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(54) Abstract Title
FUSED BICYCLIC OR TRICYCLIC AMINO ACIDS

(57) The compounds of the instant invention are bicyclic or tricyclic amino acids useful in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, arthritis, neuropathological disorders, sleep disorders, visceral pain disorders, and gastrointestinal disorders. Processes for the preparation of the final products and intermediates useful in the process are included. Pharmaceutical compositions containing one or more of the compounds are also included.

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FUSED BICYCLIC OR TRICYCLIC AMINO ACIDS

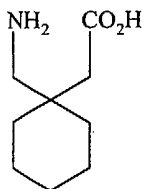
FIELD OF THE INVENTION

5 This invention relates to novel cyclic amino derivatives useful as pharmaceutical agents, to processes for their production, to pharmaceutical compositions containing them, and to their use for the treatment of the conditions set out below. It also relates to bicyclic and tricyclic ketones useful as intermediates in the production of the aforesaid compounds.

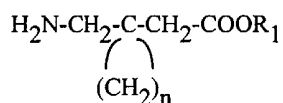
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BACKGROUND TO THE INVENTION

Gabapentin (Neurontin®) is an anti-convulsant agent that is useful in the treatment of epilepsy and that has recently been shown to be a potential treatment
15 for neurogenic pain. It is 1-(aminomethyl)-cyclohexylacetic acid of structural formula:



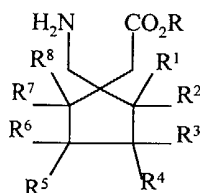
Gabapentin is one of a series of compounds of formula



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in which R_1 is hydrogen or a lower alkyl radical and n is 4, 5, or 6. These compounds are described US-A-4024175 and its divisional US-A-4087544. Their disclosed uses are: protection against thiosemicarbazide-induced cramp;
25 protection against cardiazole cramp; the cerebral diseases, epilepsy, faintness attacks, hypokinesia, and cranial traumas; and improvement in cerebral functions. The compounds are useful in geriatric patients. The disclosures of the above two patents are hereby incorporated by reference.

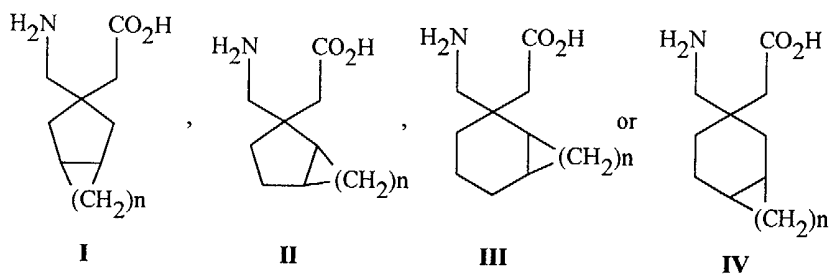
WO 99/21824, whose disclosure is also incorporated by reference, discloses further cyclic amino acids that are useful in the treatment of epilepsy, faintness attacks, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, gastrointestinal disorders such as irritable bowel syndrome (IBS) and inflammation, especially arthritis. The compounds disclosed include those of the formula:



and salts thereof, in which: R is hydrogen or a lower alkyl; and R¹ to R⁸ are each independently selected from hydrogen, straight or branched alkyl of from 1 to 6 carbons, phenyl, benzyl, fluorine, chlorine, bromine, hydroxy, hydroxymethyl, amino, aminomethyl, trifluoromethyl, -CO₂H, -CO₂R¹⁵, -CH₂CO₂H, -CH₂CO₂R¹⁵, -OR¹⁵ wherein R¹⁵ is a straight or branched alkyl of from 1 to 6 carbons, phenyl, or benzyl, R¹ to R⁸ not being simultaneously hydrogen.

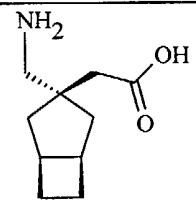
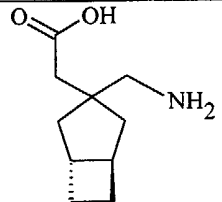
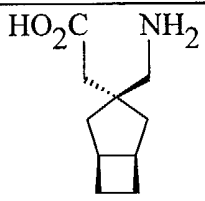
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Patent Application No. US 60/160725 describes a series of novel bicyclic amino acids, their pharmaceutically acceptable salts, and their prodrugs of formula:



wherein n is an integer of from 1 to 4, where there are stereocenters, each center may be independently R or S, preferred compounds being those of Formulae I-IV above in which n is an integer of from 2 to 4. The compounds are disclosed as being useful in treating a variety of disorders including epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety,

panic, pain, neuropathological disorders, and sleep disorders. Certain of the compounds disclosed in that patent have high activity as measured in a radioligand binding assay using [^3H]gabapentin and the $\alpha_2\delta$ subunit derived from porcine brain tissue (Gee N.S., Brown J.P., Dissanayake V.U.K., Offord J., Thurlow R., Woodruff G.N., *J. Biol. Chem.*, 1996;271:5879-5776). Results for some of the compounds are set out in the following table:

TABLE 1		
Compound	Structure	$\alpha_2\delta$ binding affinity (μM)
(1 α ,3 α ,5 α)(3-Aminomethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid		0.038
(+/-)-(1 α ,5 β)(3-Aminomethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid		2.86
((1 α ,3 β ,5 α)(3-Aminomethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid		0.332

10 Patent application number EP 01400214.1 discloses the use of compounds of formula I to IV above for preventing and treatment of visceral pain, and gastrointestinal disorders.

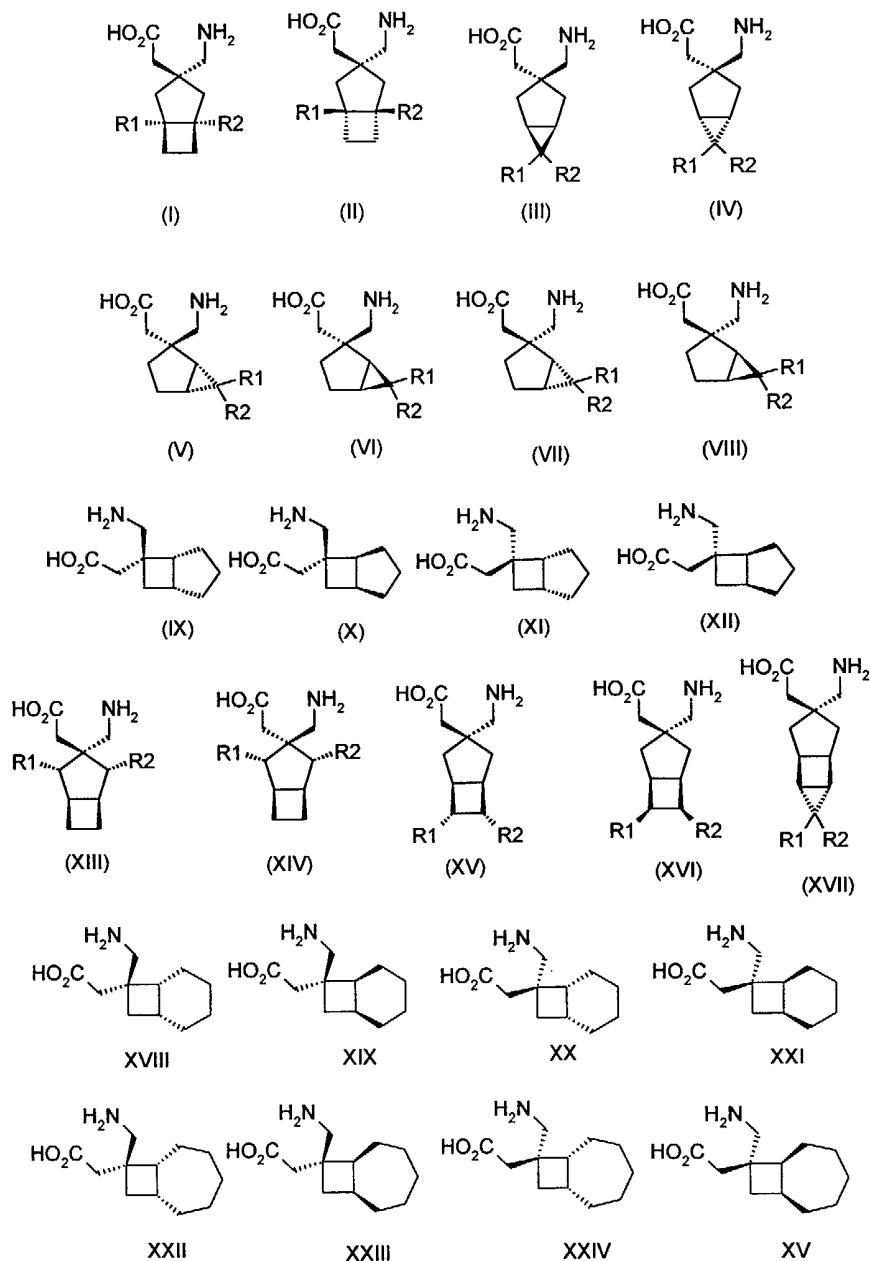
SUMMARY OF THE INVENTION

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We believe that certain analogues of the above compounds which derived e.g. from 1-(aminomethyl)-cyclopentaneacetic acid by fusion of a 3- or 4-

membered ring to the cyclopentane ring and which are substituted with one or more substituents may exhibit similar high activity. We also believe that amino acids based on bicyclo[3.2.0]heptane, bicyclo[4.2.0]octane and bicyclo[5.2.0]nonane in which the amino and carboxyl moieties are attached to one of the atoms of the four-membered ring may also exhibit high activity.

The present invention provides bicyclic amino acid analogues and their derivatives, prodrugs, and pharmaceutically acceptable salts useful in the treatment of a variety of disorders including epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, sleep disorders, osteoarthritis, rheumatoid arthritis, and neuropathological disorders. The compounds provided may also be useful in the treatment of visceral pain, functional bowel disorders such as gastro-esophageal reflux, dyspepsia, irritable bowel syndrome and functional abdominal pain syndrome, and inflammatory bowel diseases such as Crohn's disease, ileitis, and ulcerative colitis, and other types of visceral pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis. They may also be used for the treatment of premenstrual syndrome. They are compounds of any of the general formulae below:



wherein R^1 and R^2 are each independently selected from H, straight or branched alkyl of 1-6 carbon atoms, cycloalkyl of from 3-6 carbon atoms, phenyl and benzyl, subject to the proviso that, except in the case of a tricyclooctane compound of formula (XVII), R^1 and R^2 are not simultaneously hydrogen.

Preferred compounds (including salts and pro-drugs thereof) are:

((1R,5S)-3-Aminomethyl-1,5-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic

10 acid;

- ((1S,5R)-3-Aminomethyl-1,5-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid;
- ((1R,5S)-3-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-3-yl)-acetic acid;
- 5 ((1S,5R)-3-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-3-yl)-acetic acid;
- ((1S,2S,5R)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid;
- ((1R,2S,5S)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid;
- 10 ((1S,2R,5R)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid;
- ((1R,2R,5S)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid;
- 15 ((1R,5R,6S)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid;
- ((1S,5S,6S)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid;
- ((1R,5R,6R)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid;
- ((1S,5S,6R)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid;
- cis-((1S,2R,4S,5R)-3-Aminomethyl-2,4-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid;
- 20 trans-((1S,2R,4S,5R)-3-Aminomethyl-2,4-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid;
- ((1S,5R,6S,7R)-3-Aminomethyl-6,7-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid;
- 25 ((1S,5R,6R,7S)-3-Aminomethyl-6,7-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid;
- ((1R,2S,5S)-7-Aminomethyl-3,3-dimethyl-tricyclo[3.3.0.0,^{2,4}]oct-7-yl)-acetic acid;
- ((1R,6R,7S)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid;
- 30 ((1S,6S,7S)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid;
- ((1R,6R,7R)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid;
- ((1S,6S,7R)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid;

((1R,7R,8S)-8-Aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid;
((1S,7S,8S)-8-Aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid;
((1R,7R,8R)-8-Aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid; and
((1S,7S,8R)-8-Aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid.

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The present compounds can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

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Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

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Since amino acids are amphoteric, pharmacologically compatible salts can be salts of appropriate inorganic or organic acids, for example, hydrochloric, sulphuric, phosphoric, acetic, oxalic, lactic, citric, malic, salicylic, malonic, maleic, succinic, and ascorbic. Starting from corresponding hydroxides or carbonates, salts with alkali metals or alkaline earth metals, for example, sodium, potassium, magnesium, or calcium can be formed. Salts with quaternary ammonium ions can also be prepared with, for example, the tetramethyl-ammonium ion.

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Prodrugs of the above compounds are included in the scope of the instant invention. The effectiveness of an orally administered drug is dependent upon the drug's efficient transport across the mucosal epithelium and its stability in entero-hepatic circulation. Drugs that are effective after parenteral administration but less effective orally, or whose plasma half-life is considered too short, may be chemically modified into a prodrug form. A prodrug is a drug which has been chemically modified and may be biologically inactive at its site of action, but which may be degraded or modified by one or more enzymatic or other in vivo

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processes to the parent bioactive form. This chemically modified drug, or prodrug, should have a different pharmacokinetic profile to the parent, enabling easier absorption across the mucosal epithelium, better salt formulation and/or solubility, improved systemic stability (for an increase in plasma half-life, for example).

5 These chemical modifications may be

- 10 (1) Ester or amide derivatives which may be cleaved by, for example, esterases or lipases. For ester derivatives, the ester is derived from the carboxylic acid moiety of the drug molecule by known means. For amide derivatives, the amide may be derived from the carboxylic acid moiety or the amine moiety of the drug molecule by known means.
- 15 (2) Peptides which may be recognized by specific or nonspecific proteinases. A peptide may be coupled to the drug molecule via amide bond formation with the amine or carboxylic acid moiety of the drug molecule by known means.
- 20 (3) Derivatives that accumulate at a site of action through membrane selection of a prodrug form or modified prodrug form.
- (4) Any combination of 1 to 3.

Research has shown that the oral absorption of certain drugs may be increased by the preparation of "soft" quaternary salts. The quaternary salt is
25 termed a "soft" quaternary salt since, unlike normal quaternary salts, e.g., $R-N^+(CH_3)_3$, it can release the active drug on hydrolysis. "Soft" quaternary salts have useful physical properties compared with the basic drug or its salts. Water solubility may be increased compared with other salts, such as the hydrochloride, but more important there may be an increased absorption of the drug from the
30 intestine. Increased absorption is probably due to the fact that the "soft" quaternary salt has surfactant properties and is capable of forming micelles and unionized ion pairs with bile acids, etc., which are able to penetrate the intestinal

epithelium more effectively. The prodrug, after absorption, is rapidly hydrolyzed with release of the active parent drug.

Aminoacyl-glycolic and -lactic esters are known as prodrugs of amino acids (Wermuth C.G., *Chemistry and Industry*, 1980:433-435). The carbonyl group of the amino acids can be esterified by known means. Prodrugs and soft drugs are known in the art (Palomino E., *Drugs of the Future*, 1990;15(4):361-368). The last two citations are hereby incorporated by reference.

10 The invention also relates to therapeutic use of the present compounds as agents for treating or relieving the symptoms of neurodegenerative disorders. Such neurodegenerative disorders include, for example, Alzheimer's disease, Huntington's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis. The present invention also covers treating neurodegenerative disorders termed
15 acute brain injury. These include but are not limited to: stroke, head trauma, and asphyxia. Stroke refers to a cerebral vascular disease and may also be referred to as a cerebral vascular accident (CVA) and includes acute thromboembolic stroke. Stroke includes both focal and global ischemia. Also, included are transient cerebral ischemic attacks and other cerebral vascular problems accompanied by
20 cerebral ischemia. These vascular disorders may occur in a patient undergoing carotid endarterectomy specifically or other cerebrovascular or vascular surgical procedures in general, or diagnostic vascular procedures including cerebral angiography and the like. Other incidents are head trauma, spinal cord trauma, or injury from general anoxia, hypoxia, hypoglycemia, hypotension as well as
25 similar injuries seen during procedures from embole, hyperfusion, and hypoxia. The instant invention would be useful in a range of incidents, for example, during cardiac bypass surgery, in incidents of intracranial hemorrhage, in perinatal asphyxia, in cardiac arrest, and status epilepticus.

30 The compounds of the invention are useful for the treatment of acute as well as chronic pain. Acute pain is usually short-lived and is associated with hyperactivity of the sympathetic nervous system. Examples are postoperative pain

and allodynia. Chronic pain is usually defined as pain persisting from 3 to 6 months and includes somatogenic pains and psychogenic pains. Other pain is nociceptive. Still other pain is caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Neuropathic pain includes, but is not limited to, pain caused by nerve injury such as, for example, diabetic pain. Psychogenic pain is that which occurs without an organic origin such as low back pain, atypical facial pain, and chronic headache. Other types of pain are: inflammatory pain, osteoarthritic pain, trigeminal neuralgia, cancer pain, diabetic neuropathy, restless leg syndrome, acute herpetic and postherpetic neuralgia, causalgia, brachial plexus avulsion, occipital neuralgia, gout, phantom limb, burn, and other forms of neuralgia, neuropathic and idiopathic pain syndrome.

A skilled physician will be able to determine the appropriate situation in which subjects are susceptible to or at risk of, for example, stroke as well as suffering from stroke for administration by methods of the present invention.

The compounds of the invention are also expected to be useful in the treatment of depression. Depression can be the result of organic disease, secondary to stress associated with personal loss, or idiopathic in origin. There is a strong tendency for familial occurrence of some forms of depression suggesting a mechanistic cause for at least some forms of depression. The diagnosis of depression is made primarily by quantification of alterations in patients' mood. These evaluations of mood are generally performed by a physician or quantified by a neuropsychologist using validated rating scales, such as the Hamilton Depression Rating Scale or the Brief Psychiatric Rating Scale. Numerous other scales have been developed to quantify and measure the degree of mood alterations in patients with depression, such as insomnia, difficulty with concentration, lack of energy, feelings of worthlessness, and guilt. The standards

for diagnosis of depression as well as all psychiatric diagnoses are collected in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) referred to as the DSM-IV-R manual published by the American Psychiatric Association, 1994.

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The compounds of the invention are also expected to be useful in the treatment of visceral pain, and gastrointestinal disorders. The viscera encompasses the organs of the abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain associated with the viscera can be divided into digestive visceral pain and non-digestive visceral pain. Commonly encountered gastrointestinal (GI) disorders include the functional bowel disorders (FBD) and the inflammatory bowel diseases (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including – for FBD, gastro-esophageal reflux, dyspepsia, the irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and – for IBD, Crohn’s disease, ileitis, and ulcerative colitis, and all regularly produce visceral pain. It has been shown recently in these pathologies, in particular the irritable bowel syndrome and dyspepsia, that the visceral pain threshold is decreased, indicating a visceral hypersensitivity. Other types of visceral pain include the pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis.

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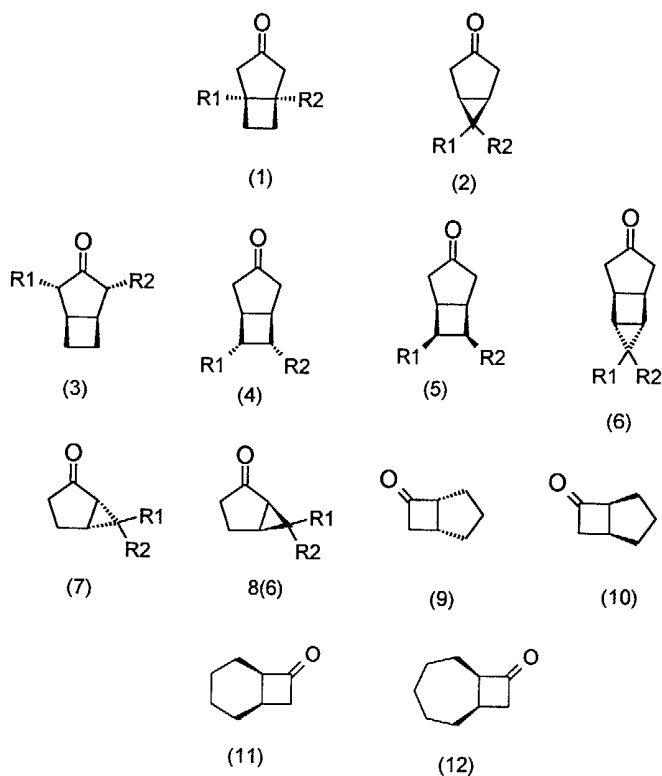
Few drugs are known to act selectively upon GI disorder-associated hypersensitivity (Farthing M.J. (1998) Drugs 56:11-21). Available treatments of pain fall into two main categories: (1) nonsteroidal anti-inflammatory drugs, used to treat mild pain, but whose therapeutic use is limited by GI adverse effects (gastric erosion, peptic ulcer formation, inflammation of the duodenum and colon); (2) morphine and related opioids, used to treat moderate to severe pain but whose therapeutic use is limited by undesirable side effects including constipation, respiratory depression, tolerance, and abuse potential.

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The compounds of the instant invention are also expected to be useful in the treatment of anxiety and of panic as demonstrated by means of standard pharmacological procedures.

5 Starting materials and their synthesis

The above compounds can be synthesised from the ketones (1) – (12) below, in which R^1 and R^2 have the same meanings as give above:

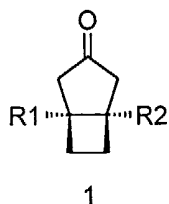


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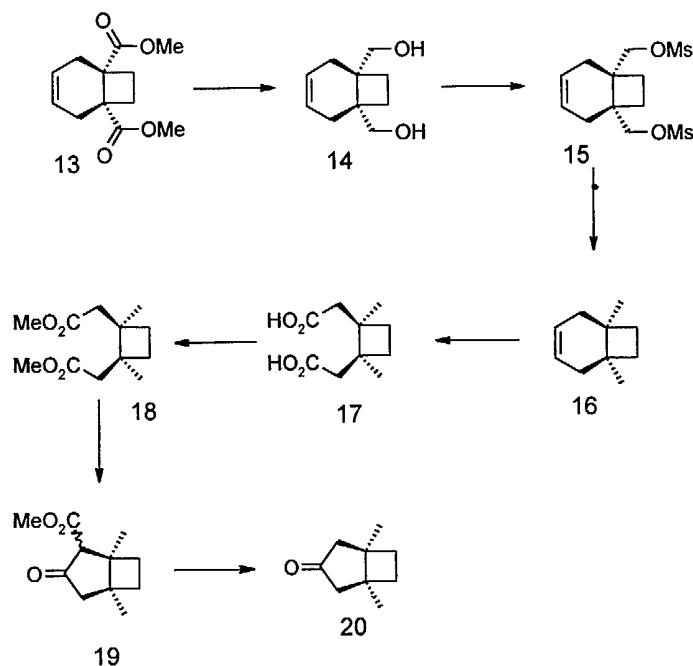
Intermediates of formulae (1) to (6) above are believed to be novel.

15 Synthetic methods for the above ketones

Various methods for synthesizing the above ketones are set out below:

(1) *Synthesis of Ketones of type 1.*

An example of the synthesis of a ketone of the above type is set out below.



(a) The known diester (13) is reduced to diol (14) e.g. by lithium aluminium hydride in an organic solvent e.g. tetrahydrofuran or diethyl ether at a temperature of 0°C to reflux.

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(b) The diol (14) is added to methylsulfonyl chloride in pyridine or triethylamine in dichloromethane a -60°C to 40°C to produce a dimesylate of formula (15).

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(c) The dimesylate (15) is added to a solution of lithium aluminium hydride in a solvent such as tetrahydrofuran or diethyl ether at a temperature of from 0°C to reflux to produce an alkene of formula (16).

(d) The alkene (16) above is added

- to a mixture of carbon tetrachloride or ethyl acetate and acetonitrile to which water, sodium periodate and ruthenium (III) chloride were added, and stirred at a temperature from $-40\text{ }^{\circ}\text{C}$ to $80\text{ }^{\circ}\text{C}$ to produce carboxylic acid of formula (17); or
- to a mixture of potassium permanganate in water and dichloromethane in the presence of a phase transfer catalyst such as tetrabutylammonium bromide to produce (17).

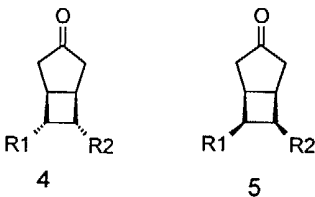
10 (e) The carboxylic acid (17) is added to a mixture of an alcohol such as methanol and a concentrated acid such as sulphuric acid or hydrochloric acid at a temperature of room temperature to reflux to produce diester of formula (18).

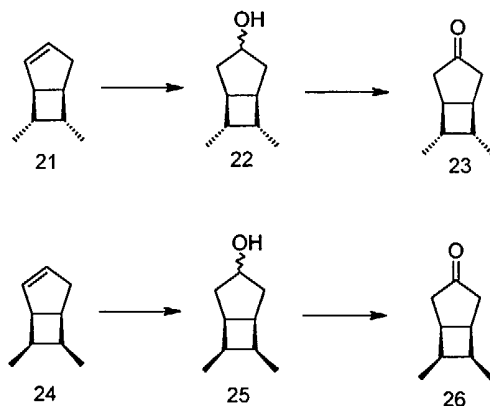
15 (f) The diester (18) above is added to a strong base such as sodium hydride or potassium *tert*-butoxide in a solvent such as tetrahydrofuran at reflux temperature to give ketone (19).

(g) The ketone (19) above is added to a mixture of dimethyl sulphoxide and water at a temperature of $100\text{-}180^{\circ}\text{C}$ to produce ketone of formula (20).

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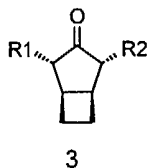
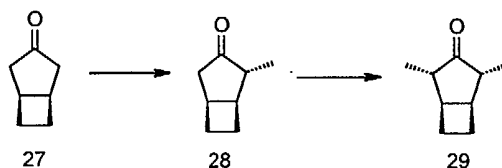
(2) *Synthesis of ketones 4 and 5.*



Examples:

- (a) The known alkene (21), see B.D. Kramer, P.D. Bartlett, *J. Am. Chem. Soc.*, 1972, 94, 3934, is mixed with an organoborane such as disiamylborane, 5
thexylborane or 9-BBN in a solvent such as diethyl ether or tetrahydrofuran at a temperature of 0°C to room temperature. The resulting organoborane is mixed with a solution of concentrated sodium hydroxide and hydrogen peroxide to give an alcohol of formula (22).
- 10 (b) The alcohol (22) is oxidized, e.g. with an oxidising agent such as chromium trioxide, pyridinium dichromate or pyridinium chlorochromate in a solvent such as dichloromethane or acetone to give the ketone of formula (23).

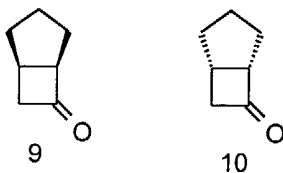
A similar process can be used for ketone (25) except that the starting 15
material is the known alkene (24), see B.D. Kramer, P.D. Bartlett, *supra*.

3). Synthesis of ketones of type (3)**Example:**

(a) The known ketone (27) see patent application US 60/160725, is added to a strong base such as lithium diisopropylamide or lithium hexamethyldisilazide followed by a methylating agent such as methyl iodide in a solvent such as tetrahydrofuran or diethyl ether at a temperature of between -100°C and room temperature to give the ketone of formula (28).

(b) The ketone of formula (46) above is further methylated with a methylating agent such as methyl iodide in the presence of a strong base such as lithium diisopropylamide or lithium hexamethyldisilazide in a solvent such as tetrahydrofuran or diethyl ether at a temperature of between -100°C and room temperature to give the product ketone of formula (29).

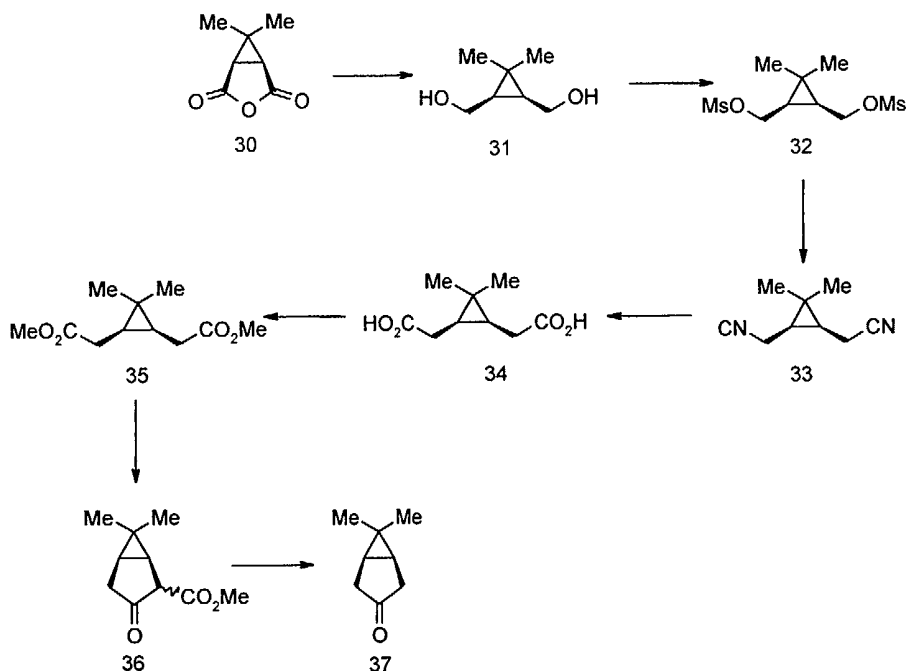
4). Synthesis of ketones (9) and (10).



These ketones are known compounds, see L.Y.Chen, L.Ghosez, *Tetrahedron Letters*, 1990, **31**, 4467; C. Houge, A.M.Frisque-Hesbain, A. Mockel, L. Ghosez, J.P.Declercq, G.Germain, M.Van Meerssche, *J. Am. Chem. Soc.*, 1982, **104**, 2920.

5). Synthesis of ketones of type (2).

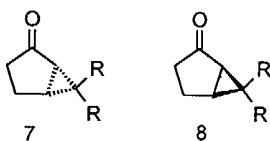


Example:

- (a) The known carbamate (30), see W. Von der Saal, R.Reinhardt, H.M. Seidenspinner, J. Stawitz, H. Quast, *Liebigs Ann. Chem.*, 1989, 703; Z. Cekovic, R. Matovic, *J. Serb. Chem. Soc.*, 1988, **53**, 595, is reduced using lithium aluminium hydride in a solvent such as tetrahydrofuran or diethyl ether at a temperature of 0°C to reflux to give diol (31).
- (b) The diol (31) is added to methylsulphonyl chloride in pyridine or triethylamine in dichloromethane at a temperature of -60°C to 40°C to produce dimesylate of formula (32).
- (c) The dimesylate (32) is added to sodium or potassium cyanide in a solvent such as tetrahydrofuran, diethyl ether, dimethylsulphoxide or dimethylformamide at a temperature of 0°C to reflux to give the dicyanide of structure (33).
- (d) The dicyanide (33) is added to a concentrated solution of potassium or sodium hydroxide at a temperature of 50°C to reflux to give diacid (34).
- (e) The diacid (34) is esterified to diester (35) by addition:

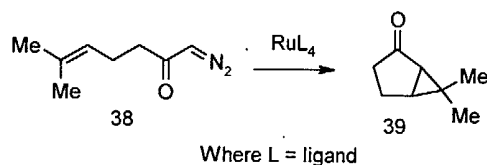
- to a mixture of iodomethane in a solvent selected from dichloromethane, chloroform, tetrahydrofuran, toluene or 1,4-dioxane to which a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) is added and stirred at a temperature from $-40\text{ }^{\circ}\text{C}$ to $110\text{ }^{\circ}\text{C}$; or
 - to a mixture of methanol and a concentrated acid such as sulphuric acid or hydrochloric acid at a temperature ranging from $0\text{ }^{\circ}\text{C}$ to $100\text{ }^{\circ}\text{C}$; or
 - to trimethylsilyldiazomethane and methanol in benzene or toluene at a temperature from $-40\text{ }^{\circ}\text{C}$ to $100\text{ }^{\circ}\text{C}$; or
 - to diazomethane in a solvent such as benzene, toluene, dichloromethane at a temperature from $-40\text{ }^{\circ}\text{C}$ to $40\text{ }^{\circ}\text{C}$.
- (f) The diester (35) is added to a strong base such as sodium hydride or potassium *tert*-butoxide in a solvent such as tetrahydrofuran at reflux temperature to give ketone (36).
- (g) The ketone (36) above is added to a mixture of dimethyl sulphoxide and water at a temperature of $100\text{-}180\text{ }^{\circ}\text{C}$ to produce ketone of formula (37).

6). *Synthesis of ketones of type 7 and 8*



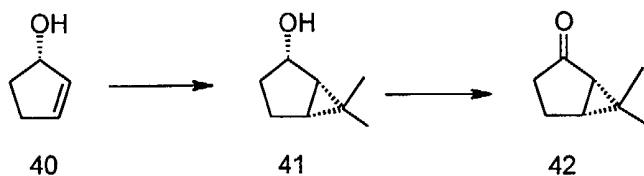
Ketones of this type can be made using ruthenium complexes, see S-W. Park, J-H.Son, S-G.Kim, K.H.Ahn, *Tetrahedron: Asymmetry*, 1999, **10**, 1903.

Example 1:



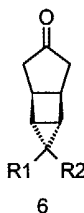
The known alkene (38), see H.Nishiyama, Y.Itoh, H.Matsumoto, S.B.Park, K.Itoh, *J. Am. Chem. Soc.*, 1994, **116**, 2223, was stirred with a ruthenium catalyst such as $\text{Cl}_2\text{Ru}(\text{pybox-ip})(\text{CH}_2=\text{CH}_2)$ in a solvent such as dichloromethane or chloroform at a temperature of 0°C to room temperature to give ketone of structure (39).

Example 2:



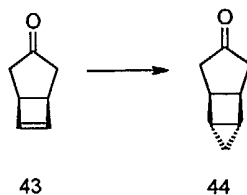
- (a) The known alcohol (40), see M.Asami, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 721; T.Sato, Y.Gotoh, Y.Wakabayashi, T.Fujisawa, *Tetrahedron Letters*, 1983, **24**, 4123, is mixed with diiodomethane and an alkylzinc such as dimethylzinc or diethylzinc or a zinc-copper couple in a solvent such as toluene or benzene at a temperature of -60°C to reflux to give an alcohol of formula (41).
- (b) The alcohol of formula (41) is added to an oxidising agent such as chromium trioxide, pyridinium dichromate or pyridinium chlorochromate in a solvent such as dichloromethane or acetone to give the ketone of formula (42).

7). Synthesis of ketones of type (6).



20

Example:



The known ketone (43), see W.A.Wilczak, D.I.Schuster, *Tetrahedron Letters*, 1986, **27**, 5331; D.I.Schuster, J.Eriksen, *J. Org. Chem.*, 1979, **44**, 4254, is mixed with diiodomethane and an alkylzinc such as dimethylzinc or diethylzinc or a zinc-copper couple in a solvent such as toluene or benzene at a temperature of -
5 60°C to reflux to give ketone of structure (44).

Synthesis of ketones (11) and (12)

Preparation of (11) can be found in the following references:

10

- Ogino, Toshio. **Preparation of bicyclo[4.2.0]octan-7-ones.** *Niigata Daigaku Kyoikugakubu Kiyo, Shizen Kagaku Hen* (1973), 15 26-33.
- Marko, Istvan; Ronsmans, Bruno; Hesbain-Frisque, Anne Marie; Dumas,
15 Stephane; Ghosez, Leon; Ernst, Beat; Greuter, Hans. **Intramolecular [2+2] cycloadditions of ketenes and keteniminium salts to olefins.** *J. Am. Chem. Soc.* (1985), 107(7), 2192-4.
- Chen, Lian Yong; Ghosez, Leon. **Study of chiral auxiliaries for the
20 intramolecular [2+2] cycloaddition of a keteniminium salt to an olefinic double bond. A new asymmetric synthesis of cyclobutanones.** *Tetrahedron Lett.* (1990), 31(31), 4467-70.

25

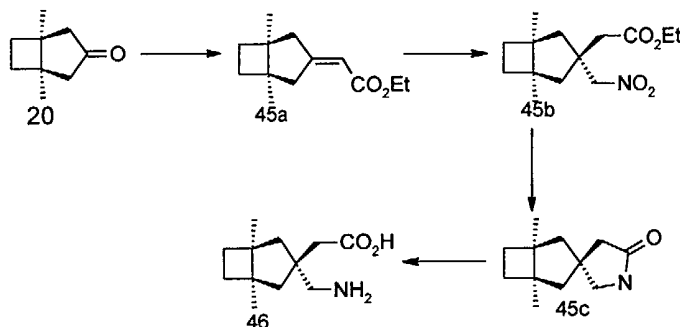
Preparation of (14) can be found in Marko *et al.*, *supra*.

Conversion of ketone starting materials into amino acids of the invention

The above ketones can be transformed into amino acids using one of the following methods A to E, illustrated below for ketone (1) where $R^1=R^2$ =methyl.

5

Method A



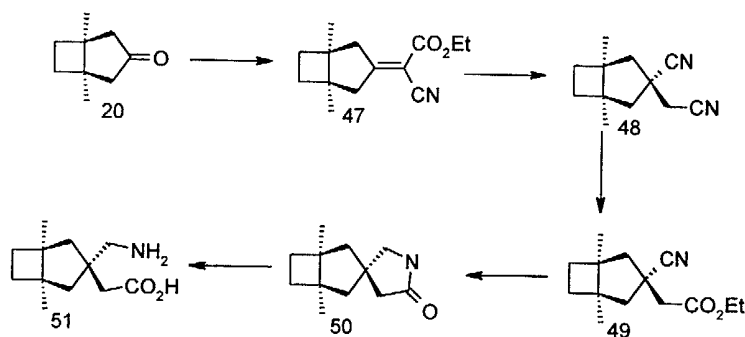
- (a) The ketone (20) is converted to unsaturated ester (45a) by reaction with with a trialkylphosphonoacetate such as triethylphosphonoacetate in the presence of a base. Suitable bases include sodium hydride, potassium hydride, lithium- or sodium- or potassium-hexamethyldisilazide, butyllithium or potassium *tert*-butoxide. The reaction may be carried out in a polar aprotic organic solvent such as tetrahydrofuran, dimethylformamide, diethyl ether or dimethylsulfoxide at a temperature in the range from -78°C to 100°C .
- (b) Nitromethane is added to the unsaturated ester (45a) by a Michael addition reaction in the presence of a base and in a polar aprotic organic solvent at a temperature of -20°C to 100°C to give the nitroester (45b). Suitable bases include tetrabutylammonium fluoride, tetramethylguanidine, 1,5-diazabicyclo[4,3,0]non-5-ene, 1,8-diazabicyclo[5,4,0]undec-7-ene, a sodium or potassium alkoxide such as potassium *tert*-butoxide, potassium carbonate, sodium hydride or potassium fluoride. Suitable organic solvents include tetrahydrofuran, diethyl ether, dimethylformamide, dimethylsulphoxide, benzene, toluene, dichloromethane, chloroform or tetrachloromethane.

25

(c) Reduction of the nitro ester (45b) and ring closure by reaction of the resulting amino group with the ester group gives the cyclic lactam (45c). Hydrogenation may be in the presence of a catalyst such as Raney nickel, palladium on charcoal or rhodium catalyst or other nickel or palladium containing catalyst in a solvent such as methanol, ethanol, isopropanol, ethyl acetate, acetic acid, 1,4-dioxane, chloroform or diethyl ether at a temperature in the range from 20°C to 80°C.

(d) Hydrolysis of the cyclic lactam (45c) e.g. using aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M and optionally in the presence of a solvent such as 1,4-dioxane, acetic acid or water produces the amino acid (46).

Method B



(a) The ketone (20) is condensed with an alkyl cyanoacetate, for example ethyl cyanoacetate in an organic solvent selected from toluene, benzene, xylenes or *n*-heptane to which acetic acid and β -alanine or ammonium acetate, or piperidine are added. The mixture is stirred at a temperature from 0 °C to 150°C with removal of water by, for example, use of a Dean-Stark trap or activated molecular sieves, to produce the cyanoester of formula (47).

(b) The cyanoester (47) is converted to dicyanide (48) by treatment with potassium cyanide or sodium cyanide in water and ethanol or methanol. The mixture is refluxed and water is removed by, for example, use of a Dean-Stark trap.

(c) The cyanomethyl group of dicyanide (48) converted to an ethoxycarbonylmethyl group by reaction with ethanol in toluene or benzene saturated with gaseous hydrochloric acid. The reaction temperature may be from $-30\text{ }^{\circ}\text{C}$ to $40\text{ }^{\circ}\text{C}$.

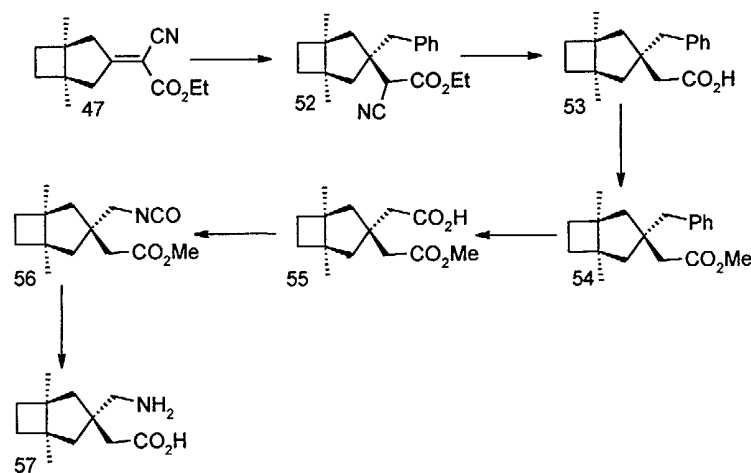
5

(d) The cyano-group of the resulting cyanoester (49) is reduced by hydrogenation in methanol, ethanol or ethyl acetate using a catalyst such as nickel, palladium, platinum or rhodium at a temperature from $15\text{ }^{\circ}\text{C}$ to $60\text{ }^{\circ}\text{C}$, after which ring closure gives lactam (50).

10

(e) Hydrolysis of the lactam (50) e.g. using aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M and optionally in the presence of a solvent such as 1,4-dioxane, acetic acid or water produce the amino acid (51).

15 Method C



(a) Cyanoester (47) is added to a mixture of benzylmagnesium chloride, bromide or iodide, in a dry solvent e.g. tetrahydrofuran, 1,4-dioxane, *n*-heptane, toluene, diethyl ether, or *tert*-butyl methyl ether at a temperature from -100°C to 110°C resulting in cyanoester of formula (52).

20

(b) The cyano group of cyanoester (52) is removed by means of a base e.g. potassium hydroxide, sodium hydroxide, lithium hydroxide or cesium hydroxide in a solvent e.g. ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane

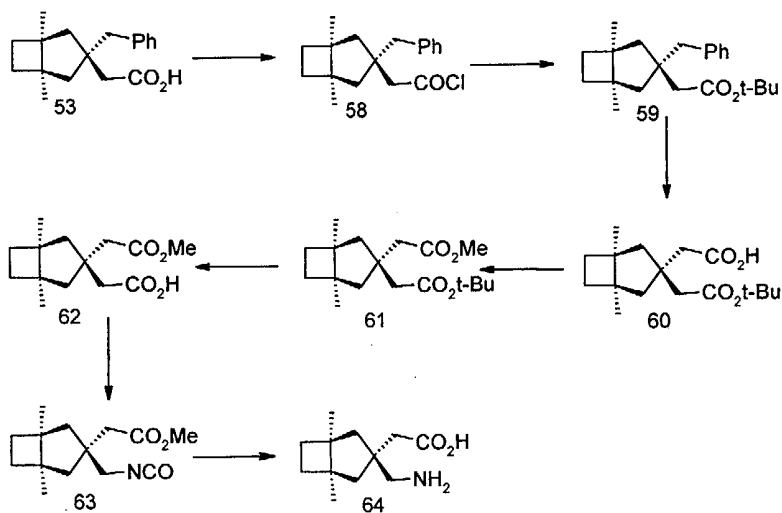
or diethylene glycol. The mixture is stirred at a temperature from 25°C to 250°C to produce the carboxylic acid of formula (53).

- (c) The carboxylic acid group of acid (53) is protected by conversion to its methyl ester (54). For this purpose, acid (53) may be added
- 5 • to a mixture of iodomethane in a solvent selected from dichloromethane, chloroform, tetrahydrofuran, toluene or 1,4-dioxane to which a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) is added and stirred at a temperature
 - 10 from -40 °C to 110 °C; or
 - to a mixture of methanol and a concentrated acid such as sulphuric acid or hydrochloric acid at a temperature ranging from 0 °C to 100 °C; or
 - to trimethylsilyldiazomethane and methanol in benzene or toluene at a temperature from -40 °C to 100 °C; or
 - 15 • to diazomethane in a solvent such as benzene, toluene, dichloromethane at a temperature from -40 °C to 40 °C.
- (d) The phenyl group of the resulting ester (54) is oxidized to a carboxylic acid group by treatment with sodium periodate and ruthenium (III) chloride in a
- 20 mixture of carbon tetrachloride or ethyl acetate and acetonitrile to which water is added. The mixture is stirred at a temperature from -40 °C to 80 °C to give carboxylic acid (55).
- (e) The carboxylic acid group of acid (55) is converted to isocyanate by addition
- 25 • to a mixture of a base selected from triethylamine or diisopropylethylamine and a solvent selected from toluene, benzene, xylenes, tetrahydrofuran, diethyl ether or *n*-heptane to which diphenylphosphoryl azide (DPPA) is added and stirring at a temperature from 0 °C to 150 °C to produce the isocyanate of formula (26); or
 - 30 • to ethyl chloroformate or isobutyl chloroformate and a base such as triethylamine or diisopropylethylamine in tetrahydrofuran or acetone or diethyl ether at a temperature of -40 °C to 78 °C followed by addition of

sodium azide in water and tetrahydrofuran or acetone followed by addition of toluene or benzene and refluxing.

- (f) The isocyanate and ester groups of compound (56) are simultaneously hydrolysed to amino and carboxylic acid groups, e.g. by aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M optionally in the presence of a solvent such as 1,4-dioxane, acetic acid or water to produce the amino acid (57).

10

Method D

- (a) As a first stage in protecting the carboxylic acid group of acid (53), it is converted to its chloride (58) by reaction at a temperature of from -40°C to 110°C with e.g. oxalyl chloride or thionyl chloride in an aprotic organic solvent e.g. dichloromethane, chloroform, diethyl ether, toluene or *tert*-butyl methyl ether to which 0.01 mol percent to 10 mol percent of *N,N*-dimethylformamide (DMF) is added.
- (b) The chloride (58) is converted to its *tert*-butyl ester, e.g. by reaction with *tert*-butyl alcohol in an aprotic organic solvent e.g. dichloromethane, chloroform, diethyl ether, toluene, or *tert*-butyl methyl ether to which *N,N*-diisopropylethylamine (DIPEA) or triethylamine is added. The reaction

mixture is stirred at a temperature from -40°C to 110°C to produce the ester of formula (59).

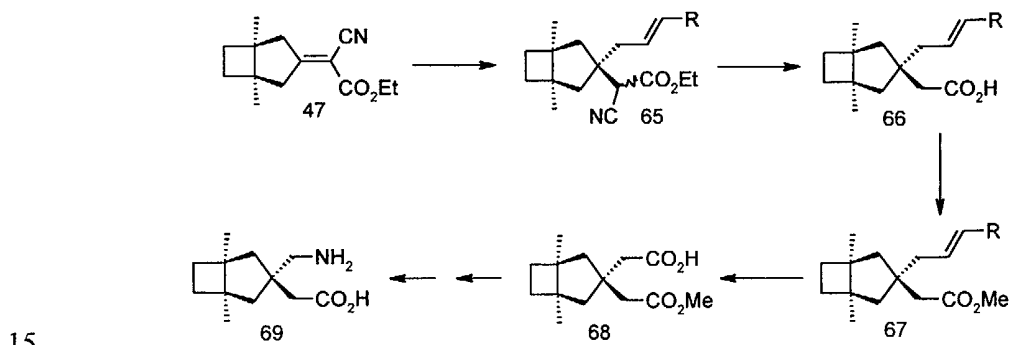
- 5 (c) The phenyl group of ester (59) is oxidized to a carboxylic acid group by reaction with , sodium periodate and ruthenium (III) chloride in a mixture of carbon tetrachloride or ethyl acetate and acetonitrile to which water is added. The reaction mixture is stirred at a temperature from -40°C to 80°C to produce carboxylic acid of formula (60).
- 10 (d) The carboxyl group of acid (60) is converted to an ester group by addition
- to a mixture of iodomethane in a solvent selected from dichloromethane, chloroform, tetrahydrofuran, toluene or 1,4-dioxane to which a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) is added and stirred at a temperature
 - 15 from -40°C to 110°C to produce the ester of formula (61); or
 - to a mixture of methanol and a concentrated acid such as sulphuric acid or hydrochloric acid at a temperature ranging from 0°C to 100°C ; or
 - to trimethylsilyldiazomethane and methanol in benzene or toluene at a temperature from -40°C to 100°C ; or
 - 20 • to diazomethane in a solvent such as benzene, toluene, dichloromethane at a temperature from -40°C to 40°C .
- (e) The *tert*-butoxy group is removed from diester (61) by reaction with trifluoroacetic acid in a solvent e.g. dichloromethane, chloroform, 1,4-dioxane, tetrahydrofuran, diethyl ether, or *tert*-butyl methyl ether. The reaction mixture
- 25 is stirred from a temperature from -40°C to 110°C to give carboxylic acid of formula (62).
- (f) The ester group of acid (62) is converted to isocyanate (63) by addition
- 30 • to a mixture of a base selected from triethylamine or diisopropylethylamine and a solvent selected from toluene, benzene, xylenes, tetrahydrofuran, diethyl ether or *n*-heptane to which

diphenylphosphoryl azide (DPPA) is added and stirring at a temperature from 0 °C to 150 °C; or

- to ethyl chloroformate or isobutyl chloroformate and a base such as triethylamine or diisopropylethylamine in tetrahydrofuran or acetone or diethyl ether at a temperature of -40 °C to 78 °C followed by addition of sodium azide in water and tetrahydrofuran or acetone followed by addition of toluene or benzene and refluxing.

- (g) Simultaneous hydrolysis of the isocyanate and ester groups of compound (63) e.g. by aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M in the presence or absence of a solvent such as 1,4-dioxane, acetic acid or water gives the amino acid (64).

Method E



- (a) Cyanoester (47) is reacted with allylmagnesium chloride or bromide or 2-butenylmagnesium chloride and a dialkylzinc such as dimethylzinc or a copper (I) salt such as copper (I) iodide or copper (I) cyanide in a dry organic solvent e.g. tetrahydrofuran, 1,4-dioxane, *n*-heptane, toluene, diethyl ether or *tert*-butyl methyl ether at a temperature from -100 °C to 110 °C to give an unsaturated addition product of formula (65).
- (b) The cyano group of addition product (65) is removed by reaction with a base, e.g. potassium hydroxide, sodium hydroxide, lithium hydroxide or cesium hydroxide in an organic solvent selected from ethylene glycol, 2-methoxyethyl

ether, 1,4-dioxane or diethylene glycol. The reaction mixture is stirred at a temperature from 25°C to 250°C to give a carboxylic acid of formula (66).

(c) The carboxylic acid group of acid (66) is converted to an ester group by addition

- 5 • to a mixture of iodomethane in a solvent selected from dichloromethane, chloroform, tetrahydrofuran, toluene or 1,4-dioxane to which a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) was added and stirred at a
- 10 • to a mixture of methanol and a concentrated acid such as sulphuric acid or hydrochloric acid at a temperature ranging from 0 °C to 100 °C; or
- to trimethylsilyldiazomethane and methanol in benzene or toluene at a temperature from -40 °C to 100 °C; or
- 15 • to diazomethane in a solvent such as benzene, toluene, dichloromethane at a temperature from -40 °C to 40 °C.

(d) The unsaturated group in ester (67) is oxidized by sodium periodate and ruthenium (III) chloride in a mixture of carbon tetrachloride or ethyl acetate and acetonitrile to which water is added. The mixture is stirred at a

20 temperature from -40 °C to 80 °C to give a carboxylic acid of formula (68).

(e) Carboxylic acid (68) is converted to amino acid (69) as in method C.

25 **Pharmaceutical compositions**

The compounds of the invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously,

30 intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the

compounds of the invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of the invention or a corresponding pharmaceutically acceptable salt of a compound of the invention.

5

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid.

10

Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier is a finely divided solid which is in a mixture with the finely
15 divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin,
20 dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus
25 in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

30

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture

is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

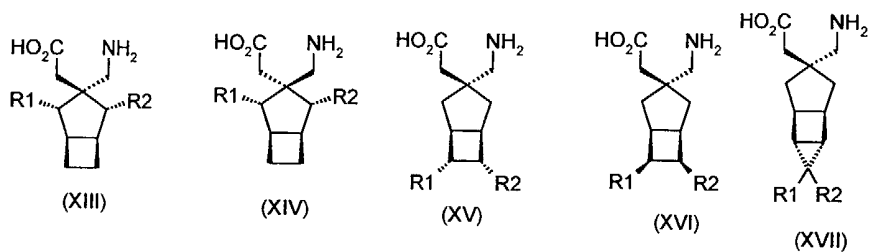
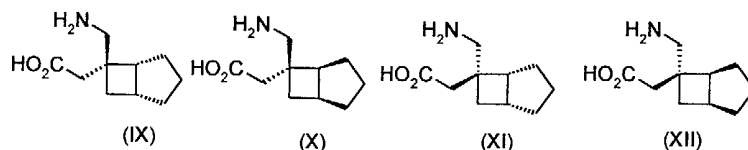
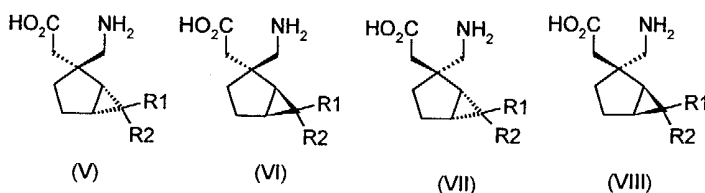
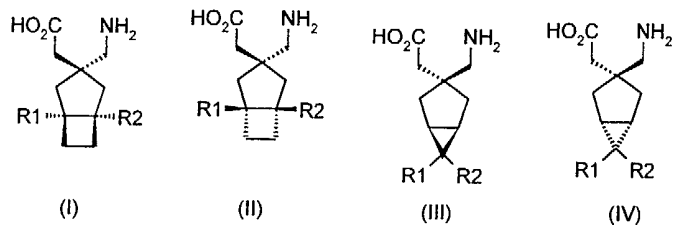
Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1 g according to the particular application and the potency of the active component. In medical use the drug may be administered three times daily as, for example, capsules of 100 or 300 mg. The composition can, if desired, also contain other compatible therapeutic agents. In therapeutic use, the compounds utilized in

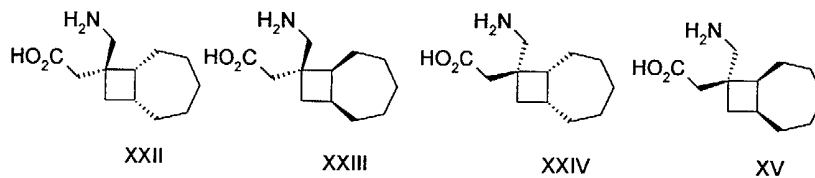
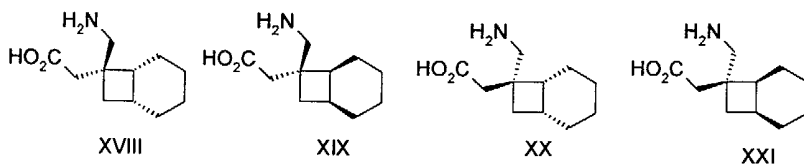
the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 100 mg/kg daily. A daily dose range of about 0.01 mg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

CLAIMS

1. A compound of any of the formulae I - XVII:



5



wherein R^1 and R^2 are each independently selected from hydrogen, straight or branched alkyl of 1-6 carbon atoms, cycloalkyl of from 3-6 carbon atoms, phenyl and benzyl, subject to the proviso that except in the

case of a tricyclooctane compound of formula (XVII) R^1 and R^2 are not simultaneously hydrogen;

or a pharmaceutically acceptable salt thereof;

or a prodrug thereof.

5

2. A compound according to claim 1, wherein R^1 and R^2 represent the same group.

10

3. A compound according to claim 1, wherein R^1 and R^2 both represent methyl.

4. Any of the compounds set out below, or an acid addition salt or prodrug thereof:

15

((1R,5S)-3-Aminomethyl-1,5-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid;

((1S,5R)-3-Aminomethyl-1,5-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid;

((1R,5S)-3-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-3-yl)-acetic acid;

20

((1S,5R)-3-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-3-yl)-acetic acid;

((1S,2S,5R)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid;

25

((1R,2S,5S)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid;

((1S,2R,5R)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid;

((1R,2R,5S)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid;

30

((1R,5R,6S)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid;

((1S,5S,6S)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid;

((1R,5R,6R)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid;

((1S,5S,6R)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid;
 cis-((1S,2R,4S,5R)-3-Aminomethyl-2,4-dimethyl-bicyclo[3.2.0]hept-3-yl)-
 acetic acid;
 trans-((1S,2R,4S,5R)-3-Aminomethyl-2,4-dimethyl-bicyclo[3.2.0]hept-3-
 5 yl)-acetic acid;
 ((1S,5R,6S,7R)-3-Aminomethyl-6,7-dimethyl-bicyclo[3.2.0]hept-3-yl)-
 acetic acid;
 ((1S,5R,6R,7S)-3-Aminomethyl-6,7-dimethyl-bicyclo[3.2.0]hept-3-yl)-
 acetic acid;
 10 ((1R,2S,5S)-7-Aminomethyl-3,3-dimethyl-tricyclo[3.3.0.0,^{2,4}]oct-7-yl)-
 acetic acid:
 ((1R,6R,7S)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid;
 ((1S,6S,7S)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid;
 ((1R,6R,7R)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid;
 15 ((1S,6S,7R)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid;
 ((1R,7R,8S)-8-Aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid;
 ((1S,7S,8S)-8-Aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid;
 ((1R,7R,8R)-8-Aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid; and
 ((1S,7S,8R)-8-Aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid.

20

5. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any preceding claim and a pharmaceutically acceptable carrier.
6. A method for treating epilepsy comprising administering a therapeutically
 25 effective amount of a compound according to any of claims 1-4 to a mammal in need of said treatment.
7. A method for treating faintness attacks, hypokinesia, and cranial disorders comprising administering a therapeutically effective amount of a

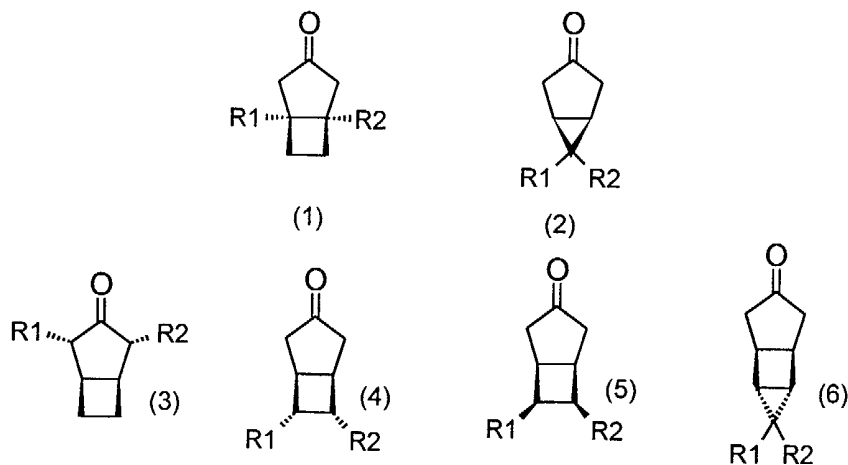
compound according to any of claims 1-4 to a mammal in need of said treatment.

- 5 8. A method for treating neurodegenerative disorders comprising administering a therapeutically effective amount of a compound according to any of claims 1-4 to a mammal in need of said treatment.
9. A method for treating depression comprising administering a therapeutically effective amount of a compound according to any of claims 1-4 to a mammal in need of said treatment.
- 10 10. A method for treating anxiety comprising administering a therapeutically effective amount of a compound according to any of claims 1-4 to a mammal in need of said treatment.
11. A method for treating panic comprising administering a therapeutically effective amount of a compound according to any of claims 1-4 to a mammal in need of said treatment.
- 15 12. A method for treating pain comprising administering a therapeutically effective amount of a compound according to any of claims 1-4 to a mammal in need of said treatment.
- 20 13. A method for treating neuropathological disorders comprising administering a therapeutically effective amount of a compound according to any of claims 1-4 to a mammal in need of said treatment.
- 25 14. A method for treating premenstrual syndrome comprising administering a therapeutically effective amount of a compound according to any of claims 1-4 to a mammal in need of said treatment.
15. A method for treating visceral pain, functional bowel disorders, inflammatory bowel diseases, pain associated with dysmenorrhea, pelvic

pain, cystitis and pancreatitis comprising administering a therapeutically effective amount of a compound according to any of claims 1-4 to a mammal in need of said treatment.

- 5 16. Use of a compound as claimed in any of claims 1-4 in the manufacture of a medicament for the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, irritable bowel syndrome, sleep disorders, osteoarthritis, rheumatoid arthritis, neuropathological disorders, visceral pain, functional bowel disorders, inflammatory bowel diseases, pain associated with
- 10 dysmenorrhea, pelvic pain, cystitis and pancreatitis.

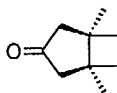
17. Compounds of any of the formulae below:



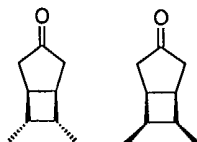
- 15 in which R^1 and R^2 are each independently selected from hydrogen, straight or branched alkyl of 1-6 carbon atoms, cycloalkyl of from 3-6 carbon atoms, phenyl and benzyl, subject to the proviso that R^1 and R^2 are not simultaneously hydrogen.

- 20 18. A compound according to claim 17, wherein R^1 and R^2 represent the same group.
19. A compound according to claim 17, wherein R^1 and R^2 both represent methyl.

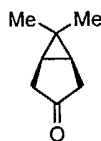
20. The compound below:



5 21. Either of the compounds below:

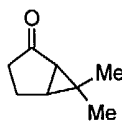


22. The compound below:



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23. The compound below:





INVESTOR IN PEOPLE

Application No: GB 0109635.3
Claims searched: 1-5,16

38

Examiner: S.I. AHMAD
Date of search: 26 October 2001

**Patents Act 1977
Search Report under Section 17**

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK CI (Ed.S):

Int CI (Ed.7): C07C-215/20

Other: DATA-BASE : CAS-ON-LINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
	NO RELEVANT DOCUMENT	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.