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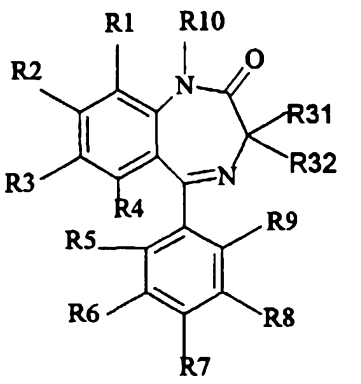
(54) Title: NOVEL 1,4-BENZODIAZEPINE COMPOUNDS AND DERIVATIVES THEREOF



(I)

(57) Abstract: The present invention relates to therapeutically active novel 1,4-benzodiazepine compounds and derivatives thereof, of formula (I), wherein R31 or/and R32 contain at least a carboxy, or an amino group or both. Also provided is a method of preparing compounds of formula (I), and pharmaceutical compositions comprising the compounds. The novel compounds act as modulators of metabotropic glutamate receptors and, as such, are useful in treating diseases of the central nervous system related to the metabotropic glutamate receptor system.

NOVEL 1,4-BENZODIAZEPINE COMPOUNDS AND DERIVATIVES THEREOF

FIELD OF THE INVENTION

This invention pertains to the field of therapeutically active 1,4-benzodiazepine compounds and is particularly concerned with 1,4-benzodiazepine compounds containing a carboxy or an amino group, or both.

BACKGROUND OF THE INVENTION

The billions of cells (neurons) in the brain and spinal cord, or the Central Nervous System (CNS), of mammals transmit information from cell to cell by releasing chemicals known as neurotransmitters through their cell membranes. Subsequent to their release, the neurotransmitters evoke a response from their target cell by interacting with different classes of receptors on the target cell's membrane. The evoked response can be inhibitory, excitatory or modulatory, and occurs as a result of the controlled movement of ions such as sodium, potassium, chloride and calcium across the cell membrane.

Errors in neurotransmission or the uncontrolled movements of ions across the cell membrane can lead to neuropathological conditions and *vice versa*. Sodium and calcium overload of neurons is thought to be a critical factor in the initiation of the pathological conditions leading to cell death following the cerebral ischemia (anoxia) that occurs during strokes or traumatic head injuries, for example. Ischemia of neurons leads to depolarization, potassium loss, sodium uptake with associated cellular swelling, calcium uptake, calcium accumulation in mitochondria with associated damage, liberation of neurotransmitters and activation of calcium-dependent enzymes.

The need for new pharmaceuticals to treat acute neurological disorders is critical. For example, in Canada alone it is estimated that approximately 50,000 Canadians suffer from strokes each year and of these 15,000 will die. The remainder, like the 15,000 who suffer from some form of head injury each year, are left with varying degrees of permanent disability that inflicts extraordinary hardships on the individual and costs the country a staggering amount in health care costs.

The current pharmaceutical options for treating neurological disorders also tend to be very general and non-specific in their actions in that, although they may reduce the clinical symptoms associated with a specific neurological disorder, they may also negatively impact normal function of the Central Nervous System of patients. Thus new cellular targets and drugs that are more specific in their actions need to be identified and developed.

The acidic amino acid L-glutamic acid (L-Glu) is recognized as the major excitatory neurotransmitter in the CNS. Research has revealed that L-Glu has both "fast" (ionotropic) neurotransmitter actions, and slower (metabotropic), modulatory effects, evoked through eight distinct receptor subclasses.

Ionotropic glutamate receptors contain integral, cation-specific ion channels, whereas the metabotropic receptors are coupled to G proteins and modulate the production of intracellular messengers. The ionotropic receptors can be subdivided into N-methyl-D-aspartate (NMDA) receptors and the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)-kainate receptors according to their selective agonists.

Much of the current research in this area is focused on developing chemicals that will interact at a new class of brain receptors. These metabotropic glutamate receptors (mGluRs), of which there are eight distinct types, were only identified within the last ten years. The receptor subtypes are differentiated by their pharmacological profiles as well as by the intracellular second messenger effects that they evoke. For example, L-Glu's interaction at the mGluR1 and mGluR5 subclass of receptor activates phospholipase C and a subsequent inositol phosphate cascade via a G-protein.

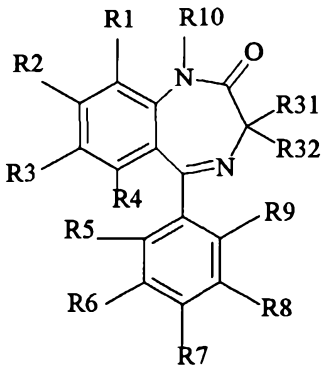
Research directed towards mGluRs is beginning to show that mGluRs may be implicated in a number of normal as well as pathological mechanisms in the brain and spinal cord. For example, activation of these receptors on neurons can: influence levels of alertness, attention and cognition; protect nerve cells from excitotoxic damage resulting from ischemia, hypoglycemia and anoxia; modulate the level of neuronal excitation; influence central mechanisms involved in controlling movement; reduce sensitivity to pain; reduce levels of anxiety.

The consequence of designing chemicals which interact at these receptor sites is that it will be possible to develop therapeutics with the potential to target areas such as: learning and memory; stroke and head injuries; epilepsy; movement disorders associated with Parkinson's Disease and Huntington's chorea; pain; anxiety; AIDS dementia; Alzheimer's disease.

Thus, a need remains for chemical compounds that demonstrate specific binding characteristics towards mGluRs, in addition to the ongoing research into ligands for ionotropic glutamate receptors.

SUMMARY OF THE INVENTION

An object of the present invention is to provide novel 1,4-benzodiazepine compounds and derivatives thereof, that demonstrate activity at the various metabotropic glutamate receptors. In accordance with an aspect of the invention, there is provided a compound of formula (I):



(I)

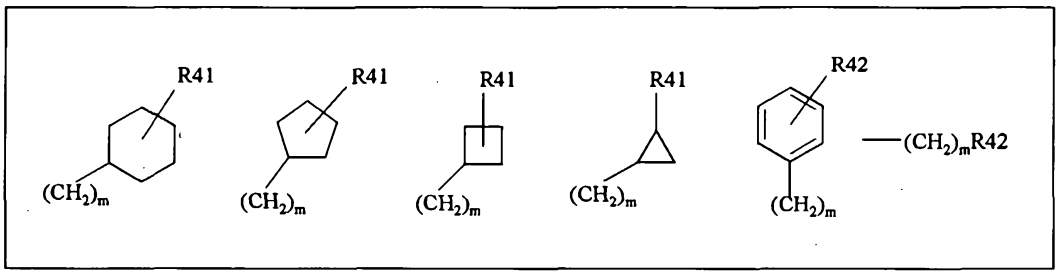
stereoisomers thereof, or pharmaceutically acceptable salt or hydrates thereof, wherein:

R1, R2, R3, R4, R5, R6, R7, R8, R9 are same or different and selected from the group comprising H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl or acceptable esters thereof;

R10 is selected from group comprising: (C_1-C_6) alkyl (straight chain or branched); (C_6-C_{10}) aryl [optionally substituted with (C_1-C_6) alkyl], aryl alkyl group where aryl group is optionally substituted with (C_1- C_6) alkyl, (C_1- C_6) alkoxy, halogen, carboxy, or nitro group; heteroaromatic group; or -O-C(O)R where R is (C_1- C_6) alkyl, (C_6- C_{10}) aryl;

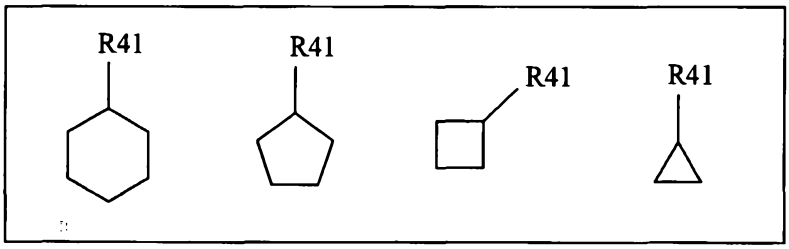
R31 is either H or taken together with **R32** to form a spirocycle;

R32 is selected from the group comprising:



wherein: **m** = 0,1

or when **R31** and **R32** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R41 is **XY** or **–CR11XY**

R42 is **X** or **Y** or **-CR11XY**

R11 is H, (C_1- C_6) alkyl (straight chain or branched); (C_6- C_{10}) aryl [optionally substituted with (C_1- C_6) alkyl], aryl alkyl group where aryl group is optionally substituted with (C_1-

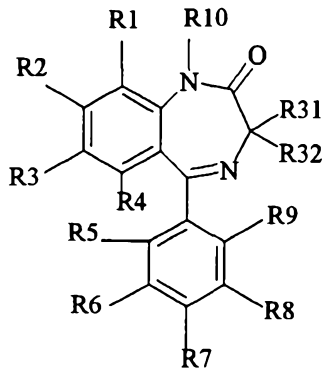
C_6) alkyl, (C_1- C_6) alkoxy, halogen, carboxy, or nitro group; (C_4- C_9) heterocyclic group (aromatic or nonaromatic);

X is H or an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, where n = 2, 3, 4, 5, or 6; or:

Y is H or a basic group selected from the group comprising 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea, with the proviso that, (i) at least one of **X** or **Y** is other than **H** and (ii) when **R32** is –$(CH_2)_m$R42, **R42** is COOH, then m is 1.

In accordance with another aspect of the present invention, there is provided a process for the preparation of a compound of Formula (I) as shown above, or a pharmaceutically acceptable metabolically labile ester or amide thereof, or a pharmaceutically acceptable salt thereof.

In accordance with another aspect of the present invention, there is provided a pharmaceutical composition, comprising a pharmaceutically acceptable carrier, diluent or excipient and a compound formula (I):



(I)

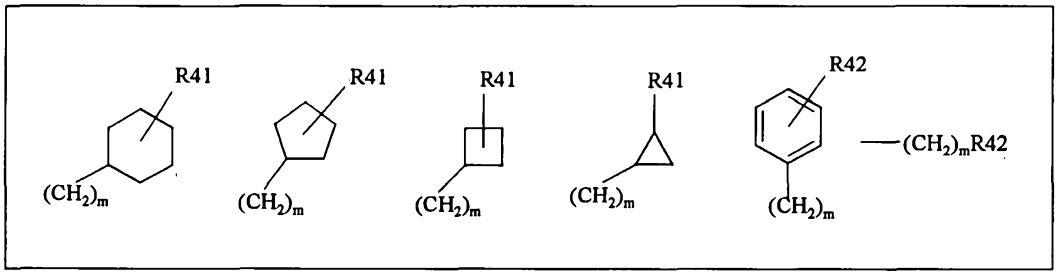
stereoisomers thereof, or pharmaceutically acceptable salt or hydrates thereof, wherein:

R1, R2, R3, R4, R5, R6, R7, R8, R9 are same or different and selected from the group comprising H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl or acceptable esters thereof;

R10 is selected from group comprising: (C_1-C_6) alkyl (straight chain or branched); (C_6-C_{10}) aryl [optionally substituted with (C_1-C_6) alkyl], aryl alkyl group where aryl group is optionally substituted with (C_1- C_6) alkyl, (C_1- C_6) alkoxy, halogen, carboxy, or nitro group; heteroaromatic group; or -O-C(O)R where R is (C_1- C_6) alkyl, (C_6- C_{10}) aryl;

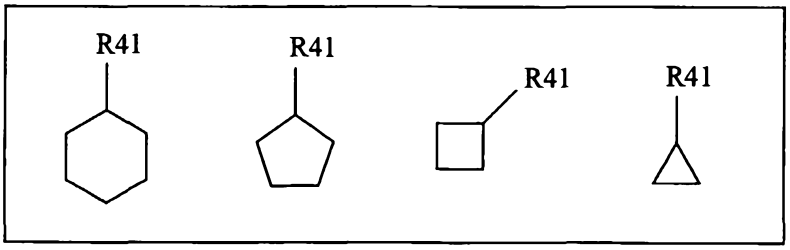
R31 is either H or taken together with **R32** to form a spirocycle;

R32 is selected from the group comprising:



wherein: **m** = 0,1

or when **R31** and **R32** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R31 is **XY** or **–CR11XY**

R41 is **X** or **Y** or **-CR11XY**

R11 is H, (C_1- C_6) alkyl (straight chain or branched); (C_6- C_{10}) aryl [optionally substituted with (C_1- C_6) alkyl], aryl alkyl group where aryl group is optionally substituted with (C_1- C_6) alkyl, (C_1- C_6) alkoxy, halogen, carboxy, or nitro group; (C_4- C_9) heterocyclic group (aromatic or nonaromatic);

X is H or an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, where n = 2, 3, 4, 5, or 6; or:

Y is H or a basic group selected from the group comprising 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea.

In accordance with another aspect of the present invention, there is provided a method of modulating the activity of metabotropic glutamate receptors in mammals, which comprises administering to a mammal requiring modulated excitatory amino acid neurotransmission a pharmacologically-effective amount of compound of formula (I).

In accordance with another aspect of the present invention, there is provided the use of the pharmaceutical composition containing compound of formula (I), in treating diseases of the central nervous system related to the metabotropic glutamate receptor system.

DETAILED DESCRIPTION OF THE INVENTION

The terms and abbreviations used in the instant examples have their normal meanings unless otherwise designated. For example "°C" refers to degrees Celsius; "N" refers to normal or normality; "mmol" refers to millimole or millimoles; "g" refers to gram or grams; "ml" means milliliter or milliliters; "M" refers to molar or molarity; "p-" refers to

para, "MS" refers to mass spectrometry; "IR" refers to infrared spectroscopy; and "NMR" refers to nuclear magnetic resonance spectroscopy.

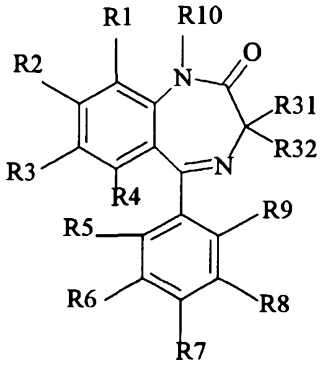
As would be understood by the skilled artisan, throughout the synthesis of the compounds of Formula I it may be necessary to employ an amino-protecting group or a carboxy-protecting group in order to reversibly preserve a reactively susceptible amino or carboxy functionality while reacting other functional groups on the compound.

Examples of such amino-protecting groups include formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, and urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4- fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, *t*-butoxycarbonyl, 2-(4-xenyl)-isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)-prop-2-yloxycarbonyl, cyclopentanyloxy-carbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, fluorenylmethoxycarbonyl ("FMOC"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decycloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonlyl and the like; benzoylmethylsulfonyl group, 2-nitrophenylsulfenyl, diphenylphosphine oxide and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the condition of subsequent reaction(s) on other positions of the intermediate molecule and can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other amino-protecting group(s). Preferred amino-protecting groups are *t*-butoxycarbonyl (*t*-Boc), allyloxycarbonyl and

benzyloxycarbonyl (CbZ). Further examples of these groups are found in E. Haslam, *Protecting Groups in Organic Chemistry*, (J. G. W. McOmie, ed., 1973), at Chapter 2; and T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, (1991), at Chapter 7.

Examples of such carboxy-protecting groups include methyl, *p*-nitrobenzyl, *p*-methylbenzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxybenzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, *t*-butyl, *t*-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, *t*-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, β-(di(n-butyl)methylsilyl)ethyl, *p*-toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl and like moieties. Preferred carboxy-protecting groups are allyl, benzyl and *t*-butyl. Further examples of these groups are found in E. Haslam, supra, at Chapter 5; and T. W. Greene and P. G. M. Wuts, supra, at Chapter 5.

The present invention provides a compound of the formula (I):



(I)

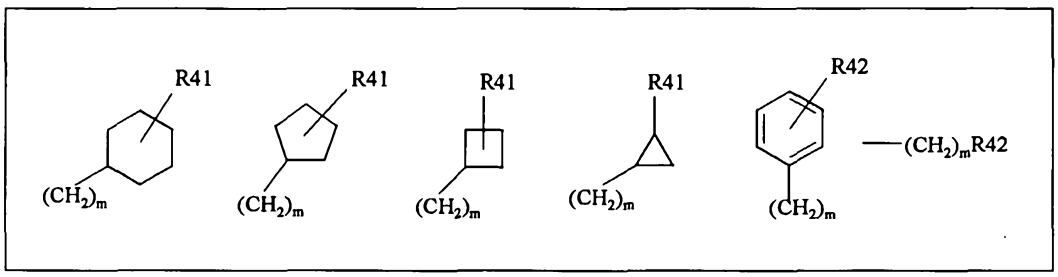
stereoisomers thereof, or pharmaceutically acceptable salt or hydrates thereof, wherein:

R1, R2, R3, R4, R5, R6, R7, R8, R9 are same or different and selected from the group comprising H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl or acceptable esters thereof;

R10 is selected from group comprising: (C_1-C_6) alkyl (straight chain or branched); (C_6-C_{10}) aryl [optionally substituted with (C_1-C_6) alkyl], aryl alkyl group where aryl group is optionally substituted with (C_1- C_6) alkyl, (C_1- C_6) alkoxy, halogen, carboxy, or nitro group; heteroaromatic group; or -O-C(O)R where R is (C_1- C_6) alkyl, (C_6- C_{10}) aryl;

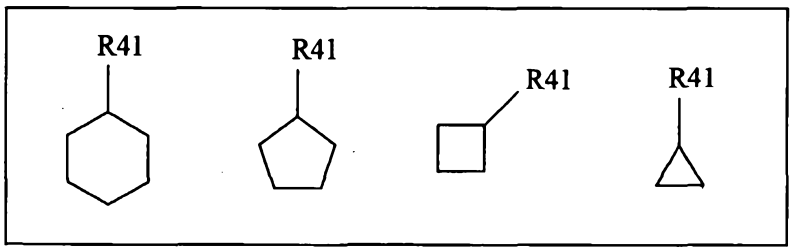
R31 is either H or taken together with **R32** to form a spirocycle;

R32 is selected from the group comprising:



wherein: **m** = 0,1

or when **R31** and **R32** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R41 is **XY** or **–CR11XY**

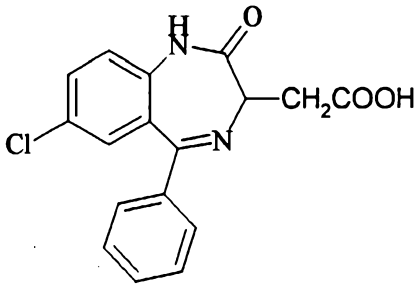
R42 is **X** or **Y** or **-CR11XY**

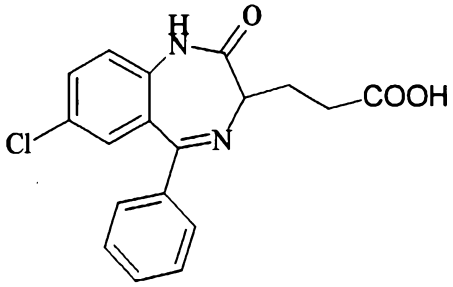
R11 is H, (C_1- C_6) alkyl (straight chain or branched); (C_6- C_{10}) aryl [optionally substituted with (C_1- C_6) alkyl], aryl alkyl group where aryl group is optionally substituted with (C_1-C_6) alkyl, (C_1- C_6) alkoxy, halogen, carboxy, or nitro group; (C_4- C_9) heterocyclic group (aromatic or nonaromatic);

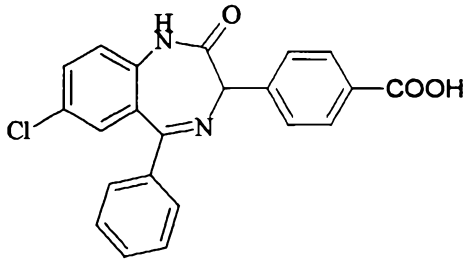
X is H or an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, where n = 2, 3, 4, 5, or 6; or:

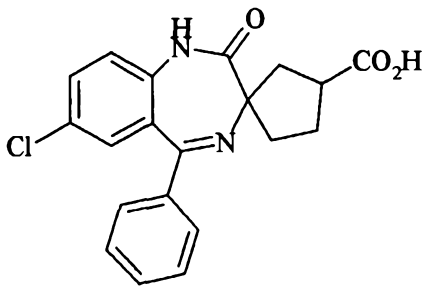
Y is H or a basic group selected from the group comprising 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea, with the proviso that (i) at least one of **X** or **Y** is other than **H** and (ii) when **R32** is –$(CH_2)_m$R42, **R42** is COOH, then m is 1.

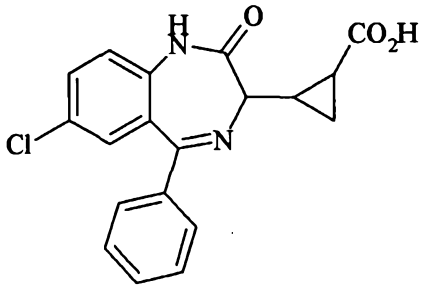
Compounds of the present invention include, but are not limited to the following exemplary molecules:











While all of the compounds of Formula I are believed to demonstrate activity at the metabotropic glutamate receptors (mGluRs), certain groups of Formula I compounds are more preferred for such use.

As noted supra, this invention includes the pharmaceutically acceptable salts of the compounds defined by Formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of organic and inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride,

isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, γ-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, napththalene-2-sulfonate, mandelate and the like.

Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

Salts of amine groups may also comprise quarternary ammonium salts in which the amino nitrogen carries a suitable organic group such as an alkyl, alkenyl, alkynyl, or aralkyl moiety.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, as long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

This invention further encompasses the pharmaceutically acceptable solvates of the compounds of Formula I. Many of the Formula I compounds can combine with solvents such as water, methanol, ethanol and acetonitrile to form pharmaceutically acceptable solvates such as the corresponding hydrate, methanolate, ethanolate and acetonitrilate.

The compounds of the present invention have multiple asymmetric (chiral) centers. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All asymmetric forms, individual isomers and combinations thereof, are within the scope of the present invention.

The prefixes "*R*" and "*S*" are used herein as commonly used in organic chemistry to denote the absolute configuration of a chiral center, according to the Cahn-Ingold-Prelog system. The stereochemical descriptor *R* (*rectus*) refers to that configuration of a chiral center with a clockwise relationship of groups tracing the path from highest to second-lowest priorities when viewed from the side opposite to that of the lowest priority group. The stereochemical descriptor *S* (*sinister*) refers to that configuration of a chiral center with a counterclockwise relationship of groups tracing the path from highest to second-lowest priority when viewed from the side opposite to the lowest priority group. The priority of groups is decided using sequence rules as described by Cahn *et al.*, *Angew. Chem.*, 78, 413-447, 1966 and Prelog, V. and Helmchen, G.; *Angew. Chem. Int. Ed. Eng.*, 21, 567-583, 1982).

In addition to the *R,S* system used to designate the absolute configuration of a chiral center, the older D-L system is also used in this document to denote relative configuration, especially with reference to amino acids and amino acid derivatives. In this system a Fischer projection of the compound is oriented so that carbon-1 of the parent chain is at the top. The prefix "D" is used to represent the relative configuration of the isomer in which the functional (determining) group is on the right side of the carbon atom at the chiral center and "L", that of the isomer in which it is on the left.

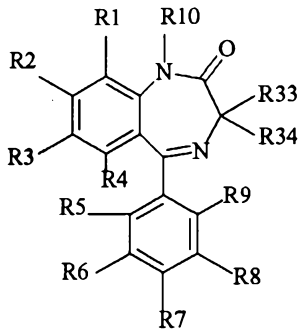
As would be expected, the stereochemistry of the Formula I compounds is critical to their potency as agonists. The relative stereochemistry is preferably established early during synthesis, which avoids stereoisomer separation problems later in the process. Subsequent synthetic steps then employ stereospecific procedures so as to maintain the preferred configuration. The preferred methods of this invention are the methods employing those preferred compounds.

Non-toxic metabolically labile esters and amides of compounds of Formula I are ester or amide derivatives of compounds of Formula I that are hydrolyzed in vivo to afford said compounds of Formula I and a pharmaceutically acceptable alcohol or amine. Examples of metabolically labile esters include esters formed with (C_1-C_6) alkanols in which the alkanol moiety may be optionally substituted by a (C_1-C_8) alkoxy group, for example methanol, ethanol, propanol and methoxyethanol. Examples of metabolically labile amides include amides formed with amines such as methylamine.

Preparation of Compounds of Formula (I)

According to another aspect, the present invention provides a process for the preparation of a compound of Formula I, or a pharmaceutically acceptable metabolically labile ester or amide thereof, or a pharmaceutically acceptable salt thereof, which comprises:

(a) hydrolyzing a compound of formula (II):

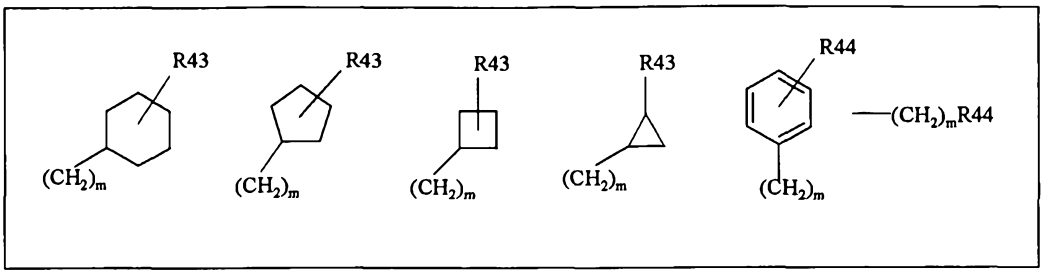


(II)

wherein: **R1-R10** are as defined above,

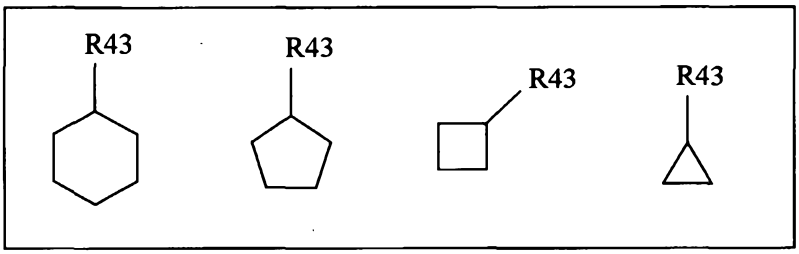
R33 is H or taken together with **R34** to form a spirocycle,

R34 is selected from the group comprising:



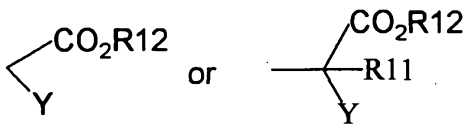
wherein: **m** = 0

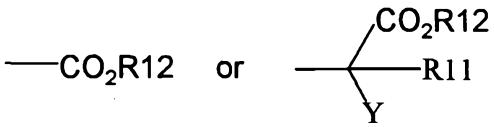
or when **R33** and **R34** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R43 is:

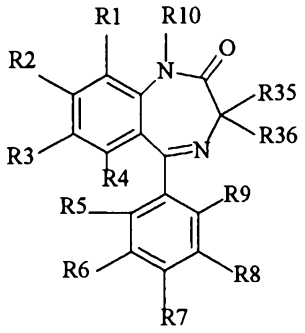
R44 is:





wherein: **R11** is as defined above, **R12** is an acid ester, **Y** is as defined above. Preferred values for Y is H or NH_2; or

(b) deprotecting a compound of formula (III):

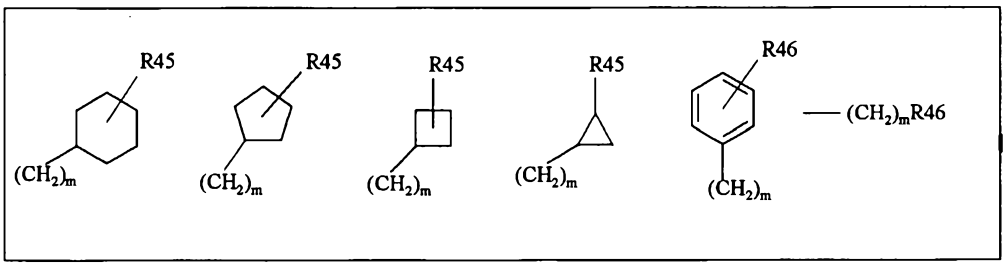


(III)

wherein: **R1-R10** are as defined above,

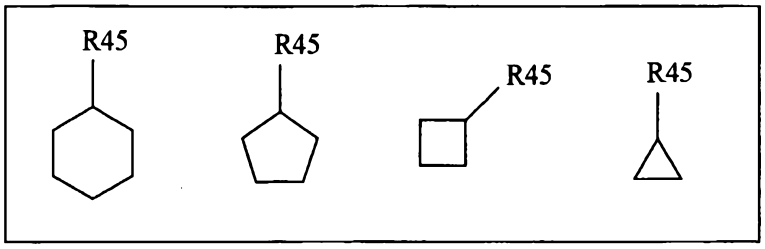
R35 is H or taken together with **R36** to form a spirocycle,

R36 is selected from the group comprising:

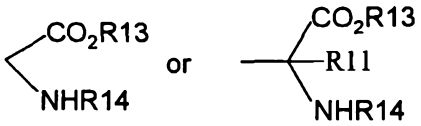


wherein: **m** = 0,1

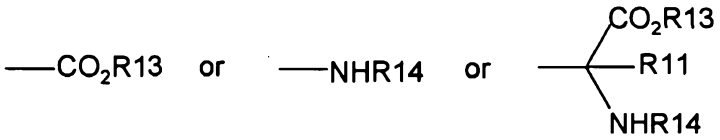
or when **R35** and **R36** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R45 is

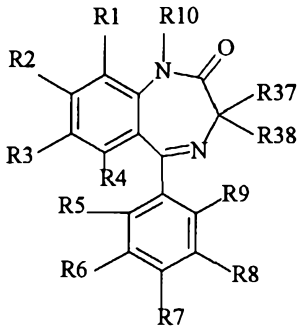


R46 is



wherein: **R11** is as defined above, **R13** represents a hydrogen atom or a carboxyl protecting group, or a salt thereof, and **R14** represents a hydrogen atom or a nitrogen protecting group;

(c) hydrolyzing a compound of formula (IV):

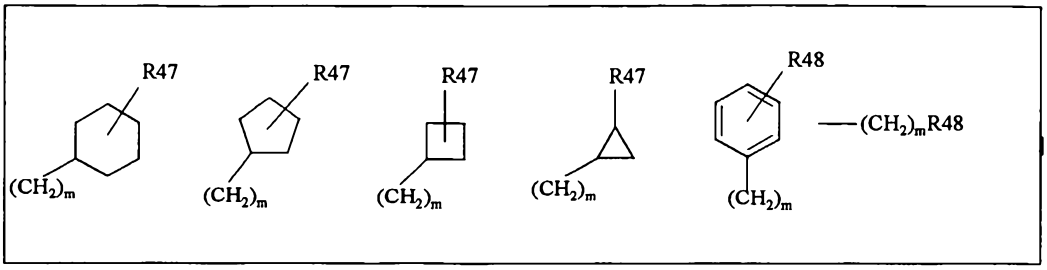


(IV)

wherein: **R1-R10** are as defined above

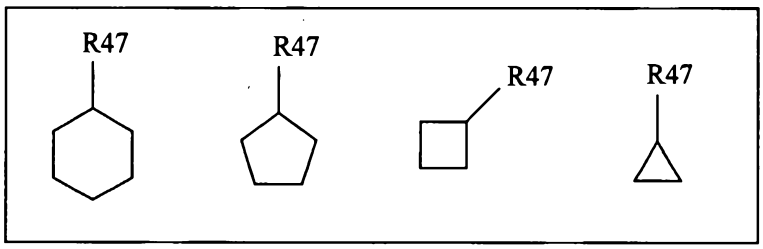
R37 is H or taken together with **R38** to form a spirocycle;

R38 is selected from the group comprising:

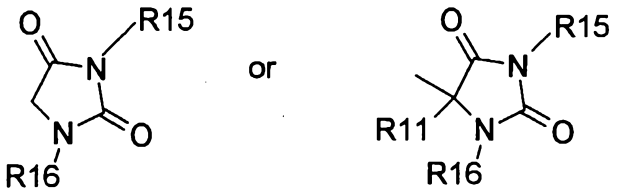


wherein: **m** = 0,1

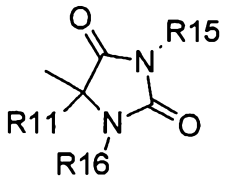
or when **R37** and **R38** taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R47 is:

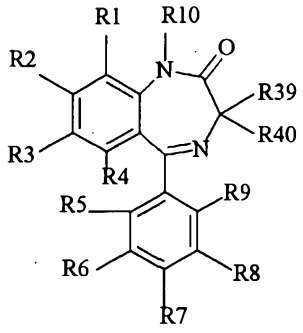


R48 is



wherein: **R11** is as defined above, **R15** and **R16** each independently represent a hydrogen atom, a (C_2-C_6) alkanoyl group, a (C_1-C_4) alkyl group, a (C_3-C_4) alkenyl group or a phenyl (C_1-C_4) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (C_1-C_4) alkyl or (C_1-C_4) alkoxy, or a salt thereof; or:

(d) hydrolyzing a compound of formula (V):

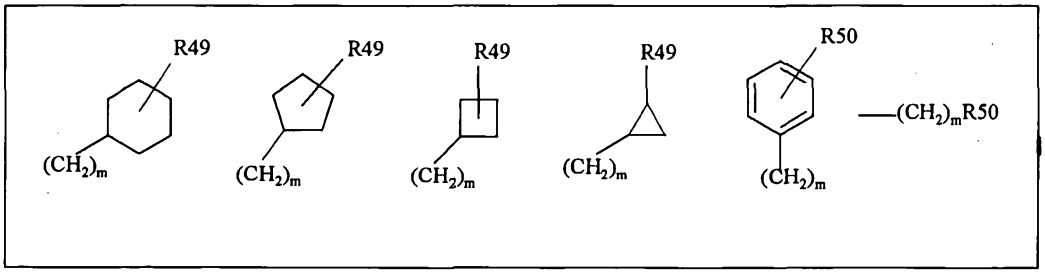


(V)

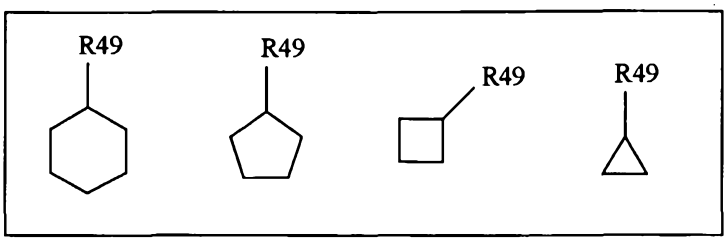
wherein: **R1-R10** are as defined above

R39 is H or taken together with **R40** to form a spirocycle;

R40 is selected from the group comprising:

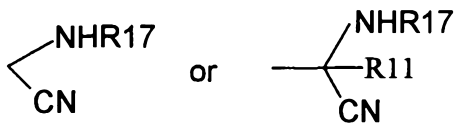


or when **R39** are **R40** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



wherein: **m** = 0,1

R49 is:



R50 is:

wherein: **R11** is as defined above, **R17** represents a hydrogen atom or an acyl group. Preferred values for **R17** are hydrogen and (C_2-C_6) alkanoyl groups, such as acetyl; whereafter, if necessary and/or desired, the following steps are carried out:

(i) resolving the compound of Formula I;

(ii) converting the compound of Formula I into a non-toxic metabolically labile ester or amide thereof; and/or;

(iii) converting the compound of Formula I or a non-toxic metabolically labile ester or amide thereof into a pharmaceutically acceptable salt thereof.

The protection of carboxylic acid and amine groups is generally described in McOmie, *Protecting Groups in Organic Chemistry*, Plenum Press, NY, 1973, and Greene and Wuts, *Protective Groups in Organic Synthesis*, 2nd. Ed., John Wiley & Sons, NY, 1991. Examples of carboxy protecting groups include alkyl groups such as methyl, ethyl, *t*-butyl and *t*-amyl; aralkyl groups such as benzyl, 4-nitrobenzyl, 4-methoxybenzyl,

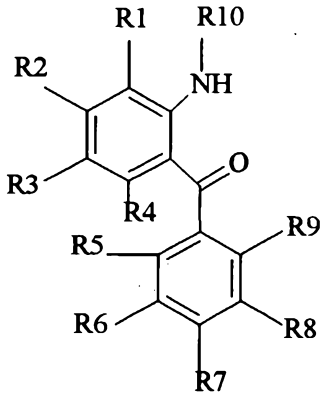
3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, benzhydryl and trityl; silyl groups such as trimethylsilyl and *t*-butyldimethylsilyl; and allyl groups such as allyl and 1-(trimethylsilylmethyl)prop-1-en-3-yl. Examples of amine protecting groups include acyl groups, such as groups of formula **–C(O)R14** in which **R14** represents (C_1-C_6) alkyl, (C_3-C_{10})) cycloalkyl, phenyl (C_1-C_6) alkyl, phenyl (C_1-C_6) alkoxy, or a (C_3-C_{10}) cycloalkoxy, wherein a phenyl group may optionally be substituted by one or two substituents independently selected from amino, hydroxy, nitro, halogeno, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, carboxy, (C_1-C_6) alkoxycarbonyl, carbamoyl, (C_1-C_6) alkanoylamino, (C_1-C_6) alkylsulphonylamino, phenylsulphonylamino, toluenesulphonylamino, and (C_1-C_6) fluoroalkyl.

The compounds of Formula II are conveniently hydrolyzed in the presence of an acid, such as hydrochloric acid or sulfuric acid, or a base, such as an alkali metal hydroxide, for example sodium hydroxide. The hydrolysis is conveniently performed in an aqueous solvent such as water and at a temperature in the range from 50 to 200 °C.

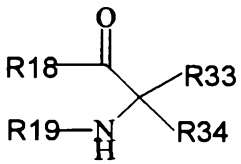
The compounds of Formula IV may be deprotected by conventional methods. Thus, an alkyl carboxyl protecting group may be removed by hydrolysis. The hydrolysis may conveniently be performed by heating the compound of Formula IV in the presence of either a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline metal hydroxide, such as barium hydroxide, or an acid such as hydrochloric acid. The hydrolysis is conveniently performed at a temperature in the range from 10 to 300 °C. An arylalkyl carboxyl-protecting group may conveniently be removed by hydrogenolysis. The hydrogenolysis may conveniently be effected by reacting the compound of Formula IV with hydrogen in the presence of a Group VIII metal catalyst, for example a palladium catalyst such as palladium on charcoal. Suitable solvents for the reaction include alcohols such as ethanol. The reaction is conveniently performed at a temperature in the range from 0 to100 °C. An acyl amine protecting group is also conveniently removed by hydrolysis, for example as described for the removal of an alkyl carboxyl protecting group.

The compounds of Formula V are conveniently hydrolyzed in the presence of a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline earth metal hydroxide such as barium hydroxide. Suitable reaction media include water. The temperature is conveniently in the range from 50 to 150 °C.

Compounds of formula (II) may be synthesized by condensing compounds of formula (VI) with a compound of general formula (VII):



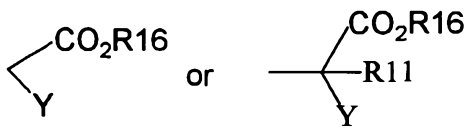
(VI)



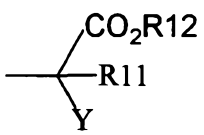
(VII)

wherein: **R1-R10**, **R33** and **R34** are as defined above, **R18** is OH or F and **R19** is H or Fmoc.

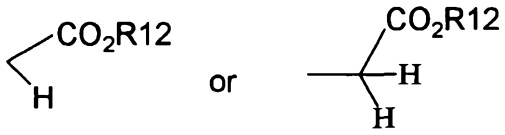
Compounds of formula (II), wherein **R43** is:



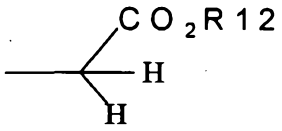
and **R44** is:



wherein: **Y** and **R12** are as defined above, **R11** is as defined above, but other than H can be prepared from compounds of formula (II), wherein **R43** is:



and **R44** is:

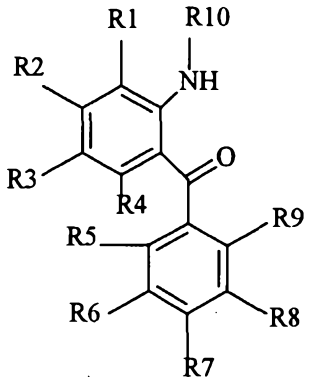


respectively, by standard procedures known to a worker skilled in the relevant art. For example:

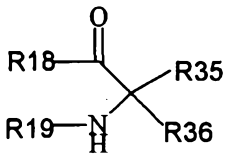
(a) by α-halogenation, followed by ammonolysis of the resulting halides by ammonia or an appropriate amine. When required, by further alkylation or acylation or halogenation of the obtained compounds, followed by further manipulations of the resulting compounds using standard procedures known to a worker skilled in the art, or

(b) by α- alkylation or acylation or halogenation , followed by α-halogenation of the obtained products, followed by ammonolysis of the resulting halides by ammonia or an appropriate amine.

Compounds of formula (III) may be synthesized by condensing compounds of formula (VI) with a compound of general formula (VIII):



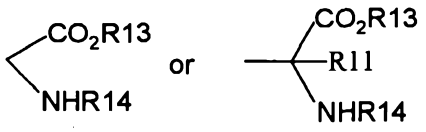
(VI)



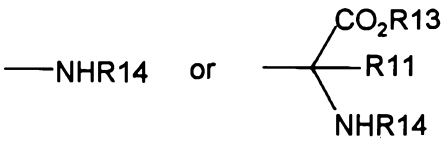
(VIII)

wherein **R1-R10, R18, R19, R35 and R36** are as defined above;

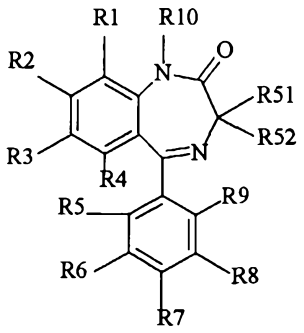
Compounds of formula (III), wherein **R45** is:



and **R46** is:



wherein: **R13** and **R14** are as defined above, **R15** is as defined above, but other than H can also be prepared from compounds of formula (IX) using standard reaction conditions known to a worker skilled in the art:

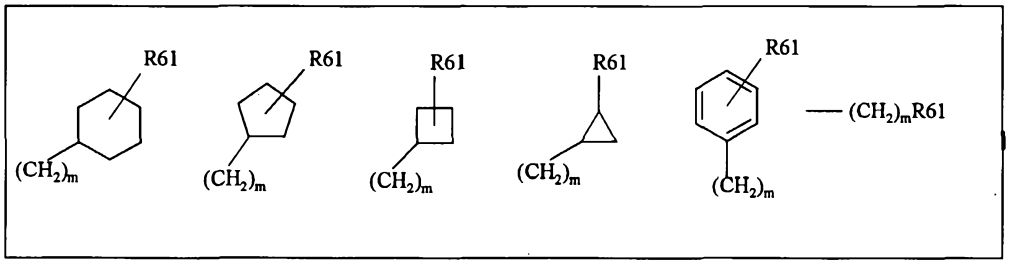


(IX)

wherein: **R1-R10** are as defined above,

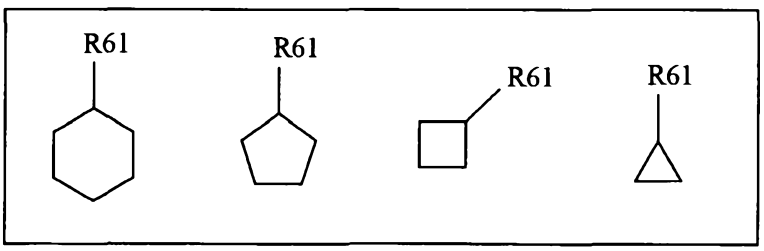
R51 is H or taken together with **R52** to form a spirocycle,

R52 is selected from the group comprising:



wherein: **m** = 0,1

or when **R51** and **R52** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R61 is

—(CH2)m-R20

wherein: m' is 0-3, **R20** is -CO_2R13 or OH and **R13** is as defined above. For example:

(a) by α-halogenation, of compound IX, wherein **R20** is -CO_2R13, followed by ammonolysis of the resulting halides. When required, by further alkylation or acylation or halogenation of the obtained compounds, followed by further manipulations of the resulting compounds using standard procedures known to a worker skilled in the art, or

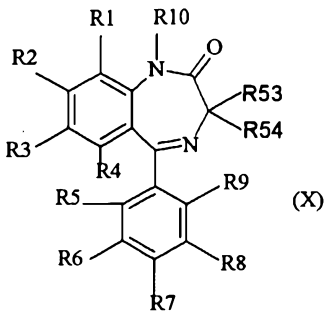
(b) by alkylation or acylation or halogenation of compound IX, wherein **R20** is -CO_2R13, followed by α-halogenation of the resulting compound and then ammonolysis of resulting halides by using ammonia or appropriate amine.

(c) by hydrolysis of compound IX, wherein **R20** is -CO_2R13 and where R13 is other than H, followed by amide formation and then subjecting the resulting compounds to Hofmann degradation conditions, followed by further manipulations of the resulting compounds, using the standard procedures known to a person skilled in the art or

(d) by α-alkylation or acylation or halogenation of compound IX, wherein **R20** is -CO_2R13, hydrolyzing the resulting compounds where R13 is other than H, , followed by amide formation and then subjecting the resulting compounds to Hofmann degradation reaction, followed by further manipulations of the resulting compounds, using the standard procedures known to a person skilled in the art, or

(e) by halogenation of the compound IX, wherein **R20** is OH, followed by ammonolysis of the resulting halide with ammonia or an appropriate amine or by reaction of the halide with anion generated from malonic ester or diethyacetamido malonate and related compounds, followed by further manipulations of the resulting compounds using standard reaction known to a worker skilled in the art.

Compounds of formula IV may be formed by reacting compound X with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and ammonium carbonate or ammonium carbamate. Common solvents include alcohols, such as methanol, aqueous methanol and aqueous ethanol. Conveniently the reaction is performed at a temperature in the range of from 10 to 150 °C. If desired, the compounds of Formula IV may then be alkylated, for example using an appropriate alkyl, aryl or acyl chloride.

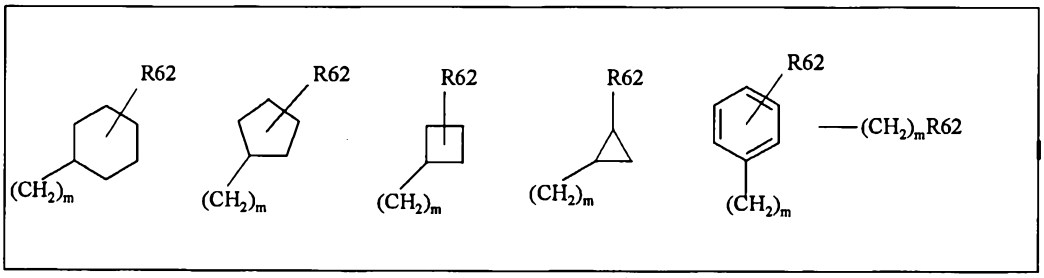


(X)

wherein: **R1-R10** are defined above;

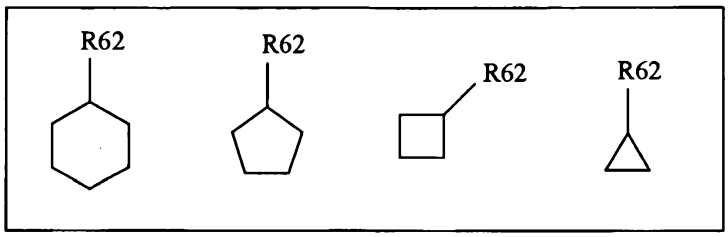
R53 is H or taken together with **R54** to form a spirocycle;

R54 is selected from the group comprising:

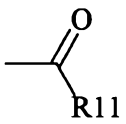


wherein: **m** = 0,1

or when **R53** and **R54** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



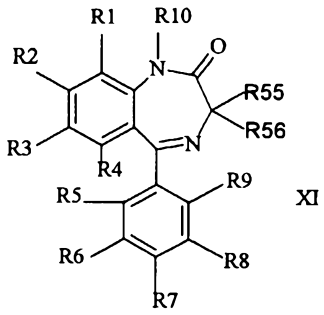
R62 is:



wherein: **R11** is as defined above.

The compounds of formula V may be prepared by reacting a compound of formula X with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and either ammonium carbonate in an aqueous alcohol, such as aqueous ethanol, or with an ammonium halide, such as ammonium chloride, conveniently in the presence of ultrasound. If the reaction is conducted with ammonium carbonate, the reaction is conveniently performed at a temperature in the range from 35 to 150 °C. If desired, the compounds of Formula V may then be alkylated, for example using an appropriate alkyl, aryl or acyl chloride. As described in more detail hereinafter, the alkylated compounds may be readily separated into their diastereomers. If the reaction is conducted with an ammonium halide in the presence of ultrasound, the ammonium halide is mixed with chromatography grade alumina in the presence of a suitable diluent such as acetonitrile.

Individual isomers of compounds of Formula V may be made by reacting a compound of the Formula X with the stereoisomers of the chiral agent (S)- and (R)-phenylglycinol and a reactive cyanide such as trimethylsilyl cyanide to form the intermediate compounds of Formula XI.

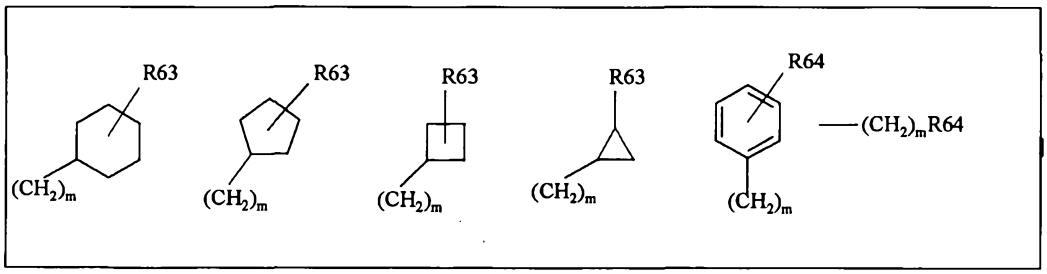


XI

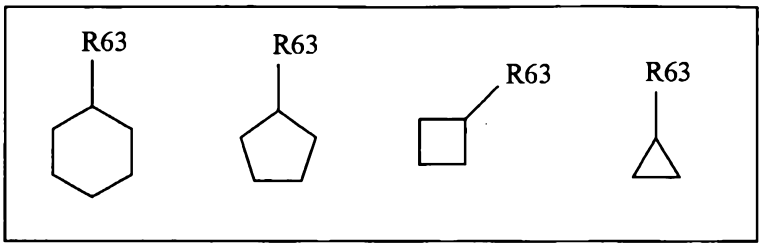
wherein: **R1-R10** are defined above;

R55 is H or taken together with **R56** to form a spirocycle;

R56 is selected from the group comprising:

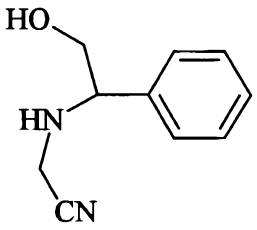


or when **R55** and **R56** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:

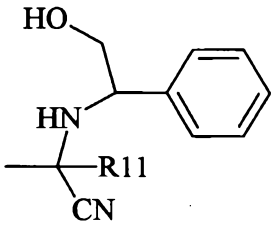


wherein: **m** = 0,1

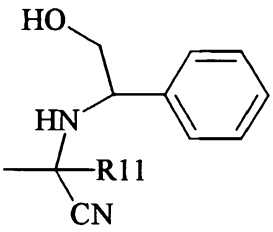
R63 is



or

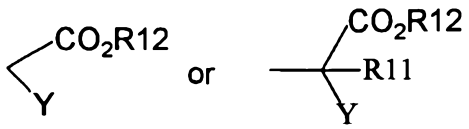


R64 is

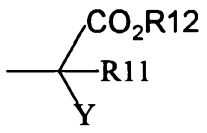


wherein: **R11** is as defined above.

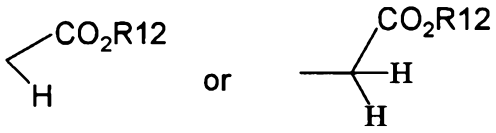
Compounds of formulae (VI), (VII) and (VIII) are either commercially available or may be prepared from other commercially available starting materials, using standard procedures known to a person skilled in the art. For example, compounds of formula (VII), wherein **R43** is:



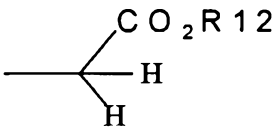
and **R44** is:



wherein: **R12** and **Y** is as defined above, **R11** is as defined above, but other than H, can be prepared from compounds of formula (II), wherein **R43** is:



and **R44** is:

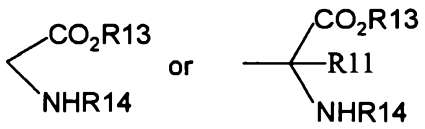


respectively, by:

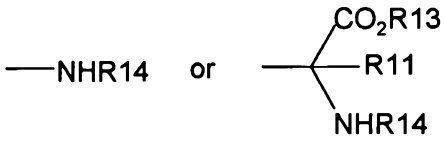
(a) α-halogenation, followed by ammonolysis of the resulting halides by ammonia or appropriate amine. When required, by further alkylation or acylation or halogenation of the obtained compounds, followed by further manipulations of the resulting compounds using standard procedures known to a worker skilled in the art, or

(b) α- alkylation or acylation or halogenation , followed by α-halogenation of the obtained products, followed by ammonolysis of the resulting halides by ammonia or appropriate amine.

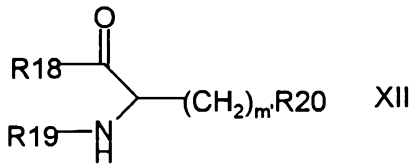
Compounds of formula (VIII), wherein **R45** is:



and **R46** is:



wherein: **R11**, **R13** and **R14** are as defined above, can be prepared from compounds of formula (XII):



XII

wherein: m' is 0-3, **R18**, **R19** and **R20** are as defined above, by:

(a) α-halogenation, of compound IX, wherein **R20** is -CO_2R13, followed by ammonolysis of the resulting halides with ammonia or an appropriate amine. When required, by further alkylation or acylation or halogenation of the obtained compounds, followed by further manipulations of the resulting compounds using standard procedures known to a worker skilled in the art, or

(b) α-alkylation or acylation or halogenation of compound IX, wherein **R20** is – CO_2R13, followed by α-halogenation of the resulting compound and then ammonolysis of resulting halides by using ammonia or an appropriate amine.

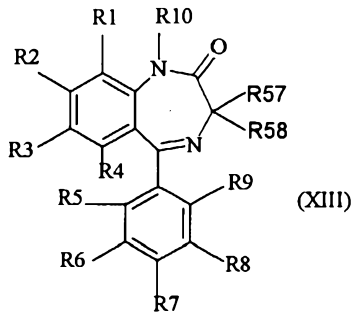
(c) hydrolysis of compound IX, wherein **R20** is -CO_2R13 and where R13 is other than H, followed by amide formation and then subjecting the resulting compounds to Hofmann degradation conditions, followed by further manipulations of the resulting compounds, using the standard procedures known to a person skilled in the art or

(d) alkylation or acylation or halogenation of compound IX, wherein **R20** is -CO_2R13, hydrolyzing the resulting compounds where R13 is other than H, followed by amide formation and then subjecting the resulting compounds to Hofmann degradation reaction, followed by further manipulations of the resulting compounds, using the standard procedures known to a person skilled in the art, or

(e) halogenation of the compound IX, wherein **R20** is OH, followed by ammonolysis of the resulting halide with ammonia or an appropriate amine or by reaction of the halide with anion generated from malonic ester or diethyacetamido malonate and related compounds, followed by further manipulations of the resulting compounds using standard reaction known to a worker skilled in the art.

Some compounds of the formula X may be can be prepared by:

(a) reduction of compound of formula XIII:

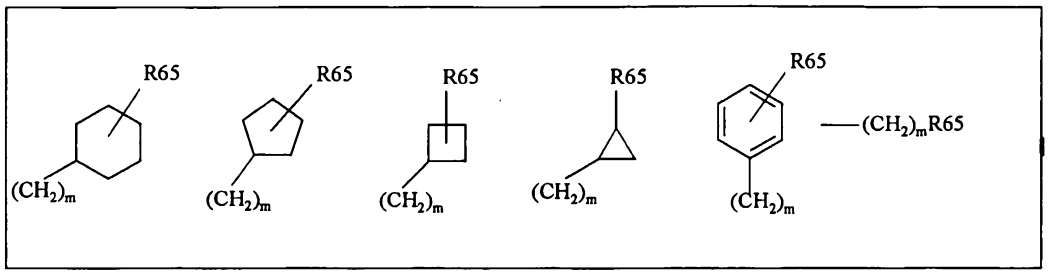


(XIII)

wherein: **R1-R10** are defined above;

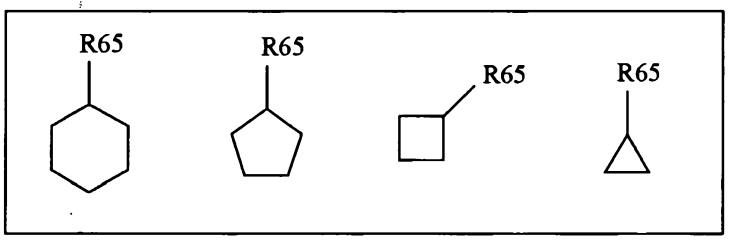
R57 is H or taken together with **R58** to form a spirocycle;

R58 is selected from the group comprising:

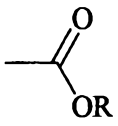


wherein: **m** = 0,1

or when **R57** are **R58** taken together to form a spirocycle, then the spirocycle is selected from the group comprising:

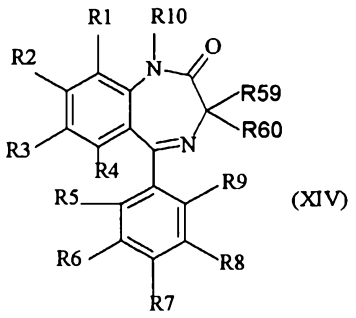


R65 is:



wherein: R is H, (C_1-C_6) alkyl, phenyl, benzyl or any other carboxyl protecting group; or

(b) oxidation of compound of formula XIV:

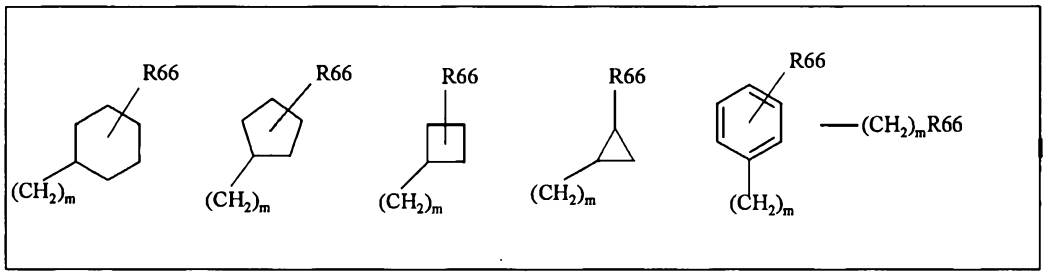


(XIV)

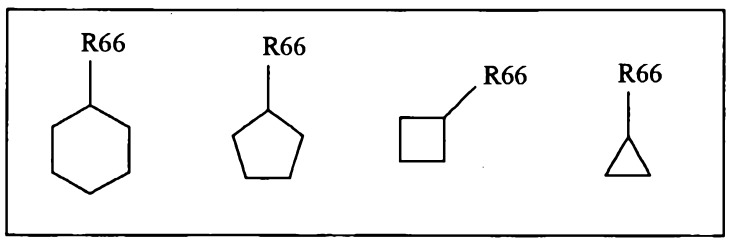
wherein: **R1-R10** are defined above;

R59 is H or taken together with **R60** to form a spirocycle;

R60 is selected from the group comprising:

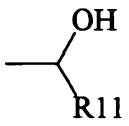


or when **R59** and **R60** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



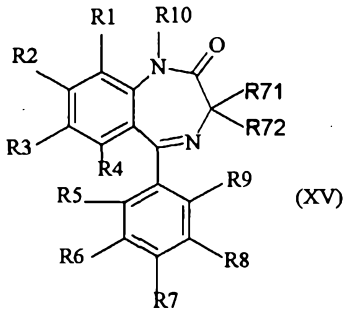
wherein: **m** = 0,1

R66 is



wherein: **R11** is as defined above; or

(c) treating a compound of formula XV with $SOCl_2$, followed by alkylation of the resulting compound with an appropriate alkylating agent:

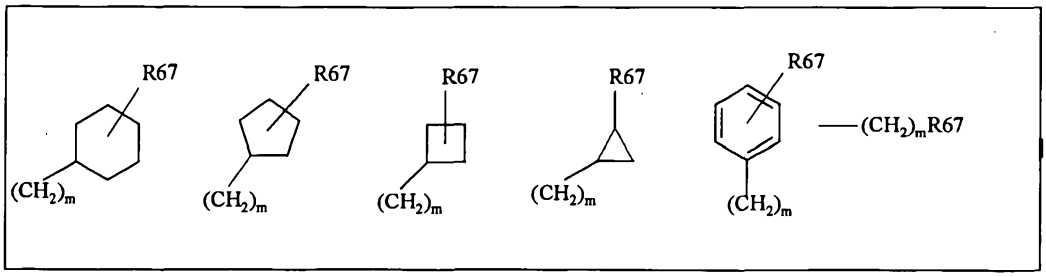


(XV)

wherein: **R1-R10** are defined above;

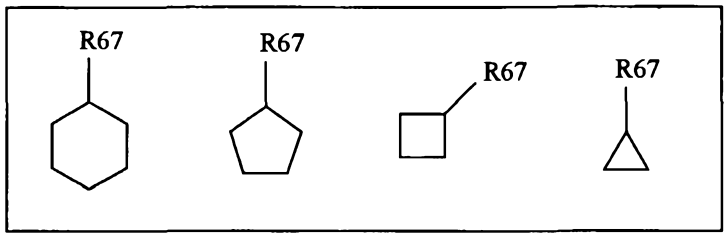
R71 is H or taken together with **R72** to form a spirocycle;

R72 is selected from the group comprising:

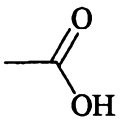


wherein: m = 0,1

or when **R71** are **R72** taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R67 is



Functional Assays Employing Cloned Subtypes of Metabotropic Receptors

The pharmacological properties of the compounds of the present invention can be determined *via* appropriate functional assays using recombinant metabotropic glutamate receptors. For example adenylate cyclase assays or phosphatidylinositol hydrolysis assays, performed using standard procedures, can be used to determine agonist or antagonist activity towards mGluRs.

In Vitro Testing:

General *in vitro* assay methods include monitoring of adenylate cyclase activity and phosphatidyl inositol hydrolysis in a cell line that expresses the appropriate mGluR. Many in vitro assays exist which can be used to study adenylate cycliase activity and phosphatidyl inositol hydrolysis, a few examples of which are provided below.

(a) Adenylate Cyclase Activity

Adenylate cyclase activity is determined in initial experiments in transfected mammalian cells, using standard techniques. See, e.g., N. Adham, *et al.*, Supra; R. L. Weinshank, *et al.* Proc. Natl. Acad. Sci. (USA), 89:3630-3634 (1992), and the references cited therein.

Mammalian cells (the cell line AV12-664 is especially preferred) are stably transfected with a plasmid comprising a cloned metabotropic glutmate receptor. The cells are maintained in an appropriate medium, for example one consisting of Dulbecco's Modified Eagle's Medium (DMEM) containing 5% dialyzed fetal calf serum, 10 mM HEPES buffer (pH 7.3), 1 mM sodium pyruvate, 1 mM glutamine, and 200 μ.g/mL hygromycin.

For the assay the cells are released from stock culture flasks with trypsin, and plated in 24-well plastic tissue culture dishes (15 mm wells) at a density of 500,000-700,000 cells per well using the same culture medium. After a twenty four hour incubation in a humidified CO_2 incubator, the cell monolayers are washed with buffer (for example Dulbecco's phosphate-buffered saline containing 0.5 mM IBMX and 3 mM glucose) and then incubated in the same buffer at 37 °C for 30 minutes. The monolayers are then washed with six exchanges of buffer.

Test compound(s) and forskolin, or forskolin alone, dissolved in buffer, are added after the final wash. After incubating for 20 minutes at 37 °C, 0.5 mL of 8 mM EDTA is added to each well. The plates are then placed in a boiling water bath for about four minutes. The supernatant fluids are recovered from the wells and lyophilized. Cyclic AMP (cAMP) determinations are carried out on the lyophilized samples using commercially available radioimmunoassay kits, following the manufacturer's instructions. The cAMP levels in wells containing test compound(s) are then compared to the forskolin controls.

(b) Phosphatidylinositol Assay

Phosphatidylinositol hydrolysis is measured in clonal cell lines (for example AV12) harbouring a plasmid expressing the cloned metabotropic glutamate receptor in response to addition of glutamate agonists, as a functional assay for metabotropic glutamate receptor activity according to D. Schoepp, Trends in Pharmaceutical Sciences, 11:508, 1990.

Twenty four well tissue culture vessels are seeded with approximately 250,000 cells per well in an appropriate medium, for example Dulbecco's Minimal Essential Media (D-MEM) (in the absence of glutamic acid) containing 2 mM glutamine and 10% dialyzed fetal calf serum. After 24 hours growth at 37 °C, the media is removed and replaced with fresh media containing four microcuries of [^{3} H]myoinositol per well and the cultures are

incubated a further 16 to 20 hours. The media is then removed and the cells in each well are washed with serum free medium containing 10 mM lithium chloride, 10 mM myoinositol, and 10 mM HEPES (2 × 1 mL washes). After the final wash, 0.5 mL of washing solution is added containing the appropriate concentration(s) of test compound(s).

If the particular assay is also testing antagonists, a ten minutes incubation is performed prior to antagonist induction. Cells are incubated for about one hour at 37 °C. in 95%:5% O_2 :CO_2 or as appropriate for time course. The reactions are terminated by removing media and adding 1 mL of cooled 1:1 acetone:methanol followed by incubation on ice for a minimum of twenty minutes.

These extracts are then collected and placed in 1.5 mL centrifuge tubes. Each well is washed with 0.5 mL water and this wash is added to the appropriate extract. After mixing and centrifugation, each aqueous supernatant is processed by chromatography on a QMA SEP-PAK® column, which is prewetted and equilibrated by passing 10 mL of water, followed by 8 mL of 1 M triethylammonium hydrogen carbonate (TEAB), followed by 10 mL of water through the column.

The assay supernatants containing the water soluble [^{3}H]inositol phosphate are passed over the columns. This is followed by a 10 mL water wash and a 4 mL wash with 0.02 M TEAB to remove [^{3}H]inositol precursors. [^{3}H]inositol phosphate is eluted with 4 mL of 0.1 M TEAB into scintillation vials and counted in the presence of scintillation cocktail. Total protein in each sample is measured using standard techniques. Measurements are taken as the amount of [^{3}H]inositol phosphate released per milligram of protein.

The assays are carried out in the absence and in the presence of the compound being tested. The measurements of [^{3}H]inositol phosphate per milligram of protein are compared in order to confirm agonist and antagonist activity of the compound being tested.

These types of assays, employing cell lines expressing different subtype of cloned metabotropic receptors, may be used to determine which compounds have selective affinity in that they modulate one subtype of receptor with a greater activity than another subtype.

(c) Testing in Chinese hamster cell lines

The Chinese hamster ovary cell lines expressing $mGluR_{1\alpha}$, $mGluR_2$ and $mGluR_{4\alpha}$ receptors have been described previously (Amarori and Nakanishi, Neuron 8, 757-765, 1992; Tanabe *et al.*, Neuron 8, 169-179, 1992, and J. Neurochem. 63, 2038-2047, 1993). They are maintained at 37 °C in a humidified 5% CO_2 incubator in Dubecco's Modified Eagle Medium (DMEM) containing a reduced concentration of (S)-glutamine (2mM) and are supplemented with 1% proline, penicillin (100 U/mL), streptomycin (100 mg/mL) and 10% dialyzed fetal calf serum (all GIBCO, Paisley). Two days before assay 1.8×10^6 cells are evenly distributed into the wells of 24 well plates.

Phosphatidylinositol (PI) hydrolysis can be measured as described previously (Hayashi *et al.*, Nature 366, 687-690,1992, and J. Neuroscience 14, 3370-3377, 1994). Briefly, the cells are labeled with [^{3}H]inositol (2μ Ci/mL) 24 h prior to the assay. For agonist assays, the cells are incubated with test compound dissolved in phosphate-buffered saline (PBS)-LiCl for 20 min, and agonist activity is determined from the level of ^{3}H-labeled mono-, bis- and tris-inositol phosphates generated, as measured following ion-exchange chromatography, compared with the level generated in the absence of the test compound. For antagonist assays, the cells are preincubated with ligand dissolved in PBS-LiCl for 20 min prior to incubation with test compound and 10 μ M (S)-Glu for 20 min. The antagonist activity is then determined as the inhibitory effect of the (S)-Glu mediated response.

The assay of cyclic AMP formation can be performed as described previously (Hayashi *et al.*, 1992, 1994). Briefly, the cells are incubated for 10 min in PBS containing test coumpound and 10 μM forskolin and 1 mM 3-isobutyl-1-methylxanthine (IBMX) (both Sigma, St. Louis, MO, USA). The agonist activity is then determined as the inhibitory effect on the forskolin-induced cyclic AMP formation. For antagonist assay, the cells are

preincubated with ligand dissolved in PBS containing 1 mM IBMX for 20 min prior to a 10 min incubation in PBS containing test compound, 20 μ M(mGlu2) or 50 μ M (mGlu4a) (S)-Glu, 10 μ M forskolin and 1 mM IBMX. The antagonist activity is then determined as the potentiating effect on the forskolin-induced cyclic AMP formation.

In Vivo Testing:

In *vivo* testing for demonstration of the pharmacological activity of certain compounds on representative mGlu receptor subtypes can be performed using Sprague Dawley rat tissues. It should be readily appreciated by a worker skilled in the art that any animal tissue that expresses mGluRs may be used as described herein, for Sprague dawley rat tissues.

Phosphatidylinositol (PI) hydrolysis can be measured as described below:

Briefly, cross-chopped slices are prepared from neonatal Sprague Dawley rat tissue (age: p7-p14). The slices are pre-labelled with [^{3}H] myo-inositol. Following pre-labelling, the slices are incubated with the test drugs and standard (known Group I agonists *i.e.* ACPD) for a period of 45 minutes. The incubation is terminated by the addition of chloroform/methanol/HCl (100:200:2). The resulting mixture is separated into two phases by the addition of chloroform and distilled water. The aqueous fraction is applied to ion exchange columns, and inositol phosphates are eluted using 800 mM Ammonium Formate/100 mM Formic Acid. The eluent is then analyzed using liquid scintillation counting. The amount of inositol phosphate accumulation is expressed as a percentage of that induced by ACPD.

The assay of cyclic AMP formation can be performed as described previously (Tovey *et al.*, *Clinica Chimica Acta*, 56, 221-234, 1974). The assay can be modelled on the cyclic AMP assay kit available from Amersham, which in turn, is based on the assay created by Tovey *et al.* Briefly, samples are prepared from Sprague Dawley rat (225-250g) cortical slices. Slices are incubated with the drug, and then challenged with forskolin to induce cyclic AMP release. Following termination of the reaction by boiling, the slices are homogenized and centrifuged. Samples of supernatant are then incubated for 2-3 hours with a known quantity of [^{3}H]cAMP and a binding protein. When the incubation is

complete, the bound cyclic AMP is separated from the free cyclic AMP by centrifugation with charcoal. The resulting supernatant (containing free cyclic AMP) is then analyzed by liquid scintillation counting. The amount of unbound cyclic AMP can be calculated from a standard curve previously determined with various samples of free cyclic AMP.

In performing such experiments with some of the compounds of the present invention, it has been demonstrated that some compounds of the present invention act as modulators of the cAMP-linked metabotropic glutamate receptors, while showing less activity with phosphatidylinositol-linked metabotropic glutamate receptors and *vice versa*.

Biological and Therapeutic Activity Of Compounds Of Formula (I)

The compounds of formula I of the present invention exhibit agonistic or antagonistic activity toward certain metabotropic glutamate receptors (mGluRs). Therefore, another aspect of the present invention provides a method of modulating the activity of mGluRs in mammals, which comprises administering to a mammal requiring modulated excitatory amino acid neurotransmission a pharmacologically-effective amount of a compound of Formula I. The term "pharmacologically-effective amount" is used to represent an amount of the compound of the present invention that is capable of affecting the mGluRs. By modulating mGluR activity, a compound of the present invention is acting as an agonist or antagonist of mGluR. When a compound of the present invention acts as an agonist, the interaction of the compound with the excitatory amino acid receptor mimics the response for the interaction of this receptor with its natural ligand, (i.e. L-Glutamic acid). When a compound of the invention acts as an antagonist, the interaction of the compound with the excitatory amino acid receptor blocks or attenuates the response from the interaction of this receptor with its natural ligand, (i.e. L-Glutamic acid).

The particular dose of compound administered according to the present invention will, of course, be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and similar considerations. The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, or intranasal routes. Alternatively, the compound may be administered by continuous infusion. A typical daily dose will contain from about 0.001 mg/kg to about 100 mg/kg

of the active compound of this invention. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 20 mg/kg.

A variety of physiological functions have been shown to be subject to influence by excessive or inappropriate stimulation of excitatory amino acid transmission. The Formula I compounds of the present invention can be used (through their interactions at the mGluRs) to treat a variety of neurological disorders in a warm-blooded mammals associated with abnormal excitatory amino acid transmission, including but not limited to acute neurological disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, cerebral ischemia (e.g. stroke and cardiac arrest), spinal cord trauma, head trauma, perinatal hypoxia, and hypoglycemic neuronal damage. Similarly, the Formula I compounds of the present invention, through their modulation of mGluR activity can be used to treat a variety of chronic neurological disorders, such as Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, ocular damage and retinopathy, cognitive disorders, and idiopathic and drug-induced Parkinson's disease. The present invention also provides methods for treating these disorders which comprises administering to a patient, in need thereof, an effective amount of a compound of Formula I.

The Formula I compounds of the present invention, through their modulation of mGluR activity can be used to treat a variety of other neurological disorders in mammals that are associated with glutamate dysfunction, including muscular spasms, convulsions, migraine headaches, urinary incontinence, psychosis, drug tolerance, withdrawal, and cessation (i.e. opiates, benzodiazepines, nicotine, cocaine, or ethanol), smoking cessation, anxiety and related disorders (e.g. panic attack), emesis, brain edema, chronic pain, sleep disorders, Tourette's syndrome, attention deficit disorder, and tardive dyskinesia. Therefore, the present invention also provides methods for treating these disorders which comprise administering to a patient in need thereof an effective amount of the compound of Formula I.

The Formula I compounds of the present invention, through their modulation of mGluR activity can be used to treat a variety of psychiatric disorders, such as schizophrenia, anxiety and related disorders (e.g. panic attack), depression, bipolar disorders, psychosis,

and obsessive compulsive disorders. The present invention also provides methods for treating these disorders which comprises administering to a patient in need thereof an effective amount of a compound of Formula I.

Administration of Compounds of Formula (I)

According to another aspect, the present invention provides a method of modulating one or more mGluR functions in a warm-blooded mammal which comprises administering an effective amount of a compound of Formula I, or a non-toxic metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof.

The compounds of the present invention are preferably formulated prior to administration. Therefore, another aspect of the present invention is a pharmaceutical formulation comprising a compound of Formula I and a pharmaceutically-acceptable carrier, diluent, or excipient. The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active ingredient.

The compounds of Formula I are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

The present invention also provides pharmaceutical compositions containing compounds as disclosed in the claims in combination with one or more pharmaceutically acceptable, inert or physiologically active, diluents or adjuvants. The compounds of the invention can be freeze dried and, if desired, combined with other pharmaceutically acceptable excipients to prepare formulations for administration. These compositions may be

presented in any form appropriate for the administration route envisaged. The parenteral and the intravenous route are the preferential routes for administration.

Compounds of the general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any procedure known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate: granulating and disintegrating agents for example, corn starch, or alginic acid: binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methyl cellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia: dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethyene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example hepta-decaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or *n*-propyl *p*-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents or one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oils phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulation according to known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compound(s) of the general Formula I may be administered, together or separately, in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compound(s) of general Formula I may be administered, together or separately, parenterally in sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants

such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle.

The mode, dosage and schedule of administration of taxol in human cancer patients has been studied extensively (see Ann. Int. Med. **111**:273 1989). For the compounds of this invention, the dose to be administered, whether a single dose, multiple dose, or a daily dose, will vary with the particular compound being used. Factors to consider when deciding upon a dose regimen include potency of the compound, route of administration, size of the recipient and the nature of the patient's condition.

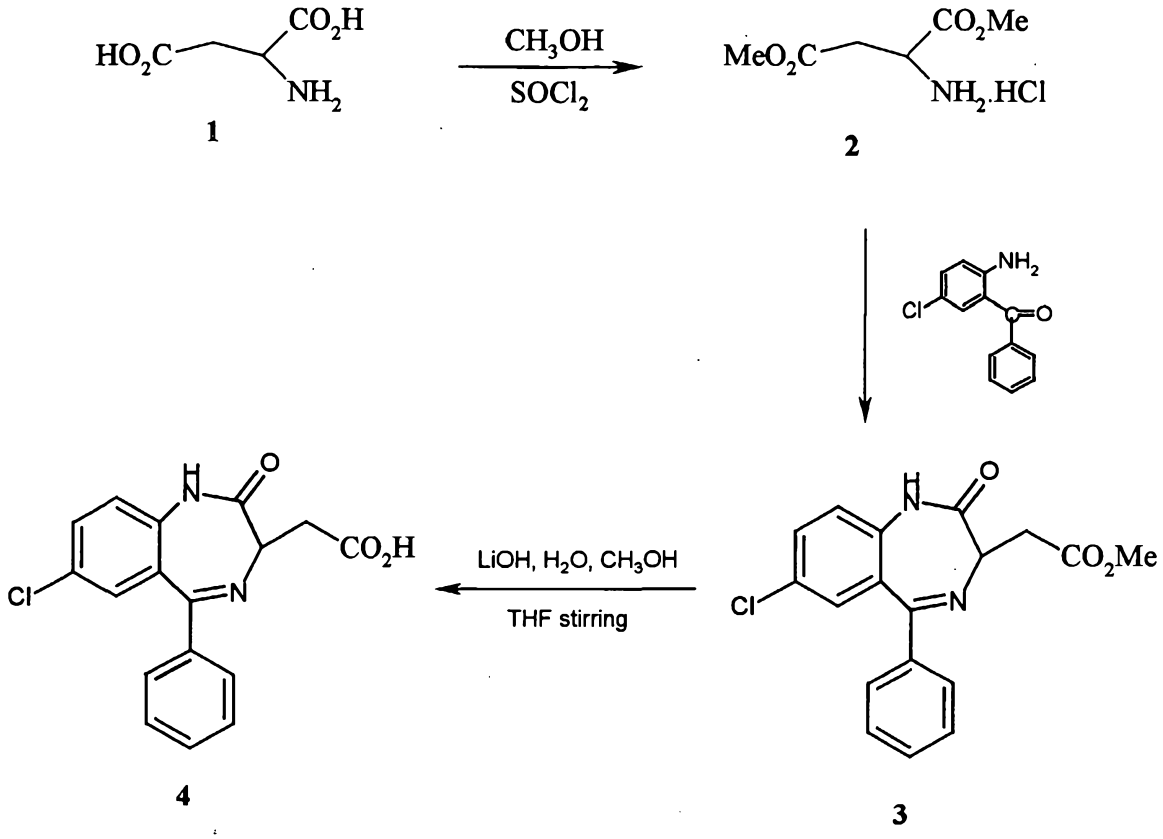
The dosage to be administered is not subject to defined limits, but in will usually be an effective amount. It will usually be the equivalent, on a molar basis of the pharmacologically active free form produced from a dosage formulation upon the metabolic release of the active free drug to achieve its desired pharmacological and physiological effects.

Examples

To gain a better understanding of the invention described herein, the following examples are set forth. It should be understood that these examples are for illustrative purposes only. Therefore, they should not limit the scope of this invention in any way.

The following abbreviations are used in the Examples: EtOAc, ethyl acetate; THF, tetrahydrofuran; EtOH, ethanol; TLC, thin layer chromatography; GC, gas chromatography; HPLC, high pressure liquid chromatography; DMF; *N*,*N*-dimethylformamide; Fmoc; 9-flurenylmethoxycarbonyl; Et_2O, diethyl ether; DMSO, dimethyl sulfoxide; DBU, 1,8-diazabicyclo-[5.4.0]undec-7-ene, MTBE, methyl *t*-butyl ether; and FDMS, field desorption mass spectrometry.

Example 1:



Preparation of dimethyl-L-aspartate hydrochloride (compound **2**)

8.35 g of thionyl chloride was added dropwise, to a suspension of 6.65 g of L-aspartic acid in methanol (38 mL) at 0 °C and the resulting mixture was allowed to stir at room temperature for 45 hours. The residual oil was concentrated and triturated with ether. The resulting white solid was filtered and washed with cold ether, and dried to obtain 7.65 g (95%) of compound **2**.

Preparation of (7-chloro-5-phenyl-1,3-dihydro-2H,-1,4-benzodiazepin-2-keto)-3-methyl acetate (compound **3**)

A solution of 4.63 g (0.1 mol) of 5-chloro-2-aminobenzophenone, and 5.92g (0.15 mol) of dimethyl L-aspartate hydrochloride (compound **2**) was refluxed in 200 mL of pyridine, for 15 hours. During the first four hours, 20-50 mL of the solvent was distilled slowly and replaced with fresh dry pyridine (to remove some of the water and alcohol formed during the reaction). After 15 hours, the mixture was concentrated *in vacuo* and partitioned between water and ether. The aqueous layer was made alkaline with 2 N

NaOH and then extracted with ether. The ether layers were combined, washed and dried over $MgSO_4$. The reddish oily product was dissolved in some ethyl acetate and then run through column chromatography using silica gel, and eluted with ethyl acetate and hexane (1:1). 2.36g (24%) compound **3** was isolated as an oil which was solidified by the addition of ether/hexanes to give a yellow-white solid.

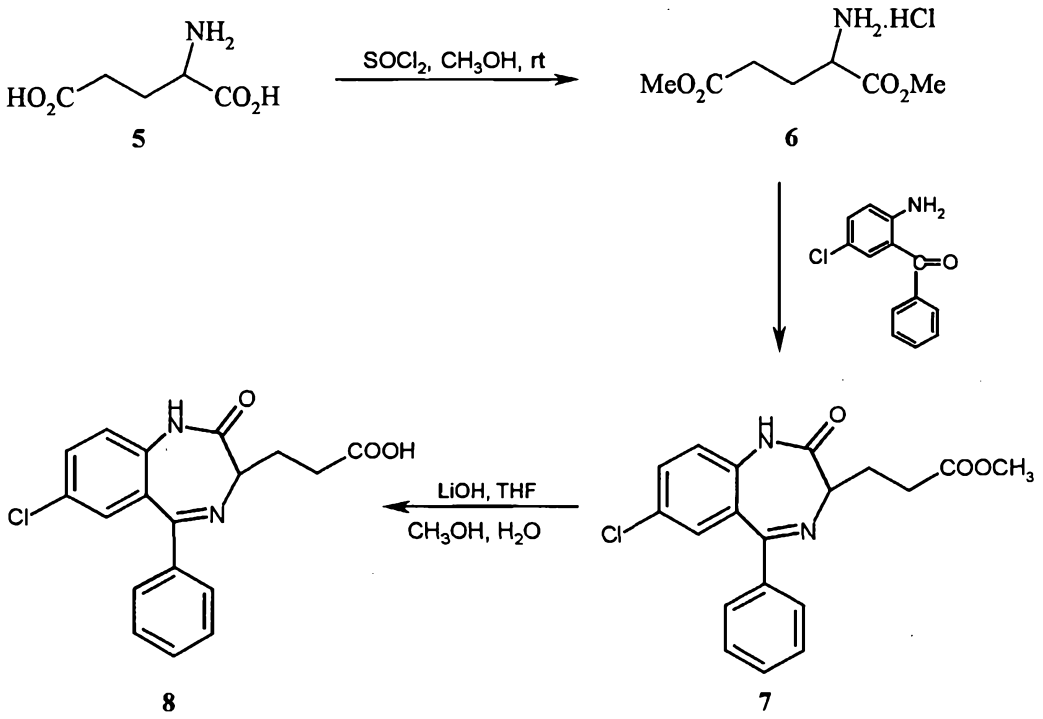
Preparation of (7-chloro-5phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-keto)-3-acetic acid (compound **4**)

To 250 mg of compound **3**, in (3:1:1) THF: CH_3OH: H_2O, was added 91.89 mg (2.19 mmol) $LiOH.H_2O$. The reaction was stirred at 4 °C for 15 minutes and at room temperature for 6 h. The mixture was concentrated *in vacuo* and dissolved in water, acidified with 1 N HCl to pH 2 to precipitate an orange solid, which was filtered, and washed with cold hexane. The product was purified with silica gel chromatography (230-400 mesh), and eluted with ethyl acetate and hexane. (1:1), then with EtOAc + Hexanes + Methanol (2:2:1) and finally, with 2:1:1. EtOAc + Hexanes + Methanol. The product was isolated as a yellow solid. Yield 2.27 (100%).

Anal. Calculated for compound **4**: C; 62.11, H; 3.99, N; 8.52. Found: C; 61.87, H; 4.20, N; 8.35.

^1H NMR (D_2O) δ2.8-3.1 (t, 2H), 3.95-4.2 (dd, 1H), 7.5-8.1 (m, 8H).

Example 2



Preparation of dimethyl L-glutamate hydrochloride (compound **6**)

8.33 g of thionyl chloride was added drop wise to a suspension of 7.35 g of L-glutamic acid in 40 mL of methanol at 0 °C and the solution was allowed to stir at room temperature for 45 h. After concentration the residual oil was triturated with ether and the resulting white solid was filtered and washed with cold ether and dried to give 8.3 g (95%) of compound **6**.

Preparation of [7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-keto]3-methyl propionate (compound 7)

A solution of 4.6 g (0.1 mol) of 5-chloro-2-aminobenzophenone, and 6.4 g (0.15 mol) of compound **6** was refluxed in 200 mL of pyridine for 15 hours. During the first four hours, 20-50 mL of the solvent was distilled slowly and replaced with fresh dry pyridine (This was done in order to remove some of the water and alcohol formed during the reaction). After 15 hours, the mixture was concentrated *in vacuo* and partitioned between water and ether. The aqueous layer was made alkaline with 2 N NaOH and then extracted with

ether. The ether layers were combined, washed and dried over $MgSO_4$. The reddish oily product was dissolved in ethyl acetate and then run through column chromatography using silica gel, and eluted with ethyl acetate and hexane (1:1) to give 1.95g (15%) of the expected compound 7.

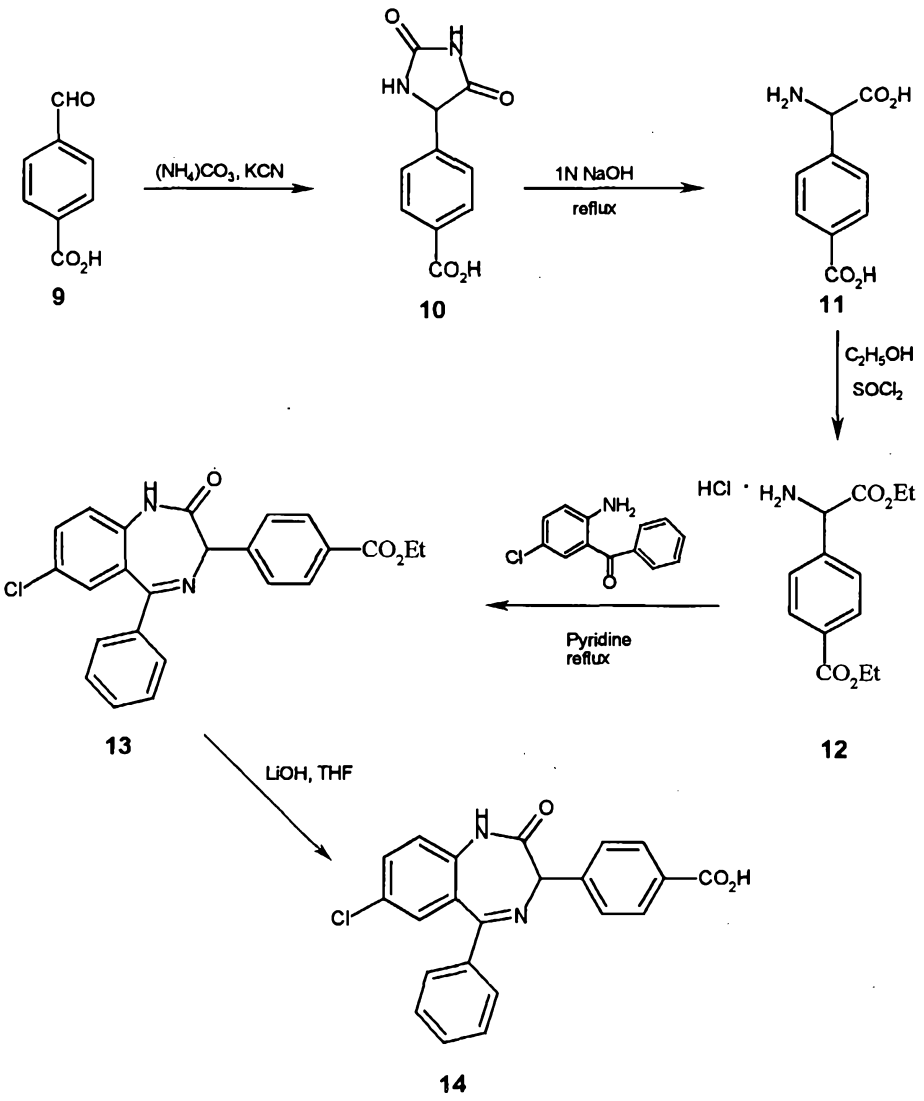
Preparation of [7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-keto]-3-propionic acid (compound **8**)

400 mg of compound 7 in 3 mL of THF, 1mL of methanol and 1mL of water, were treated with 141 mg (3.36 mmol) of $LiOH.H_2O$. The mixture was stirred at room temperature for 3 hours, concentrated *in vacuo* and re-dissolved in water and acidified with 1N HCl to pH 3. The product was filtered and purified on [ethyl acetate: hexanes: Methanol (2: 2: 1)] to yield 0.38 g (100%) of desired compound **8**.

Anal. Calculated for compound **8**: C; 63.07, H; 4.41, N; 8.17. Found: C; 62.77, H; 4.65, N; 8.01.

^1H NMR (D_2O) δ 2.2-2.8 (m, 4H), 3.6-3.7 (dd, 1H), 7.3-7.4 (m, 3H), 7.6 (s, 5H).

Example 3



Preparation of 4-carboxyphenyl-5'-hydantoin (compound **10**)

A solution of 3.65 g (0.024 mol) of 4-carboxybenzaldehyde (compound 9), 9.0 g of ammonium carbonate and 3.2 g of KCN in 100 mL of 1:1 ethanol:water was stirred at 70 °C for 5 hours. The solution was acidified with concentrated HCl until a solid formed. The product was collected by filtration to yield, 4.5 g of hydantoin (compound **10**), that was used without further purification.

Preparation of4-carboxyphenylglycine (compound **11**)

The crude compound **10** (4g) was refluxed with 100 mL of 1 N NaOH overnight. The resulting solution was acidified with, HCl to pH 2 to obtain precipitates, that were collected by filtration to give 3.2 g of desired compound **11**.

Preparation ofdiethyl-4-carboxyphenylglycine hydrochloride (compound **12**)

0.85 g of thionyl chloride, and 1 g (0.01 mol) of compound **11** in 15 mL of absolute ethanol was stirred at room temperature for 30 hours. Evaporation yielded 1.5g of desired compound **12** as a solid, that was used without further purification.

Preparation of ethyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-keto] 3,4'-benzoate (compound **13**)

1.3 g (0.004 mol) of compound **12** and 0.61 g (0.0026 mol) of 5-chlorobenzophenone in 15 mL of pyridine were refluxed overnight. The mixture was evaporated *in vacuo* and the product was purified on silica gel using hexane: EtOAc (3:1), to remove unwanted materials. The elution was continued using hexane: EtOAc (1:1) to isolate 300 mg (12%) of the desired compound **13**.

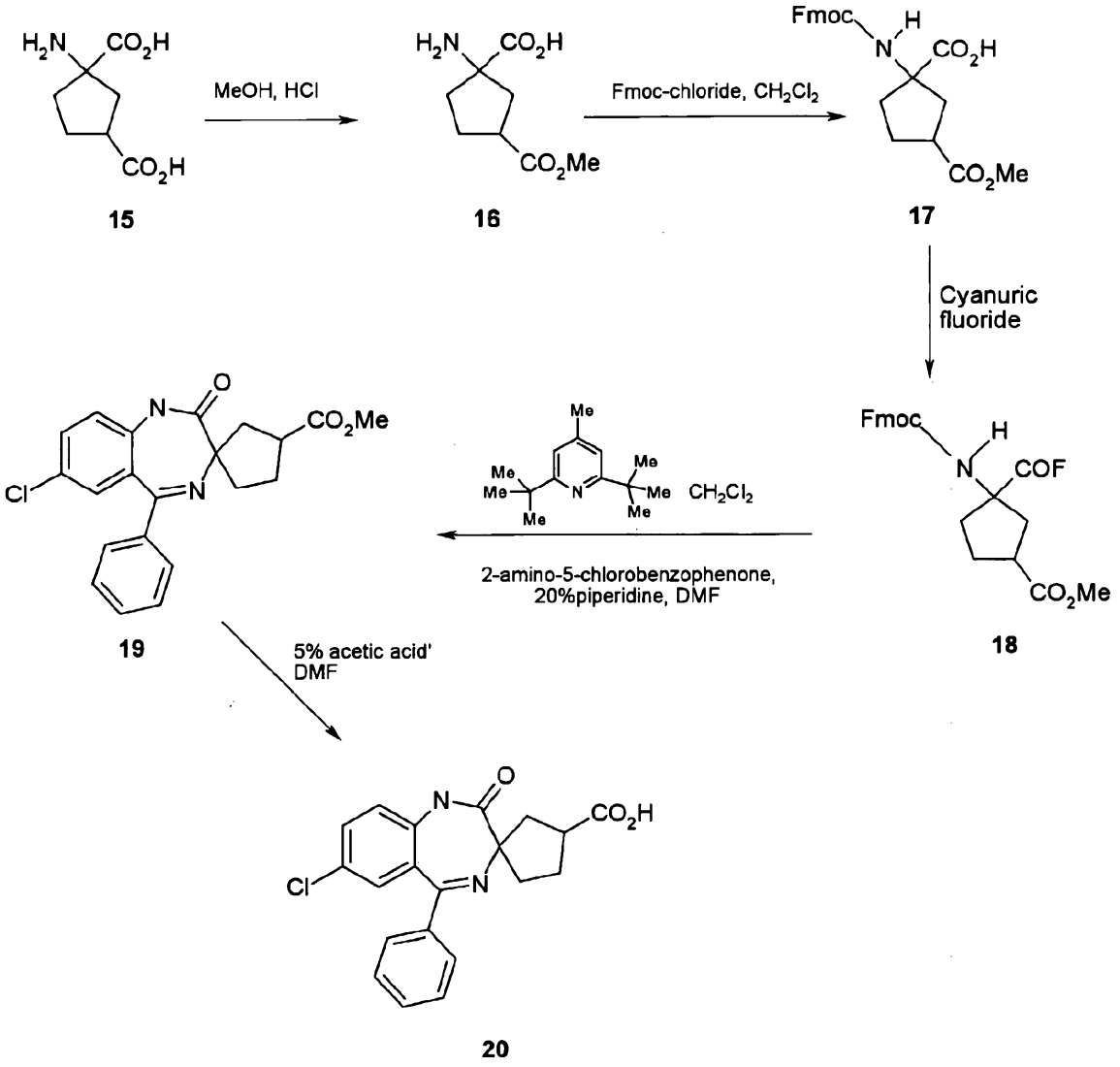
Preparation of 3-(4-carboxyphenyl)-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazapin-2-one (compound **14**)

300 mg of compound **13** was dissolved in THF:H_2O (4mL: 2mL) with 90 mg of LiOH-H_2O and stirred overnight. After evaporation of the solvents, the residue was dissolved in 15 mL of water and acidified to pH 2 with 2 N HCl to precipitate crude compound **14** as a yellow solid. The product was purified on silica gel using hexane-EtOAc (1:2) to yield 280 mg (100%) of compound **14**.

Anal. Calculated for compound **14**: C; 67.61, H; 3.87, N; 7.17. Found: C; 67.24, H; 3.95, N; 6.98.

^{1}H NMR (D_2O) δ 5.05 (s, 1H), 7.3-8.4 (m, 12H).

Example 4



15 16 17 18 19 20

Preparation of (compound **16***)*

1.73 g of 1-amino-1,3-cyclopentane dicarboxylic acid (compound **15**) was dissolved in 10 mL of HCl saturated methanol and stirred overnight. The resulting solution was evaporated to dryness to give 1.54 g (80.2%) of mono methyl ester (compound **16**).

Preparation of (compound 17)

Compound **16** from above was dissolved in 10 mL of CH_2Cl_2 with Et_3N (0.1 mL) at 0 °C and a solution of 9-fluorenylmethylcarbonylchloride (2.33 g) in 5 mL of CH_2Cl_2 was added with stirring. The mixture was stirred overnight at room temperature. The resulting solution was taken up in a further 50 mL of CH_2Cl_2 and extracted with 1 M HCl (3 x 10 mL), dried and concentrated to give a gum, which was purified on silica (EtOAc: hexanes, 1:9-5:5) to afford 2.87 g (85%) of compound **17**.

Preparation of (compound **18**)

The Fmoc amino acid ester (compound **17**) was dissolved in 5 mL of dry CH_2Cl_2 and 50 µL of dry pyridine, then 0.66 g of cyanuric fluoride was added and the mixture was refluxed under N_2 for 4 h. A white precipitate separated and the mixture was extracted with water (2 x 10 mL). The organic layer was dried over $MgSO_4$ and evaporated to give a white solid which was recrystallized to give 2.01 g (70%) of the compound **18**.

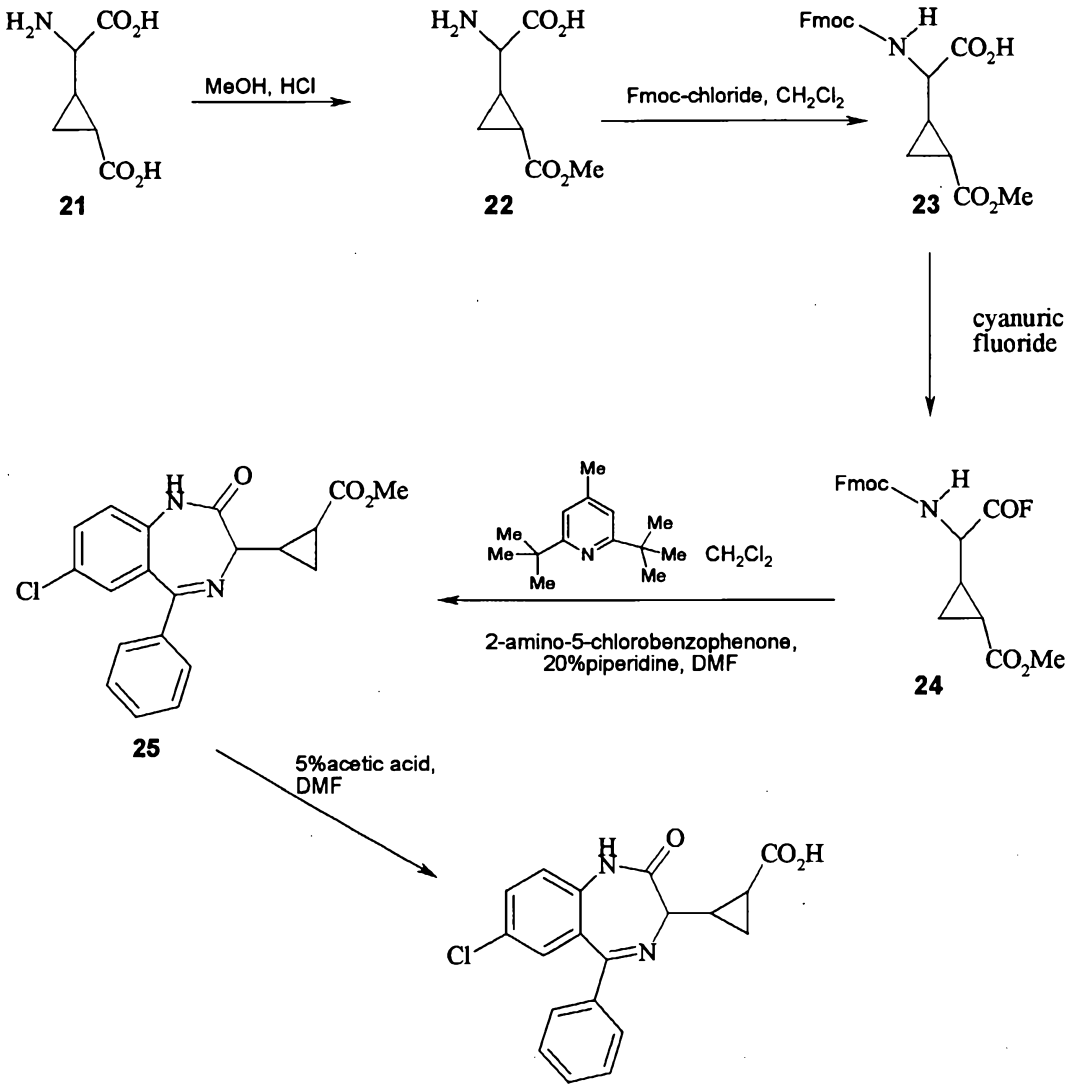
Preparation of (compound **20**)

The Fmoc amino acid fluoride ester (compound **18**) was dissolved in 10 mL of dry CH_2Cl_2 with 30 µL of 4-methyl-2,6-di-tert-butylpyridine and 1.15 g of 2-amino-5-chlorobenzophenone. The resulting solution was stirred overnight under N_2 and evaporated to dryness. The residue was taken up into 5 mL of 20% piperidine in DMF and stirred for 30 min to remove the N-protecting group. The mixture was diluted with 50 mL of water and extracted with CH_2Cl_2, the organic extract was dried over $MgSO_4$ and evaporated. The residue was taken up in 5% acetic acid in DMF and stirred for 2 days. The reaction mixture was poured into water (50 mL) to obtain precipitates of compound **20**, that were collected by filtration. The obtained product was purified by recrystallization from methanol/ water.

Anal. Calculated for compound **20**: C, 65.13; H, 4.65; N, 7.60. Found: C, 64.93; H, 4.76; N, 7.60.

^{1}H NMR (D_2O) δ 1.8-2.6 (m 6H), 2.8-3.3 (m 1H), 6.9-8.0 (m 8H).

Example 5



21 22 23 24 25 26

Preparation of (compound **22**)

1.59 g (10 mmol) of the amino acid **21** was dissolved in 10 mL of HCl saturated methanol and stirred overnight. The resulting solution was evaporated to dryness to give 1.47g (85%) of mono methyl ester (compound **22**).

Preparation of (compound **23**)

Compound **22** from above was dissolved in 10 mL CH_2Cl_2 with Et_3N (0.1 mL) at 0 °C and 9-fluorenylmethylcarbonylchloride (2.33 g) in 5 mL of CH_2Cl_2 was added with

stirring. The mixture was stirred overnight at room temperature. The resulting solution was taken up in 50 mL of CH_2Cl_2 and extracted with 1 M HCl (3x10 mL), dried and concentrated to give a gum which was purified on silica (EtOAc:hexanes, 1:9-5:5) to yield 3.3 g (90%) of desired compound **23**.

Preparation of (compound **24**)

The Fmoc amino acid ester (compound **23**) was dissolved in 5 mL of dry CH_2Cl_2 and 50 µL of dry pyridine. Then, 0.66 g of cyanuric fluoride was added and the mixture refluxed under N_2 for 4 h. A white precipitate separated and the mixture was extracted with water (2 x 10 mL). The organic layer was dried over $MgSO_4$ and evaporated to give a white solid which was recrystallized from CH_2Cl_2/hexanes to give 2.38 g (72%) of the desired compound **24**.

Preparation of (compound **26**)

The Fmoc amino acid fluoride ester (compound **24**) was dissolved in 10 mL of dry CH_2Cl_2 with 30µL of 4-methyl-2,6-di-tert-butylpyridine and 1.15g of 2-amino-5-chlorobenzophenone. The resulting solution was stirred overnight under N_2 and evaporated to dryness. The residue is taken up into 5 mL of 20% piperidine in DMF and stirred for 30 min to remove the N-protecting group. The mixture was diluted with 50 mL of water and extracted with CH_2Cl_2, the organic extract was dried over $MgSO_4$ and evaporated. The residue was taken up in 5% acetic acid in DMF and stirred for 2 days. The reaction mixture was poured into 50 mL of water to precipitate the product which was collected by filtration. The crude product was purified by recrystallization from methanol/ water to afford 1.56 g (80%)of compound **26**.

Anal. Calculated for compound **26**: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.14; H, 4.36; N, 7.66.

^1H NMR (D_2O) δ 1.1-1.5 (m 2H), 1.6-2.05 (m 2H), 3.8 (d 1H), 6.9-8.0 (m 8H) (mixture of isomers).

Example 6: *In Vivo* Testing of Exemplary Compounds:

Cyclic AMP assay:

Rationale:

Group II/III metabotropic glutamate receptors (mGluRs) are negatively coupled to adenylate cyclase, and agonists of these receptors lead to a decrease in intracellular cyclic AMP accumulation.

Method:

The assay has been modeled on the cyclic AMP assay kit available from Amersham. This kit, in turn, is based on the assay created by Tovey *et al.* (1974). Briefly, the samples were prepared from Sprague Dawley rat (225-250g) cortical slices. Slices were incubated with the test compound (drug), and then challenged with forskolin to induce cyclic AMP release. Following termination of the reaction by boiling, the slices were homogenized and centrifuged. Samples of supernatant were then incubated for 2-3 hours with a known quantity of [^{3}H]cAMP and a binding protein. When the incubation was complete, the bound cyclic AMP was separated from the free cyclic AMP by centrifugation with charcoal. The resulting supernatant (containing free cyclic AMP) was then analyzed by liquid scintillation counting. The amount of unbound cyclic AMP was calculated from a standard curve previously determined with various samples of free cyclic AMP.

Results Interpretation:

If the drugs tested inhibit forskolin-induced cyclic AMP accumulation, they are considered to be Group II/III agonists. Conversely, if they inhibit the decrease in forskolin-induced cyclic AMP accumulation caused by glutamate, they are considered to be Group II/III antagonists.

Results:

Benzodiazepines	Group II/III Agonist	EC_{50} (M)	Group II/III Antagonist	EC_{50} (M)
7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-keto-3-acetic acid (compound **4**)	Yes	2.8×10^{-5}	Yes	3.6×10^{-11}
7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-keto-3-propionic acid (compound **8**)	Yes	2.5×10^{-9}	No	-
7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-keto-3-carboxylic acid	Yes	3.1×10^{-11}	No	-
3-(4-carboxyphenyl)-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one (compound **14**)	Yes	1.1×10^{-9}	No	

Phosphatidylinositol Assay

Rationale:

Group I metabotropic glutamate receptors (mGluRs) are positively coupled on inositol phosphate metabolism. Agonists at these receptors lead to an increase in intracellular free inositol phosphates, while antagonists inhibit the increase in intracellular free inositol phosphate induced by standard agonists (*i.e.* ACPD).

Method:

Cross-chopped slices were prepared from neonatal Sprague Dawley rat tissue (age: p7-p14). The slices were pre-labelled with [^{3}H]myo-inositol. Following pre-labelling, the slices were incubated with the test compounds and standard (known Group I agonists *i.e.* ACPD) for a period of 45 minutes. The incubation was terminated by the addition of chloroform/methanol/HCl (100:200:2). The resulting mixture was separated into two phases by the addition of chloroform and distilled water. The aqueous fraction was applied to ion exchange columns, and inositol phosphates were eluted using 800 mM

Ammonium Formate/100 mM Formic Acid. The eluent was then analyzed using liquid scintillation counting. The amount of inositol phosphate accumulation was expressed as a percentage of that induced by ACPD.

Results Interpretation:

If the drugs cause an increase in intracellular free inositol phosphate accumulation, they are considered to be Group I agonists. If they inhibit the increase in intracellular free inositol phosphate accumulation induced by ACPD, they are considered to be Group II antagonists.

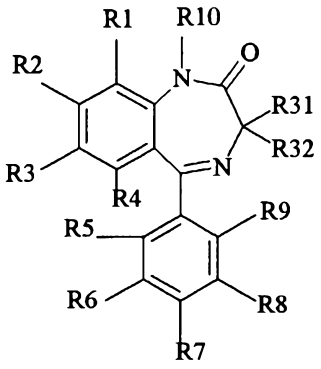
Results:

Benzodiazepine	Group I Agonist	EC_{50} (M)	Group I Antagonist	EC_{50} (M)
7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-keto-3-acetic acid (compound **4**)	No	-	Yes	1.1×10^{-10}
7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-keto-3-propionic acid (compound **8**)	No	-	No	-
7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-keto-3-carboxylic acid	No	-	Yes	2.3×10^{-9}
3-(4-carboxyphenyl)-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one (compound **14**)	No	-	Yes	1.7×10^{-5}

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A compound of formula (I):



(I)

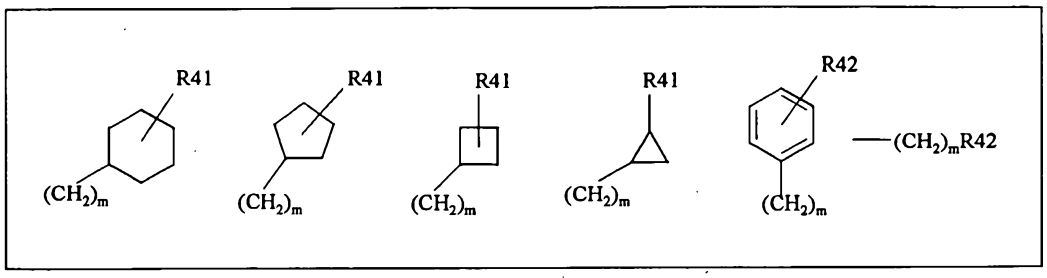
stereoisomers thereof, or pharmaceutically acceptable salt or hydrates thereof, wherein:

R1, R2, R3, R4, R5, R6, R7, R8, R9 are same or different and selected from the group comprising H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl or acceptable esters thereof;

R10 is selected from group comprising: (C_1-C_6) alkyl (straight chain or branched); (C_6-C_{10}) aryl [optionally substituted with (C_1-C_6) alkyl], aryl alkyl group where aryl group is optionally substituted with (C_1- C_6) alkyl, (C_1- C_6) alkoxy, halogen, carboxy, or nitro group; heteroaromatic group; or -O-C(O)R where R is (C_1- C_6) alkyl, (C_6- C_{10}) aryl;

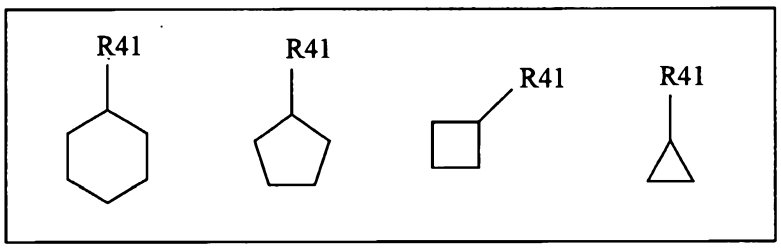
R31 is either H or taken together with **R32** to form a spirocycle;

R32 is selected from the group comprising:



wherein: **m** = 0,1

or when **R31** and **R32** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R31 is **XY** or **–CR11XY**

R41 is **X** or **Y** or **-CR11XY**

R11 is H, (C_1- C_6) alkyl (straight chain or branched); (C_6- C_{10}) aryl [optionally substituted with (C_1- C_6) alkyl], aryl alkyl group where aryl group is optionally substituted with (C_1- C_6) alkyl, (C_1- C_6) alkoxy, halogen, carboxy, or nitro group; (C_4- C_9) heterocyclic group (aromatic or nonaromatic);

X is H or an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, where n = 2, 3, 4, 5, or 6; or:

Y is H or a basic group selected from the group comprising 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea, with the proviso that, (i) at least one of **X** or **Y** is other than **H** and (ii) when **R32** is $-(CH_2)_mR42$, **R42** is COOH, then m is 1.

2. The compound as claimed in claim 1, wherein **Y** is H, **X** is an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, $-(CH_2)_n$-carboxy, $-(CH_2)_n$-phosphono, $-(CH_2)_n$-phosphino, $-(CH_2)_n$-sulfono,$-(CH_2)_n$-sulfino, $-(CH_2)_n$-borono, $-(CH_2)_n$-tetrazol, and $-(CH_2)_n$-isoxazol, where n = 2, 3, 4, 5, or 6; or:

3. The compound as claimed in claim 1, wherein **X** is H, **Y** is a basic group selected from the group comprising 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic.

4. The compound according to claim 2, wherein, **Y** is H, **X** is CO_2H, CH_2CO_2H.

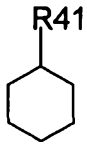
5. The compound according to claim 2, wherein, **R1-R2** and **R4-R10**, **R31** = H, **R3** = Cl, **R32** = $-(CH_2)_mR42$, wherein m = 0, **R42** =X, **X** is CH_2CO_2H.

6. The compound according to claim 2, wherein, **R1-R2** and **R4-R10**, **R31** = H, **R3** = Cl, **R32** = $-(CH_2)_mR42$, wherein m = 1, **R42** =X, **X** is CH_2CO_2H.

7. The compound according to claim 2, wherein, **R1-R2** and **R4-R10**, **R31** = H, **R3** = Cl, **R32** = $-(CH_2)_mC_6H_4R42$, wherein m = 0, **R42** =X, **X** is CO_2H.

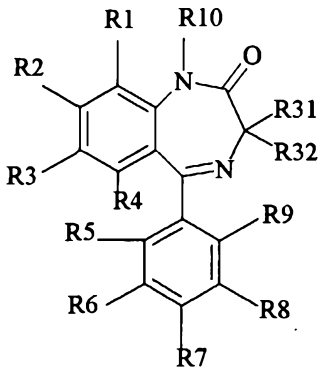
8. The compound according to claim 2, wherein, **R1-R2** and **R4-R10**, **R31** = H, **R3** = Cl, **R32** = $-(CH_2)_mC_3H_4R41$, wherein m = 0, C_3H_4 is a cyclopropyl group, **R41** =XY, **X** is $-CO_2H$.

9. The compound according to claim 2, wherein, **R1-R2** and **R4-R10**, **R31** = H, **R3** **R3** = Cl, **R31** and **R32** are taken together to form a spirocycle, wherein spriroycle is:



wherein: **R41** is XY, **X** is COOH and **Y** is H.

10. A process for the preparation of a compound of Formula (I):



(I)

stereoisomers thereof, or pharmaceutically acceptable salt or hydrates thereof, wherein:

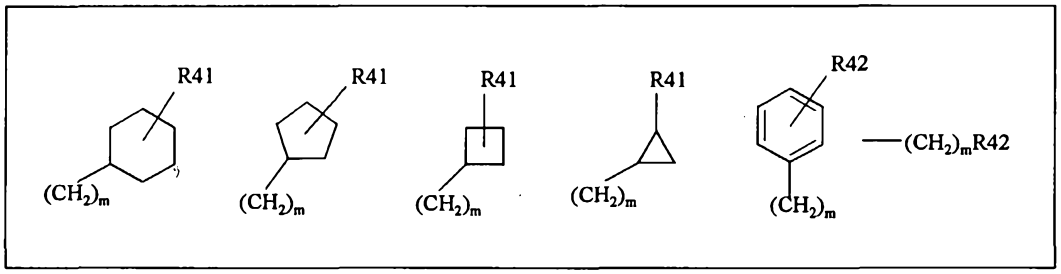
R1, R2, R3, R4, R5, R6, R7, R8, R9 are same or different and selected from the group comprising H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl or acceptable esters thereof;

R10 is selected from group comprising: (C_1-C_6) alkyl (straight chain or branched); (C_6-C_{10}) aryl [optionally substituted with (C_1-C_6) alkyl], aryl alkyl group where aryl group is

optionally substituted with (C_1- C_6) alkyl, (C_1- C_6) alkoxy, halogen, carboxy, or nitro group; heteroaromatic group; or -O-C(O)R where R is (C_1- C_6) alkyl, (C_6- C_{10}) aryl;

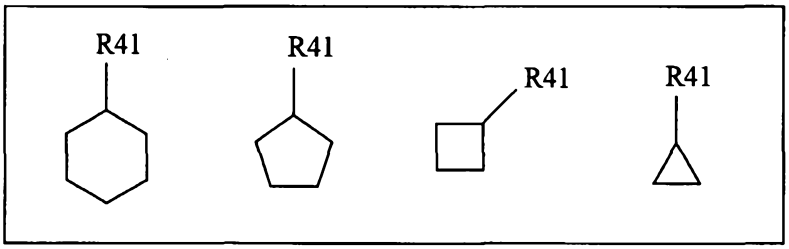
R31 is either H or taken together with **R32** to form a spirocycle;

R32 is selected from the group comprising:



wherein: **m** = 0,1

or when **R31** and **R32** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R41 is **XY** or **–CR11XY**

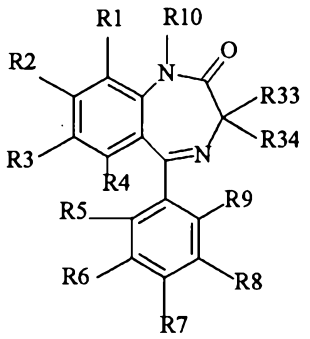
R42 is **X** or **Y** or **-CR11XY**

R11 is H, (C_1- C_6) alkyl (straight chain or branched); (C_6- C_{10}) aryl [optionally substituted with (C_1- C_6) alkyl], aryl alkyl group where aryl group is optionally substituted with (C_1- C_6) alkyl, (C_1- C_6) alkoxy, halogen, carboxy, or nitro group; (C_4- C_9) heterocyclic group (aromatic or nonaromatic);

X is H or an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, where n = 2, 3, 4, 5, or 6; or:

Y is H or a basic group selected from the group comprising 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea, with the proviso that, (i) at least one of **X** or **Y** is other than **H** and (ii) when **R32** is –$(CH_2)_m$R42, **R42** is COOH, then m is 1, which comprises:

(a) hydrolyzing a compound of formula (II):

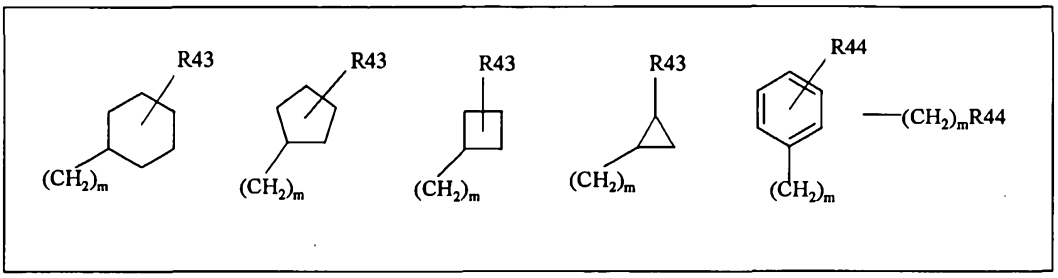


(II)

wherein: **R1-R10** are as defined above,

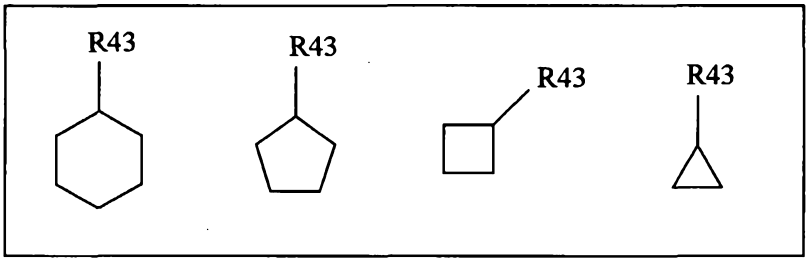
R33 is H or taken together with **R34** to form a spirocycle,

R34 is selected from the group comprising:

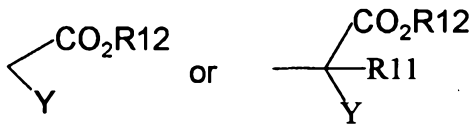


wherein: **m** = 0

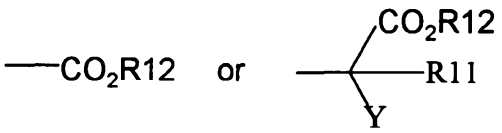
or when **R33** and **R34** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R43 is:

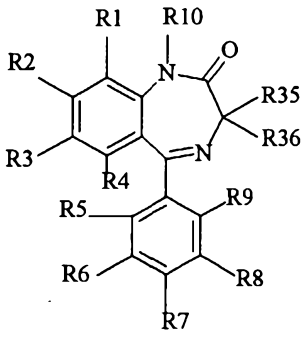


R44 is:



wherein: **R11** is as defined above, **R12** is an acid ester, **Y** is as defined above. Preferred values for Y is H or NH_2; or

(b) deprotecting a compound of formula (III):

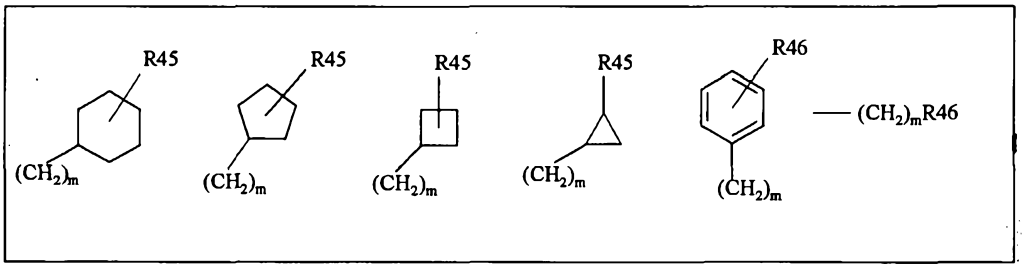


(III)

wherein: **R1-R10** are as defined above,

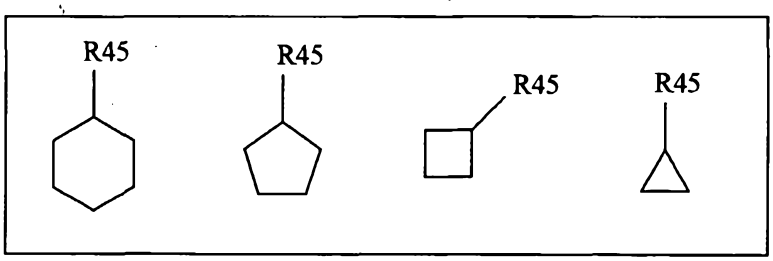
R35 is H or taken together with **R36** to form a spirocycle,

R36 is selected from the group comprising:

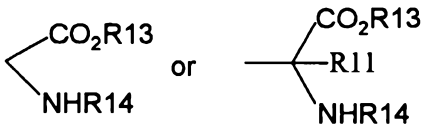


wherein: **m** = 0,1

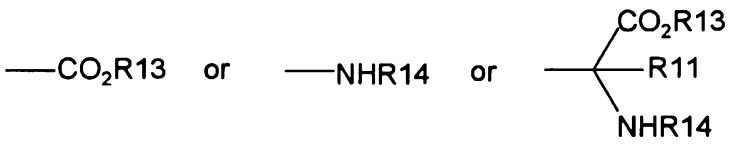
or when **R35** and **R36** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R45 is

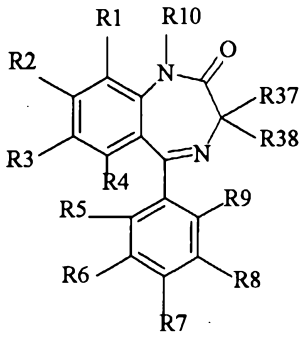


R46 is



wherein: **R11** is as defined above, **R13** represents a hydrogen atom or a carboxyl protecting group, or a salt thereof, and **R14** represents a hydrogen atom or a nitrogen protecting group;

(c) hydrolyzing a compound of formula (IV):

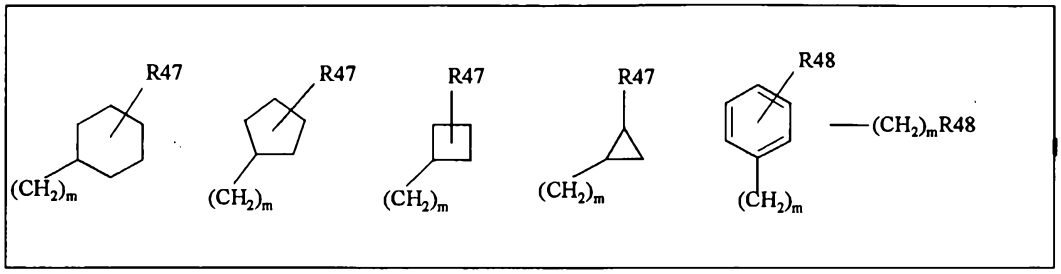


(IV)

wherein: **R1-R10** are as defined above

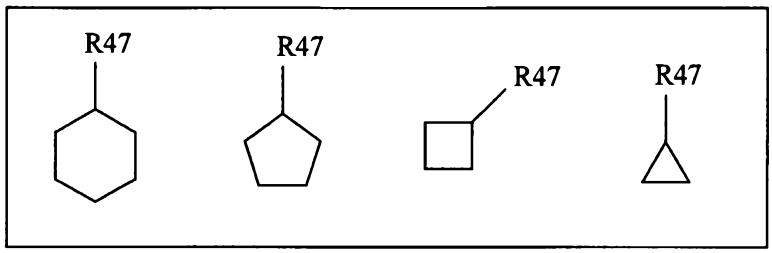
R37 is H or taken together with **R38** to form a spirocycle;

R38 is selected from the group comprising:

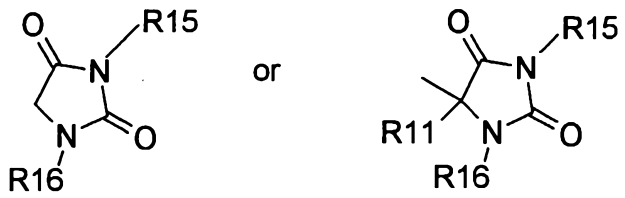


wherein: **m** = 0,1

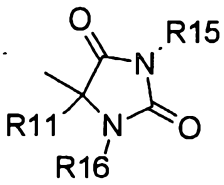
or when **R37** and **R38** taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R47 is:

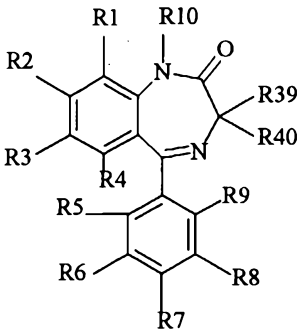


R48 is



wherein: **R11** is as defined above, **R15** and **R16** each independently represent a hydrogen atom, a (C_2-C_6) alkanoyl group, a (C_1-C_4) alkyl group, a (C_3-C_4) alkenyl group or a phenyl (C_1-C_4) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (C_1-C_4) alkyl or (C_1-C_4) alkoxy, or a salt thereof; or:

(d) hydrolyzing a compound of formula (V):

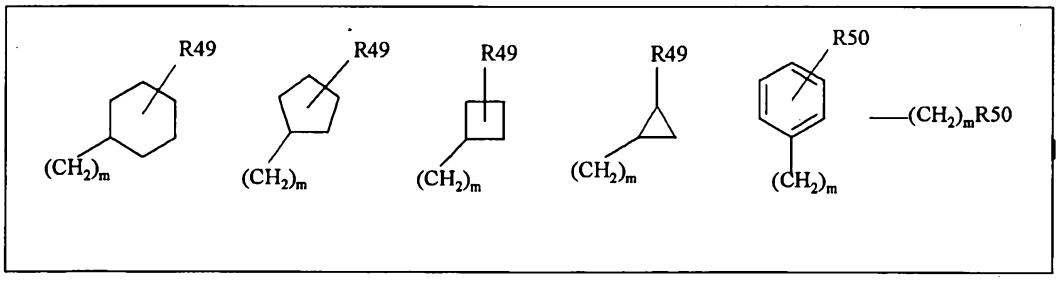


(V)

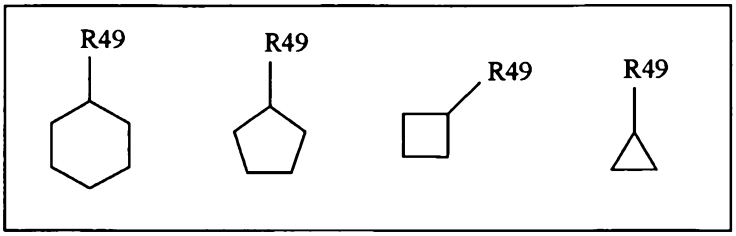
wherein: **R1-R10** are as defined above

R39 is H or taken together with **R40** to form a spirocycle;

R40 is selected from the group comprising:

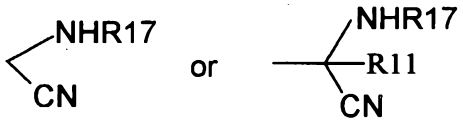


or when **R39** are **R40** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



wherein: **m** = 0,1

R49 is:



R50 is:

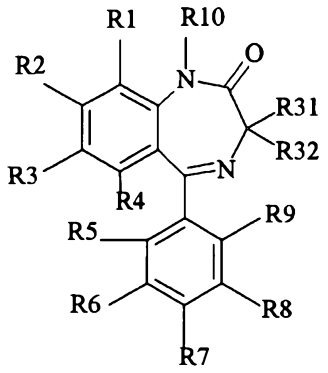
wherein: **R11** is as defined above, **R17** represents a hydrogen atom or an acyl group. Preferred values for **R17** are hydrogen and (C_2-C_6) alkanoyl groups, such as acetyl; whereafter, if necessary and/or desired, the following steps are carried out:

(i) resolving the compound of Formula I;

(ii) converting the compound of Formula I into a non-toxic metabolically labile ester or amide thereof; and/or;

(iii) converting the compound of Formula I or a non-toxic metabolically labile ester or amide thereof into a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier, diluent or excipient and a compound formula (I):



(I)

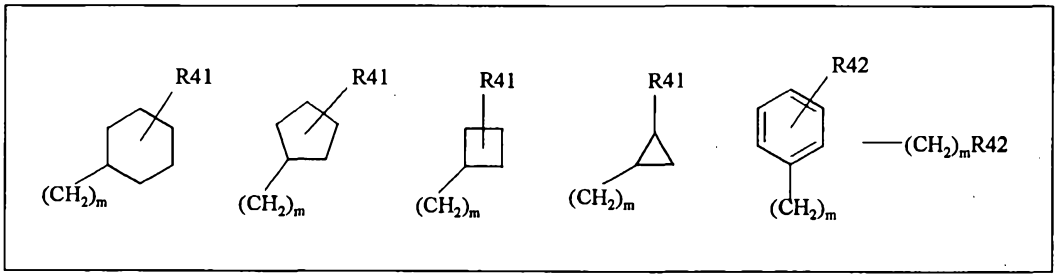
stereoisomers thereof, or pharmaceutically acceptable salt or hydrates thereof, wherein:

R1, R2, R3, R4, R5, R6, R7, R8, R9 are same or different and selected from the group comprising H, nitro, amino, halogen, tritium, trifluoromethyl, trifluoroacetyl, sulfo, carboxy, carbamoyl, sulfamoyl or acceptable esters thereof;

R10 is selected from group comprising: (C_1-C_6) alkyl (straight chain or branched); (C_6- C_{10}) aryl [optionally substituted with (C_1-C_6) alkyl], aryl alkyl group where aryl group is optionally substituted with (C_1- C_6) alkyl, (C_1- C_6) alkoxy, halogen, carboxy, or nitro group; heteroaromatic group; or -O-C(O)R where R is (C_1- C_6) alkyl, (C_6- C_{10}) aryl;

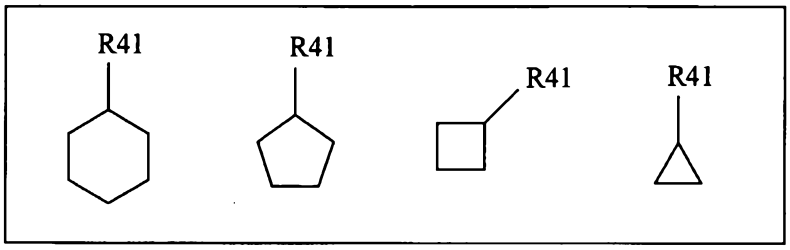
R31 is either H or taken together with **R32** to form a spirocycle;

R32 is selected from the group comprising:



wherein: **m** = 0,1

or when **R31** and **R32** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R41 is **XY** or **–CR11XY**

R42 is **X** or **Y** or **-CR11XY**

R11 is H, (C_1- C_6) alkyl (straight chain or branched); (C_6- C_{10}) aryl [optionally substituted with (C_1- C_6) alkyl], aryl alkyl group where aryl group is optionally substituted with (C_1- C_6) alkyl, (C_1- C_6) alkoxy, halogen, carboxy, or nitro group; (C_4- C_9) heterocyclic group (aromatic or nonaromatic);

X is H or an acidic group selected from the group comprising carboxy, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -$(CH_2)_n$-carboxy, -$(CH_2)_n$-phosphono, -$(CH_2)_n$-phosphino, -$(CH_2)_n$-sulfono,-$(CH_2)_n$-sulfino, -$(CH_2)_n$-borono, -$(CH_2)_n$-tetrazol, and -$(CH_2)_n$-isoxazol, where n = 2, 3, 4, 5, or 6; or:

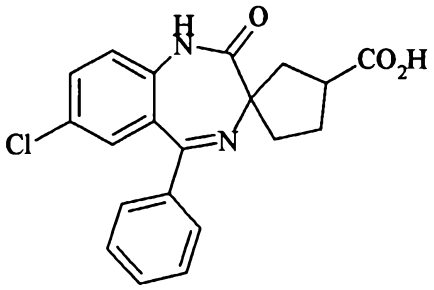
Y is H or a basic group selected from the group comprising 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea.

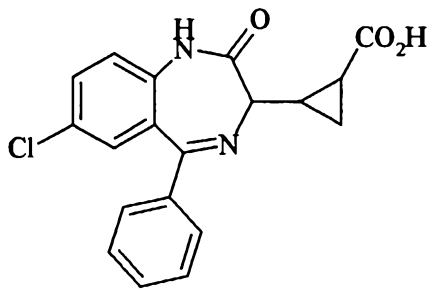
12. The use of the pharmaceutical composition according to claim 11, in modulating one or more metabotropic glutamate receptor functions in warm blooded mammals, wherein said use comprises the administration of an effective amount of said pharmaceutical composition .

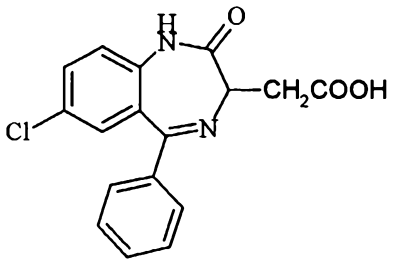
13. 13. The use of the pharmaceutical composition according to claim 11, in treating a neurological disease or disorder selected from the group comprising: cerebral deficits subsequent to cardiac bypass surgery and grafting, cerebral ischemia, stroke, cardiac arrest, spinal cord trauma, head trauma, perinatal hypoxia, and hypoglycemic neuronal damage, Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms, convulsions, migraine headaches, urinary incontinence, psychosis, drug tolerance, withdrawal, and cessation (i.e. opiates, benzodiazepines, nicotine, cocaine, or ethanol), smoking cessation, anxiety and related disorders (e.g. panic attack), emesis, brain edema, chronic pain, sleep disorders, Tourette's syndrome, attention deficit disorder, and tardive dyskinesia, wherein said use comprises the administration of an effective amount of said pharmaceutical composition .

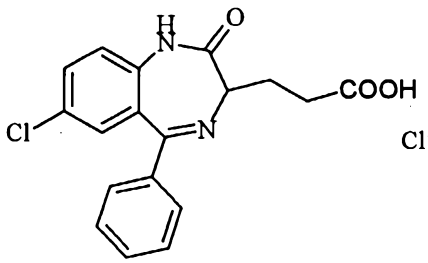
14. 14. The use of the pharmaceutical composition according to claim 11, in treating a psychiatric disease or disorder selected from the group comprising: schizophrenia, anxiety and related disorders (e.g. panic attack), depression, bipolar disorders, psychosis, and obsessive compulsive disorders, wherein said use comprises the administration of an effective amount of said pharmaceutical composition

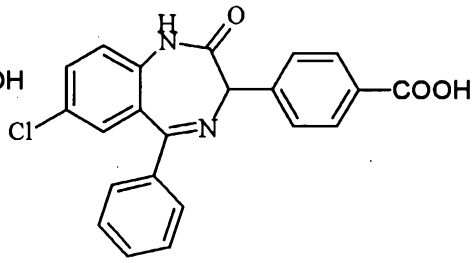
15. The use according to any one of claims 12, 13 or 14 wherein said compound is selected from the group of compounds comprising





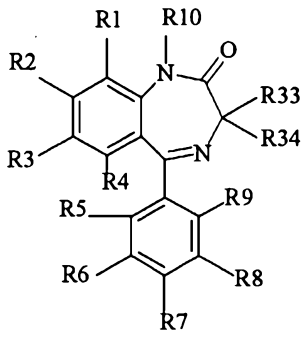






16. A method of modulating the activity of metabotropic glutamate receptors in mammals, which comprises administering to a mammal, requiring modulated excitatory amino acid neurotransmission, a therapeutically effective amount of the pharmaceutical composition according to claim 11

17. A compound of formula (II):

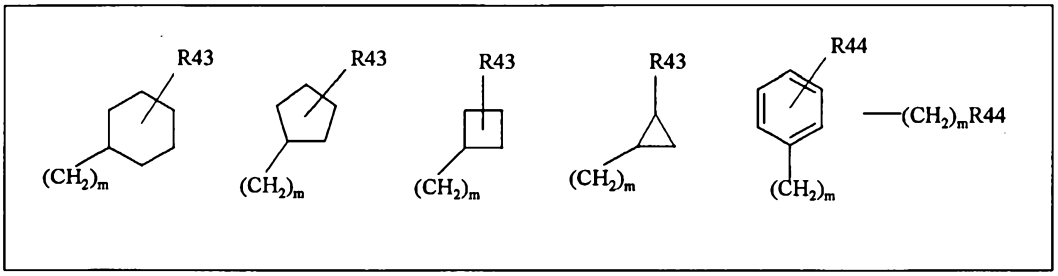


(II)

wherein: **R1-R10** are as defined above,

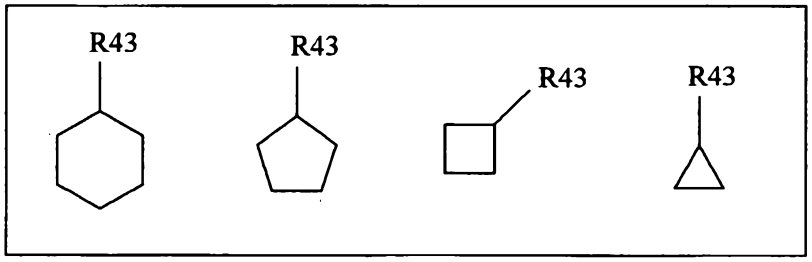
R33 is H or taken together with **R34** to form a spirocycle,

R34 is selected from the group comprising:

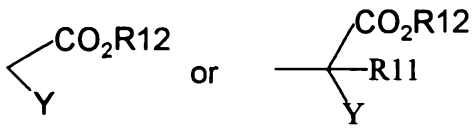


wherein: **m** = 0

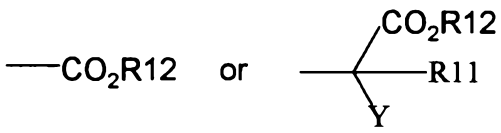
or when **R33** and **R34** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R43 is:



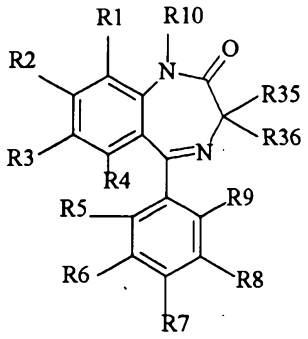
R44 is:



wherein: **R11** is as defined above, **R12** is an acid ester, **Y** is as defined above. Preferred values for Y is H or NH_2; or

18. The compound according to claim 17, wherein Y is H or NH_2.

19. A compound of formula (III):

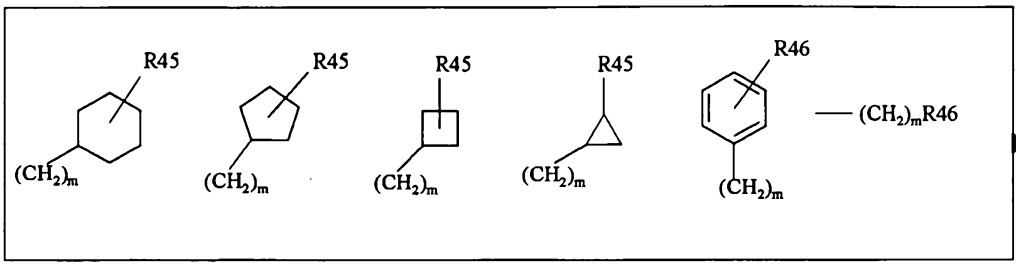


(III)

wherein: **R1-R10** are as defined above,

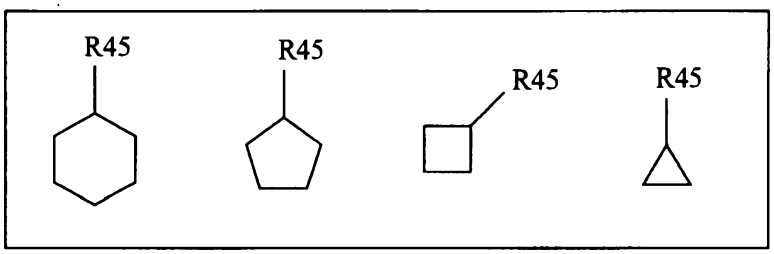
R35 is H or taken together with **R36** to form a spirocycle,

R36 is selected from the group comprising:

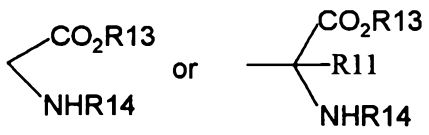


wherein: **m** = 0,1

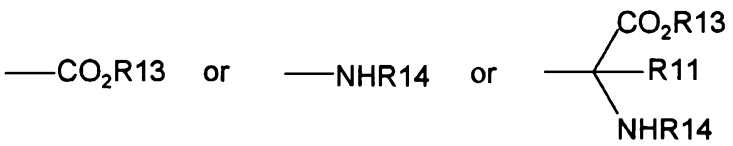
or when **R35** and **R36** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R45 is

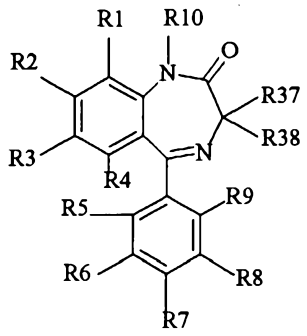


R46 is



wherein: **R11** is as defined above, **R13** represents a hydrogen atom or a carboxyl protecting group, or a salt thereof, and **R14** represents a hydrogen atom or a nitrogen protecting group;

20. A compound of formula (IV):

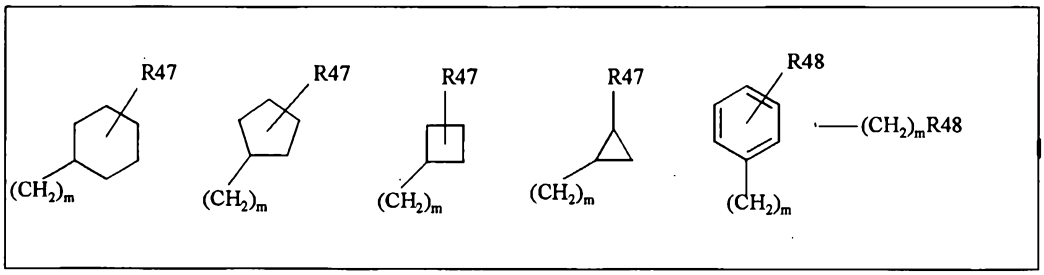


(IV)

wherein: **R1-R10** are as defined above

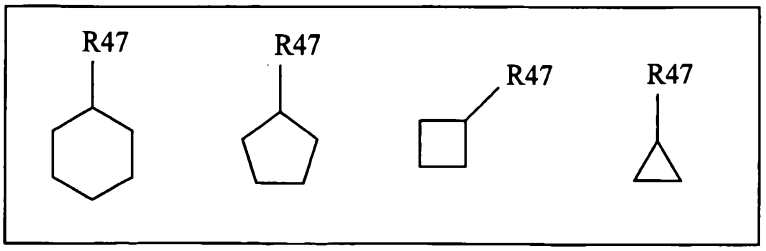
R37 is H or taken together with **R38** to form a spirocycle;

R38 is selected from the group comprising:

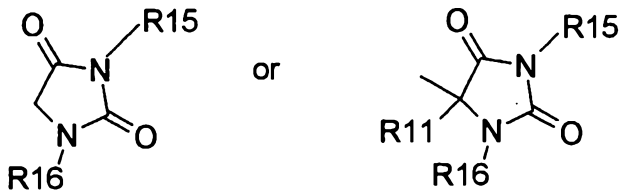


wherein: **m** = 0, 1

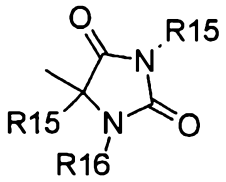
or when **R37** and **R38** taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



R47 is:

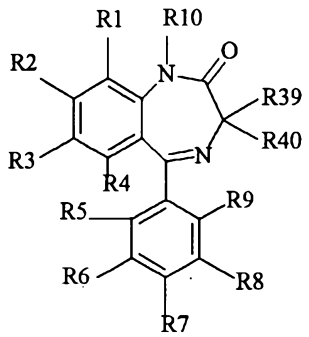


R48 is



wherein: **R11** is as defined above, **R15** and **R16** each independently represent a hydrogen atom, a (C_2-C_6) alkanoyl group, a (C_1-C_4) alkyl group, a (C_3-C_4) alkenyl group or a phenyl (C_1-C_4) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (C_1-C_4) alkyl or (C_1-C_4) alkoxy, or a salt thereof; or:

21. A compound of formula (V):

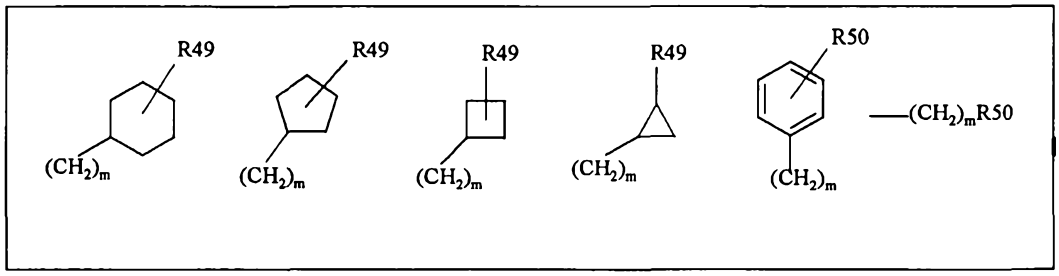


(V)

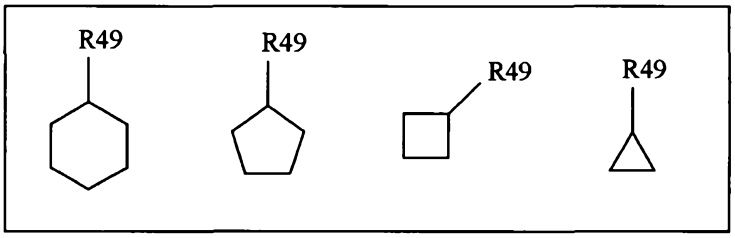
wherein: **R1-R10** are as defined above

R39 is H or taken together with **R40** to form a spirocycle;

R40 is selected from the group comprising:

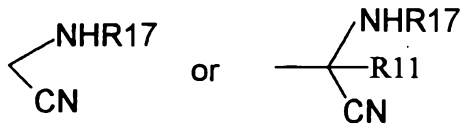


or when **R39** are **R40** are taken together to form a spirocycle, then the spirocycle is selected from the group comprising:



wherein: **m** = 0,1

R49 is:



R50 is:

wherein: **R11** is as defined above, **R17** represents a hydrogen atom or an acyl group. Preferred values for **R17** are hydrogen and (C_2-C_6) alkanoyl groups.