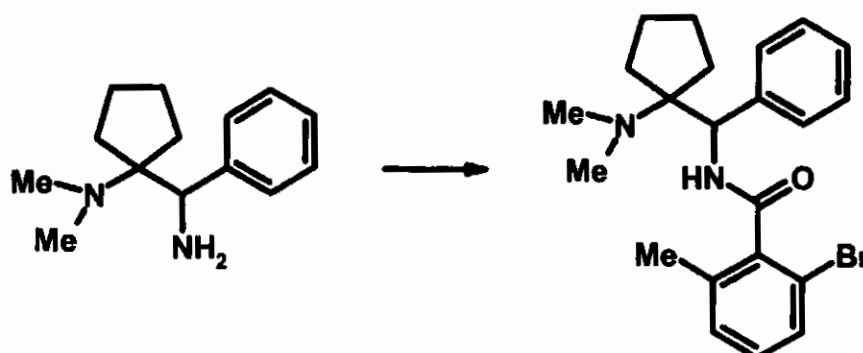


5 [2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine R(-)-α methoxy phenyl acetic acid salt from step 2 (22g; 57.3mmol) was suspended in DCM at 0°C, treated with 1M NaOH solution (86mL) and stirred at room temperature for 20 minutes. To the mixture water (250mL) was added, the phases separated and the aqueous one extracted with DCM (2x300mL). The collected organics were dried over Na₂SO₄ and evaporated in vacuo to get 12.3g of white solid that was diluted with dry DCM (200mL) under nitrogen and cooled at 0°C. To this solution was added triethylamine (23.92mL; 172mmol) and a solution of 2-(methoxy)-4,6-bis(trifluoromethyl)benzoyl chloride from Step 3 in dry DCM (190ml of a 200mL solution in DCM of the step 3 material) over 30 minutes. The reaction was left stirring at room temperature for 2 hours and then quenched with a saturated solution of NaHCO₃ (ca.450mL). The phases were separated and the organic one washed with water (500mL), dried over Na₂SO₄ and evaporated in vacuo to get crude material that was purified by silica gel flash chromatography eluting with DCM/methanol 97/3. Evaporation of the solvent afforded the title material (26g) as a pale yellow solid.

Step 5: 2-(Methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide hydrochloride chiral

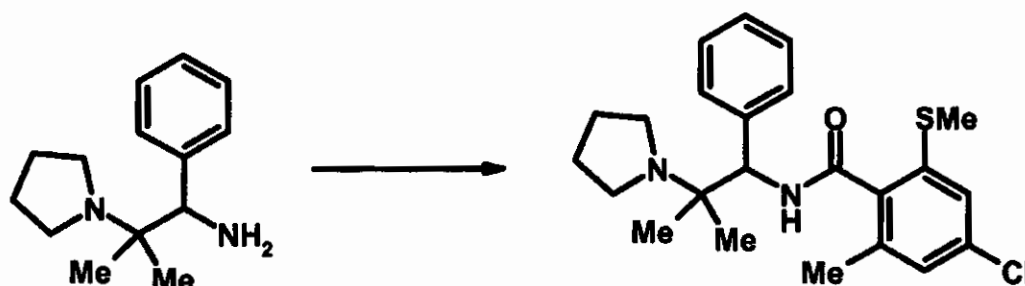
20 2-(Methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide E15 from step 4 (10g; 20.47mmol) was dissolved in dry ethyl ether (200mL), cooled to 0°C and treated with 1M solution of HCl in ethyl ether (21.5mL; 21.49mmol). After 0.5h the solid was collected by filtration, washed with diethyl ether and dried at 45°C overnight to get the title material (9.1g) as a pale yellow solid.

Example 16: 2-Bromo-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-6-methylbenzamide chiral



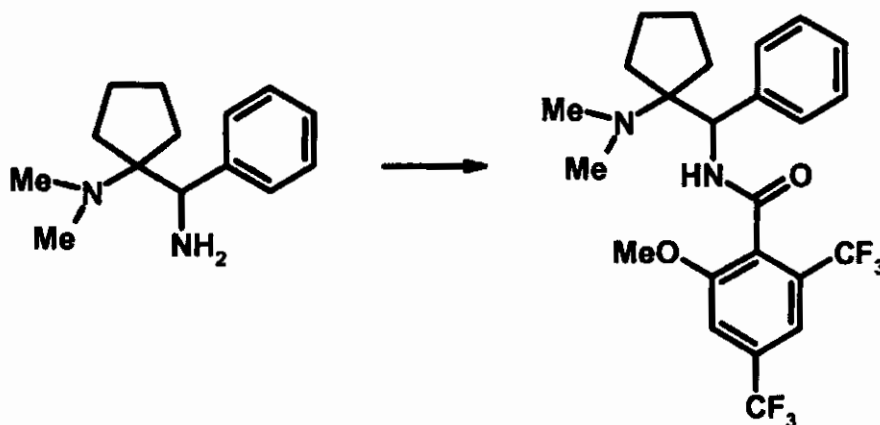
To {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (50mg, 0.23 mmol) in DCM (5ml) was added 2-bromo-6-methylbenzoic acid (108mg; 0.5mmol), followed by 1-hydroxybenzotriazole (45mg; 0.3mmol) and PS-DCC (400mg of 1.3 mmol/g loading, 0.52mmol) and the mixture shaken at room temperature for ca.2 days. The reaction mixture was filtered through a phase-separation cartridge and the filtrate stirred with saturated aqueous sodium bicarbonate for 30min. The lower layer was removed, passed through another phase-separation cartridge and loaded onto an SCX cartridge which was eluted with 2 column volumes each of DCM, 50% methanol-DCM, methanol and 1M ammonia in methanol. The product containing fractions were evaporated to afford the title product (82mg; 82%). ¹H NMR (CDCl₃) δ: 0.95 - 1.10 (2H, m), 1.40 - 1.60 (2H, m), 1.60 - 1.80 (2H, m), 1.80 - 1.90 (2H, m), 2.23 (6H, s), 2.33 (3H, m), 5.13 (1H, d J = 6Hz), 6.97 (1H, br s), 7.10 - 7.15 (2H, m), 7.24 - 7.34 (3H, m), 7.38 - 7.41 (1H, m), 7.46 - 7.48 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 415 (MH⁺). C₂₂H₂₇⁷⁹BrN₂O requires 414. Ret. time 1.93 min.

Example 17: 4-Chloro-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-6-(methylthio)benzamide chiral



A mixture of (+)- [2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D6 (262mg; 1.2mmol), 4-chloro-2-methyl-6-(methylthio)benzoic acid (388mg; 1.8mmol), 1-hydroxybenzotriazole hydrate (276mg; 1.8mmol) and EDC (345mg; 1.8mmol) in DCM (16ml) was stirred for 16h. The reaction mixture was then partitioned between DCM and saturated aqueous sodium hydrogen carbonate and the organic layer separated, washed with brine, dried and evaporated. The residue was chromatographed on silica gel eluting with an ethyl acetate – hexane 0 to 100% gradient to give the title compound as a colourless oil (332mg; 66%). ¹H NMR (CDCl₃) δ: 0.90 (3H, s), 0.98 (3H, s), 1.66 – 1.75 (4H, m), 2.31 (3H, s), 2.44 (3H, s), 2.60 – 2.65 (2H, m), 2.69 – 2.74 (2H, m), 4.82 (1H, d J = 3Hz), 7.00 (1H, m), 7.09 (1H, m), 7.11 (1H, br s), 7.23 – 7.33 (3H, m), 7.41 – 7.43 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 417 (MH⁺). C₂₃H₂₉³⁵ClN₂OS requires 416. Ret. time 2.08 min. The product was dissolved in methanol and 1M HCl/diethylether solution was added dropwise to the stirred solution. After stirring at room temperature for 5 minutes, the mixture was evaporated at reduced pressure. It was redissolved in DCM and evaporated again at reduced pressure to yield the hydrochloride salt as a white foam (320mg).

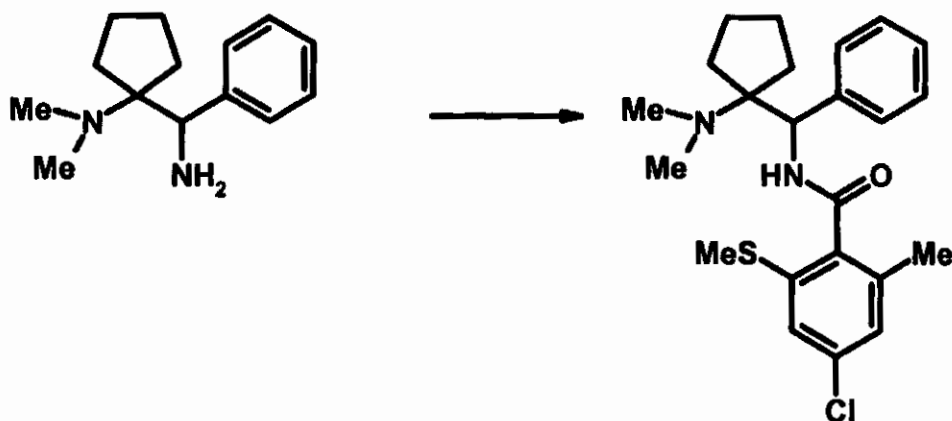
Example 18: N-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide chiral



To a stirred solution of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (0.8g; 3.67mmol) and triethylamine (1.02ml; 7.34mmol) in DCM (35ml) was added 2,4-ditrifluoromethyl-6-methoxy-benzoyl chloride (1.12g; 3.67mmol) in DCM (5ml) dropwise over 5 min. The resulting solution was allowed to stand for 66h at room temperature and then saturated aqueous sodium bicarbonate solution (40ml) added. After stirring at room temperature for 0.5h. the reaction mixture was loaded onto a phase separation cartridge and the eluted organic phase evaporated under reduced pressure. The residue was

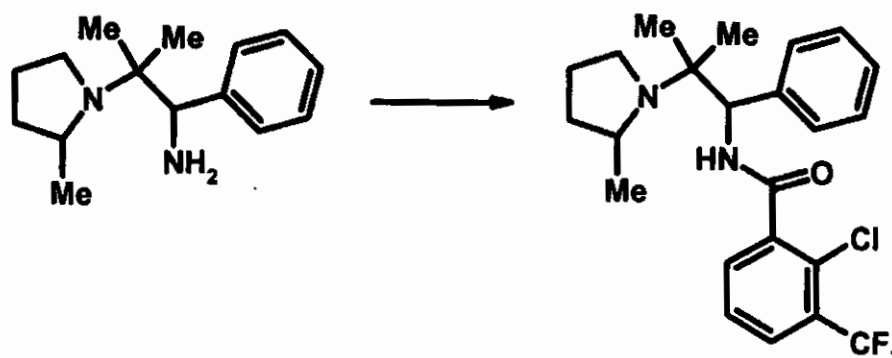
dissolved in a minimum of DCM and chromatographed on silica gel eluting with 0 to 95% ethyl acetate-pentane mixtures. After evaporating the collected fractions under reduced pressure, redissolving in DCM and evaporating under reduced pressure the title compound was obtained as a colourless solid (1.33g; 74%). ^1H NMR (CDCl_3) δ : 0.90 – 1.05 (1H, m), 1.25 – 1.60 (3H, m), 1.60 – 1.75 (2H, m), 1.80 – 1.90 (2H, m), 2.20 (6H, s), 3.93 (3H, s), 5.07 (1H, d, $J = 5\text{Hz}$), 7.14 (1H, br s), 7.20 – 7.35 (4H, m), 7.44 (2H, m), 7.53 (1H, s). Mass Spectrum (Electrospray LC/MS): Found 489 (MH^+). $\text{C}_{24}\text{H}_{26}\text{F}_6\text{N}_2\text{O}_2$ requires 488. Ret. time 2.17min.

10 **Example 19: 4-Chloro-*N*-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-6-(methylthio)benzamide chiral**



A mixture of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (203mg; 0.93mmol), 4-chloro-2-methyl-6-(methylthio)benzoic acid (obtainable as described in F.P. Doyle, J.H.C. Nayler, H.R.J. Waddington, J.C. Hanson and G.R. Thomas. J.Chem.Soc. 1963, 497) (202mg; 0.93mmol), EDC (178mg; 0.93mmol) and HOBt (143mg; 0.93mmol) in DCM (20ml) was stirred at room temperature for 4h and then stood at room temperature for 90h. The resulting reaction mixture was washed with saturated aqueous sodium bicarbonate (50ml) and the organic layer separated by passage through a phase separation cartridge. The organic layer was evaporated, the residue dissolved in a minimum of DCM and chromatographed on silica gel, eluting with 0 – 100% ethyl acetate – pentane. The fractions were combined and evaporated under reduced pressure to afford the title compound (200mg; 52%). ^1H NMR (CDCl_3) δ : 0.90 – 1.10 (1H, m), 1.38 – 1.55 (3H, m), 1.60 – 1.76 (2H, m), 1.80 – 1.90 (2H, m), 2.21 (6H, s), 2.26 (3H, s), 2.47 (3H, s), 5.11 (1H, d, $J = 6\text{Hz}$), 6.94 (1H, d, $J = 5.2\text{Hz}$), 7.00 (1H, m), 7.09 (1H, m), 7.20 – 7.35 (3H, m), 7.40 – 7.50 (2H, m). Mass spectrum (Electrospray LC/MS), ES^+ : Found 417 (MH^+). $\text{C}_{23}\text{H}_{29}^{35}\text{ClN}_2\text{OS}$ requires 416. Ret. time 2.03min. The title product was converted to its corresponding hydrochloride salt (210mg).

Example 20: ($\pm$)-2-Chloro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-3-(trifluoromethyl)benzamide Diastereomers

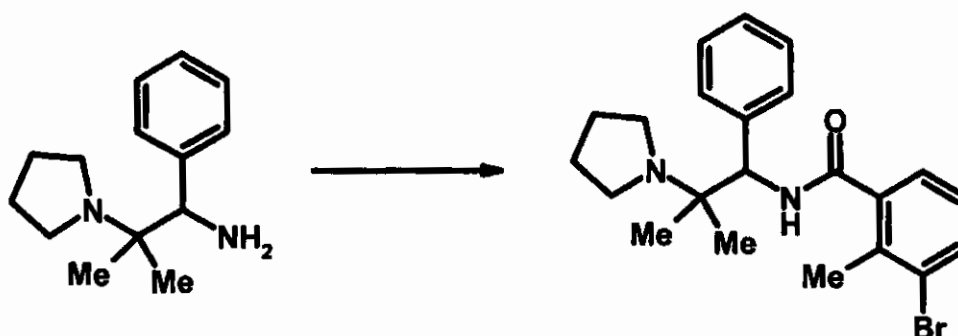


A mixture of [2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]amine D26 (0.150g; 0.647mmol), 2-chloro-3-(trifluoromethyl)benzoic acid (0.174g; 0.775mmol), EDC (0.149g; 0.777mmol) and HOBt (0.020g; 0.148mmol) in DCM (4ml) was shaken at room temperature for 66 hours. Saturated sodium hydrogen carbonate (8ml) was added and shaking continued for 0.5 hours. The organic layer was passed through a phase separation cartridge and applied to a 2g SCX column. The column was washed with DCM and methanol and the product eluted with 1M ammonia in methanol. The crude product was purified by chromatography on silica gel (20g) eluting with 0 – 100% ethyl acetate in pentane gradient to afford the title compound as two pairs of enantiomers.

For the less polar pair of enantiomers (0.170g; 60%). ^1H NMR (CDCl_3) δ : 0.97 (6H, s), 1.05 (3H, d, $J = 6\text{Hz}$), 1.50 (1H, br m), 1.70 – 1.85 (3H, br m), 2.76 – 2.83 (1H, m), 2.90 – 2.97 (1H, m), 3.15 – 3.20 (1H, m), 4.73 (1H, d, $J = 2\text{Hz}$), 7.20 – 7.42 (5H, m), 7.43 (1H, t, $J = 8\text{Hz}$), 7.75 – 7.79 (2H, m), 7.84 (1H, br s). Mass spectrum (Electrospray LC/MS), ES^+ : Found 439 (MH^+). $\text{C}_{23}\text{H}_{26}^{35}\text{ClF}_3\text{N}_2\text{O}$ requires 438. Ret. time 2.17min. The title product was converted to its corresponding hydrochloride salt.

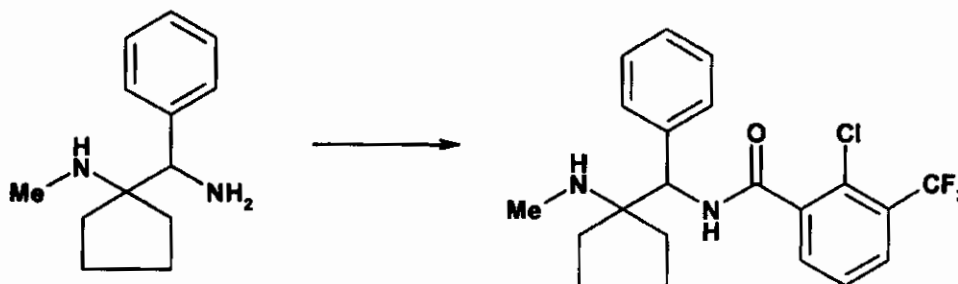
For the more polar pair of enantiomers (0.100g; 35%). ^1H NMR (CDCl_3) δ : 0.95 – 1.10 (9H, m), 1.45 (1H, br m), 1.65 – 1.82 (3H, br m), 2.60 – 2.67 (1H, m), 2.85 – 2.93 (1H, m), 3.35 – 3.40 (1H, m), 4.76 (1H, d, $J = 3.2\text{Hz}$), 7.20 – 7.45 (5H, m), 7.60 (1H, br m), 7.70 – 7.80 (2H, m), 7.84 (1H, m). Mass spectrum (Electrospray LC/MS), ES^+ : Found 439 (MH^+). $\text{C}_{23}\text{H}_{26}^{35}\text{ClF}_3\text{N}_2\text{O}$ requires 438. Ret. time 2.17min. The title product was converted to its corresponding hydrochloride salt.

Example 21: (±)-3-Bromo-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidiny)propyl]benzamide



- 5 To PS-EDC (0.068g; 0.1mmol; 1.42mmol/g) was added a solution of HOAt (0.01mmol in 0.8ml (THF:DCM,1:1)) followed by the addition of 3-bromo-2-methyl-benzoic acid (0.011g; 0.05mmol) in 1:3 NMP:THF(0.25ml) and then [2-methyl-1-phenyl-2-(1-pyrrolidiny)propyl]amine D5 (0.011g 0.05mmol) in DCM (0.25ml). The reaction was allowed to mix for 60h. Following this PS-isocyanate (0.068g, 0.1mmol, 1.5mmol/g) and PS-CO3 (0.068g, 0.1mmol, 1.5mmol/g) were added and allowed to mix for another 24h.
- 10 The reaction mixture was filtered and passed through an SCX block (500mg) (pre-wetted with DCM). The content of the Robbins block was washed with more solvent (DCM:THF, 1:1) and allowed to pass through the SCX which was then washed with DCM (2ml x2) and methanol (2ml x 2). The SCX was then eluted with 0.5M ammonia in methanol and the product containing eluent evaporated to afford the title product (17.4mg; 84%). Mass
- 15 Spectrum (Electrospray LC/MS): Found 414 (MH⁺). C₂₂H₂₇⁷⁹BrN₂O requires 415; Ret. time 2.64min*

Example 22: (±)-2-Chloro-N-[[1-(methylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide

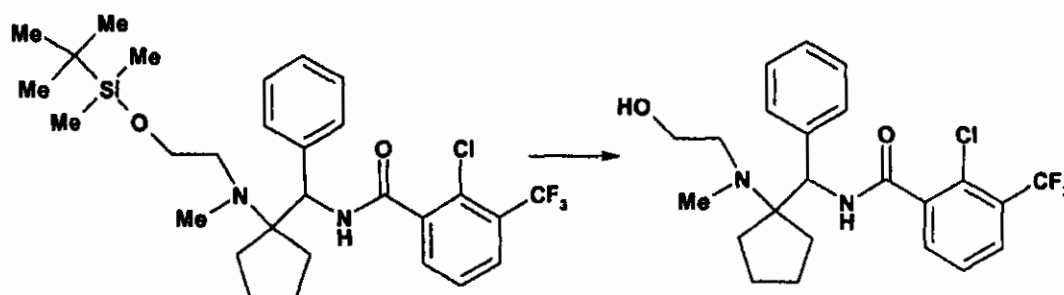


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To a solution of 2-chloro-3-(trifluoromethyl)benzoic acid (0.728g; 3.24mmol) in DMF (20ml) and DIPEA (2.5ml) was added (±)-[[amino(phenyl)methyl]cyclopentyl] methylamine D29 (1.0g; 3.60mmol) and HATU (1.23g; 3.24mmol). The resulting mixture was allowed to stir at room temperature overnight and then DMF evaporated off in vacuo. Residual

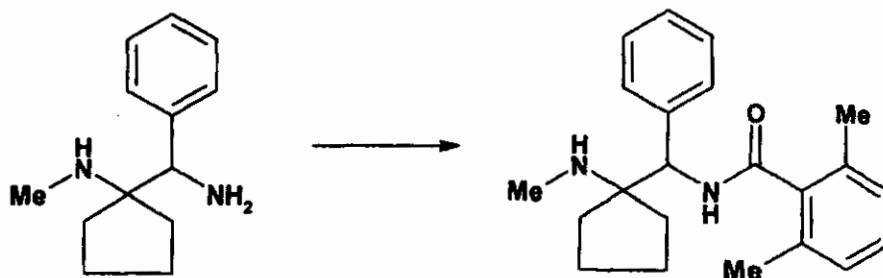
material was partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4) and the filtrate evaporated in vacuo. The desired product was isolated by column chromatography on silica gel using 20% diethyl ether to 100% diethyl ether in n-pentane to afford the title compound as a white solid (0.908g; 61%). ^1H NMR (CDCl_3) δ : 1.47-1.83 (9H, m), 2.21 (3H, s), 5.1 (1H, m), 7.23-7.43 (6H, m), 7.58 (1H, m), 7.65 (1H, m), 7.73 (1H, m); Mass Spectrum (Electrospray LC/MS), API^+ : Found 411 (MH^+). $\text{C}_{21}\text{H}_{22}^{35}\text{ClF}_3\text{N}_2\text{O}$ requires 410. Ret. time 2.04min.

Example 23: ($\pm$)-2-Chloro-N-[[1-[(2-hydroxyethyl)(methyl)amino]cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide



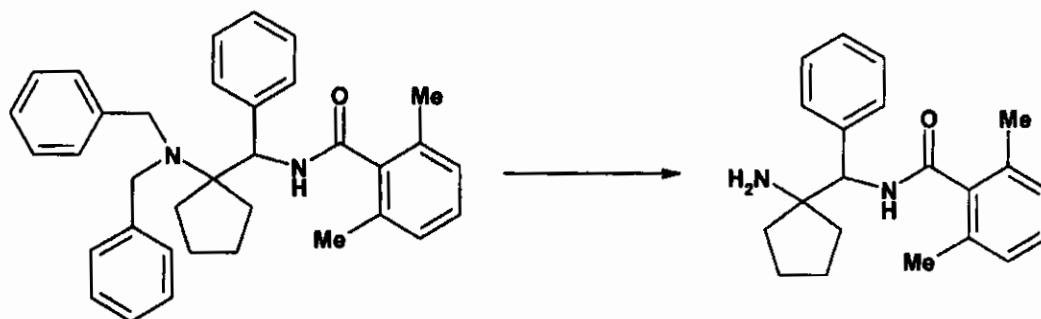
To a solution of ($\pm$)-2-chloro-N-[[1-[(2-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)ethyl](methyl)amino]cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide D30 (0.390g; 0.685mmol) in THF (10ml) was added tetrabutylammonium fluoride (1M solution in THF 1.6ml; 1.6mmol). The reaction mixture was allowed to stir at room temperature for 4 h. The desired product was isolated by column chromatography on silica using 20% to 50% ether in n-pentane, the solvent was reduced in volume by evaporation in vacuo and loaded onto an SCX cartridge. Washing with DCM, then methanol followed by elution with 1M ammonia in methanol afforded the title product (170mg, 73%). Mass Spectrum (Electrospray LC/MS). Found 455 (MH^+). $\text{C}_{23}\text{H}_{26}^{35}\text{ClF}_3\text{N}_2\text{O}_2$ requires 454. Ret. time: 2.09min.

Example 24: 2,6-Dimethyl-N-[[1-(methylamino)cyclopentyl](phenyl)methyl]benzamide chiral



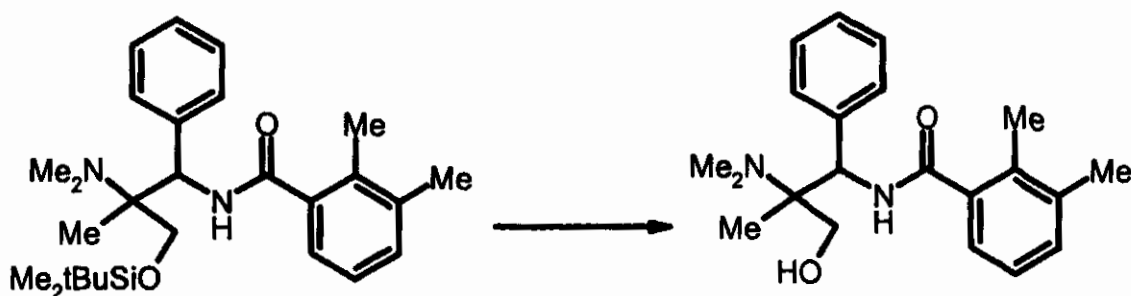
To a solution of 2,6-dimethylbenzoic acid (0.100g; 0.668mmol) in DMF (5ml) and DIPEA (0.12ml) was added {[amino(phenyl)methyl]cyclopentyl} methylamine D31 enantiomer 2 (0.124g; 0.608mmol) and HATU (0.254g; 0.668mmol). The resulting mixture was allowed to stir at room temperature for 3 days and then the DMF was evaporated off under reduced pressure. Residual material was partitioned between ethyl acetate and water, washed with water and the organic layer was dried (Na_2SO_4) and evaporated. The residual material was dissolved in DCM (2ml) and loaded onto an SCX cartridge. Washing with DCM, then methanol followed by elution with 1M ammonia in methanol afforded the title product (155mg; 76%). ^1H NMR (CDCl_3) δ : 1.3-1.8 (9H, m), 2.21 (3H, s), 2.28 (6H, s), 5.07 (1H, m), 7.0 (2H, m), 7.1-7.4 (7H, m). Mass Spectrum (Electrospray LC/MS). Found 337 (MH^+). $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}$ requires 336. Ret. time: 1.86min.

Example 25: ($\pm$)-N-[(1-aminocyclopentyl)(phenyl)methyl]-2,6-dimethylbenzamide



The title compound (1.14g; 71%) was prepared from the catalytic hydrogenation of ($\pm$)-N-[[1-[bis(phenylmethyl)amino]cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide D34 (2.51g; 5mmol) over 10% Pd/Carbon (0.4g) in 3M HCl (8ml) and ethanol (150ml) in a similar manner to that described in D29. The ethanol was evaporated off in vacuo and the residual material was partitioned between DCM and sodium bicarbonate solution and dried (Na_2SO_4). The filtrate was reduced in volume by evaporation in vacuo and loaded onto an SCX cartridge. Washing with DCM, then methanol followed by elution with 1M ammonia in methanol afforded the title product (90mg, 88%). ^1H NMR (CDCl_3) δ : 0.98-1.96 (10H, m), 2.23 (6H, s), 4.97 (1H, m), 7.0 (2H, m), 7.16 (1H, m), 7.22-7.41 (6H, m); Mass Spectrum (Electrospray LC/MS). Found 323 (MH^+). $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}$ requires 322. Ret. time 1.69min.

Example 26: ($\pm$)-N-[2-(Dimethylamino)-3-hydroxy-2-methyl-1-phenylpropyl]-2,3-dimethylbenzamide diastereomeric mixture



- 5 A solution of ($\pm$)-N-(2-(dimethylamino)-3-[(1,1-dimethylethyl)(dimethyl)silyloxy]-2-methyl-1-phenylpropyl)-2,3-dimethylbenzamide D49 (56 mg; 0.12mmol) in THF (5ml) was treated with a solution of tetrabutylammonium fluoride (1.0M solution in THF; 0.2ml, 0.2mmol) and the mixture stirred at room temperature overnight. The mixture was poured directly onto a chromatography column (Flashmaster II; eluent 0-100% ethyl acetate / pentane) to afford
- 10 the title compound (38mg; 63%). ^1H NMR (CDCl_3) δ : 0.73 and 1.14 (3H, 2 x s), 1.70-2.50 (1H, br s), 2.26 (6H, q), 2.38 and 2.48 (6H, 2 x s), 3.17, 3.39, and 3.55 (2H, 3 x d), 5.26 and 5.46 (1H, 2 x d), 6.83 and 7.89 (1H, 2 x br d), 7.07-7.46 (8H, br m). Mass spectrum (Electrospray LC/MS), API^+ : Found 341 (MH^+), $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2\text{Si}$ requires 340. Ret. time 1.71 and 1.76 min.

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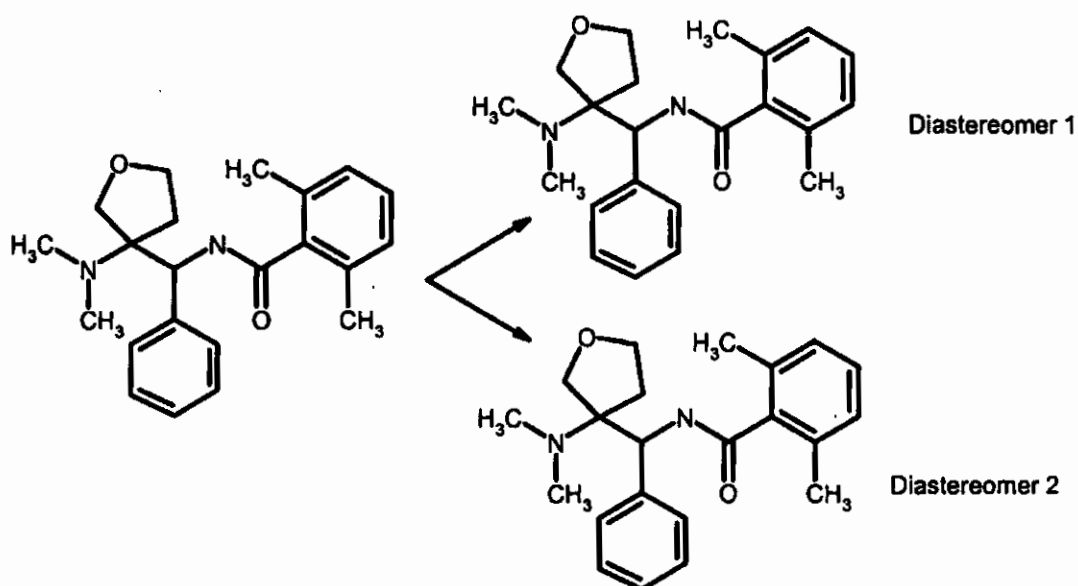
The examples in Table 3 were prepared in a manner similar to that described in example E26.

Table 3

Example	Structure	Mass spectrum (Electrospray LC/MS), API^+ Ret.time (min)	Name
27		Found 341 (MH^+) $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2$ requires 340; 1.78 and 1.83.	($\pm$)-N-[2-(dimethylamino)-3-hydroxy-2-methyl-1-phenylpropyl]-2,6-dimethylbenzamide

28		Found 415 (MH ⁺) C ₂₀ H ₂₂ ³⁵ ClF ₃ N ₂ O ₂ requires 414; 1.91 and 1.94.	(±)-2-chloro- <i>N</i> -[2-(dimethylamino)-3-hydroxy-2-methyl-1-phenylpropyl]-3-(trifluoromethyl)benzamide
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Example 29: (±)-*N*-[[3-(Dimethylamino)tetrahydro-3-furanyl](phenyl)methyl]-2,6-dimethylbenzamide: Diastereomer 1 and Diastereomer 2



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Racemic *N*-[[3-(dimethylamino)tetrahydro-3-furanyl](phenyl)methyl]-2,6-dimethylbenzamide E204 (40 mg, 0.11 mmol) was separated by preparative chiral HPLC to afford the title product diastereomer 1 (13 mg); Chiral HPLC: >95% de; Mass spectrum (Electrospray LC/MS): Found 353 (MH⁺). Ret. time 1.67 min. C₂₂H₂₈N₂O₂ requires 352 and diastereomer 2 (14 mg); Chiral HPLC: >95% de; Mass spectrum (Electrospray LC/MS): Found 353 (MH⁺) Ret. time 1.69 min. C₂₂H₂₈N₂O₂ requires 352.

Preparative HPLC conditions:

15 Column: S.F.C. Ethyl Pyridyl 150 mm x 21.1 mm i.d; 6 micron particle size

Mobile phase: Carbon Dioxide: Ethanol (95:5) v/v; pump-mixed isocratic

Flow rate: 50 ml/min

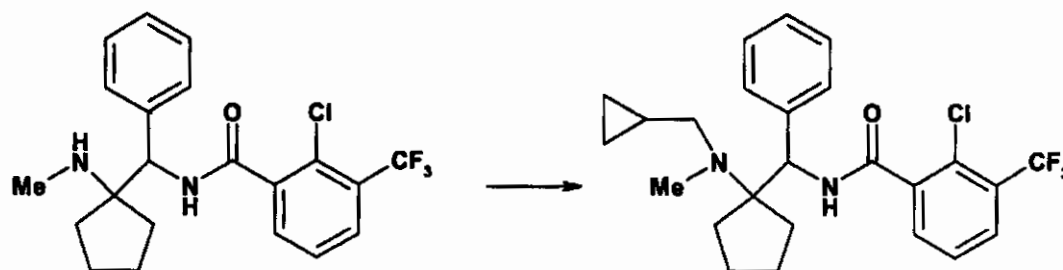
- Pressure: 100 bar
 Temperature: 40°C
 UV wavelength range: 220nm
 Elution time: 10 min
 5 Ret. Time: 6.3 min (Diastereomer 1); 7.1 min (Diastereomer 2)

Analytical chromatography conditions:

- Column: S.F.C. Ethyl Pyridyl 150 mm x 4.6 mm i.d; 6 micron particle size
 10 Mobile phase: Carbon Dioxide: Ethanol (98:2) v/v; pump-mixed isocratic
 Flow rate: 2.35 ml/min
 Pressure: 100 bar
 Temperature: 38°C
 UV wavelength range: 254 nm
 15 Elution time: 15 min
 Ret. Time: 12.2 min (Diastereomer 1); 13.4 min (Diastereomer 2)

Example 30: (±)-2-Chloro-N-[[1-[(cyclopropylmethyl)(methyl)amino]cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide hydrochloride

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- To a solution (±)-2-chloro-N-[[1-(methylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide E22 (143g; 0.35mmol), cyclopropanecarboxaldehyde (0.026ml; 0.035mmol) and acetic acid (3 drops) in 1,2-dichloroethane (10ml) was added sodium triacetoxyborohydride (303mg; 1.4mmol). The resulting mixture was allowed to stir at room temperature under argon overnight. Then the reaction mixture was diluted with DCM (20ml), washed with saturated potassium carbonate solution and brine, dried (Na₂SO₄) and evaporated in vacuo. The mixture was separated by column chromatography on silica gel using 20% ether in n-pentane to 2% methanol in ether. The
- 25
30

oil obtained was treated with 1M HCl in ether to give the title product as an off white hydrochloride salt (0.054g; 33%). Mass Spectrum (Electrospray LC/MS). Found 465 (MH⁺). C₂₅H₂₈³⁵ClF₃N₂O requires 464. Ret. time: 2.30 min.

- 5 The compounds in Table 4 below were prepared using similar methods to those described for Example 30 above.

Table 4

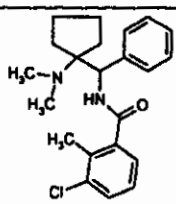
Example	Structure	Mass spectrum (Electrospray LC/MS), API ⁺ Ret.time (min)	Name
31		Found 365 (MH ⁺). C ₂₄ H ₃₂ N ₂ O requires 364; 1.96.	(±)-N-[[1-ethyl(methyl)amino]cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide
32		Found 377 (MH ⁺). C ₂₅ H ₃₂ N ₂ O requires 376; 2.07	(±)-N-[[1-[(cyclopropylmethyl)amino]cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide
33		Found 439 (MH ⁺). C ₂₃ H ₂₆ ³⁵ ClF ₃ N ₂ O requires 438; 2.23.	(±)-2-Chloro-N-[[1-ethyl(methyl)amino]cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide
34		Found 351 (MH ⁺). C ₂₃ H ₃₀ N ₂ O requires 350; 1.82.	(±)-2-Chloro-N-[[1-(ethylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide
35		Found 391 (MH ⁺). C ₂₆ H ₃₄ N ₂ O requires 390; 2.19	(±)-N-[[1-[(cyclopropylmethyl)(methyl)amino]cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide

The compounds in Table 5 below were prepared using similar methods to those described for the Examples above. Coupling method: A = Acid chloride (using method similar to that in Example 13); E = EDC(using method similar to that in Example 17); H = HATU(using method similar to that in Example 15); P = Polymer-supported DCC (using method similar to that in Example 1); PE = Polymer-supported EDC (using method similar to that in Example 21). Work-up and purification was carried out using appropriate methods similar to those described in the examples above.

Benzoic acid starting materials were obtained commercially except for 2,6-dichloro-3-trifluoromethylbenzoic acid used for the examples indicated with a #, which was obtained by the method described in DE1924766. 4-chloro-2-methyl-6-(methylthio)benzoic acid is obtainable as described in F.P. Doyle, J.H.C. Nayler, H.R.J. Waddington, J.C. Hanson and G.R. Thomas. J.Chem.Soc. 1963, 497.

For the example compound names, those denoted by (±)- are derived from the corresponding racemic amine D2, D8, D10, D12, D14, D16, D18, D20, D22, D24, D26, D29, D36, D38, D40, D42, D43, D46, D48 and those without are from the corresponding chiral amines D3 enantiomer 2, D6, D31 enantiomer 2. LCMS retention times were generally measured using analytical LC/MS chromatography conditions method A. Compounds annotated with * are compounds prepared using array format described in Example 23 and they were analysed using analytical LC/MS chromatography conditions method B.

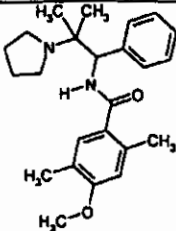
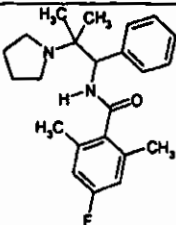
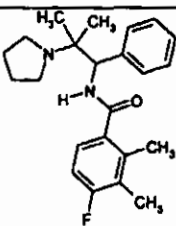
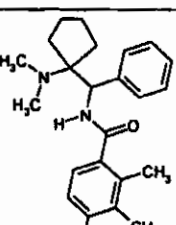
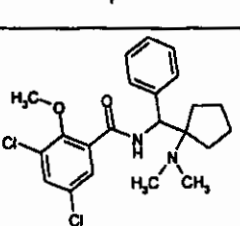
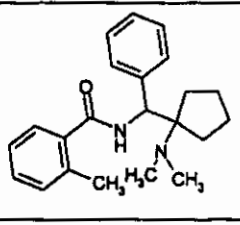
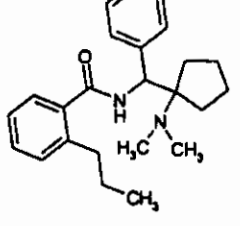
Table 5

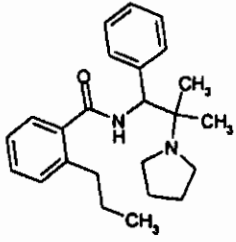
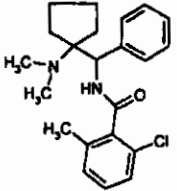
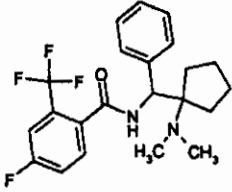
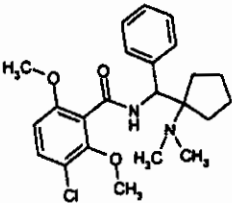
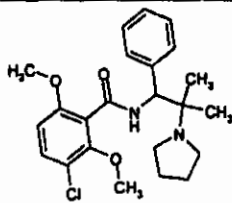
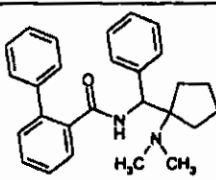
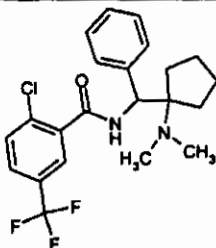
Ex	Structure	Method	Mass spectrum (Electrospray LC/MS), API ⁺ Ret.time (min)	Name
36		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 2.08	3-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methylbenzamide chiral

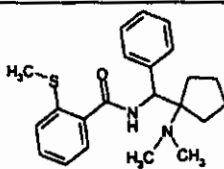
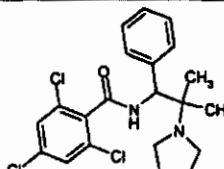
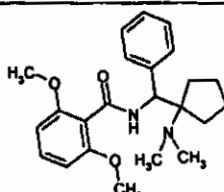
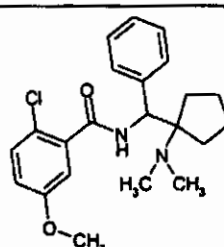
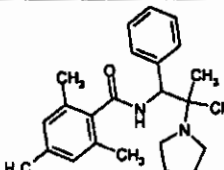
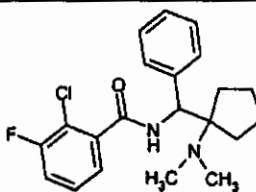
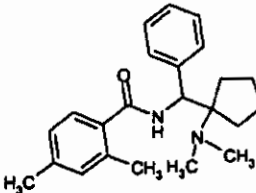
37		P	Found 415 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O requires 414; 2.09	3-bromo-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methylbenzamide chiral
38		P	Found 367 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₂ requires 366; 1.84	2-methyl-6-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
39		P	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 2.03	(±)-2,5-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
40		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 2.01	2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-methylbenzamide chiral
41		P	Found 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requires 404; 2.20	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-5-(trifluoromethyl)benzamide chiral
42		P	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 2.04	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-5-(trifluoromethyl)benzamide chiral
43		PE	Found 429 (MH ⁺) C ₂₃ H ₂₉ ⁷⁹ BrN ₂ O requires 428; 2.68*	(±)-3-bromo-2-methyl-N-[2-methyl-2-(2-methyl-1-phenylpropyl)-1-pyrrolidinyl]benzamide
44		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 1.98	(±)-2-chloro-3-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide

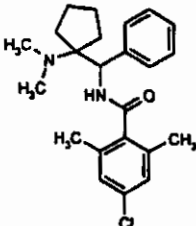
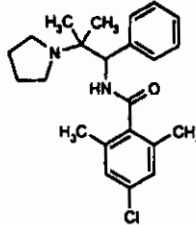
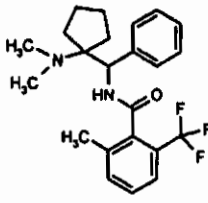
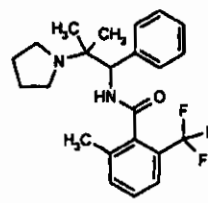
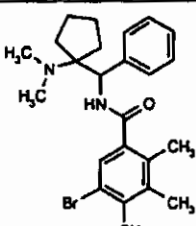
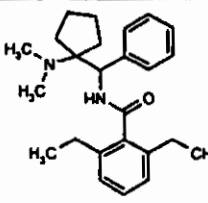
45		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 1.90	(±)-2-chloro-6-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
46		PE	Found 431 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ OS requires 430; 2.57*	(±)-4-chloro-2-methyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-6-(methylthio)benzamide
47		P	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 1.88	2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-6-(methoxy)benzamide chiral
48		P	Found 355 (MH ⁺) C ₂₂ H ₂₇ FN ₂ O requires 354; 1.96	(±)-3-fluoro-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
49		P	Found 415 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O requires 414; 1.92	(±)-2-bromo-6-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
50		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 2.08	(±)-3-chloro-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
51		P	Found 355 (MH ⁺) C ₂₂ H ₂₇ FN ₂ O requires 354; 1.97	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-fluoro-2-methylbenzamide chiral

52		PE	Found 383 (MH ⁺) C ₂₃ H ₃₀ N ₂ OS requires 382; 2.62*	(±)-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-2-(methylthio)benzamide
53		PE	Found 429 (MH ⁺) C ₂₃ H ₂₉ ⁷⁹ BrN ₂ O requires 428; 2.44*	(±)-2-bromo-6-methyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
54		P	Found 367 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₂ requires 366; 1.84	(±)-2-methyl-6-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
55		PE	Found 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requires 384; 2.65*	(±)-2-chloro-3-methyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
56		P	Found 425 (MH ⁺) C ₂₁ H ₂₃ ³⁵ Cl ₃ N ₂ O requires 424; 2.08	2,4,6-trichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]benzamide chiral
57		P	Found 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requires 404; 2.18	(±)-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-5-(trifluoromethyl)benzamide
58		P	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 2.10	2,3-Dimethyl-4-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral

59		P	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 2.14	2,5-Dimethyl-4-(methoxy)- N-[2-methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e chiral
60		A	Found 369 (MH ⁺) C ₂₃ H ₂₉ FN ₂ O requires 368; 2.00	4-Fluoro-2,6-dimethyl-N-[2- methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e chiral
61		P	Found 369 (MH ⁺) C ₂₃ H ₂₉ FN ₂ O requires 368; 2.02	4-Fluoro-2,3-dimethyl-N-[2- methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e chiral
62		P	Found 369 (MH ⁺) C ₂₃ H ₂₉ FN ₂ O requires 368; 2.05	N-[[1- (Dimethylamino)cyclopentyl](phenyl)methyl]-4-fluoro-2,3- dimethylbenzamide chiral
63		PE	Found 421 (MH ⁺) C ₂₂ H ₂₈ ³⁵ Cl ₂ N ₂ O ₂ requires 420; 2.55*	3,5-dichloro-N-[[1- (dimethylamino)cyclopentyl](phenyl)methyl]-2- (methoxy)benzamide chiral
64		PE	Found 337 (MH ⁺) C ₂₂ H ₂₈ N ₂ O requires 336; 2.34*	N-[[1- (dimethylamino)cyclopentyl](phenyl)methyl]-2- methylbenzamide chiral
65		PE	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.48*	N-[[1- (dimethylamino)cyclopentyl](phenyl)methyl]-2- propylbenzamide chiral

66		PE	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.45*	(±)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-2-propylbenzamide
67		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 1.93	2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-6-methylbenzamide chiral
68		PE	Found 409 (MH ⁺) C ₂₂ H ₂₄ F ₄ N ₂ O requires 408; 2.44*	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-4-fluoro-2-(trifluoromethyl)benzamide chiral
69		PE	Found 417 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O ₃ requires 416; 2.43*	3-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-bis(methoxy)benzamide chiral
70		PE	Found 417 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O ₃ requires 416; 2.4*	(±)-3-chloro-2,6-bis(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
71		PE	Found 399 (MH ⁺) C ₂₇ H ₃₀ N ₂ O requires 398; 2.51*	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-biphenylcarboxamide chiral
72		PE	Found 425 (MH ⁺) C ₂₂ H ₂₄ ³⁵ ClF ₃ N ₂ O requires 424; 2.48*	2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-5-(trifluoromethyl)benzamide chiral

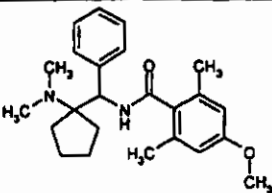
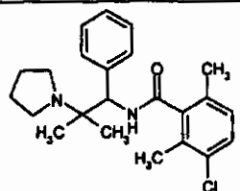
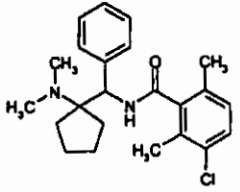
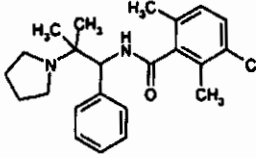
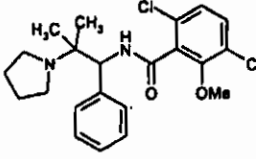
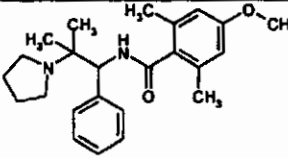
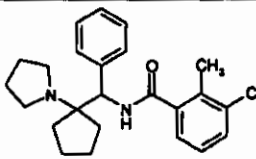
73		PE	Found 369 (MH ⁺) C ₂₂ H ₂₈ N ₂ OS requires 368; 2.58*	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(methylthio)benzamide chiral
74		PE	Found 425 (MH ⁺) C ₂₁ H ₂₃ ³⁵ Cl ₃ N ₂ O requires 424; 2.93*	(±)-2,4,6-trichloro-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
75		PE	Found 383 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₃ requires 382; 2.88*	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-bis(methoxy)benzamide chiral
76		PE	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 2.56*	2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-5-methoxybenzamide chiral
77		PE	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.46*	(±)-2,4,6-trimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
78		PE	Found 375 (MH ⁺) C ₂₁ H ₂₄ ³⁵ ClFN ₂ O requires 374; 2.99*	2-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-fluorobenzamide chiral
79		PE	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 2.96*	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,4-dimethylbenzamide chiral

80		E	Found 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requires 384; 2.19	4-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide chiral
81		E	Found 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requires 384; 2.07	4-chloro-2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
82		E	Found 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requires 404; 1.91	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-6-(trifluoromethyl)benzamide chiral
83		E	Found 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requires 404; 1.91	2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-6-(trifluoromethyl)benzamide chiral
84		A	Found 443 (MH ⁺) C ₂₄ H ₃₁ ⁷⁹ BrN ₂ O requires 442; 2.27	5-bromo-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,3,4-trimethylbenzamide chiral
85		E	Found 379 (MH ⁺) C ₂₅ H ₃₄ N ₂ O requires 378; 2.07	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-diethylbenzamide chiral

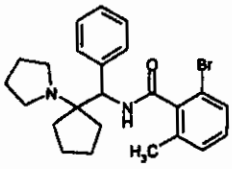
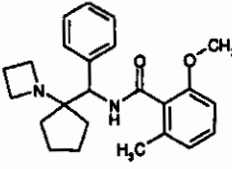
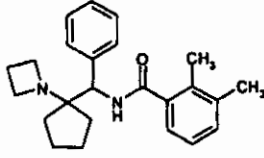
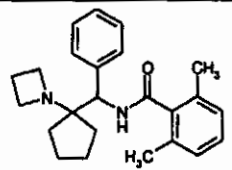
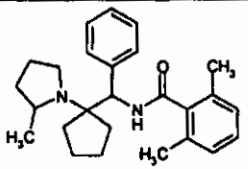
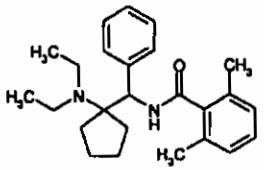
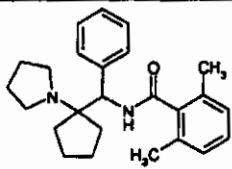
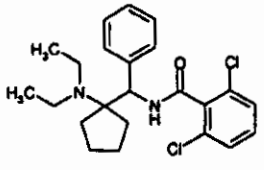
86		E	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.06	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,3,4-trimethylbenzamide chiral
87		E	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 2.00	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,5-dimethyl-4-(methoxy)benzamide chiral
88		E	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 1.96	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,3-dimethyl-4-(methoxy)benzamide chiral
89		E	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.02	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(1-methylethyl)benzamide chiral
90		P	Found 413 (MH ⁺) C ₂₈ H ₃₂ N ₂ O requires 412;	(±)-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-3-biphenylcarboxamide
91		P#	Found 459 (MH ⁺) C ₂₂ H ₂₃ ³⁵ Cl ₂ F ₃ N ₂ O requires 458; 2.11	2,6-dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide chiral
92		H	Found 337 (MH ⁺) C ₂₂ H ₂₈ N ₂ O requires 336; 1.88	(±)-2,6-dimethyl-N-[[1-(methylamino)cyclopentyl](phenyl)methyl]benzamide

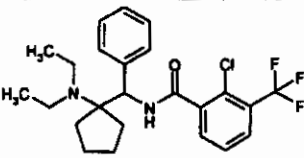
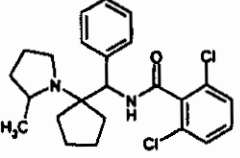
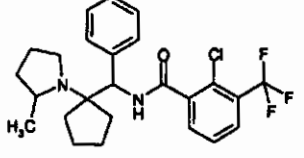
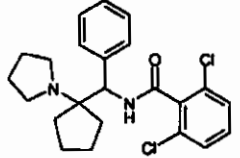
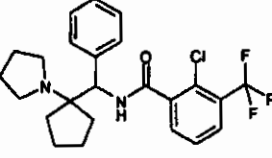
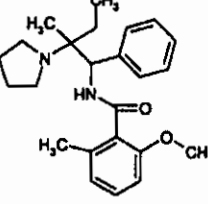
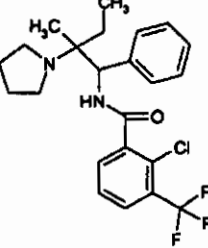
93		P	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 1.97	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,4,6-trimethylbenzamide chiral
94		P	Found 407 (MH ⁺) C ₂₇ H ₃₈ N ₂ O requires 406; 2.34	(±)-4-(1,1-dimethylethyl)-2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
95		P	Found 461 (MH ⁺) C ₂₃ H ₂₉ ⁷⁹ BrN ₂ O ₃ requires 460; 1.98	(±)-3-bromo-2,6-bis(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
96		P	Found 415 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ O ₂ requires 414; 2.36	(±)-5-chloro-4-ethyl-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
97		A	Found 395 (MH ⁺) C ₂₅ H ₃₄ N ₂ O ₂ requires 394; 2.14	(±)-2,6-dimethyl-N-[(1-{methyl[2-(methoxy)ethyl]amino}cyclopentyl)(phenyl)methyl]benzamide
98		A	Found 471 (MH ⁺) C ₂₄ H ₂₄ F ₆ N ₂ O requires 470; 2.29	(±)-N-[2-(3-azabicyclo[3.1.0]hex-3-yl)-2-methyl-1-phenylpropyl]-2,4-bis(trifluoromethyl)benzamide
99		H	Found 501 (MH ⁺) C ₂₅ H ₂₆ F ₆ N ₂ O ₂ requires 500; 2.30	(±)-N-[2-(3-azabicyclo[3.1.0]hex-3-yl)-2-methyl-1-phenylpropyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide

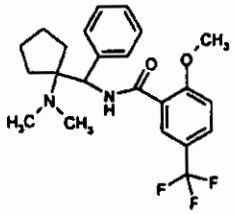
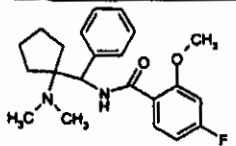
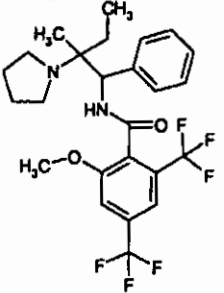
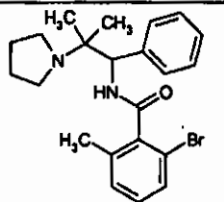
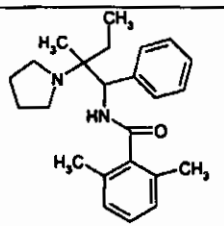
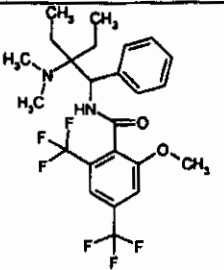
100		A	Found 363 (MH ⁺) C ₂₄ H ₃₀ N ₂ O requires 362; 1.94	(±)-N-[2-(3-azabicyclo[3.1.0]hex-3-yl)-2-methyl-1-phenylpropyl]-2,6-dimethylbenzamide
101		H	Found 375 (MH ⁺) C ₂₅ H ₃₀ N ₂ O requires 374; 1.94	(±)-N-[[1-(2,5-dihydro-1H-pyrrol-1-yl)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide
102		H	Found 513 (MH ⁺) C ₂₈ H ₂₆ F ₆ N ₂ O ₂ requires 512; 2.35	(±)-N-[[1-(2,5-dihydro-1H-pyrrol-1-yl)cyclopentyl](phenyl)methyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide
103		H	Found 429 (MH ⁺) C ₂₃ H ₂₈ ⁷⁹ BrN ₂ O requires 428; 2.02	(±)-2-bromo-6-methyl-N-[2-methyl-1-phenyl-2-(1-piperidinyl)propyl]benzamide
104		H	Found 473 (MH ⁺) C ₂₄ H ₂₆ F ₆ N ₂ O requires 472; 2.18	(±)-N-[2-methyl-1-phenyl-2-(1-piperidinyl)propyl]-2,4-bis(trifluoromethyl)benzamide
105		H	Found 503 (MH ⁺) C ₂₅ H ₂₈ F ₆ N ₂ O ₂ requires 502; 2.28	(±)-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-piperidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide
106		H	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 1.88	(±)-2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-piperidinyl)propyl]benzamide
107		H	Found 405 (MH ⁺) C ₂₂ H ₂₈ ³⁵ Cl ₂ N ₂ O requires 404;	2,4-dichloro-6-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide

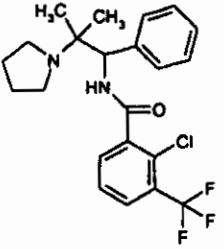
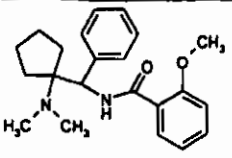
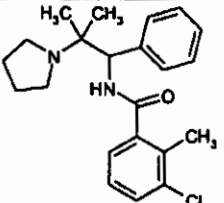
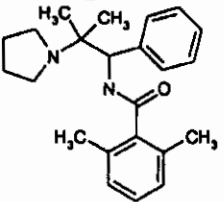
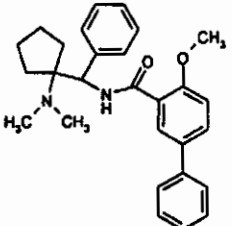
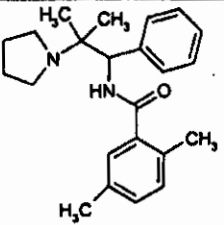
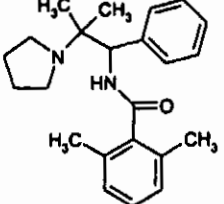
			2.10	e chiral
108		H	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 1.89	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethyl-4-(methoxy)benzamide chiral
109		P	Found 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requires 384; 2.11	3-chloro-2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
110		P	Found 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requires 384; 2.12	3-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide chiral
111		H	Found 385 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O requires 384; 2.02	(±)-3-chloro-2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
112		H	Found 421 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O ₂ requires 420; 2.02	(±)-3,6-dichloro-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
113		H	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 1.86	(±)-2,6-dimethyl-4-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
114		H	Found 397 (MH ⁺) C ₂₄ H ₂₉ ³⁵ ClN ₂ O requires 396; 2.13	(±)-3-chloro-2-methyl-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide

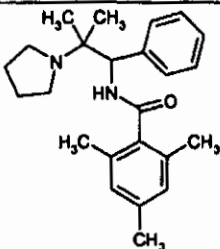
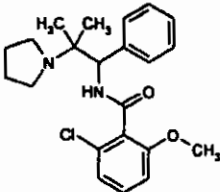
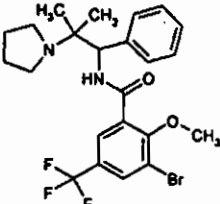
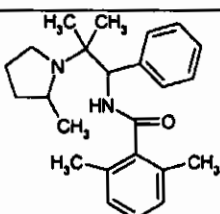
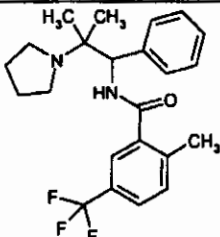
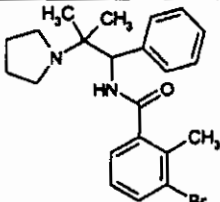
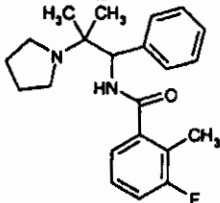
115		H	Found 441 (MH ⁺) C ₂₄ H ₂₉ ⁷⁹ BrN ₂ O requires 440; 2.15	(±)-3-bromo-2-methyl-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide
116		H	Found 451 (MH ⁺) C ₂₃ H ₂₅ ³⁵ Cl ₃ N ₂ O requires 450; 2.14	(±)-2,4,6-trichloro-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide
117		H	Found 377 (MH ⁺) C ₂₅ H ₃₂ N ₂ O requires 376; 2.02	(±)-2,3-dimethyl-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide
118		H	Found 393 (MH ⁺) C ₂₅ H ₃₂ N ₂ O ₂ requires 392; 1.95	(±)-2-methyl-6-(methyloxy)-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide
119		H	Found 391 (MH ⁺) C ₂₆ H ₃₄ N ₂ O requires 390; 2.08	(±)-2,4,6-trimethyl-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide
120		H	Found 443 (MH ⁺) C ₂₅ H ₃₁ ³⁵ ClN ₂ OS requires 442; 2.18	(±)-4-chloro-2-methyl-6-(methylthio)-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide
121		H	Found 397 (MH ⁺) C ₂₄ H ₂₉ ³⁵ ClN ₂ O requires 396; 2.08	(±)-2-chloro-6-methyl-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide
122		H	Found 413 (MH ⁺) C ₂₄ H ₂₉ ³⁵ ClN ₂ O ₂ requires 412; 1.92	(±)-2-chloro-6-(methyloxy)-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide

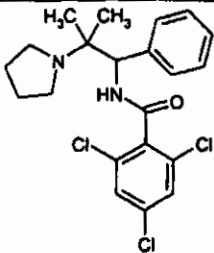
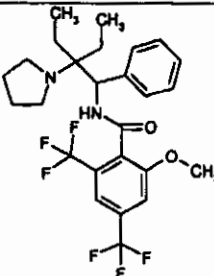
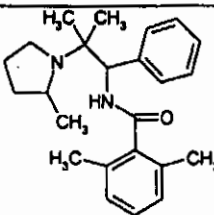
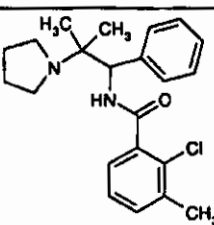
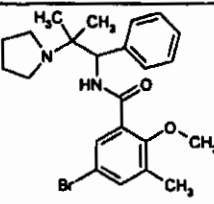
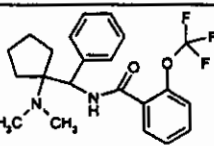
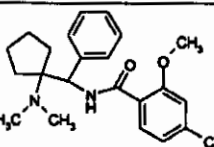
123		H	Found 441 (MH ⁺) C ₂₄ H ₂₉ ⁷⁹ BrN ₂ O requires 440; 1.97	(±)-2-bromo-6-methyl-N- {phenyl[1-(1- pyrrolidinyl)cyclopentyl]meth yl}benzamide
124		H	Found 379 (MH ⁺) C ₂₄ H ₃₀ N ₂ O ₂ requires 378; 1.97	(±)-N-[[1-(1- azetidyl)cyclopentyl](pheny l)methyl]-2-methyl-6- (methoxy)benzamide
125		A	Found 363 (MH ⁺) C ₂₄ H ₃₀ N ₂ O requires 362; 1.99	(±)-N-[[1-(1- azetidyl)cyclopentyl](pheny l)methyl]-2,3- dimethylbenzamide
126		A	Found 363 (MH ⁺) C ₂₄ H ₃₀ N ₂ O requires 362; 1.90	(±)-N-[[1-(1- azetidyl)cyclopentyl](pheny l)methyl]-2,6- dimethylbenzamide
127		A	Found 391 (MH ⁺) C ₂₆ H ₃₄ N ₂ O requires 390; 2.06	(±)-2,6-dimethyl-N-[[1-(2- methyl-1- pyrrolidinyl)cyclopentyl](phen yl)methyl]benzamide
128		A	Found 379 (MH ⁺) C ₂₅ H ₃₄ N ₂ O requires 378; 2.04	(±)-N-[[1- (diethylamino)cyclopentyl](p henyl)methyl]-2,6- dimethylbenzamide
129		A	Found 377 (MH ⁺) C ₂₅ H ₃₂ N ₂ O requires 376; 1.90	(±)-2,6-dimethyl-N-{phenyl[1- (1- pyrrolidinyl)cyclopentyl]meth yl}benzamide
130		H	Found 419 (MH ⁺) C ₂₃ H ₂₈ ³⁵ Cl ₂ N ₂ O requires 418; 2.15	(±)-2,6-dichloro-N-[[1- (diethylamino)cyclopentyl](p henyl)methyl]benzamide

131		H	Found 453 (MH ⁺) C ₂₄ H ₂₈ ³⁵ ClF ₃ N ₂ O requires 452; 2.25	(±)-2-chloro-N-[[1-(diethylamino)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide
132		H	Found 431 (MH ⁺) C ₂₄ H ₂₈ ³⁵ Cl ₂ N ₂ O requires 430; 1.93	(±)-2,6-dichloro-N-[[1-(2-methyl-1-pyrrolidinyl)cyclopentyl](phenyl)methyl]benzamide
133		H	Found 465 (MH ⁺) C ₂₅ H ₂₈ ³⁵ ClF ₃ N ₂ O requires 464; 2.15	(±)-2-chloro-N-[[1-(2-methyl-1-pyrrolidinyl)cyclopentyl](phenyl)methyl]-3-(trifluoromethyl)benzamide
134		H	Found 417 (MH ⁺) C ₂₃ H ₂₆ ³⁵ Cl ₂ N ₂ O requires 416; 1.99	(±)-2,6-dichloro-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}benzamide
135		H	Found 451 (MH ⁺) C ₂₄ H ₂₆ ³⁵ ClF ₃ N ₂ O requires 450	(±)-2-chloro-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}-3-(trifluoromethyl)benzamide
136		E	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 1.83 & 1.87	(±)-2-methyl-6-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]benzamide
137		A	Found 439 (MH ⁺) C ₂₃ H ₂₆ ³⁵ ClF ₃ N ₂ O requires 438; 2.11 & 2.17.	(±)-2-chloro-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-3-(trifluoromethyl)benzamide

138		P	Found 421 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O ₂ requires 420; 2.19.	(±)-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(methoxy)-5-(trifluoromethyl)benzamide
139		P	Found 371 (MH ⁺) C ₂₂ H ₂₇ FN ₂ O ₂ requires 370; 1.99.	(±)-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-4-fluoro-2-(methoxy)benzamide
140		E	Found 503 (MH ⁺) C ₂₅ H ₂₈ F ₆ N ₂ O ₂ requires 502; 2.23 & 2.27.	(±)-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-4,6-bis(trifluoromethyl)benzamide
141		E	Found 415 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O requires 414; 1.84.	2-bromo-6-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
142		A	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 1.86 & 1.94.	(±)-2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]benzamide
143		E	Found 491 (MH ⁺) C ₂₄ H ₂₈ F ₆ N ₂ O ₂ requires 490; 2.26.	(±)-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide

144		P	Found 425 (MH ⁺) C ₂₂ H ₂₄ ³⁵ ClF ₃ N ₂ O requires 424; 2.0.	(±)-2-chloro-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-3-(trifluoromethyl)benzamide
145		P	Found 353 (MH ⁺) C ₂₂ H ₂₈ N ₂ O ₂ requires 352; 1.93 .	(±)-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(methoxy)benzamide
146		E	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 1.98 .	3-chloro-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
147		E	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 1.89 .	2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
148		P	Found 429 (MH ⁺) C ₂₈ H ₃₂ N ₂ O ₂ requires 428; 2.32 .	(±)-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-4-(methoxy)-3-biphenylcarboxamide
149		E	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 1.94 .	2,5-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
150		P	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350 1.80 .	(±)-2,6-dimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide

151		E	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 1.88 .	2,4,6-trimethyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
152		E	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 1.84 .	2-chloro-6-(methyloxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
153		E	Found 499 (MH ⁺) C ₂₃ H ₂₈ ⁷⁹ BrF ₃ N ₂ O ₂ requires 498; 2.28 .	3-bromo-2-(methyloxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-5-(trifluoromethyl)benzamide chiral
154		E	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.00 .	(±)-2,6-dimethyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
155		E	Found 405 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O requires 404; 2.19 .	2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-5-(trifluoromethyl)benzamide chiral
156		E	Found 415 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O requires 414; 2.12	3-bromo-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
157		E	Found 355 (MH ⁺) C ₂₂ H ₂₇ FN ₂ O requires 354; 1.96 .	3-fluoro-2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral

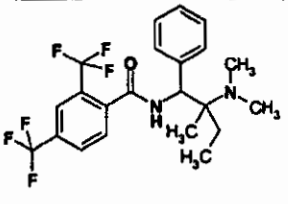
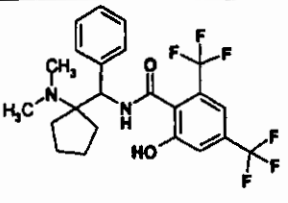
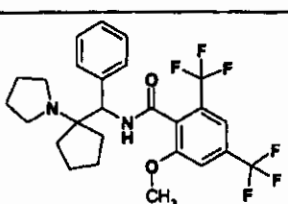
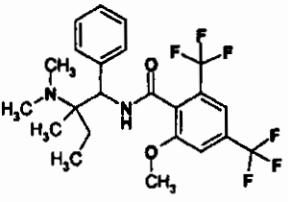
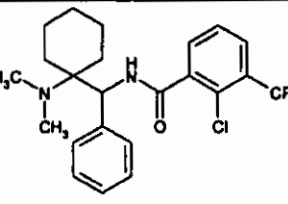
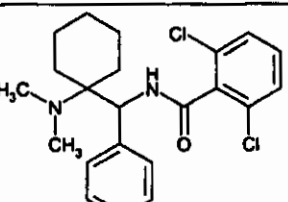
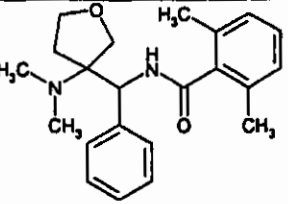
158		E	Found 425 (MH ⁺) C ₂₁ H ₂₃ ³⁵ Cl ₃ N ₂ O requires 424; 2.11 .	2,4,6-trichloro-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
159		E	Found 517 (MH ⁺) C ₂₈ H ₃₀ F ₆ N ₂ O ₂ requires 516; 2.32 .	(±)-N-[2-ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide
160		E	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 1.96 .	(±)-2,6-dimethyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
161		E	Found 371 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O requires 370; 1.89 .	2-chloro-3-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
162		E	Found 445 (MH ⁺) C ₂₃ H ₂₉ ⁷⁹ BrN ₂ O ₂ requires 444; 2.15	5-bromo-3-methyl-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral
163		P	Found 407 (MH ⁺) C ₂₂ H ₂₅ F ₃ N ₂ O ₂ requires 406; 2.05 .	(±)-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-[(trifluoromethyl)oxy]benzamide
164		P	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 2.10 .	(±)-4-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(methoxy)benzamide

165		E	Found 503 (MH ⁺) C ₂₅ H ₂₆ F ₆ N ₂ O ₂ requires 502; 2.21 .	2-(ethyloxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide chiral
166		A	Found 339 (MH ⁺) C ₂₂ H ₃₀ N ₂ O requires 338; 1.75 .	(±)-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2,6-dimethylbenzamide
167		PE	Found 463 (MH ⁺) C ₂₃ H ₂₈ ⁷⁹ BrFN ₂ O ₂ requires 462; 2.44* .	(±)-6-bromo-2-fluoro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-3-(methoxy)benzamide
168		P	Found 339 (MH ⁺) C ₂₂ H ₃₀ N ₂ O requires 338; 1.71 & 1.76 .	(±)-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2,6-dimethylbenzamide
169		E	Found 367 (MH ⁺) C ₂₄ H ₃₄ N ₂ O requires 366; 1.87 .	(±)-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-2,4,6-trimethylbenzamide
170		E	Found 373 (MH ⁺) C ₂₂ H ₂₉ ³⁵ ClN ₂ O requires 372; 1.85 .	(±)-3-chloro-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-2-methylbenzamide
171		E	Found 393 (MH ⁺) C ₂₈ H ₃₈ N ₂ O requires 392; 2.02 .	(±)-N-[2-ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2,4,6-trimethylbenzamide
172		E	Found 425 (MH ⁺) C ₂₁ H ₂₃ ³⁵ Cl ₃ N ₂ O requires 424; 2.25 .	(±)-2,3,6-trichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]benzamide

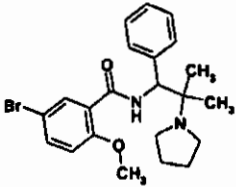
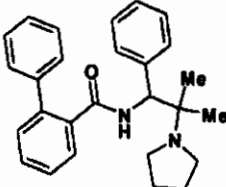
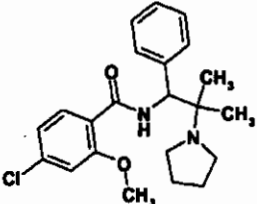
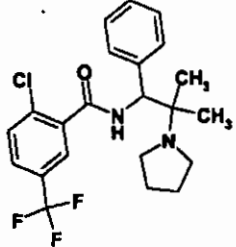
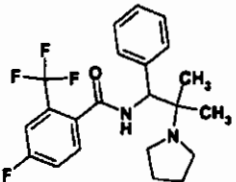
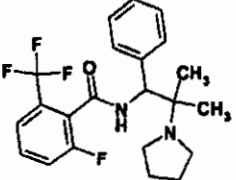
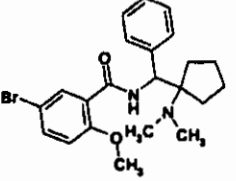
173		E	Found 503 (MH ⁺) C ₂₅ H ₂₈ F ₆ N ₂ O ₂ requires 502; 2.18 .	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(ethoxy)-4,6-bis(trifluoromethyl)benzamide chiral
174		E	Found 399 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ O requires 398; 2.12 .	(±)-3-chloro-N-[2-ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2-methylbenzamide
175		E	Found 417 (MH ⁺) C ₂₂ H ₂₉ ⁷⁹ BrN ₂ O requires 416; 1.81 .	(±)-2-bromo-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-6-methylbenzamide
176		A	Found 339 (MH ⁺) C ₂₂ H ₃₀ N ₂ O requires 338; 1.63 .	(±)-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2,6-dimethylbenzamide
177		P	Found 393 (MH ⁺) C ₂₂ H ₂₇ F ₃ N ₂ O requires 392; 1.95 & 2.03 .	(±)-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2-methyl-5-(trifluoromethyl)benzamide
178		E	Found 395 (MH ⁺) C ₂₅ H ₃₄ N ₂ O ₂ requires 394; 1.86 .	(±)-N-[2-ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2-methyl-6-(methoxy)benzamide
179		A	Found 379 (MH ⁺) C ₂₅ H ₃₄ N ₂ O requires 378; 1.89 .	(±)-N-[2-ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2,6-dimethylbenzamide
180		P	Found 339 (MH ⁺) C ₂₂ H ₃₀ N ₂ O requires 388; 1.90 .	N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2,3-dimethylbenzamide chiral

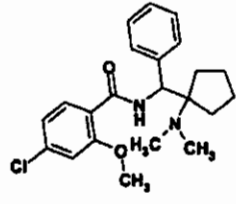
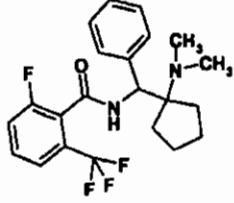
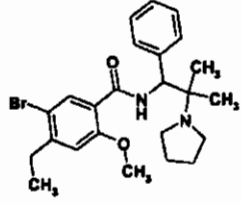
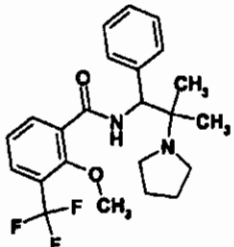
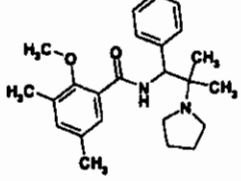
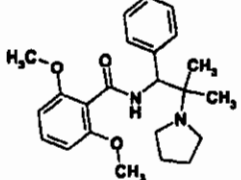
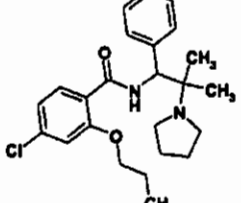
181		E	Found 443 (MH ⁺) C ₂₄ H ₃₁ ⁷⁹ BrN ₂ O requires 442; 2.00 .	(±)-2-bromo-N-[2-ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-6-methylbenzamide
182		A	Found 353 (MH ⁺) C ₂₃ H ₃₂ N ₂ O requires 352; 1.82 .	(±)-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-2,6-dimethylbenzamide
183		P	Found 359 (MH ⁺) C ₂₁ H ₂₇ ³⁵ ClN ₂ O requires 358; 1.88 & 1.91.	(±)-2-chloro-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-6-methylbenzamide
184		P	Found 413 (MH ⁺) C ₂₁ H ₂₄ ³⁵ ClF ₃ N ₂ O requires 412; 2.09 & 2.21.	(±)-2-chloro-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-3-(trifluoromethyl)benzamide
185		E	Found 433 (MH ⁺) C ₂₅ H ₃₁ F ₃ N ₂ O requires 432; 2.20 .	(±)-N-[2-ethyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2-methyl-5-(trifluoromethyl)benzamide
186		E	Found 369 (MH ⁺) C ₂₃ H ₃₂ N ₂ O ₂ requires 368; 1.74 .	(±)-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-2-methyl-6-(methoxy)benzamide
187		P	Found 467 (MH ⁺) C ₂₇ H ₂₈ ³⁵ Cl ₂ N ₂ O requires 466; 2.3	(±)-3',5-dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-biphenylcarboxamide
188		E	Found 407 (MH ⁺) C ₂₃ H ₂₈ F ₃ N ₂ O requires 406; 2.08 .	(±)-N-[2-(dimethylamino)-2-ethyl-1-phenylbutyl]-2-methyl-5-(trifluoromethyl)benzamide

189		P	Found 433 (MH ⁺) C ₂₇ H ₂₉ ³⁵ ClN ₂ O requires 432; 2.0	(±)-3'-chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-biphenylcarboxamide
190		P	Found 421 (MH ⁺) C ₂₂ H ₂₈ ³⁵ Cl ₂ N ₂ O ₂ requires 420; 2.12	(±)-3,5-dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(methoxy)benzamide
191		P	Found 468 (MH ⁺) C ₂₇ H ₂₈ ³⁵ Cl ₂ N ₂ O requires 467; 2.3	(±)-3',4-dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-biphenylcarboxamide
192		A	Found 473 (MH ⁺) C ₂₄ H ₂₈ F ₆ N ₂ O requires 472; 1.97 .	(±)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2,6-bis(trifluoromethyl)benzamide
193		A	Found 459(MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O Requires 458; 2.20	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,4-bis(trifluoromethyl)benzamide chiral
194		A	Found 459(MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O Requires 458; 2.21	N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-2,4-bis(trifluoromethyl)benzamide chiral
195		A	Found 471(MH ⁺) C ₂₄ H ₂₄ F ₆ N ₂ O Requires 470; 2.24	(±)-N-[[1-(1-azetidiny)cyclopentyl](phenyl)methyl]-2,4-bis(trifluoromethyl)benzamide
196		A	Found 485(MH ⁺) C ₂₅ H ₂₆ F ₆ N ₂ O Requires 484; 2.28	(±)-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}-2,4-bis(trifluoromethyl)benzamide

197		A	Found 447(MH ⁺) C ₂₂ H ₂₄ F ₆ N ₂ O Requires 446; 2.16	(±)-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2,4-bis(trifluoromethyl)benzamide
198		A	Found 475(MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O ₂ Requires 475; 1.97	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-hydroxy-4,6-bis(trifluoromethyl)benzamide chiral
199		P	Found 515(MH ⁺) C ₂₆ H ₂₈ F ₆ N ₂ O ₂ Requires 514; 2.33	(±)-2-(methoxy)-N-{phenyl[1-(1-pyrrolidinyl)cyclopentyl]methyl}-4,6-bis(trifluoromethyl)benzamide
200		P	Found 477(MH ⁺) C ₂₃ H ₂₆ F ₆ N ₂ O ₂ Requires 476; 2.21	(±)-N-[2-(dimethylamino)-2-methyl-1-phenylbutyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide
201		P	Found 439 (MH ⁺) C ₂₃ H ₂₆ ³⁵ ClF ₃ N ₂ O requires 438; 2.16.	(±)-2-chloro-N-[[1-(dimethylamino)cyclohexyl](phenyl)methyl]-3-(trifluoromethyl)benzamide
202		P	Found 405 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O requires 404; 1.90.	(±)-2,6-dichloro-N-[[1-(dimethylamino)cyclohexyl](phenyl)methyl]benzamide
203		P	Found 353 (MH ⁺) C ₂₂ H ₂₈ N ₂ O ₂ requires 352; 1.70 and 1.72.	(±)-N-[[3-(dimethylamino)tetrahydro-3-furanyl](phenyl)methyl]-2,6-dimethylbenzamide

204		P	Found 369 (MH ⁺) C ₂₂ H ₂₈ N ₂ O ₃ requires 368; 1.75 and 1.77.	(±)-N-[[3-(dimethylamino)tetrahydro-3-furanyl](phenyl)methyl]-2-methyl-6-(methoxy)benzamide
205		P	Found 427 (MH ⁺) C ₂₁ H ₂₂ ³⁵ ClF ₃ N ₂ O ₂ requires 426; 1.94 and 1.96.	(±)-2-chloro-N-[[3-(dimethylamino)tetrahydro-3-furanyl](phenyl)methyl]-3-(trifluoromethyl)benzamide
206		P	Found 353 (MH ⁺) C ₂₂ H ₂₈ N ₂ O ₂ requires 352; 1.74 and 1.76.	(±)-N-[[3-(dimethylamino)tetrahydro-3-furanyl](phenyl)methyl]-2,3-dimethylbenzamide
207		A	Found 459 (MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O requires 458; 1.97 .	N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-bis(trifluoromethyl)benzamide chiral
208		A	Found 459 (MH ⁺) C ₂₃ H ₂₄ F ₆ N ₂ O requires 458; 1.92 .	N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-2,6-bis(trifluoromethyl)benzamide chiral
209		A	Found 473 (MH ⁺) C ₂₄ H ₂₆ F ₆ N ₂ O requires 472; 2.05 & 2.09.	(±)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-2,6-bis(trifluoromethyl)benzamide
210		PE	Found 421 (MH ⁺) C ₂₂ H ₂₆ ³⁵ Cl ₂ N ₂ O ₂ requires 420; 2.53*.	(±)-3,5-dichloro-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide

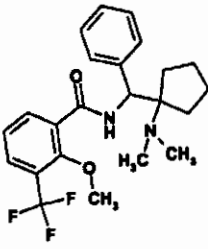
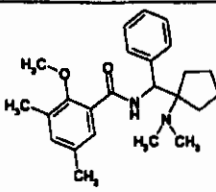
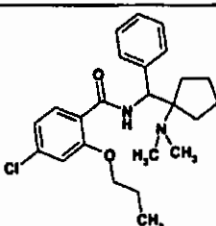
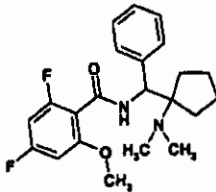
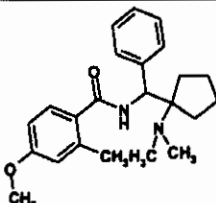
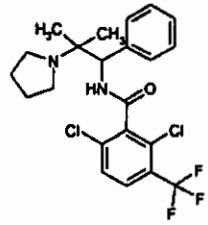
211		PE	Found 431 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O ₂ requires 430; 2.57*.	(±)-5-bromo-2-(methoxy)- <i>N</i> -[2-methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
212		PE	Found 399 (MH ⁺) C ₂₇ H ₃₀ N ₂ O requires 398; 2.47*.	(±)- <i>N</i> -[2-methyl-1-phenyl-2- (1-pyrrolidinyl)propyl]-2- biphenylcarboxamide
213		PE	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 2.49*.	(±)-4-chloro-2-(methoxy)- <i>N</i> -[2-methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
214		PE	Found 425 (MH ⁺) C ₂₂ H ₂₄ ³⁵ ClF ₃ N ₂ O requires 424; 2.45*.	(±)-2-chloro- <i>N</i> -[2-methyl-1- phenyl-2-(1- pyrrolidinyl)propyl]-5- (trifluoromethyl)benzamide
215		PE	Found 409 (MH ⁺) C ₂₂ H ₂₄ F ₄ N ₂ O requires 408; 2.39*.	(±)-4-fluoro- <i>N</i> -[2-methyl-1- phenyl-2-(1- pyrrolidinyl)propyl]-2- (trifluoromethyl)benzamide
216		PE	Found 409 (MH ⁺) C ₂₂ H ₂₄ F ₄ N ₂ O requires 408; 2.56*.	(±)-2-fluoro- <i>N</i> -[2-methyl-1- phenyl-2-(1- pyrrolidinyl)propyl]-6- (trifluoromethyl)benzamide
217		PE	Found 431 (MH ⁺) C ₂₂ H ₂₇ ⁷⁹ BrN ₂ O ₂ requires 430; 2.54*.	5-bromo- <i>N</i> -[[1- (dimethylamino)cyclopentyl](phenyl)methyl]-2- (methoxy)benzamide chiral

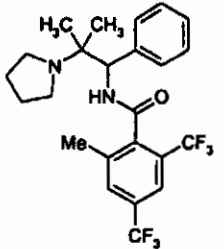
218		PE	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 2.54*.	4-chloro-N-[[1-(dimethylamino)cyclopentyl]phenyl)methyl]-2-(methoxy)benzamide chiral
219		PE	Found 409 (MH ⁺) C ₂₂ H ₂₄ F ₄ N ₂ O requires 408; 2.47*.	N-[[1-(dimethylamino)cyclopentyl]phenyl)methyl]-2-fluoro-6-(trifluoromethyl)benzamide chiral
220		PE	Found 459 (MH ⁺) C ₂₄ H ₃₁ ⁷⁹ BrN ₂ O ₂ requires 458; 2.81*.	(±)-5-bromo-4-ethyl-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
221		PE	Found 421 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O ₂ requires 420; 2.63*.	(±)-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-3-(trifluoromethyl)benzamide
222		PE	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 2.52*.	(±)-3,5-dimethyl-2-(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
223		PE	Found 383 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₃ requires 382; 2.77*.	(±)-2,6-bis(methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide
224		PE	Found 415 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ O ₂ requires 414; 3.05*.	(±)-4-chloro-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-2-(propyloxy)benzamide

225		PE	Found 387 (MH ⁺) C ₂₂ H ₂₇ ³⁵ ClN ₂ O ₂ requires 386; 2.53*.	(±)-2-chloro-5-(methoxy)- <i>N</i> -[2-methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
226		PE	Found 397 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₃ requires 396; 2.58*.	(±)-2-(ethoxy)-4- (methoxy)- <i>N</i> -[2-methyl-1- phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
227		PE	Found 389 (MH ⁺) C ₂₂ H ₂₆ F ₂ N ₂ O ₂ requires 388; 2.47*.	(±)-2,4-difluoro-6- (methoxy)- <i>N</i> -[2-methyl-1- phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
228		PE	Found 375 (MH ⁺) C ₂₁ H ₂₄ ³⁵ ClFN ₂ O requires 374; 2.86*.	(±)-2-chloro-3-fluoro- <i>N</i> -[2- methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
229		PE	Found 351 (MH ⁺) C ₂₃ H ₃₀ N ₂ O requires 350; 2.84*.	(±)-2,4-dimethyl- <i>N</i> -[2-methyl- 1-phenyl-2-(1- pyrrolidinyl)propyl]benzamid e
230		PE	Found 449 (MH ⁺) C ₂₂ H ₂₆ ⁷⁹ BrFN ₂ O ₂ requires 448; 2.45*	6-bromo- <i>N</i> -[[1- (dimethylamino)cyclopentyl](phenyl)methyl]-2-fluoro-3- (methoxy)benzamide chiral
231		PE	Found 443 (MH ⁺) C ₂₂ H ₂₃ ³⁵ ClF ₄ N ₂ O requires 442; 2.94*.	(±)-3-chloro-2-fluoro- <i>N</i> -[2- methyl-1-phenyl-2-(1- pyrrolidinyl)propyl]-6- (trifluoromethyl)benzamide

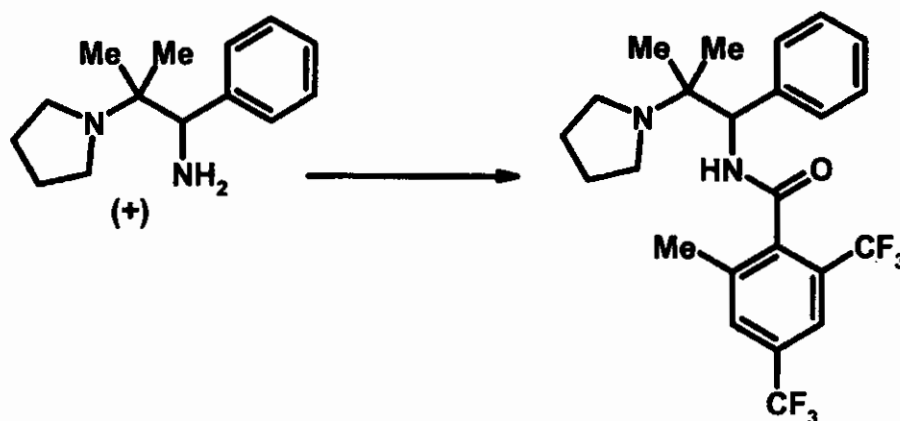
232		P	Found 337 (MH ⁺) C ₂₂ H ₂₈ N ₂ O requires 336; 1.86.	(±)-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methylbenzamide
233		A	Found 517 (MH ⁺) C ₂₈ H ₃₀ F ₆ N ₂ O ₂ requires 516; 2.32.	(±)-N-[2-(hexahydro-1H-azepin-1-yl)-2-methyl-1-phenylpropyl]-2-(methoxy)-4,6-bis(trifluoromethyl)benzamide
234		A	Found 453 (MH ⁺) C ₂₄ H ₂₈ ³⁵ ClF ₃ N ₂ O requires 452; 2.21.	(±)-2-chloro-N-[2-methyl-2-(hexahydro-1H-azepin-1-yl)-2-methyl-1-phenylpropyl]-3-(trifluoromethyl)benzamide
235		PE	Found 401 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O ₂ requires 400; 2.48*.	(±)-2-chloro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-6-(methoxy)benzamide
236		PE	Found 397 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₃ requires 396; 2.79*.	(±)-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-2,6-bis(methoxy)benzamide
237		PE	Found 401 (MH ⁺) C ₂₃ H ₂₉ ³⁵ ClN ₂ O ₂ requires 400; 2.53*.	(±)-2-chloro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-5-(methoxy)benzamide
238		PE	Found 403 (MH ⁺) C ₂₃ H ₂₈ F ₂ N ₂ O ₂ requires 402; 2.52*.	(±)-2,4-difluoro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-6-(methoxy)benzamide

239		PE	Found 389 (MH ⁺) C ₂₂ H ₂₆ ³⁵ ClFN ₂ O requires 388; 2.89*.	(±)-2-chloro-3-fluoro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
240		PE	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.66*.	(±)-2,5-dimethyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
241		PE	Found 365 (MH ⁺) C ₂₄ H ₃₂ N ₂ O requires 364; 2.94*.	(±)-2,4-dimethyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
242		PE	Found 379 (MH ⁺) C ₂₅ H ₃₄ N ₂ O requires 378; 2.5*.	(±)-2,4,6-trimethyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
243		PE	Found 439 (MH ⁺) C ₂₂ H ₂₅ ³⁵ Cl ₃ N ₂ O requires 438; 2.91*.	(±)-2,4,6-trichloro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]benzamide
244		PE	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 2.84*.	(±)-2-methyl-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-4-(methoxy)benzamide
245		PE	Found 457 (MH ⁺) C ₂₃ H ₂₅ ³⁵ ClF ₄ N ₂ O requires 456; 2.97*.	(±)-3-chloro-2-fluoro-N-[2-methyl-2-(2-methyl-1-pyrrolidinyl)-1-phenylpropyl]-6-(trifluoromethyl)benzamide
246		PE	Found 459 (MH ⁺) C ₂₄ H ₃₁ ⁷⁹ BrN ₂ O ₂ requires 458; 2.84*.	5-bromo-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-4-ethyl-2-(methoxy)benzamide chiral

247		PE	Found 421 (MH ⁺) C ₂₃ H ₂₇ F ₃ N ₂ O ₂ requires 420; 2.67*.	<i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(methoxy)-3-(trifluoromethyl)benzamide chiral
248		PE	Found 381 (MH ⁺) C ₂₄ H ₃₂ N ₂ O ₂ requires 380; 2.54*.	<i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-3,5-dimethyl-2-(methoxy)benzamide chiral
249		PE	Found 415 (MH ⁺) C ₂₄ H ₃₁ ³⁵ ClN ₂ O ₂ requires 414; 3.21*.	4-chloro- <i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-(propyloxy)benzamide chiral
250		PE	Found 389 (MH ⁺) C ₂₂ H ₂₆ F ₂ N ₂ O ₂ requires 388; 2.51*.	<i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,4-difluoro-6-(methoxy)benzamide chiral
251		PE	Found 367 (MH ⁺) C ₂₃ H ₃₀ N ₂ O ₂ requires 366; 2.98*.	<i>N</i> -[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-4-(methoxy)benzamide chiral
252		P#	Found 459 (MH ⁺) C ₂₂ H ₂₃ ³⁵ Cl ₂ F ₃ N ₂ O requires 458; 2.07	2,6-dichloro- <i>N</i> -[2-methyl-1-(pyrrolidinyl)propyl]-3-(trifluoromethyl)benzamide chiral

253		A	Found 473 (MH ⁺) C ₂₄ H ₂₆ F ₆ N ₂ O requires 472; 2.22.	2-methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide chiral
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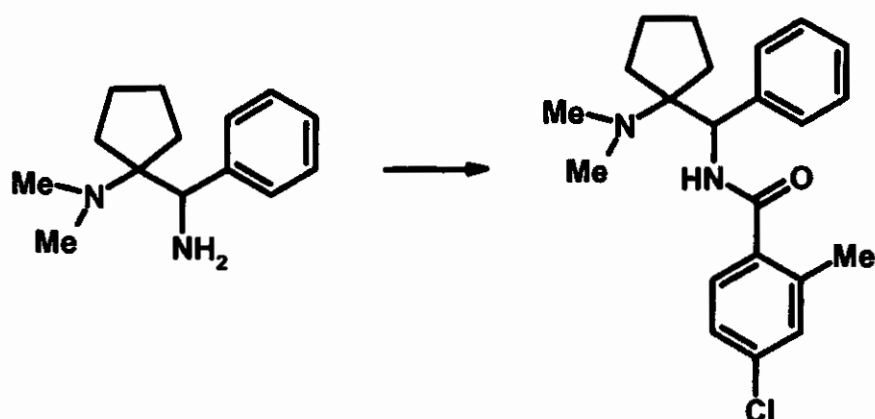
Example 253: 2-Methyl-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide chiral – alternative method



- 5 A mixture of 2-methyl-4,6-bis(trifluoromethyl)benzoyl chloride and methyl 2,4-bis(trifluoromethyl)benzoate (approximately 0.5mmol) prepared as described in D53 was dissolved in dry DCM (3ml) and treated with (+)-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D6 (109mg, 0.50mmol) and triethylamine (140ul, 1.00 mmol) and left overnight at room temperature. The volatile components were removed under reduced pressure and the residue chromatographed on silica gel. Elution with 0-80% ethyl acetate in pentane gave the title product as an gum (127mg, ca.54%). ¹H NMR (CDCl₃) δ: 0.90 (3H, s), 1.01 (3H, s), 1.70 (4H, overlapping m), 2.47 (3H, s), 2.63 (4H, overlapping m), 4.84 (1H, d, J = 2.8 Hz), 7.16 (1H, br s), 7.26 – 7.38 (5H, overlapping m) 7.67 (1H, s), 7.77 (1H, s). Mass Spectrum (Electrospray LC/MS): Found 473 (MH⁺)
- 15 C₂₄H₂₆F₆N₂O requires 472. Ret time 2.24 min.

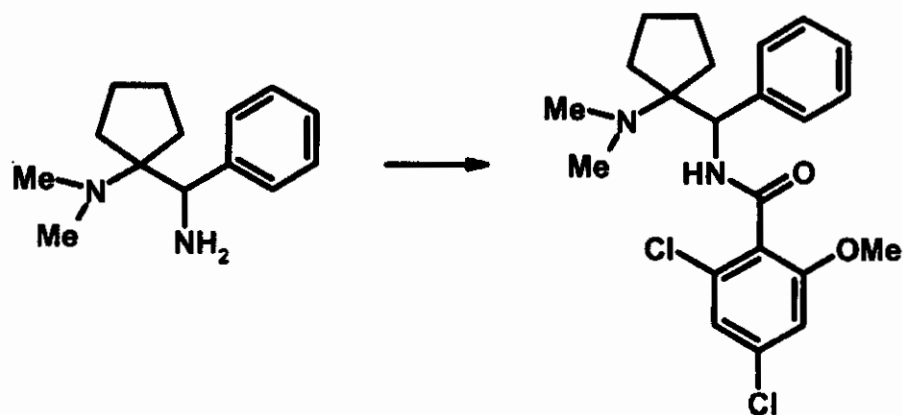
This was converted to the hydrochloride salt (white solid, 140mg) by addition of excess 1M HCl in ether to a chloroform solution of the amine and removal of the solvent under reduced pressure.

Example 254: 4-Chloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2-methylbenzamide chiral



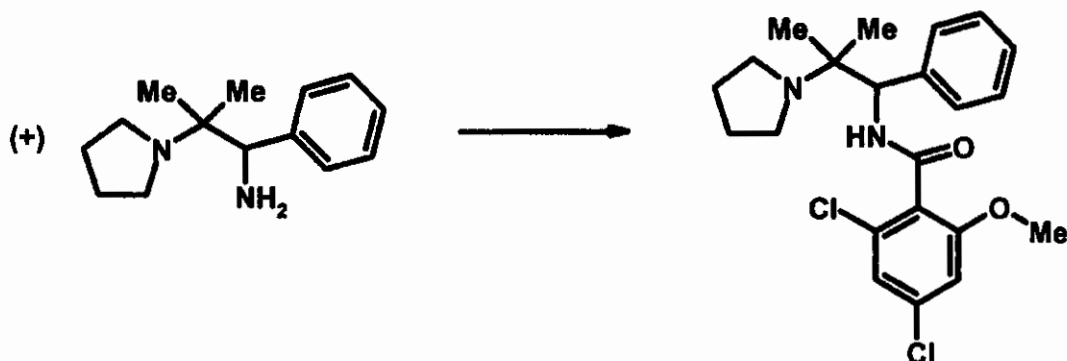
- 5 A mixture of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (80mg, 0.37 mmol), 4-chloro-2-methylbenzoic acid (68mg; 0.40mmol), HOBt (61mg; 0.40mmol) and PS-DCC (310mg of 1.3 mmol/g loading, 0.40mmol) in DCM (4ml) was shaken overnight. Saturated aqueous sodium bicarbonate was added and the mixture separated with a phase-sep cartridge and the organics applied directly to SCX resin. Elution with
- 10 DCM, methanol and then 1M ammonia in methanol, followed by chromatography eluting with 12 – 100% ethyl acetate – pentane (SP4 Biotage) afforded the title product (64mg; 43%). ¹H NMR (CDCl₃) δ: 0.9 – 1.0 (1H, m), 1.25 – 1.40 (1H, m), 1.4 – 1.6 (2H, m), 1.6 – 1.75 (2H, m), 1.8 – 1.9 (2H, m), 2.22 (6H, s), 2.41 (3H, s), 5.09 (1H, d, J = 5Hz), 7.07 (1H, d, J = 5Hz), 7.2 – 7.4 (8H, m). Mass Spectrum (Electrospray LC/MS): Found 371 (MH⁺).
- 15 C₂₂H₂₇³⁵ClN₂O requires 370. Ret. time 2.26 min. The title product was converted to the corresponding hydrochloride salt.

Example 255: 2,4-Dichloro-N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-6-(methoxy)benzamide chiral



A mixture of {1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (80mg, 0.37 mmol), 2,4-dichloro-6-(methyloxy)benzoic acid (88mg; 0.40mmol), HOBT (61mg; 0.40mmol) and PS-DCC (310mg of 1.3 mmol/g loading, 0.40mmol) in DCM (4ml) was shaken overnight. Saturated aqueous sodium bicarbonate was added and the mixture separated with a phase-sep cartridge and the organics applied directly to SCX resin. Elution with DCM, methanol and then 1M ammonia in methanol, followed by chromatography eluting with 12 – 100% ethyl acetate – pentane (SP4 Biotage) afforded the title product (133mg; 79%). ¹H NMR (CDCl₃) δ: 0.95 – 1.10 (1H, m), 1.25 – 1.35 (1H, m), 1.40 – 1.60 (2H, m), 1.60 – 1.75 (2H, m), 1.80 – 1.90 (2H, m), 2.22 (6H, s), 3.82 (3H, s), 5.08 (1H, d, J = 5Hz), 6.82 (1H, d, J = 2Hz), 7.02 (1H, d, J = 2Hz), 7.07 (1H, m), 7.22 – 7.33 (3H, m), 7.44 – 7.46 (2H, m). Mass Spectrum (Electrospray LC/MS): Found 421 (MH⁺). C₂₂H₂₆³⁵Cl₂N₂O₂ requires 420. Ret. time 2.34 min. The title product was converted to the corresponding hydrochloride salt. 2,4-Dichloro-6-(methyloxy)benzoic acid can be prepared as described by G. E. Stokker, A. W. Alberts, P. S. Anderson, E. J. Cragoe Jr., A. A. Deana, J. L. Gilfillan, J. Hirshfield, W. J. Holtz, W. F. Hoffman, J.W. Huff, T.J. Lee, F.C. Novello, J.D. Prugh, C.S. Rooney, R.L. Smith, A.K. Willard J Med Chem, 1986, 29(2), 170.

Example 256: 2,4-Dichloro-6-(methyloxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]benzamide chiral

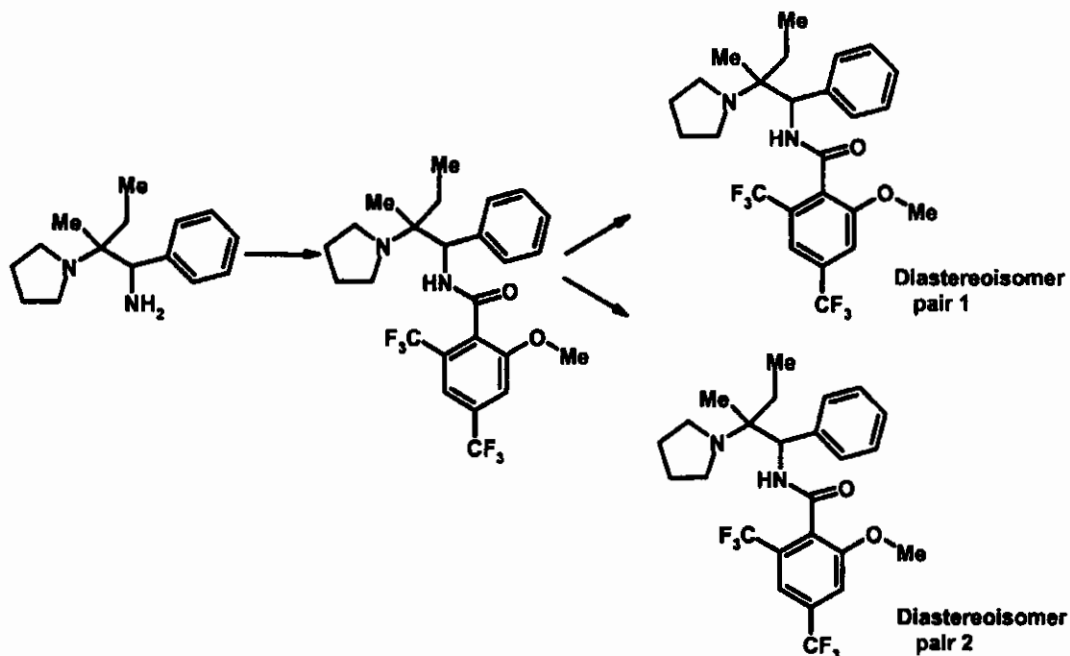


To a solution of (+)-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D6 (0.10g; 0.459mmol) and triethylamine (0.15ml; 1mmol) in DCM (3ml) was added a solution of 2,4-dichloro-6-methoxybenzoyl chloride (0.13g; 0.540mmol) in DCM (2ml). After 1 h. saturated aqueous sodium hydrogen carbonate (8ml) was added and the mixture shaken for 2 minutes. The organic layer was passed through a phase separation cartridge and the solvent removed under reduced pressure. The residue was dissolved in the minimum of DCM and applied to a 10g silica gel column. Elution with 0 – 100% ethyl acetate in pentane gradient and removal of solvent under reduced pressure afforded the title

compound as a colourless gum (0.14g; 72%). ^1H NMR (CDCl_3) δ : 0.91 (3H, s), 0.96 (3H, s), 1.60-1.80 (4H, m), 2.55-2.75 (4H, m), 3.82 (3H, s), 4.76 (1H, d, $J = 2.4\text{Hz}$), 6.81 (1H, d, $J = 1.6\text{Hz}$), 7.02 (1H, d, $J = 1.6\text{Hz}$), 7.20-7.50 (6H, m). Mass spectrum (Electrospray LC/MS). Found 421 (MH^+). $\text{C}_{22}\text{H}_{28}^{35}\text{Cl}_2\text{N}_2\text{O}_2$ requires 420. Ret. Time: 1.97min.

5

Examples 257: ($\pm$)-2-(Methoxy)-N-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]-4,6-bis(trifluoromethyl)benzamide Diastereoisomer Pair 1 and Diastereoisomer Pair 2

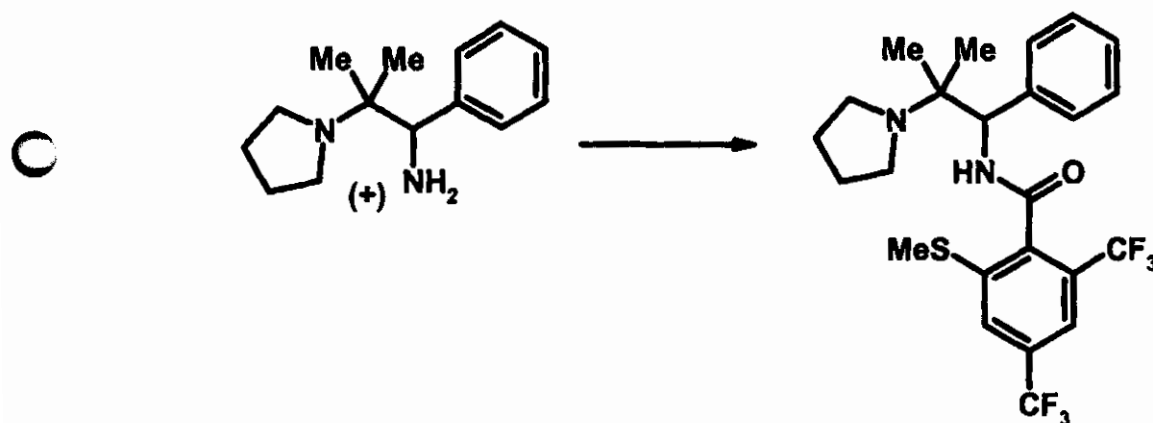


To a stirred solution of ($\pm$)-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)butyl]amine D22 (2.32g; 10mmol) and triethylamine (2.78ml; 20mmol) in DCM (75ml) at room temperature was added a solution of 2-(methoxy)-4,6-bis(trifluoromethyl)benzoyl chloride (3.10g; 10mmol) in DCM (25ml) dropwise over 10 minutes. After 20 h. saturated aqueous sodium hydrogen carbonate (100ml) was added and stirring continued for 0.5 h. The layers were separated and the aqueous layer extracted with DCM (150ml). The combined organics were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to afford a pale orange foam (4.8g). The sample was dissolved in the minimum of DCM and one half of the solution applied to a 40M silica column. Elution with 2% MeOH in DCM (2.5L) then 3% MeOH in DCM (2.4L) afforded the title compound diastereoisomer pair 1 (0.16g) ^1H NMR (CDCl_3) δ : 0.97 (3H, s), 1.01 (3H, t, $J = 7.6\text{Hz}$), 1.25-1.35 (2H, q, $J = 8\text{Hz}$), 1.55-1.75 (4H, m), 2.55-2.70 (4H, m), 3.93 (3H, s), 4.84 (1H, d, $J = 0.9\text{Hz}$), 7.20-7.45 (7H, m), 7.54 (1H, s). Mass spectrum (Electrospray LC/MS). Found 503 (MH^+). $\text{C}_{25}\text{H}_{28}\text{F}_6\text{N}_2\text{O}_2$ requires 502. Ret. Time: 2.27min.

Further elution with 5% MeOH in DCM afforded the title compound diastereoisomer pair 2 (0.36g). ^1H NMR (CDCl_3) δ : 0.75-0.85 (3H, t), 1.03 (3H, s), 1.35-1.55 (1H, m), 1.60-1.72 (4H, m), 1.72-1.90 (1H, m), 2.70-2.85 (4H, m), 3.92 (3H, s), 4.83 (1H, d, $J = 3.6\text{Hz}$) 7.20-7.40 (7H, m), 7.53 (1H, s). Mass spectrum (Electrospray LC/MS). Found 503 (MH^+).

5 $\text{C}_{25}\text{H}_{28}\text{F}_6\text{N}_2\text{O}_2$ requires 502. Ret. Time: 2.30min.

Example 258: *N*-[2-Methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-2-(methylthio)-4,6-bis(trifluoromethyl)benzamide chiral



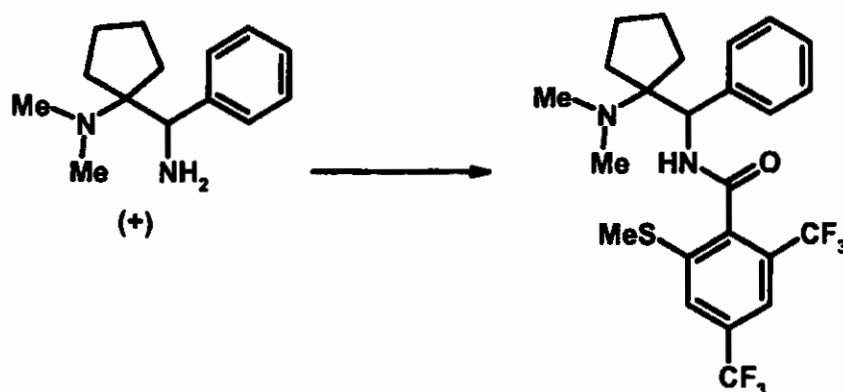
10 A solution of 2-(methylthio)-4,6-bis(trifluoromethyl)benzoyl chloride D55 (60mg; 0.19mmol) in dry DCM (1ml) was treated with (+)-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]amine D6 (60mg, 0.27mmol) followed by triethylamine (5drops) and left overnight at room temperature. The volatile components were removed under reduced pressure and the residue chromatographed on silica gel. Elution with 0-80% ethyl acetate

15 in pentane gave the title product as an oil (80mg, 85%). ^1H NMR (CDCl_3) δ : 0.94 (3H, s), 1.00 (3H, s), 1.69 (4H, overlapping m), 2.54 (3H, s), 2.62 (2H, m), 2.72 (2H, m), 4.78 (1H, s), 7.25 – 7.45 (6H, overlapping m), 7.68 (1H, s), 7.72 (1H, s). Mass Spectrum (Electrospray LC/MS): Found 505 (MH^+) $\text{C}_{24}\text{H}_{28}\text{F}_6\text{N}_2\text{OS}$ requires 504. Ret time 2.24 min.

C

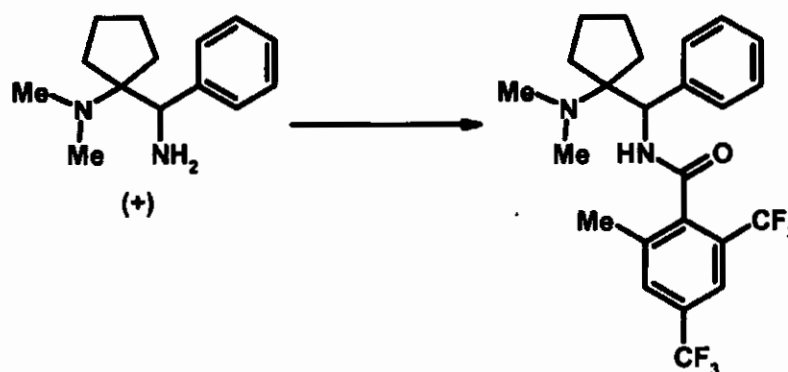
20 The title product was converted to the hydrochloride salt (85mg) by addition of excess 1M HCl in ether to a DCM solution of the amine and removal of the solvent under reduced pressure.

Example 259: *N*-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2-(methylthio)-4,6-bis(trifluoromethyl)benzamide chiral



- A mixture of 2-(methylthio)-4,6-bis(trifluoromethyl)benzoyl chloride and methyl 2,4-bis(trifluoromethyl)benzoate (112mg) prepared as described in D55 was dissolved in dry DCM (2ml) and treated with (+)-[1-[amino(phenyl)methyl] cyclopentyl]dimethylamine D3 enantiomer 2 (33mg; 0.15mmol) and triethylamine (42ul, 0.30mmol) and left overnight at room temperature. The volatile components were removed under reduced pressure and the residue chromatographed on silica gel. Elution with 0-80% ethyl acetate in pentane gave the title product as a crisp foam (60mg; 86%). ¹H NMR (CDCl₃) δ: 0.90 (1H, m), 1.4 – 1.9 (7H, overlapping m), 2.22 (6H, s), 2.52 (3H, s), 5.05 (1H, d, J = 4.4 Hz), 7.22 – 7.5 (6H, overlapping m), 7.68 (1H, s), 7.71 (1H, s). Mass Spectrum (Electrospray LC/MS): Found 505 (MH⁺) C₂₄H₂₆F₆N₂OS requires 504. Ret time 2.35 min.
- The title product was converted to the hydrochloride salt (60mg) by addition of excess 1M HCl in ether to a DCM solution of the amine and removal of the solvent under reduced pressure.

Example 260: *N*-[[1-(Dimethylamino)cyclopentyl](phenyl)methyl]-2-methyl-4,6-bis(trifluoromethyl)benzamide chiral



A mixture of 2-methyl-4,6-bis(trifluoromethyl)benzoyl chloride and methyl 2,4-bis(trifluoromethyl)benzoate (approximately 0.5mmol) prepared as described in D53 was dissolved in dry DCM (3ml) and treated with (+)-{1-[amino(phenyl)methyl]cyclopentyl}dimethylamine D3 enantiomer 2 (109mg, 0.50 mmol) and triethylamine (140ul, 1.00 mmol) and left overnight at room temperature. The volatile components were removed under reduced pressure and the residue chromatographed on silica gel. Elution with 0-80% ethyl acetate in pentane gave the title product (86mg, ca.36%). ¹H NMR (CDCl₃) δ: 0.95 (1H, br m), 1.44 – 1.86 (7H, overlapping m), 2.20 (6H, s), 2.41 (3H, br s), 5.10 (1H, d, J = 5.6 Hz), 7.07 (1H, br s), 7.26 – 7.42 (5H, overlapping m), 7.67 (1H, s), 7.77 (1H, s). Mass Spectrum (Electrospray LC/MS): Found 473 (MH⁺) C₂₄H₂₆F₆N₂O requires 472. Ret time 2.25 min.

The title product was converted to the hydrochloride salt (90mg) by addition of excess 1M HCl in ether to a chloroform solution of the amine and removal of the solvent under reduced pressure.

The compounds of the Examples above could be converted to their corresponding hydrochloride salts by dissolving the parent free base in DCM or DCM / methanol mixtures and adding 1M hydrogen chloride in ether, followed by evaporation and drying *in vacuo*. Compounds purified by Mass Directed Auto-Purification were isolated as the formate salt which could be converted to the free base via an SCX column and to the corresponding hydrochloride salt by reaction with 1M hydrogen chloride in ether as described above.

CLAIMS

1. A composition of matter comprising 2-(methyloxy)-*N*-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide as a racemic mixture, or stereoisomer thereof; or a salt thereof.
2. The composition of claim 1 wherein the salt form is a pharmaceutically acceptable salt.
3. The composition of claim 1 comprising 2-(methyloxy)-*N*-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide as a racemic mixture, or stereoisomer thereof.
4. The composition of claim 1 comprising the hydrochloride salt form of 2-(methyloxy)-*N*-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide as a racemic mixture, or stereoisomer thereof.
5. A pharmaceutical composition comprising a composition of matter comprising 2-(methyloxy)-*N*-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide as a racemic mixture, or stereoisomer thereof, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.
6. The pharmaceutical composition of claim 5 wherein the composition of matter comprises 2-(methyloxy)-*N*-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide as a racemic mixture, or stereoisomer thereof; and a pharmaceutically acceptable excipient.
7. The pharmaceutical composition of claim 5 wherein the composition of matter comprises the hydrochloride salt form of 2-(methyloxy)-*N*-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide as a racemic mixture, or stereoisomer thereof; and a pharmaceutically acceptable excipient.
8. A composition of matter comprising a chirally enriched enantiomer of 2-(methyloxy)-*N*-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide, or a salt thereof.

9. The composition of claim 8 comprising a chirally enriched enantiomer of a pharmaceutically acceptable salt form of 2-(methyloxy)-*N*-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide.

10. The composition of claim 9 comprising a chirally enriched enantiomer of the hydrochloride salt form of 2-(methyloxy)-*N*-[2-methyl-1-phenyl-2-(1-pyrrolidinyl)propyl]-4,6-bis(trifluoromethyl)benzamide.