



CARLOS TAMAYO & ASOCIADOS
INTERNATIONAL PATENT AND TRADEMARK OFFICE

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Patent
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Marcas
Patentes
Registros Sanitarios
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Nombres Comerciales
Diseños

Indicación: 0003678 MARCAS
Fecha (MRO): 1990-07-02 (14/07/90)
Trámite: 1 QUE PATENTES 3 1 REGISTRO SIN PETICION
Dependencia: EN DIVISION DE NUEVAS CREACIONES

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

REF: EXPEDIENTE No.00-93678
PATENTE: "METODO NOVEDOSO PARA LA SINTESIS ESTEREOSELECTIVA
DE AMINOACIDOS CICLICOS"

Estimados señores:

Con fundamento jurídico en lo dispuesto por el Artículo (44) de la Decisión (488) de la Comisión de la Comunidad Andina de Naciones (CAN) ruego a ustedes disponer lo pertinente para proceder al Examen de Patentabilidad de la Solicitud citada en la referencia, para lo cual estamos adjuntando el recibo de pago correspondiente a la tasa vigente para este caso.

En consecuencia, esperamos se surta este trámite para que el expediente siga su curso normal, hasta su concesión.

Atentamente,

CARLOS ORLANDO MAYA RODRÍGUEZ
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T.P. No. 17.402- C.S.J.

Anexo.- Recibo de Pago

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E-mail: trademarks1@tutopia.com • Bogotá, Colombia, S.A.
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INDICACIONES Y LINEAS
Indicacion : 0003676 0000006 Folios: 2
Fecha (GIR): 2003-07-02 16:29:24
Procedimiento : 002 PATENTES D 1 REGISTRO/ SIN PETICION
Dependencia: 000 DIVISION DE MARCAS CIONES

BIT : 000176009-2

RECIBO OFICIAL DE CAJA : 03 - 45,721
FECHA : JULIO 2 DE 2003

00000 CONSIGNACION 00000

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PBO	VR. PAGO
CARLOS TAMAYO	CONSIGNACION	BANCO POPULAR	050-00110-6	14073320	02/07/2003	1,063,000.00

00000 C O N C E P T O 00000

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 90003-01-01 SOLICITUDEN	03 EXAMEN DE PATENTABILIDAD DE JOVEN	333,000.00
	TOTAL :	333,000.00

GIR: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.			Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: CYCLIC AMINO ACIDS AND DERIVATIVES THEREOF USEFUL AS PHARMACEUTICAL AGENTS			
(57) Abstract The invention is a novel series of cyclic amino acids which 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. A pharmaceutical composition containing a compound of the invention as well as methods of preparing the compounds and novel intermediates useful in the preparation of the final compounds are included.			

[1R-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-
acetic acid;

(1 α ,3 α ,4 α)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;

5 [1S-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic
acid;

[1R-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic
acid;

[1S-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic
acid;

10 [1R-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic
acid;

(1S-cis)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

15 (1S-cis)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

20 (1R-cis)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(S)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid;

25 (S)-(1-Aminomethyl-3,3-diethyl-cyclopentyl)-acetic acid;

(1-Aminomethyl-3,3,4,4-tetramethyl-cyclopentyl)-acetic acid;

(1-Aminomethyl-3,3,4,4-tetraethyl-cyclopentyl)-acetic acid;

(1 α ,3 β ,4 β)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid;

(1 α ,3 β ,4 β)-(1-Aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid;

30 (1 α ,3 β ,4 β)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic acid;

[1R-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-acetic
acid;

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- (1R-trans)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;
(1R-trans)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;
(1R-trans)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;
(1R-trans)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;
5 (1R-trans)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;
(1R-trans)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;
(1S-trans)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;
(1S-trans)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;
(1S-trans)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;
10 (1S-trans)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;
(1S-trans)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;
(1S-trans)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;
(R)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid;
(R)-(1-Aminomethyl-3,3-diethyl-cyclopentyl)-acetic acid;
15 cis-(1-Aminomethyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-ethyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-isopropyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-phenyl-cyclobutyl)-acetic acid;
20 cis-(1-Aminomethyl-3-benzyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-ethyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-isopropyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-tert-butyl-cyclobutyl)-acetic acid;
25 trans-(1-Aminomethyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-ethyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-isopropyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-3-methyl-cyclobutyl)-acetic acid;
30 cis-(1-Aminomethyl-3-methyl-3-phenyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-benzyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-ethyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-isopropyl-3-methyl-cyclobutyl)-acetic acid;

Pair 34

A handwritten bracket on the right side of the list groups the first six items (lines 1-6) and the next six items (lines 7-12). Arrows point from the bracket to the text 'Pair 34' at the top right.

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Results

The dose-dependent suppression of sound-induced tonic seizures in DBA/2 mice was tested, and the corresponding ED₅₀ values are shown in Table 1.

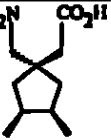
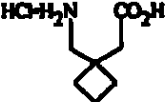
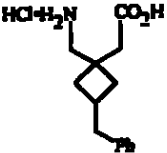
5 The present results show that the compounds of the invention given orally cause dose-related anticonvulsant effects in a sound susceptible strain (DBA/2) of mice, confirming previous data showing anticonvulsant activity in other models of experimental epilepsy. The effective dosages of drugs in this model are lower than those in the maximal electroshock test, confirming that DBA/2 mice are a
10 sensitive model for detecting anticonvulsant actions.

TABLE 1

Compound	Structure	IC ₅₀ (μM) at α ₂ δ binding site	Carrageenan Induced Thermal Hyperalgesia in the Rat		DBA/2 Audiogenic Mouse
			% MPE ^a 1 hr postdose @ 30 mg/kg PO	% MPE ^a 2 hr postdose @ 30 mg/kg PO	% Protected 1 hr postdose 30 mg/kg PO
(±)-(trans)-(1-Aminomethyl-3,4-dimethylcyclopentyl)-acetic acid hydrochloride		0.034	23	72	100
(+)-(trans)-(1-Aminomethyl-3,4-dimethylcyclopentyl)-acetic acid hydrochloride		0.022	109	118	100
(-)-(trans)-(1-Aminomethyl-3,4-dimethylcyclopentyl)-acetic acid hydrochloride		1.0			
(cis/trans)-(3R)-(1-Aminomethyl-3-methylcyclopentyl)-acetic acid hydrochloride		0.088	67	53	100

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TABLE 1 (cont'd)

Compound	Structure	IC ₅₀ (μM) at α ₂ δ binding site	Carrageenan Induced Thermal Hyperalgesia in the Rat		DBA/2 Audiogenic Mouse
			% MPE ^a 1 hr postdose @ 30 mg/kg PO	% MPE ^a 2 hr postdose @ 30 mg/kg PO	% Protected 1 hr postdose 30 mg/kg PO
(trans)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid hydrochloride		0.154	-7	-2	100
(1-Aminomethyl-cyclobutyl)-acetic acid hydrochloride		0.598	4	4	20 (2 hours postdose)
(cis/trans)-(1-Aminomethyl-3-benzyl-cyclobutyl)-acetic acid hydrochloride		>10	0	0	not tested

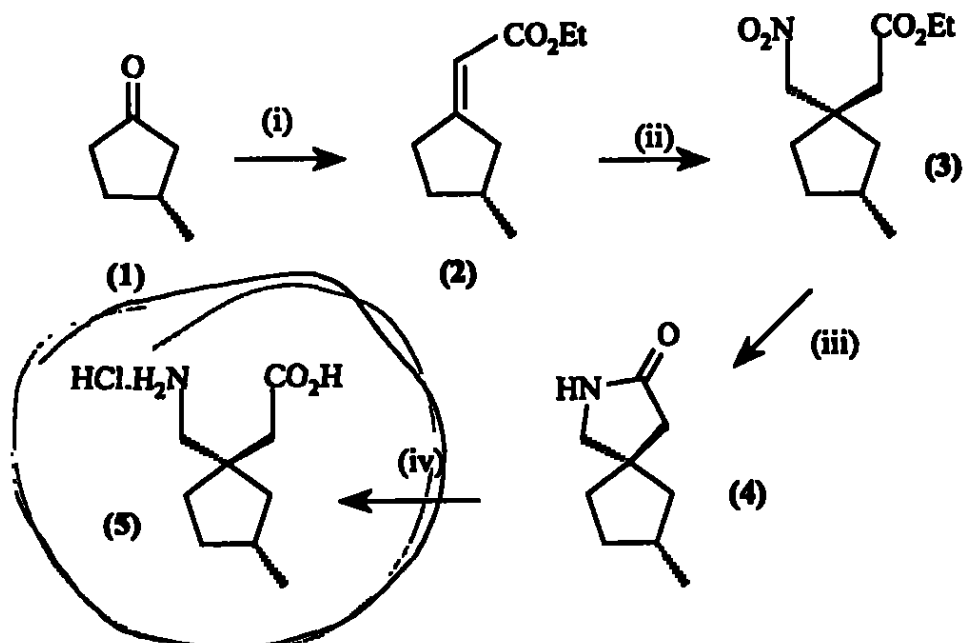
^a MPE: maximum possible effect - set as baseline value prior to treatment with carrageenan.

The radioligand binding assay using [³H]gabapentin and the α₂δ subunit derived from porcine brain tissue was used ("The Novel Anti-convulsant Drug, Gabapentin, Binds to the α₂δ Subunit of a Calcium Channel", Gee N. et al., *J. Biological Chemistry*, in press).

5 The compounds of the invention show good binding affinity to the α₂δ subunit. Gabapentin (Neurontin®) is about 0.10 to 0.12 μM in this assay. Since the compounds of the instant invention also bind to the subunit, they are expected to exhibit pharmacologic properties comparable to gabapentin. For example, as agents for convulsions, anxiety, and pain.

10 The compounds of the invention are related to Neurontin®, a marketed drug effective in the treatment of epilepsy. Neurontin® is 1-(aminomethyl)-cyclohexanecetic acid of structural formula

EXAMPLE 3



Reagents: (i) Triethylphosphonoacetate, NaH; (ii) MeNO₂, Bu₄N⁺F⁻; (iii) H₂, Ni;
(iv) HCl

5 **Synthesis of (R)-(3-Methyl-cyclopentylidene)-acetic acid ethyl ester (2)**

NaH (60% dispersion in oil, 1.86 g, 46.5 mmol) was suspended in dry tetrahydrofuran (40 mL) and cooled to 0°C. Triethylphosphonoacetate (9.69 mL, 48.8 mmol) was added and the mixture stirred at 0°C for 15 minutes. The ketone (1) (5 mL, 46.5 mmol) in THF (10 mL) was then added and the mixture
10 allowed to warm to room temperature. After 2 hours, the mixture was partitioned between diethyl ether (200 mL) and water (150 mL). The organic phase was separated, washed with brine, dried (MgSO₄) and the solvent removed in vacuo. The residue was purified by flash chromatography (silica, ethyl acetate:heptane 1:9) to give 5.45 g (70%) of (2) as a colorless oil.

15 ¹H NMR 400 MHz (CDCl₃): δ 1.04 (3H, m), 1.27 (3H, t, J = 7 Hz), 1.80-2.74 (7H, m), 2.90-3.15 (1H, m), 4.13 (2H, q, J = 7 Hz), 5.76 (1H, s).

MS (CI⁺) m/e: 169 ([MH⁺], 20%).

IR (film) ν cm⁻¹: 1205, 1371, 1653, 1716, 2955.

878 86f

Synthesis of (cis/trans)-(3R)-(3-Methyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl ester (3)

The unsaturated ester (2) (3.0 g, 17.8 mmol) was dissolved in tetrahydrofuran (20 mL) and stirred at 70°C with nitromethane (1.92 mL, 35.6 mmol) and tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 25 mL, 25.0 mmol). After 18 hours, the mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and washed with 2N HCl (30 mL) followed by brine (50 mL). The organic phase was collected, dried (MgSO₄), and the solvent removed in vacuo. The residue was purified by flash chromatography (silica, ethyl acetate:heptane 1:9) to give 2.00 g (49%) of a clear oil.

¹H NMR 400 MHz (CDCl₃): δ 1.02 (3H, d, J = 6 Hz), 1.08-1.37 (5H, m), 1.59-2.17 (5H, m), 2.64 (2H, m), 4.15 (2H, q, J = 7 Hz), 4.64 (2H, m).

MS (ES+) m/e: 230 ([MH⁺], 4%).

IR (film) ν cm⁻¹: 1183, 1377, 1548, 1732, 2956.

Synthesis of (cis/trans)-(7R)-7-Methyl-spiro[4.4]nonan-2-one (4)

The nitroester (3) (1.98 g, 8.66 mmol) was dissolved in methanol (50 mL) and shaken over Raney nickel catalyst under an atmosphere of hydrogen (40 psi) at 30°C. After 18 hours, the catalyst was removed by filtration through celite. The solvent was removed in vacuo and the residue purified by flash chromatography (silica, ethyl acetate:heptane 1:1) to give 1.05 g (79%) of a white solid.

¹H NMR 400 MHz (CDCl₃): δ 1.03 (3H, m), 1.22 (2H, m), 1.60-2.15 (5H, m), 2.22 (2H, m), 3.20 and 3.27 (2H total, 2 × s, cis, and trans), 6.18 (1H, br s).

MS (ES+) m/e: 154 ([MH⁺], 100%).

IR (film) ν cm⁻¹: 1695, 2949, 3231.

Synthesis of (cis/trans)-(3R)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride (5)

The lactam (4) (746 mg, 4.88 mmol) was heated to reflux in a mixture of 1,4-dioxan (5 mL) and 6N HCl (15 mL). After 4 hours, the mixture was cooled to room temperature, diluted with water (20 mL), and washed with dichloromethane

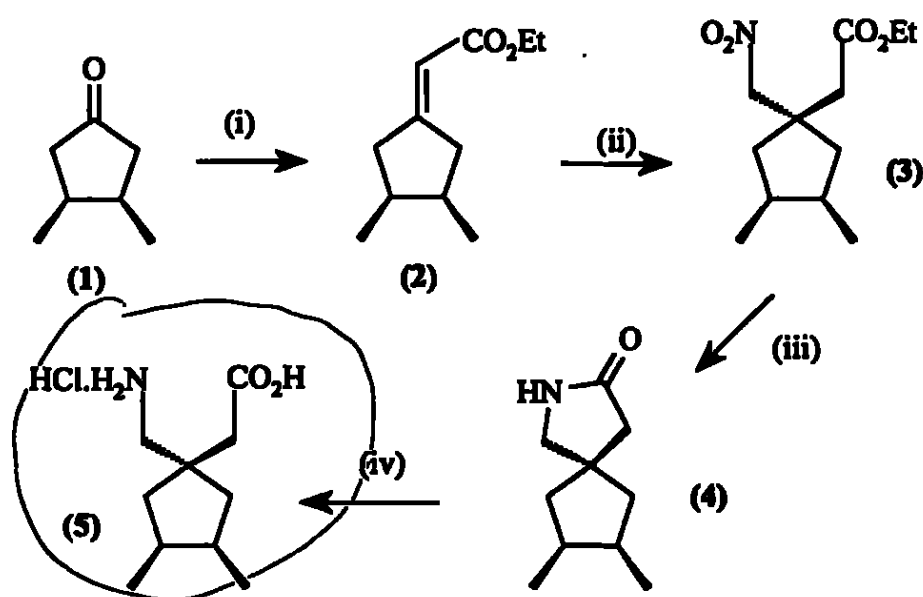
(3 × 30 mL). The aqueous phase was collected and the solvent removed in vacuo.

The residue was triturated with ethyl acetate to give a white solid which was collected and dried. This was recrystallized from ethyl acetate/methanol to give 656 mg (65%) of (5) after collection and drying.

¹H NMR 400 MHz (d₆-DMSO): δ 0.96 (3H, m), 1.01-1.24 (2H, m), 1.42-2.10 (5H, m), 2.41 and 2.44 (2H total, 2 × s, cis/trans), 2.94 (2H, m), 7.96 (3H, br s), 12.35 (1H, br s).

MS (ES+) m/e: 172 ([MH-HCl]⁺, 100%).

EXAMPLE 4



Reagents: (i) Triethylphosphonoacetate, NaH; (ii) MeNO₂, Bu₄N⁺F⁻; (iii) H₂, Ni; (iv) HCl

Synthesis of (E)-(3,4-Dimethyl-cyclopentylidene)-acetic acid ethyl ester (2)

NaH (60% dispersion in oil, 519 mg, 12.96 mmol) was suspended in dry tetrahydrofuran (30 mL) and cooled to 0°C. Triethylphosphonoacetate (2.68 mL, 13.5 mmol) was added and the mixture stirred at 0°C for 15 minutes. The ketone (1) (1.21 g, 10.80 mmol) in THF (10 mL) was then added and the mixture allowed to warm to room temperature. After 2 hours, the mixture was partitioned

Synthesis of (±)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid hydrochloride (5)

The lactam (240 mg, 1.44 mmol) in 6N HCl were heated to reflux for 24 hours. The residue was concentrated under reduced pressure and triturated with ether to give the amino acid **5** as a white solid.

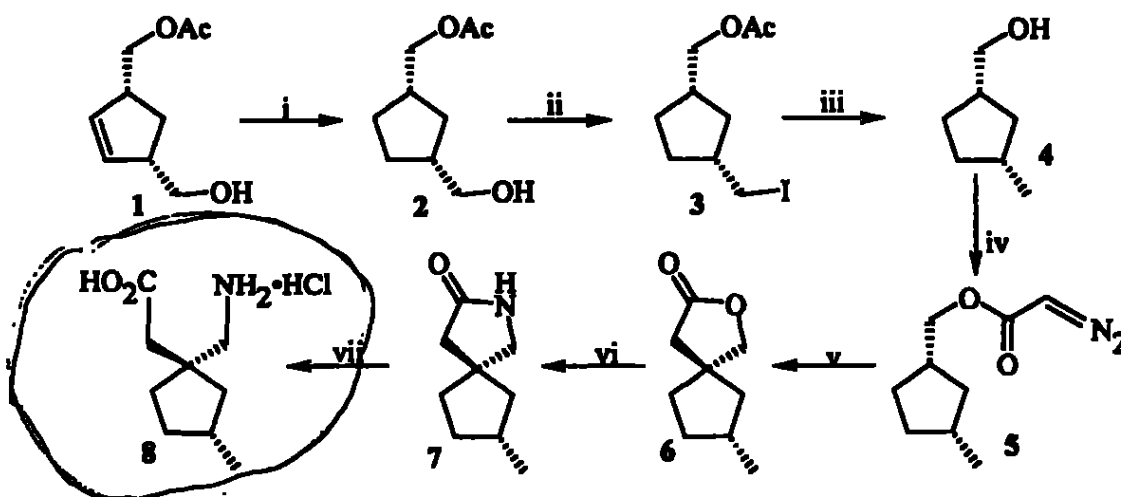
^1H NMR (400 MHz, CD_3OD): δ 2.98 (2H, s), 2.4 (2H, s), 1.5 (2H, m),

1.4-1.2 (4H, m), 0.84 (3H, s), 0.84 (3H, s).

MS (m/z): 186 (MH^+ , 100%), 168 ($\text{M}-\text{NH}_3$, 20%).

EXAMPLE 9

Synthesis of (cis)-(3R)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride



Reagents and conditions: (i) H_2 , Pd/C, MeOH; (ii) I_2 , Ph_3P , imidazole, CH_3CN ;

(iii) LAH, THF; (iv) $\text{TsNHN}=\text{CHCOCl}$, PhNMe_2 , Et_3N ; (v) $\text{Rh}_2(\text{cap})_4$,

CH_2Cl_2 , reflux; (vi) a) BBr_3 , EtOH; b) NH_3 ; (vii) 6N HCl, reflux.

The monoester **1** was prepared according to the procedure described in *Tetrahedron: Asymmetry* 3, 1992:431.

In the first step, the ester **1** is hydrogenated using catalysts 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

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acetate, acetic acid, 1,4-dioxane, chloroform or diethyl ether at a suitable temperature in the range from 20°C to 80°C.

In the second step, the alcohol 2 is treated with triphenylphosphine, imidazole, and iodine in a solvent such as ether, tetrahydrofuran, or acetonitrile at 0°C to room temperature to give the iodide 3.

In the third step, the iodide 3 is treated with a suitable reducing agent such as lithium aluminium hydride or lithium borohydride in a solvent such as ether or tetrahydrofuran at temperature between 0°C and or reflux to give the alcohol 4.

In step four, the alcohol 4 is treated with glyoxylic acid chloride (*p*-toluenesulfonyl)hydrazone and *N,N*-dimethylaniline followed by triethylamine in a solvent such as methylene chloride, chloroform, benzene, or toluene to give the diazoacetate 5.

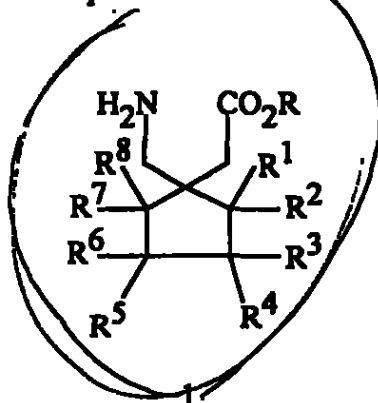
In the fifth step, the diazoacetate 5 is added to a refluxing solution or suspension of a suitable rhodium(II) catalyst such as Rh₂(cap)₄, Rh₂(5S-MEOX)₄, Rh₂(5S-MEPY)₄, Rh₂(5R-MEPY)₄, or Rh₂(OAc)₄ in a solvent such as methylene chloride, benzene, toluene, or 1,2-dichloroethane as described by Doyle and Dyatkin in *J. Org. Chem.*, 1995;60:3035 to give the spirolactone 6.

In step six, the spirolactone 6 is treated with hydrogen bromide or boron tribromide in methanol or ethanol to give a bromoester intermediate which is then reacted with ammonia to give the spirolactam 7.

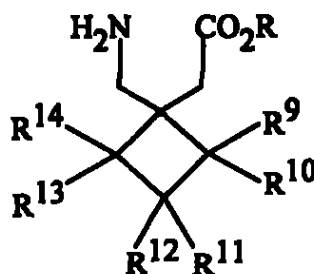
In step seven, the spirolactam 7 is treated hydrochloric acid solution (6N to 12N) at reflux to which may be added a water miscible co-solvent such as 1,4-dioxane or tetrahydrofuran to give the amino acid 8.

CLAIMS

1. A compound of formula



or



1A

or a pharmaceutically acceptable salt thereof wherein:

5

R is hydrogen or a lower alkyl;

R¹ to R¹⁴ 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,
 10 -OR¹⁵ wherein R¹⁵ is a straight or branched alkyl of from 1 to 6 carbons, phenyl, or benzyl, and R¹ to R⁸ are not simultaneously hydrogen.

10

2. A compound according to Claim 1 wherein R¹ to R¹⁴ are selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl straight or branched,
 15 phenyl, or benzyl.

15

3. A compound according to Claim 1 wherein R¹ to R¹⁴ are selected from hydrogen, methyl, ethyl, or benzyl.

4. A compound according to Claim 1 and selected from:

(±)-(trans)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid
 20 hydrochloride;

20

(1-Aminomethyl-cyclobutyl)-acetic acid hydrochloride;
(cis/trans)-(3R)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid
hydrochloride;
(cis/trans)-(1-Aminomethyl-3-benzyl-cyclobutyl)-acetic acid
5 hydrochloride;
(±)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid
hydrochloride; and
(cis)-(3R)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid
hydrochloride.

- 10 5. A compound according to Claim 1 and selected from:
(1 α ,3 α ,4 α)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic
acid;
(1 α ,3 α ,4 α)-(1-Aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid;
(1 α ,3 α ,4 α)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic
15 acid;
[1S-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-
acetic acid;
[1R-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-
acetic acid;
20 [1S-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-isopropyl-4-methyl-
cyclopentyl)-acetic acid;
[1R-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-isopropyl-4-methyl-
cyclopentyl)-acetic acid;
[1S-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-
25 cyclopentyl)-acetic acid;
[1R-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-
cyclopentyl)-acetic acid;
[1S-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-tert-butyl-4-methyl-
cyclopentyl)-acetic acid;
30 [1R-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-tert-butyl-4-methyl-
cyclopentyl)-acetic acid;

- [1S-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;
- 5 [1S-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;
- 10 (1 α ,3 α ,4 α)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;
- 15 [1S-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 α ,4 α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;
- 20 (1S-cis)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;
- (1S-cis)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;
- (1S-cis)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;
- (1S-cis)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;
- (1S-cis)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;
- (1S-cis)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;
- 25 (1R-cis)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;
- (1R-cis)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;
- (1R-cis)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;
- (1R-cis)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;
- (1R-cis)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;
- 30 (1R-cis)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;
- (S)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid;
- (S)-(1-Aminomethyl-3,3-diethyl-cyclopentyl)-acetic acid;

- (1-Aminomethyl-3,3,4,4-tetramethyl-cyclopentyl)-acetic acid;
(1-Aminomethyl-3,3,4,4-tetraethyl-cyclopentyl)-acetic acid;
(1 α ,3 β ,4 β)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid;
(1 α ,3 β ,4 β)-(1-Aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid;
5 (1 α ,3 β ,4 β)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic acid;
acid;
[1R-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-acetic acid;
[1S-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-
10 acetic acid;
[1R-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;
[1S-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;
15 [1R-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;
[1S-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;
[1R-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;
20 [1S-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;
[1R-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;
25 [1S-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;
[1R-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;
[1S-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;
30

- (1 α ,3 β ,4 β)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;
- 5 [1S-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;
- 10 (1R-trans)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;
- (1R-trans)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;
- (1R-trans)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;
- (1R-trans)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;
- 15 (1R-trans)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;
- (1R-trans)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;
- (1S-trans)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;
- (1S-trans)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;
- (1S-trans)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;
- 20 (1S-trans)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;
- (1S-trans)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;
- (1S-trans)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;
- (R)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid;
- (R)-(1-Aminomethyl-3,3-diethyl-cyclopentyl)-acetic acid;
- 25 cis-(1-Aminomethyl-3-methyl-cyclobutyl)-acetic acid;
- cis-(1-Aminomethyl-3-ethyl-cyclobutyl)-acetic acid;
- cis-(1-Aminomethyl-3-isopropyl-cyclobutyl)-acetic acid;
- cis-(1-Aminomethyl-3-tert-butyl-cyclobutyl)-acetic acid;
- cis-(1-Aminomethyl-3-phenyl-cyclobutyl)-acetic acid;
- 30 cis-(1-Aminomethyl-3-benzyl-cyclobutyl)-acetic acid;
- trans-(1-Aminomethyl-3-methyl-cyclobutyl)-acetic acid;
- trans-(1-Aminomethyl-3-ethyl-cyclobutyl)-acetic acid;

- trans-(1-Aminomethyl-3-isopropyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-tert-butyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-cyclobutyl)-acetic acid;
5 cis-(1-Aminomethyl-3-ethyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-isopropyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-methyl-3-phenyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-benzyl-3-methyl-cyclobutyl)-acetic acid;
10 trans-(1-Aminomethyl-3-ethyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-isopropyl-3-methyl-cyclobutyl)-acetic
acid;
trans-(1-Aminomethyl-3-tert-butyl-3-methyl-cyclobutyl)-acetic
acid;
15 trans-(1-Aminomethyl-3-methyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-ethyl-3-isopropyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-3-ethyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-ethyl-3-phenyl-cyclobutyl)-acetic acid;
20 cis-(1-Aminomethyl-3-benzyl-3-ethyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-ethyl-3-isopropyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-tert-butyl-3-ethyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-ethyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-ethyl-cyclobutyl)-acetic acid;
25 cis-(1-Aminomethyl-3-tert-butyl-3-isopropyl-cyclobutyl)-acetic
acid;
cis-(1-Aminomethyl-3-isopropyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-isopropyl-cyclobutyl)-acetic
acid;
30 cis-(1-Aminomethyl-3-tert-butyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-tert-butyl-cyclobutyl)-acetic
acid;

- trans-(1-Aminomethyl-3-tert-butyl-3-isopropyl-cyclobutyl)-acetic acid;
- trans-(1-Aminomethyl-3-isopropyl-3-phenyl-cyclobutyl)-acetic acid;
- 5 cis-(1-Aminomethyl-3-benzyl-3-isopropyl-cyclobutyl)-acetic acid;
- trans-(1-Aminomethyl-3-tert-butyl-3-phenyl-cyclobutyl)-acetic acid;
- cis-(1-Aminomethyl-3-benzyl-3-tert-butyl-cyclobutyl)-acetic acid;
- (1-Aminomethyl-3,3-dimethyl-cyclobutyl)-acetic acid;
- 10 (1-Aminomethyl-3,3-diethyl-cyclobutyl)-acetic acid;
- (1-Aminomethyl-3,3-diisopropyl-cyclobutyl)-acetic acid;
- (1-Aminomethyl-3,3-di-tert-butyl-cyclobutyl)-acetic acid;
- (1-Aminomethyl-3,3-diphenyl-cyclobutyl)-acetic acid;
- (1-Aminomethyl-3,3-dibenzyl-cyclobutyl)-acetic acid;
- 15 (1-Aminomethyl-2,2,4,4-tetramethyl-cyclobutyl)-acetic acid;
- (1-Aminomethyl-2,2,3,3,4,4-hexamethyl-cyclobutyl)-acetic acid;
- (R)-(1-Aminomethyl-2,2-dimethyl-cyclobutyl)-acetic acid;
- (S)-(1-Aminomethyl-2,2-dimethyl-cyclobutyl)-acetic acid;
- (1R-cis)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;
- 20 [1R-(1 α ,2 α ,3 α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;
- (1 α ,2 α ,4 α)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;
- [1R-(1 α ,2 α ,3 β)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;
- 25 (1 α ,2 α ,4 β)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;
- (1S-trans)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;
- [1S-(1 α ,2 β ,3 β)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;
- (1 α ,2 β ,4 β)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;
- 30 [1S-(1 α ,2 β ,3 α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;
- (1 α ,2 β ,4 α)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

- (1R-trans)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;
[1R-(1 α ,2 β ,3 β)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic
acid;
[1R-(1 α ,2 β ,4 β)]-(1-Aminomethyl-2-ethyl-4-methyl-cyclobutyl)-
5 acetic acid;
[1R-(1 α ,2 β ,3 α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic
acid;
(1 α ,2 β ,4 α)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;
(1S-cis)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;
10 [1S-(1 α ,2 α ,3 α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic
acid;
[1S-(1 α ,2 α ,3 α)]-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic
acid;
[1S-(1 α ,2 β ,3 α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic
15 acid;
(1 α ,2 α ,4 β)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;
(3S, 4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid;
(3R, 4R)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid;
(3S, 4S)-(1-Aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid;
20 (3R, 4R)-(1-Aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid;
(3S, 4S)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic acid;
(3R, 4R)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic
acid;
(3S, 4S)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic
25 acid;
(3R, 4R)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic
acid;
(3S, 4S)-(1-Aminomethyl-3,4-diphenyl-cyclopentyl)-acetic acid;
(3R, 4R)-(1-Aminomethyl-3,4-diphenyl-cyclopentyl)-acetic acid;
30 (3S, 4S)-(1-Aminomethyl-3,4-dibenzyl-cyclopentyl)-acetic acid;
(3R, 4R)-(1-Aminomethyl-3,4-dibenzyl-cyclopentyl)-acetic acid;

- [1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;
- 5 [1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;
- 10 [1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;
- 15 [1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;
- 20 [1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 β ,4 β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;
- 25 [1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;
- 30

[1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-
acetic acid;

[1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-
acetic acid;

5 [1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-benzyl-4-methyl-
cyclopentyl)-acetic acid;

[1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-benzyl-4-methyl-
cyclopentyl)-acetic acid;

10 [1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-
acetic acid;

[1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-
cyclopentyl)-acetic acid;

[1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-
cyclopentyl)-acetic acid;

15 [1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-
cyclopentyl)-acetic acid;

[1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-
cyclopentyl)-acetic acid;

20 [1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-
cyclopentyl)-acetic acid;

[1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-
cyclopentyl)-acetic acid;

[1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-
cyclopentyl)-acetic acid;

25 [1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-
cyclopentyl)-acetic acid;

[1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-
acetic acid;

30 [1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-
acetic acid;

- [1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;
- 5 [1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;
- 10 [1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;
- 15 [1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;
- 20 [1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;
- 25 [1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;
- 30

- [1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;
- 5 [1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-tert-butyl-4-phenyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-tert-butyl-4-phenyl-cyclopentyl)-acetic acid;
- 10 [1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-tert-butyl-4-phenyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-tert-butyl-4-phenyl-cyclopentyl)-acetic acid;
- 15 [1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-benzyl-4-tert-butyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-benzyl-4-tert-butyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-benzyl-4-tert-butyl-cyclopentyl)-acetic acid;
- 20 [1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-benzyl-4-tert-butyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-benzyl-4-phenyl-cyclopentyl)-acetic acid;
- 25 [1R-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-benzyl-4-phenyl-cyclopentyl)-acetic acid;
- [1R-(1 α ,3 α ,4 β)]-(1-Aminomethyl-3-benzyl-4-phenyl-cyclopentyl)-acetic acid;
- [1S-(1 α ,3 β ,4 α)]-(1-Aminomethyl-3-benzyl-4-phenyl-cyclopentyl)-acetic acid;
- 30 (1R-cis)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;
- (1S-cis)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;

- (1R-trans)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;
(1S-trans)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;
(R)-(1-Aminomethyl-2,2-dimethyl-cyclopentyl)-acetic acid;
(S)-(1-Aminomethyl-2,2-dimethyl-cyclopentyl)-acetic acid;
5 (1-Aminomethyl-2,2,5,5-tetramethyl-cyclopentyl)-acetic acid;
(1 α ,2 β ,5 β)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;
(2R, 5R)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;
(2S, 5S)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;
(1 α ,2 α ,5 α)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic
10 acid;
[1R-(1 α ,2 α ,3 α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-
acetic acid;
[1R-(1 α ,2 β ,3 α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-
acetic acid;
15 [1R-(1 α ,2 α ,3 β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-
acetic acid;
[1R-(1 α ,2 β ,3 β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic
acid;
[1S-(1 α ,2 α ,3 α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-
20 acetic acid;
[1S-(1 α ,2 β ,3 α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic
acid;
[1S-(1 α ,2 α ,3 β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic
acid;
25 [1S-(1 α ,2 β ,3 β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic
acid;
[1R-(1 α ,2 α ,4 α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-
acetic acid;
[1S-(1 α ,2 α ,4 α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-
30 acetic acid;
[1R-(1 α ,2 α ,4 β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-
acetic acid;

[1S-(1 α ,2 α ,4 β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1R-(1 α ,2 β ,4 α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

5 [1S-(1 α ,2 β ,4 α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1R-(1 α ,2 β ,4 β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid; and

10 [1S-(1 α ,2 β ,4 β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid.

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.
7. A method for treating epilepsy comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
8. A method for treating faintness attacks, hypokinesia, and cranial disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
9. A method for treating neurodegenerative disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
10. A method for treating depression comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

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11. A method for treating anxiety comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
- 5 12. A method for treating panic comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
13. A method for treating pain comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
- 10 14. A method for treating neuropathological disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
- 15 15. A method for treating inflammation comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
16. A method for treating gastrointestinal disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
- 20 17. A method for treating irritable bowel syndromes comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
- 25 18. A compound selected from:
(trans)-(3,4-Dimethyl-cyclopentylidene)-acetic acid ethyl ester;
(trans)-(3,4-Dimethyl-1-nitromethyl-cyclopentyl)-acetic acid;
(±)-(trans)-7,8-Dimethyl-spiro[4.4]nonane-2-one;
(1-Nitromethyl-cyclobutyl)-acetic acid ethyl ester;

(cis/trans)-(3R)-(3-Methyl-1-nitromethyl-cyclopentyl)-acetic acid
ethyl ester;

(cis/trans)-(7R)-7-Methyl-spiro[4.4]nonane-2-one;

(cis)-(3,4-Dimethyl-cyclopentylidene)-acetic acid ethyl ester;

5 (trans)-3,4-Dimethyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl
ester;

(trans)-7,8-Dimethyl-spiro[4.4]nonane-2-one;

(3-Benzyl-cyclobutylidene)-acetic acid ethyl ester; and

10 (cis/trans)-(3-Benzyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl
ester.

[54] CYCLIC AMINO ACIDS

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[22] Filed: Dec. 31, 1975

[21] Appl. No.: 648,724

[30] Foreign Application Priority Data

Dec. 21, 1974 Germany 2460891

[52] U.S. Cl. 260/468 J; 260/514 J;
260/514 K; 260/468 K; 424/30 S; 424/319

[51] Int. Cl.² C07C 101/04; C07C 101/18

[58] Field of Search 260/514 J, 468 J

[56] References Cited

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March, Advanced Organic Chemistry, pp. 816-819
(1969).

Primary Examiner—Robert Gerstl

Attorney, Agent, or Firm—Albert H. Graddis; Frank S.
Chow; George M. Yahwak

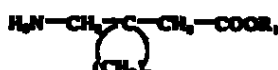
[57] ABSTRACT

The present invention is concerned with new cyclic
amino acids and with the preparation thereof.

11 Claims, No Drawings

CYCLIC AMINO ACIDS

Compounds of the general formula:



wherein R_1 is a hydrogen atom or a lower alkyl radical and n is 4, 5, or 6; and the pharmacologically compatible salts thereof, have been found to possess valuable pharmacodynamic properties.

Lower alkyl radicals according to the present invention are straight or branched chain alkyl radicals containing up to 8, and preferably up to 4 carbon atoms, especially methyl ethyl, isopropyl, and tert-butyl radicals.

The compounds of general formula (I) show hypothermic and, in some cases, narcosis-potentiating or sedating properties. They are also characterized by an extremely low toxicity. In animal experiments, there was, surprisingly, also found a remarkable protective effect against cramp induced by thiosemicarbazide. Some of the compounds according to the present invention also possess a considerable protective action against cardiac cramp. Thus these new compounds (I) can be used for the therapy of certain cerebral diseases, for example, they can be used for the treatment of certain forms of epilepsy, faintness attacks, hypokinesia and cranial traumas. They also bring about an improvement of the cerebral functions. Consequently, they are also especially useful for the treatment of geriatric patients.

The compounds of general formula (I) according to the present invention can be prepared, for example, by one of the following methods:

a. converting a compound of the general formula:



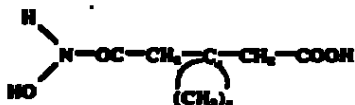
wherein R_2 is an alkyl radical containing up to 8 carbon atoms and n has the same meaning as above, via a reactive acid derivative thereof, into an azide which is then subjected to the Curtius rearrangement; or

b. subjecting a compound of the general formula:



wherein n has the same meaning as above, to the Hofmann rearrangement; or

c. subjecting a compound of the general formula:



wherein n has the same meaning as above, to the Lossen rearrangement.

When a free amino acid is obtained, it may be esterified to give a corresponding lower alkyl ester and/or the product obtained may be converted into a pharmacologically compatible salt by reaction with an acid or a base.

Since amino acids are amphoteric, pharmacologically compatible salts when R_1 is a hydrogen atom can be salts of appropriate inorganic and organic acids, for example, hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, oxalic acid, lactic acid, citric acid, malic acid, salicylic acid, malonic acid, maleic acid, succinic acid or ascorbic acid, but also, starting from the corresponding hydroxides or carbonates, salts with alkali metals or alkaline earth metals, for example, sodium, potassium, magnesium or calcium. Salts with quaternary ammonium ions can also be prepared with, for example, the tetramethyl-ammonium ion. Of course, when R_1 is a lower alkyl radical, it is only possible to form salts with acids.

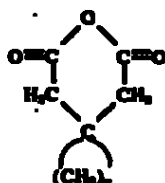
The reaction of the compounds of general formula (II) takes place according to the well-known Curtius rearrangement. The free carboxyl group is first activated by conversion into a reactive derivative, for example an acid halide or a mixed anhydride, and subsequently reacted with an appropriate azide, for example, sodium azide. The acid azide thus obtained is then subjected to thermal decomposition in an organic solvent, for example, benzene, toluene or an alcohol, such as ethanol, during which nitrogen is split off and an intramolecular rearrangement to an isocyanate or, in the presence of an alcohol, to a urethane takes place. The isocyanates and the urethanes can easily be converted into the desired primary amines by basic or acid hydrolysis.

The well-known Hofmann rearrangement of compounds of general formula (III) also takes place via isocyanates. In this case, the acid amides are reacted with alkali metal hypohalites. Upon hydrolysis of the isocyanate formed by anionotropic rearrangement, the desired amine is formed, together with carbon dioxide.

The Lossen rearrangement of hydroxamic acids of general formula (IV) also takes a similar course. In this case, formally water is split off, the corresponding isocyanate first being formed, hydrolysis of which gives the desired amine. Usually the hydroxamic acids are reacted with bases via their O-acyl derivatives as, for example, the O-acetyl-, O-benzoyl- and preferably O-sulfonyl- derivatives.

If R_1 is to be a lower alkyl radical, the carboxyl group of the amino acids obtained is esterified under known protocols. Most simply, the reaction can be carried out by dissolving a free amino acid of general formula (I) or a salt thereof in an excess of the alcohol serving as the esterification component and the solution then saturated with hydrogen chloride. The corresponding amino acid ester hydrochloride is thus directly obtained. If it is desired to work without an excess of alcohol, then it is possible to employ the esterification methods known from amino acid chemistry, with masking of the amino group.

The compounds of general formula (II) used as starting materials can be prepared by reacting an acid anhydride of the general formula:



(V)

wherein n has the same meaning as above, with one mole of an alcohol of the general formula:



wherein R_2 has the same meaning as above.

The compounds of general formula (V) are known (cf. J.C.S., 115, 686/1919; Soc., 99, 446; J.C.S., 117, 639/1920).

Some of the components of general formula (III), as well as processes for the preparation thereof, are known (cf. Austral. J.C., 13, 127/1960) and can, for example, also be prepared by reacting a compound of general formula (V) with ammonia. In this case, it is advantageous to work at the lowest possible temperature. However, it is also possible first, as described above, to prepare a hemi-ester, then to react the free carboxylic acid group with, for example, ethyl chloroformate and subsequently to carry out a reaction with ammonia.

The hydroxamic acids of general formula (IV) can be prepared analogously by reacting the anhydride of general formula (V) with hydroxylamine.

Because of their low toxicity, the compounds of general formula (I) according to the present invention can be administered enterally or parenterally within wide dosage ranges in liquid or solid form. As injection solution, water is preferably employed which contains the usual additives for injection solutions, such as stabilising agents, solubilising agents and/or buffers.

Additives of this kind include, for example, tartrate and citrate buffers, ethanol, complex-forming agents (such as ethylenediamine-tetraacetic acid and the non-toxic salts thereof), as well as high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials include, for example, starch, lactose, mannitol, methyl cellulose, talc, highly-dispersed silicic acids, high molecular weight fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats and solid high molecular weight polymers (Such as polyethylene glycol); compositions suitable for oral administration can, if desired, also contain flavouring and/or sweetening agents.

The individual dosage for the compounds according to the present invention can be 5 - 50 mg. parenterally and 20 - 200 mg. enterally.

Thus, the present invention also provides pharmaceutical compositions containing at least one compound of general formula (I) and/or at least one pharmacologically compatible salt thereof, in admixture with a solid or liquid pharmaceutical diluent or carrier.

The following Examples are given for the purpose of illustrating the present invention:

EXAMPLE 1

1-Aminomethyl-1-cyclohexane-acetic acid.

5.6 ml. Triethylamine in 16 ml. anhydrous acetone are added dropwise, with stirring and cooling to 0° C., to a solution of 7.28 g. monomethyl 1,1-cyclohexane-diacetate, whereafter a solution of 3.6 ml. ethyl chloroformate in 16 ml. anhydrous acetone is added thereto. The reaction mixture is further stirred for 30 minutes at 0° C. and then a solution of 3.4 g. sodium azide in 12 ml. water added dropwise thereto. The reaction mixture is stirred for 1 hour at 0° C., then poured into ice water and extracted three times with 50 ml. amounts of ice-cold toluene. The combined extracts

are dried over anhydrous sodium sulphate at 0° C. and subsequently introduced drop-wise into a flask preheated to 100° C. The mixture is then heated for a further hour under reflux and thereafter evaporated in a vacuum. The crude methyl 1-isocyanatomethyl-1-cyclohexane-acetate which remains behind is heated under reflux for 3 hours with 50 ml. 20% hydrochloric acid. After cooling the solution, it is extracted three times with 100 ml. amounts of chloroform to remove the 1-amino-methyl-1-cyclohexane-acetic acid lactam formed as a by-product product and the aqueous hydrochloric acid solution evaporated in a vacuum, whereby 1-aminomethyl-1-cyclohexane-acetic acid crystallises as the hydrochloride; m.p. 117°-118° C., after recrystallisation from acetone/methanol/ether. After recrystallization from methanol/ether the melting point of the product is 129°-133° C.

Analysis:

$\text{C}_8\text{H}_{15}\text{ClNO}_2$, 0.25 H_2O .

calc. : C 50.94%; H 8.79%; Cl 16.70%; N 6.60%.

found : 51.03%; 8.56%; 16.34%; 6.84%.

By treatment with a basic ion exchanger and crystallisation from ethanol/ether, there is obtained pure 1-aminomethyl-1-cyclohexane-acetic acid; m.p. 162°-166° C.

Analysis:

$\text{C}_8\text{H}_{17}\text{NO}_2$.

calc. : C 63.13%; H 10.01%; N 8.18%; O 18.69%.

found : 63.20%; 9.61%; 7.95%; 19.02%.

The monomethyl 1,1-cyclohexane-diacetate used as starting material is prepared as follows:

32.8 g. 1,1-cyclohexane-diacetic anhydride are mixed with 7 g. anhydrous methanol and heated under reflux for 1 hour. After evaporation of the reaction mixture in a vacuum, 37.5 g monomethyl 1,1-cyclohexane-diacetate remains behind in the form of a yellowish oil.

EXAMPLE 2

Ethyl 1-aminomethyl-1-cyclohexane-acetate.

10 g. of the 1-aminomethyl-1-cyclohexane-acetic acid, prepared according to Example 1, are dissolved in 50 ml. anhydrous ethanol and saturated at 0° C. with gaseous hydrogen chloride. The reaction mixture is left to stand overnight at ambient temperature, then evaporated in a vacuum and the residue recrystallised from ethanol/ether. Ethyl 1-aminomethyl-1-cyclohexane-acetate is obtained in the form of its hydrochloride; m.p. 161°-163° C.

Analysis:

$\text{C}_{11}\text{H}_{21}\text{ClNO}_2$.

calc. : C 56.04%; H 9.41%; N 5.94%.

found : 55.93%; 9.28%; 5.94%. EXAMPLE 3

EXAMPLE 3

1-Aminomethyl-1-cycloheptane-acetic acid.

15.9 g. monomethyl 1,1-cycloheptane-diacetate are dissolved in 100 ml. anhydrous acetone and, in a manner analogous to that described in Example 1, first mixed with 8.1 g. triethylamine in 30 ml. acetone, thereafter with 9.8 g. ethyl chloroformate in 30 ml. anhydrous acetone and finally with 6.5 g. sodium azide in 20 ml. water. After the reaction has taken place, the reaction mixture is extracted as in Example 1 and the solution obtained of monomethyl 1,1-cycloheptane-diacetate azide is rearranged in toluene to the isocyanate. The methyl 1-isocyanatomethyl-1-cycloheptane-acetate obtained is boiled for 3 hours under reflux in

20% hydrochloric acid. Upon evaporation in a vacuum, 1-aminomethyl-1-cycloheptane-acetic acid separates out in the form of its hydrochloride, which is recrystallized from methanol/acetone/ethyl acetate; m.p. 69°-72° C.

Analysis: $C_{12}H_{21}ClNO_2$, 0.25 H_2O .

calc.: C 53.12%; H 9.13%; Cl 15.68%; N 6.19% O 15.88%.

found: 53.29%; 9.03%; 15.73%; 6.16%; 15.77%

The monomethyl 1,1-cycloheptane-diacetate used as starting material is prepared as follows:

13.7 g. 1,1-cycloheptane-diacetic anhydride are mixed with 2.36 g. anhydrous methanol in 10 ml. benzene and boiled under reflux for 2 hours. After evaporation, there are obtained 15.9 g. monomethyl 1,1-cycloheptane-diacetate, which is further worked up directly.

EXAMPLE 4

1-Aminomethyl-1-cyclopentane-acetic acid.

Variant A:

17 g. 1,1-cyclopentane-diacetic acid monoamide are dissolved in 15 ml. water, together with 4 g. sodium hydroxide. The solution obtained is added dropwise at -10° C., while stirring, to a solution of sodium hypobromite, prepared by the dropwise addition of 19 g. bromine to a solution of 24 g. sodium hydroxide in 250 ml. water at -10° C. The reaction mixture is allowed to warm up to ambient temperature, while stirring, and thereafter heated to 60° C. for 2 hours.

After acidification with 12N hydrochloric acid, the reaction mixture is extracted three times with 150 ml. amounts of methylene chloride and the aqueous phase evaporated in a vacuum. The crude 1-aminomethyl-1-cyclopentane-acetic acid hydrochloride is obtained by digesting the residue with ethanol and evaporating the ethanolic solution. It is converted into the free amino acid by passing over anion exchanger in the OH form. After stripping off the solvent and recrystallizing the residue from ethanol/ether, there is obtained pure 1-aminomethyl-1-cyclopentane-acetic; m.p. 171°-172° C.

Analysis:

$C_6H_{11}NO_2$.

calc.: C 61.12%; H 9.62%; N 8.91%; O 20.25%.

found: 60.78%; 9.37%; 8.93%; 19.96%. The 1,1-cyclopentane-diacetic acid monoamide used as starting material is prepared as follows:

30 g. 1,1-cyclopentane-diacetic anhydride are mixed, while cooling, with 60 ml. of a 20% aqueous solution of ammonia. After the reaction has taken place, excess ammonia is removed in a vacuum and the solution is acidified with hydrochloric acid and then extracted with methylene chloride. Subsequently, the solvent is stripped off. The 1,1-cyclopentane-diacetate acid monoamide thus obtained can be further worked up directly.

Variant B:

5.88 g. 1,1-cyclopentane-diacetic anhydride are introduced, while cooling with ice water, into an ethanolic solution of hydroxylamine, prepared from 2.5 g. hydroxylamine crude benzene-sulfonate and the equivalent amount of sodium ethylate in 15 ml. anhydrous ethanol and subsequent filtration. The reaction mixture is further stirred for 1 hour at ambient temperature, the solution is evaporated in a vacuum and the crude hydroxamic acid taken up in 37 ml. 10% aqueous sodium

carbonate solution. While cooling, 4.5 ml. benzene-sulphochloride is added thereto dropwise. The reaction mixture is further stirred for 1 hour at 25° C., mixed with 14 ml. of a 10% aqueous solution of sodium hydroxide and the reaction mixture then heated for 45 minutes to 100° C. After cooling, the solution is acidified with concentrated hydrochloric acid and then evaporated to dryness in a vacuum. The residue is treated with ethanol, filtered and the ethanolic solution concentrated somewhat. 1-Aminomethyl-1-cyclopentane-acetic acid thereby crystallizes out as its benzene-sulfonate which, in the manner described in Variant A above, is converted into the free amino acid by means of an ion exchanger.

EXAMPLE 5

Sodium salt of 1-aminomethyl-1-cyclohexane-acetic acid

An aqueous solution of 1-aminomethyl-1-cyclohexane-acetic acid (Example 1) is mixed with an equimolar amount of a 1 N solution of sodium hydroxide. Thereafter the solution is evaporated in a vacuum until the beginning of crystallization. After addition of isopropanol the precipitate obtained is filtered off and dried. The sodium salt of 1-amino-methyl-1-cyclohexane-acetic acid begins to sinter at about 150° C and has a melting point of 238° C.

Analysis:

$C_8H_{15}NO_2Na \cdot \frac{1}{2} H_2O$.

calc: C 53.46%, H 8.47 %.

found: 53.48%, 8.28%.

In the same manner, by reacting a molar aqueous solution of calcium hydroxide with a solution of 1-aminomethyl-1-cyclohexane-acetic acid, there is obtained the calcium salt.

The analogous ammonium salt is manufactured by reacting an ethanolic solution of 1-aminomethyl-1-cyclohexane-acetic acid with ammonia. After evaporation in a vacuum the residue is crystallized from methanol/ether. The ammonium salt of 1-aminomethyl-1-cyclohexane-acetic acid thus obtained has a melting point of 145°-150° C.

EXAMPLE 6

Methyl 1-aminomethyl-1-cyclohexane-acetate

In an analogous manner as described in Example 2, 1-amino-methyl-1-cyclohexane-acetic acid hydrochloride is reacted with methanol in the presence of hydrogen chloride. After evaporation in a vacuum the residue is recrystallized from methanol/ether to give pure methyl 1-aminomethyl-1-cyclohexane -acetate; m.p. 150°-152° C. (hydrochloride)

Analysis:

$C_{12}H_{23}ClNO_2 \cdot \frac{1}{2} H_2O$.

calc: C 53.15%; H 9.13 %; Cl 15.69%; N 6.20%.

found: 53.26%; 8.68%; 15.39%; 6.23%.

EXAMPLE 7

n-Butyl 1-aminomethyl-1-cyclohexane-acetate

A solution of 1-aminomethyl-1-cyclohexane-acetic acid hydrochloride in n-butanol is saturated with hydrogen chloride at 0° C. The reaction mixture is then heated to 110° C for 2 hours while hydrogen chloride is passed through. The solution thus obtained is then evaporated at 60° C and the residue stirred up with hexane is filtered and dried. n-Butyl 1-aminomethyl-1-

cyclohexane acetate hydrochloride is obtained in form of a white powder having a melting point of 106°-109° C.

Analysis:

$C_{12}H_{21}Cl NO_2 \cdot \frac{1}{2} H_2O$.

calc.: C 58.20%; H 9.96%; Cl 13.21%; N 5.22%;

found: 58.21%; 9.69%; 13.45%; 5.36%.

EXAMPLE 8

Sodium salt of 1-aminomethyl-1-cycloheptane-acetic acid

1-Aminomethyl-1-cycloheptane acetic acid is obtained from the hydrochloride of Example 3 by passing an aqueous solution through a basic ion exchange resin in the OH-form. The solution of the free amino acid is evaporated in a vacuum and the 1-aminomethyl-1-cycloheptane acetic acid obtained recrystallized from ethanol; m.p. 180° C.

Analysis:

$C_{12}H_{21}NO_2$.

calc.: C 64.83%; H 10.34%; N 7.56%.

found: 64.55%; 10.32%; 7.35%.

According to Example 5 the free amino acid is reacted with a 1-molar aqueous solution of sodium hydroxide to give the sodium salt of 1-aminomethyl-1-cycloheptane-acetic acid, which after recrystallization from methanol/isopropanol sinters above 140° C under slow decomposition.

The corresponding calcium salt is crystallizing in the form of colourless platelets from water/acetone. The calcium salt of 1-aminomethyl-1-cycloheptane-acetic acid is sintering above 180° C without signs of melting.

EXAMPLE 9

Methyl 1-aminomethyl-1-cycloheptane-acetate

In an analogous manner as described in example 2 1-aminomethyl-1-cycloheptane acetic acid hydrochloride is esterified with methanol in the presence of hydrogen chloride.

After working up and crystallization from isopropanol/ether/hexane, methyl 1-aminomethyl-1-cycloheptane-acetate is obtained as hydrochloride in the form of colourless crystals having a melting point of 115°-116° C.

Analysis:

$C_{11}H_{21}ClNO_2$.

calc.: C 56.04%; H 9.41%; Cl 15.04%; N 5.94%.

found: 55.70%; 9.24%; 14.94%; 6.05%.

EXAMPLE 10

n-Butyl 1-aminomethyl-1-cycloheptane-acetate .
toluene sulfonate

In an analogous manner as described in Example 7, 1-amino-methyl-1-cycloheptane-acetic acid hydrochloride is esterified with n-butanol in the presence of hydrogen chloride to give n-butyl 1-aminomethyl-1-cycloheptane-acetate hydrochloride in the form of a syrup, which is mixed with benzene and an equivalent amount of p-toluene-sulfonic acid. The mixture is evaporated in a vacuum to dryness. After crystallization from chloroform/ether/hexane n-butyl 1-aminomethyl-1-cycloheptane-acetate.p-toluene-sulfonate is obtained. m.p. 116° - 118° C.

Analysis: $C_{21}H_{39}NO_3 S$.

calc.: C 60.99%; H 8.53%; N 3.39%.

found: 60.97%; 8.68%; 3.91%.

EXAMPLE 11

1-aminomethyl-1-cyclopentane-acetate .
benzene-sulfonate

According to Example 1, monomethyl-1,1-cyclopentane-diacetate is subjected to the Curtius rearrangement via the azide form to give 1-aminomethyl-1-cyclopentane-acetic-acid hydrochloride having a melting point of 110°-120° C after crystallization from ethanol/ether.

Analysis:

$C_8H_{15}ClNO_2$.

calc.: C 49.61%; H 8.33%; N 7.23%.

found: 49.63%; 8.12%; 7.23%.

The benzene-sulfonate of 1-aminomethyl-1-cyclopentane-acetic acid which is obtained by reaction of the free amino acid with benzene-sulfonic acid in ethanolic solution has a melting point of 171°-173° C.

Analysis:

$C_{12}H_{21}NO_3$.

calc.: C 53.31%; 6.71%; N 4.44%.

53.44%; 6.77; 4.58%.

EXAMPLE 12

n-Butyl 1-aminomethyl-1-cyclopentane-acetate

According to Example 7, 1-aminomethyl-1-cyclopentane-acetic acid hydrochloride is esterified with n-butanol to give n-butyl 1-aminomethyl-1-cyclopentane-acetate hydrochloride; m.p. 50° C.

The corresponding p-toluene sulfonate which is obtained after repeated evaporation of the benzene solution and by addition of an equimolar amount of p-toluene sulfonic acid and recrystallization from chloroform/ether/hexane has a melting point of 86°-87° C.

Analysis:

$C_{19}H_{33}NO_3 S$.

calc.: C 59.19%; H 8.11%; N 3.63%.

found: 59.35%; 7.99%; 3.88%.

We claim:

1. Compounds of the general formula:



wherein R₁ is a hydrogen atom or a lower alkyl radical and n is 4, 5 or 6; and the pharmacologically compatible salts thereof.

2. The compound according to claim 1 which is 1-Aminomethyl-1-cyclohexane-acetic acid.

3. The compound according to claim 1 which is Ethyl 1-aminomethyl-1-cyclohexane-acetate.

4. The compound according to claim 1 which is 1-Aminomethyl-1-cycloheptane-acetic acid.

5. The compound according to claim 1 which is 1-Aminomethyl-1-cyclopentane-acetic acid.

6. The compound of claim 1 which is Methyl 1-aminomethyl-1-cyclohexane-acetate.

7. The compound of claim 1 which is n-Butyl 1-aminomethyl-1-cyclohexane-acetate.

8. The compound of claim 1 which is Methyl 1-aminomethyl-1-cycloheptane-acetate.

9. The compound of claim 1 which is n-Butyl 1-aminomethyl-1-cycloheptane-acetate . toluene sulfonate.

10. The compound of claim 1 which is 1-Aminomethyl-1-cyclopentane-acetate . benzene-sulfonate.

11. The compound of claim 1 which is n-Butyl 1-aminomethyl-1-cyclopentane-acetate.

* * * * *

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[54] **TREATMENT OF CRANIAL
DYSFUNCTIONS USING NOVEL CYCLIC
AMINO ACIDS**

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[21] **Appl. No.:** 791,677

[22] **Filed:** Apr. 28, 1977

Related U.S. Application Data

[62] **Division of Ser. No. 643,724, Dec. 31, 1973, Pat. No.
4,024,173.**

[30] **Foreign Application Priority Data**

Dec. 21, 1974 Germany 2460291

[31] **Int. Cl.:** A61K 31/215; A61K 31/193

[32] **U.S. Cl.:** 424/308; 424/319

[38] **Field of Search:** 424/305, 319

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,035,507 7/1977 Bodor et al. 424/319

Primary Examiner—Frederick E. Waddell

Attorney, Agent, or Firm—Albert H. Graddis; Frank S.
Chow; George M. Yahwak.

[57] **ABSTRACT**

The present invention is concerned with new cyclic
amino acids and with the preparation thereof.

11 Claims, No Drawings

TREATMENT OF CRANIAL DYSFUNCTIONS USING NOVEL CYCLIC AMINO ACIDS

This is a division, of application Serial No. 645,724 filed Dec. 31, 1975 now U.S. Pat. No. 4,024,175 as of 17 May 1977.

Compounds of the general formula:



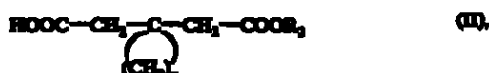
wherein R_1 is a hydrogen atom or a lower alkyl radical and n is 4, 5, or 6; and the pharmacologically compatible salts thereof, have been found to possess valuable pharmacodynamic properties.

Lower alkyl radicals according to the present invention are straight or branched chain alkyl radicals containing up to 8, and preferably up to 4 carbon atoms, especially methyl, ethyl, isopropyl and tert.-butyl radicals.

The compounds of general formula (I) show hypothermal and, in some cases, narcosis-potentiating or sedating properties. They are also characterized by an extremely low toxicity. In animal experiments, there was, surprisingly, also found a remarkable protective effect against cramp induced by thiosemicarbazide. Some of the compounds according to the present invention also possess a considerable protective action against caridazole cramp. Thus these new compounds (I) can be used for the therapy of certain cerebral diseases, for example, they can be used for the treatment of certain forms of epilepsy, faintness attacks, hypokinesia and cranial traumas. They also bring about an improvement of the cerebral functions. Consequently, they are also especially useful for the treatment of geriatric patients.

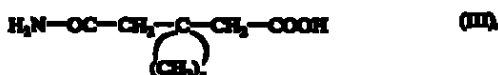
The compounds of general formula (I) according to the present invention can be prepared, for example, by one of the following methods:

(a) converting a compound of the general formula:



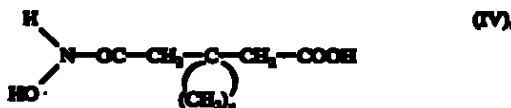
wherein R_2 is an alkyl radical containing up to 8 carbon atoms and n has the same meaning as above, via a reactive acid derivative thereof, into an amide which is then subjected to the Curtius rearrangement; or

(b) subjecting a compound of the general formula:



wherein n has the same meaning as above, to the Hofmann rearrangement; or

(c) subjecting a compound of the general formula:



wherein n has the same meanings as above, to the Lossen rearrangement.

When a free amino acid is obtained, it may be esterified to give a corresponding lower alkyl ester and/or the product obtained may be converted into a pharmacologically compatible salt by reaction with an acid or a base.

Since amino acids are amphoteric, pharmacologically compatible salts when R_1 is a hydrogen atom can be salts of appropriate inorganic and organic acids, for example, hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, oxalic acid, lactic acid, citric acid, malic acid, salicylic acid, malonic acid, maleic acid, succinic acid or ascorbic acid, but also, starting from the corresponding hydroxides or carbonates, salts with alkali metals or alkaline earth metals, for example, sodium, potassium, magnesium or calcium. Salts with quaternary ammonium ions can also be prepared with, for example, the tetramethyl-ammonium ion. Of course, when R_1 is a lower alkyl radical, it is only possible to form salts with acids.

The reaction of the compounds of general formula (II) takes place according to the well-known Curtius rearrangement. The free carboxyl group is first activated by conversion into a reactive derivative, for example an acid halide or a mixed anhydride, and subsequently reacted with an appropriate amine, for example, sodium azide. The acid azide thus obtained is then subjected to thermal decomposition in an organic solvent, for example, benzene, toluene or an alcohol, such as ethanol, during which nitrogen is split off and an intramolecular rearrangement to an isocyanate or, in the presence of an alcohol, to a urethane takes place. The isocyanates and the urethanes can easily be converted into the desired primary amines by basic or acid hydrolysis.

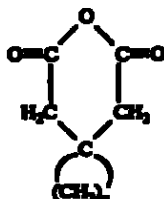
The well-known Hofmann rearrangement of compounds of general formula (III) also takes place via isocyanates. In this case, the acid amides are reacted with alkali metal hypohalites. Upon hydrolysis of the isocyanate formed by anionotropic rearrangement, the desired amine is formed, together with carbon dioxide.

The Lossen rearrangement of hydroxamic acids of general formula (IV) also takes a similar course. In this case, formally water is split off, the corresponding isocyanate first being formed, hydrolysis of which gives the desired amine. Usually the hydroxamic acids are reacted with bases via their O-acyl derivatives as, for example, the O-acetyl-, O-benzoyl- and preferably O-sulfonyl- derivatives.

If R_1 is to be a lower alkyl radical, the carboxyl group of the amino acids obtained is esterified under known protocols. Most simply, the reaction can be carried out by dissolving a free amino acid of general formula (I) or a salt thereof in an excess of the alcohol serving as the esterification component and the solution then saturated with hydrogen chloride. The corresponding amino acid ester hydrochloride is thus directly obtained. If it is desired to work without an excess of alcohol, then it is possible to employ the esterification methods known from amino acid chemistry, with masking of the amino group.

The compounds of general formula (II) used as starting materials can be prepared by reacting an acid anhydride of the general formula:

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wherein n has the same meaning as above, with one mole of an alcohol of the general formula:



wherein R_1 has the same meaning as above.

The compounds of general formula (V) are known (cf. J.C.S., 115, 686/1919; Soc., 99, 446; J.C.S., 117, 639/1920).

Some of the compounds of general formula (III), as well as processes for the preparation thereof, are known (cf. Austral. J.C., 13, 127/1960) and can, for example, also be prepared by reacting a compound of general formula (V) with ammonia. In this case, it is advantageous to work at the lowest possible temperature. However, it is also possible first, as described above, to prepare a hemi-ester, then to react the free carboxylic acid group with, for example, ethyl chloroformate and subsequently to carry out a reaction with ammonia.

The hydroxamic acids of general formula (IV) can be prepared analogously by reacting the anhydride of general formula (V) with hydroxylamine.

Because of their low toxicity, the compounds of general formula (I) according to the present invention can be administered enterally or parenterally within wide dosage ranges in liquid or solid form. As injection solution, water is preferably employed which contains the usual additives for injection solutions, such as stabilizing agents, solubilizing agents and/or buffers.

Additives of this kind include, for example, tartrate and citrate buffers, ethanol, complex-forming agents (such as ethylenediamine-tetraacetic acid and the non-toxic salts thereof), as well as high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials include, for example, starch, lactose, mannitol, methyl cellulose, talc, highly-dispersed silicic acids, high molecular weight fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats and solid high molecular weight polymers (such as polyethylene glycol); compositions suitable for oral administration can, if desired, also contain flavouring and/or sweetening agents.

The individual dosage for the compounds according to the present invention can be 5 - 50 mg. parenterally and 20 - 200 mg. enterally.

Thus, the present invention also provides pharmaceutical compositions containing at least one compound of general formula (I) and/or at least one pharmacologically compatible salt thereof, in admixture with a solid or liquid pharmaceutical diluent or carrier.

The following Examples are given for the purpose of illustrating the present invention:

EXAMPLE 1

1-Aminomethyl-1-cyclohexane-acetic acid

5.6 ml. Triethylamine in 16 ml. anhydrous acetone are added dropwise, with stirring and cooling to 0° C., to a

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solution of 7.28 g. monomethyl 1,1-cyclohexanediacetate, whereafter a solution of 3.6 ml. ethyl chloroformate in 16 ml. anhydrous acetone is added thereto. The reaction mixture is further stirred for 30 minutes at 0° C. and then a solution of 3.4 g. sodium azide in 12 ml. water added dropwise thereto. The reaction mixture is stirred for 1 hour at 0° C., then poured into ice water and extracted three times with 50 ml. amounts of ice-cold toluene. The combined extracts are dried over anhydrous sodium sulphate at 0° C. and subsequently introduced dropwise into a flask pre-heated to 100° C. The mixture is then heated for a further hour under reflux and thereafter evaporated in a vacuum. The crude methyl 1-isocyanatomethyl-1-cyclohexane-acetate which remains behind is heated under reflux for 3 hours with 50 ml. 20% hydrochloric acid. After cooling the solution, it is extracted three times with 100 ml. amounts of chloroform to remove the 1-aminomethyl-1-cyclohexane-acetic acid lactam formed as a byproduct and the aqueous hydrochloric acid solution evaporated in a vacuum, whereby 1-aminomethyl-1-cyclohexane-acetic acid crystallises as the hydrochloride; m.p. 117°-118° C., after recrystallisation from acetone/methanol/ether. After recrystallisation from methanol/ether the melting point of the product is 129°-133° C.

Analysis: $\text{C}_9\text{H}_{17}\text{ClNO}_2$, 0.25 H_2O ; calc.: C 50.94%; H 8.79%; Cl 16.70%; N 6.60%; found: 51.03%; 8.56%; 16.34%; 6.84%.

By treatment with a basic ion exchanger and crystallisation from ethanol/ether, there is obtained pure 1-aminomethyl-1-cyclohexane-acetic acid; m.p. 162° - 166° C.

Analysis: $\text{C}_9\text{H}_{17}\text{NO}_2$; calc.: C 63.13%; H 10.01%; N 8.18%; O 18.69%; found: 63.20%; 9.61%; 7.95%; 19.02%.

The monomethyl 1,1-cyclohexane-diacetate used as starting material is prepared as follows:

32.8 g. 1,1-cyclohexane-diactetic anhydride are mixed with 7 g. anhydrous methanol and heated under reflux for 1 hour. After evaporation of the reaction mixture in a vacuum, 37.5 g. monomethyl 1,1-cyclohexane-diactate remains behind in the form of a yellowish oil.

EXAMPLE 2

Ethyl 1-aminomethyl-1-cyclohexane-acetate

10 g. of the 1-aminomethyl-1-cyclohexane-acetic acid, prepared according to Example 1, are dissolved in 50 ml. anhydrous ethanol and saturated at 0° C. with gaseous hydrogen chloride. The reaction mixture is left to stand overnight at ambient temperature, then evaporated in a vacuum and the residue recrystallised from ethanol/ether. Ethyl 1-aminomethyl-1-cyclohexane-acetate is obtained in the form of its hydrochloride; m.p. 161° - 163° C.

Analysis: $\text{C}_{11}\text{H}_{22}\text{ClNO}_2$; calc.: C 56.04%; H 9.41%; N 5.94%; found: 55.93%; 9.28%; 5.94%.

EXAMPLE 3

1-Aminomethyl-1-cycloheptane-acetic acid

15.9 g. monomethyl 1,1-cycloheptane-diactate are dissolved in 100 ml. anhydrous acetone and, in a manner analogous to that described in Example 1, first mixed with 8.1 g. triethylamine in 30 ml. acetone, thereafter with 9.8 g. ethyl chloroformate in 30 ml. anhydrous acetone and finally with 6.5 g. sodium azide in 20 ml. water. After the reaction has taken place, the reaction

mixture is extracted as in Example 1 and the solution obtained of monomethyl 1,1-cycloheptane-diacetate azide is rearranged in toluene to the isocyanate. The methyl 1-isocyanatomethyl-1-cycloheptane-acetate obtained is boiled for 3 hours under reflux in 20% hydrochloric acid. Upon evaporation in a vacuum, 1-aminomethyl-1-cycloheptane-acetic acid separates out in the form of its hydrochloride, which is recrystallized from methanol/acetone/ethyl acetate; m.p. 69° - 72° C.

Analysis: $C_{10}H_{17}ClNO_2 \cdot 0.25 H_2O$; calc.: C 53.12%; H 9.13%; Cl 15.68%; N 6.19%; O 15.88%; found: 53.29%; 9.03%; 15.73%; 6.16%; 15.77%.

The monomethyl 1,1-cycloheptane-diacetate used as starting material is prepared as follows:

13.7 g. 1,1-cycloheptane-diacetic anhydride are mixed with 2.36 g. anhydrous methanol in 10 ml. benzene and boiled under reflux for 2 hours. After evaporation, there are obtained 15.9 g. monomethyl 1,1-cycloheptane-diacetate, which is further worked up directly.

EXAMPLE 4

1-Aminomethyl-1-cyclopentane-acetic acid

Variant A:

17 g. 1,1-cyclopentane-diacetic acid mononmide are dissolved in 15 ml. water, together with 4 g. sodium hydroxide. The solution obtained is added dropwise at -10° C., while stirring, to a solution of sodium hypobromite, prepared by the dropwise addition of 19 g. bromine to a solution of 24 g. sodium hydroxide in 250 ml. water at -10° C. The reaction mixture is allowed to warm up to ambient temperature, while stirring, and thereafter heated to 60° C. for 2 hours.

After acidification with 12N hydrochloric acid, the reaction mixture is extracted three times with 150 ml. amounts of methylene chloride and the aqueous phase evaporated in a vacuum. The crude 1-aminomethyl-1-cyclopentane-acetic acid hydrochloride is obtained by digesting the residue with ethanol and evaporating the ethanolic solution. It is converted into the free amino acid by passing over an ion exchanger in the OH form. After stripping off the solvent and recrystallizing the residue from ethanol/ether, there is obtained pure 1-aminomethyl-1-cyclopentane-acetic; m.p. 171° - 172° C.

Analysis: $C_6H_{11}NO_2$; calc.: C 61.12%; H 9.62%; N 8.91%; O 20.25%; found: 60.78%; 9.37%; 8.93%; 19.96%.

The 1,1-cyclopentane-diacetic acid mononmide used as starting material is prepared as follows:

30 g. 1,1-cyclopentane-diacetic anhydride are mixed, while cooling, with 60 ml. of a 20% aqueous solution of ammonia. After the reaction has taken place, excess ammonia is removed in a vacuum and the solution is acidified with hydrochloric acid and then extracted with methylene chloride. Subsequently, the solvent is stripped off. The 1,1-cyclopentane-diacetate acid mononmide thus obtained can be further worked up directly.

Variant B:

5.88 g. 1,1-cyclopentane-diacetic anhydride are introduced, while cooling with ice water, into an ethanolic solution of hydroxylamine, prepared from 2.5 g. hydroxylamine crude benzene-sulfonate and the equivalent amount of sodium ethylate in 15 ml. anhydrous ethanol and subsequent filtration. The reaction mixture is further stirred for 1 hour at ambient temperature, the solution is evaporated in a vacuum and the crude hydrazonic acid taken up in 37 ml. 10% aqueous sodium carbonate solution. While cooling, 4.5 ml. benzene-sul-

phochloride is added thereto dropwise. The reaction mixture is further stirred for 1 hour at 25° C., mixed with 14 ml. of a 10% aqueous solution of sodium hydroxide and the reaction mixture then heated for 45 minutes to 100° C. After cooling, the solution is acidified with concentrated hydrochloric acid and then evaporated to dryness in a vacuum. The residue is treated with ethanol, filtered and the ethanolic solution concentrated somewhat. 1-Aminomethyl-1-cyclopentane-acetic acid thereby crystallizes out as its benzene-sulfonate which, in the manner described in Variant A above, is converted into the free amino acid by means of an ion exchanger.

EXAMPLE 5

Sodium salt of 1-aminomethyl-1-cyclohexane-acetic acid

An aqueous solution of 1-aminomethyl-1-cyclohexane-acetic acid (Example 1) is mixed with an equimolar amount of a 1 a solution of sodium hydroxide. Thereafter the solution is evaporated in a vacuum until the beginning of crystallization. After addition of isopropanol the precipitate obtained is filtered off and dried. The sodium salt of 1-amino-methyl-1-cyclohexane-acetic acid begins to sinter at about 150° C and has a melting point of 238° C.

Analysis: $C_8H_{15}NO_2Na \cdot \frac{1}{2}H_2O$; calc.: C 53.46%, H 8.47%; found: 53.48%, 8.28%.

In the same manner, by reacting a molar aqueous solution of calcium hydroxide with a solution of 1-aminomethyl-1-cyclohexane-acetic acid, there is obtained the calcium salt.

The analogous ammonium salt is manufactured by reacting an ethanolic solution of 1-aminomethyl-1-cyclohexane-acetic acid with ammonia. After evaporation in a vacuum the residue is crystallized from methanol/ether. The ammonium salt of 1-aminomethyl-1-cyclohexane-acetic acid thus obtained has a melting point of 145° - 150° C.

EXAMPLE 6

Methyl 1-aminomethyl-1-cyclohexane-acetate

In an analogous manner as described in Example 2, 1-aminomethyl-1-cyclohexane-acetic acid hydrochloride is reacted with methanol in the presence of hydrogen chloride. After evaporation in a vacuum the residue is recrystallized from methanol/ether to give pure methyl 1-aminomethyl-1-cyclohexane-acetate; m.p. 150° - 152° C. (hydrochloride)

Analysis: $C_{10}H_{19}ClNO_2 \cdot \frac{1}{2}H_2O$; calc.: C 53.15%; H 9.13%; Cl 15.69%; N 6.20%; found: 53.26%; 8.68%; 15.39%; 6.23%.

EXAMPLE 7

n-Butyl 1-aminomethyl-1-cyclohexane-acetate

A solution of 1-aminomethyl-1-cyclohexane-acetic acid hydrochloride in n-butanol is saturated with hydrogen chloride at 0° C. The reaction mixture is then heated to 110° C for two hours while hydrogen chloride is passed through. The solution thus obtained is then evaporated at 60° C and the residue stirred up with hexane is filtered and dried. n-Butyl 1-aminomethyl-1-cyclohexane acetate hydrochloride is obtained in form of a white powder having a melting point of 106° - 109° C.

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Analysis: $C_{13}H_{23}ClNO_2 \cdot \frac{1}{2}H_2O$; calc.: C 58.20%; H 9.96%; Cl 13.21%; N 5.22%; found: 58.21%; 9.69%, 13.45%; 5.36%.

EXAMPLE 8

Sodium salt of 1-aminomethyl-1-cycloheptane-acetic acid

1-Aminomethyl-1-cycloheptane acetic acid is obtained from the hydrochloride of Example 3 by passing an aqueous solution through a basic ion exchange resin in the OH-form. The solution of the free amino acid is evaporated in a vacuum and the 1-aminomethyl-1-cycloheptane acetic acid obtained recrystallized from ethanol; m.p. 180° C.

Analysis: $C_{10}H_{19}NO_2$; calc.: C 64.83%; H 10.34%; N 7.56%; found: 64.55%; 10.32%; 7.35%.

According to Example 5 the free amino acid is reacted with a 1-molar aqueous solution of sodium hydroxide to give the sodium salt of 1-aminomethyl-1-cycloheptane-acetic acid, which after recrystallization from methanol/isopropanol slaters above 140° C under slow decomposition.

The corresponding calcium salt is crystallizing in the form of colourless platelets from water/acetone. The calcium salt of 1-aminomethyl-1-cycloheptane-acetic acid is slatering above 180° C without signs of melting.

EXAMPLE 9

Methyl 1-aminomethyl-1-cycloheptane-acetate

In an analogous manner as described in Example 2 1-aminomethyl-1-cycloheptane acetic acid hydrochloride is esterified with methanol in the presence of hydrogen chloride. After working up and crystallization from isopropanol/ether/hexane, methyl 1-aminomethyl-1-cycloheptane-acetate is obtained as hydrochloride in the form of colourless crystals having a melting point of 115° - 116° C.

Analysis: $C_{11}H_{21}ClNO_2$; calc.: C 56.04%; H 9.41%; Cl 15.04%; N 5.94%; found: 55.70%; 9.24%; 14.94%; 6.05%.

EXAMPLE 10

n-Butyl 1-aminomethyl-1-cycloheptane-acetate . toluene sulfonate

In an analogous manner as described in Example 7, 1-aminomethyl-1-cycloheptane-acetic acid hydrochloride is esterified with n-butanol in the presence of hydrogen chloride to give n-butyl 1-aminomethyl-1-cycloheptane-acetate hydrochloride in the form of a syrup, which is mixed with benzene and an equivalent amount of p-toluene-sulfonic acid. The mixture is evaporated in a vacuum to dryness. After crystallization from chloroform/ether/hexane n-butyl 1-aminomethyl-1-cycloheptane-acetate . p-toluene-sulfonate is obtained. m.p. 116° - 118° C.

Analysis: $C_{21}H_{39}NO_3S$; calc.: C 60.99%; H 8.53%; N 3.39%; found: 60.97%; 8.68%; 3.91%.

EXAMPLE 11

1-aminomethyl-1-cyclopentane-acetate . benzene-sulfonate

According to Example 1, monomethyl-1,1-cyclopentane-diacetate is subjected to the Curtius rearrangement

via the azide form to give 1-aminomethyl-1-cyclopentane-acetic acid hydrochloride having a melting point of 110° - 120° C after crystallization from ethanol/ether.

Analysis: $C_9H_{17}ClNO_2$; calc.: C 49.61%; H 8.33%; N 7.23%; found: 49.93%; 8.12%; 7.23%.

The benzene-sulfonate of 1-aminomethyl-1-cyclopentane-acetic acid which is obtained by reaction of the free amino acid with benzene-sulfonic acid in ethanolic solution has a melting point of 171° - 173° C.

Analysis: $C_{14}H_{21}NO_3S$; calc.: C 53.31%; H 6.71%; N 4.44%; found: 53.44%; 6.77%; 4.58%.

EXAMPLE 12

n-Butyl 1-aminomethyl-1-cyclopentane-acetate

According to Example 7, 1-aminomethyl-1-cyclopentane-acetic acid hydrochloride is esterified with n-butanol to give n-butyl 1-aminomethyl-1-cyclopentane-acetate hydrochloride; m.p. 50° C.

The corresponding p-toluene sulfonate which is obtained after repeated evaporation of the benzene solution and by addition of an equimolar amount of p-toluene sulfonic acid and recrystallization from chloroform/ether/hexane has a melting point of 86° - 87° C.

Analysis: $C_{19}H_{31}NO_3S$; calc.: C 59.19%; H 8.11%; N 3.63%; found: 59.35%; 7.99%; 3.88%.

We claim:

1. A method of treating certain forms of epilepsy, faintness attacks, hypokinesia and cranial traumas which comprises the enteral or parenteral administration to a mammal having such cranial dysfunction of an amount effective for such treatment of at least one compound or its pharmaceutically acceptable salt of the formula:



wherein R is hydrogen or a lower alkyl and n is 4, 5, or 6.

2. The method of claim 1 wherein the compound is 1-Aminomethyl-1-cyclohexane-acetic acid.

3. The method of claim 1 wherein the compound is Ethyl 1-aminomethyl-1-cyclohexane-acetate.

4. The method of claim 1 wherein the compound is 1-Aminomethyl-1-cycloheptane-acetic acid.

5. The method of claim 1 wherein the compound is 1-Aminomethyl-1-cyclopentane-acetic acid.

6. The method of claim 1 wherein the compound is Methyl 1-aminomethyl-1-cyclohexane-acetate.

7. The method of claim 1 wherein the compound is n-Butyl 1-aminomethyl-1-cyclohexane-acetate.

8. The method of claim 1 wherein the compound is Methyl 1-aminomethyl-1-cycloheptane-acetate.

9. The method of claim 1 wherein the compound is n-Butyl 1-aminomethyl-1-cycloheptane-acetate . toluene sulfonate.

10. The method of claim 1 wherein the compound is 1-Aminomethyl-1-cyclopentane-acetate . benzene-sulfonate.

11. The method of claim 1 wherein the compound is n-Butyl 1-aminomethyl-1-cyclopentane-acetate.

* * * * *

United States Patent [19]
Elliott et al.

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[54] **CYCLOPENTENE DERIVATIVES AS
ENDOTHELIN RECEPTOR ANTAGONISTS**

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[51] **Int. Cl.⁶** A01N 37/10; C07C 65/00

[52] **U.S. Cl.** 514/570; 562/473
[58] **Field of Search** 562/473; 514/570

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Primary Examiner—Paul J. Killos
Attorney, Agent, or Firm—Linda E. Hall; Stephen A.
Venetianer; Charles M. Kinzig

[57] **ABSTRACT**
Novel cyclopentane derivatives are described which are
endothelin receptor antagonists.

5 Claims, No Drawings

CYCLOPENTENE DERIVATIVES AS ENDOTHELIN RECEPTOR ANTAGONISTS

FIELD OF INVENTION

The present invention relates to novel cyclopentane derivatives, pharmaceutical compositions containing these compounds and their use as endothelin receptor antagonists.

BACKGROUND

Endothelin (ET) is a highly potent vasoconstrictor peptide synthesized and released by the vascular endothelium. Endothelin exists as three isoforms, ET-1, ET-2 and ET-3. [Unless otherwise stated "endothelin" shall mean any or all of the isoforms of endothelin]. Endothelin has profound effects on the cardiovascular system, and in particular, the coronary, renal and cerebral circulation. Elevated or abnormal release of endothelin is associated with smooth muscle contraction which is involved in the pathogenesis of cardiovascular, cerebrovascular, respiratory and renal pathophysiology. Elevated levels of endothelin have been reported in plasma from patients with essential hypertension, acute myocardial infarction, subarachnoid hemorrhage, atherosclerosis, and patients with uraemia undergoing dialysis.

In vivo, endothelin has pronounced effects on blood pressure and cardiac output. An intravenous bolus injection of ET (0.1 to 3 nmol/kg) in rats causes a transient, dose-related depressor response (lasting 0.5 to 2 minutes) followed by a sustained, dose-dependent rise in arterial blood pressure which can remain elevated for 2 to 3 hours following dosing. Doses above 3 nmol/kg in a rat often prove fatal.

Endothelin appears to produce a preferential effect in the renal vascular bed. It produces a marked, long-lasting decrease in renal blood flow, accompanied by a significant decrease in GFR, urine volume, urinary sodium and potassium excretion. Endothelin produces a sustained antinatriuretic effect, despite significant elevations in atrial natriuretic peptide. Endothelin also stimulates plasma renin activity. These findings suggest that ET is involved in the regulation of renal function and is involved in a variety of renal disorders including acute renal failure, cyclosporine nephrotoxicity and chronic renal failure.

Studies have shown that in vivo, the cerebral vasculature is highly sensitive to both the vasodilator and vasoconstrictor effects of endothelin. Therefore, ET may be an important mediator of cerebral vasospasm, a frequent and often fatal consequence of subarachnoid hemorrhage.

ET also exhibits direct central nervous system effects such as severe apnea and ischemic lesions which suggests that ET may contribute to the development of cerebral infarcts and neuronal death.

ET has also been implicated in myocardial ischemia (Nichols et al. *Br. J. Pharm.* 99: 597-601, 1989 and Clozel and Clozel, *Circ. Res.*, 65: 1193-1200, 1989) coronary vasospasm (Fukuda et al., *Eur. J. Pharm.* 165: 301-304, 1989 and Luscher, *Circ.* 83: 701, 1991) heart failure, proliferation of vascular smooth muscle cells, (Takagi, *Biochem. & Biophys. Res. Commun.*; 168: 537-543, 1990, Bobek et al., *Am. J. Physiol.* 258: 408-C415, 1990) and atherosclerosis, (Nakaki et al., *Biochem. & Biophys. Res. Commun.* 158: 880-881, 1989, and Lerman et al., *New Eng. J. of Med.* 325: 997-1001, 1991). Increased levels of endothelin have been shown after coronary balloon angioplasty (Kadel et al., No. 2491 *Circ.* 82: 627, 1990).

Further, endothelin has been found to be a potent constrictor of isolated mammalian airway tissue including

human bronchus (Uchida et al., *Eur. J. of Pharm.* 154: 227-228 1988, LaGente, *Clin. Exp. Allergy* 20: 343-348, 1990; and Springall et al., *Lancet*, 337: 697-701, 1991). Endothelin may play a role in the pathogenesis of interstitial pulmonary fibrosis and associated pulmonary hypertension, Glard et al., Third International Conference on Endothelin, 1993, p. 34 and ARDS (Adult Respiratory Distress Syndrome), Sanai et al., *Supra*, p. 112.

Endothelin has been associated with the induction of haemorrhagic and necrotic damage in the gastric mucosa (Whittle et al., *Br. J. Pharm.* 95: 1011-1013, 1988); Raynaud's phenomenon, Cinniniello et al., *Lancet* 337: 114-115, 1991); Crohn's Disease and ulcerative colitis, Munch et al., *Lancet*, Vol. 339, p. 381; Migraine (Edmeads, *Headache*, Feb. 1991 p 127); Sepsis (Weitzberg et al., *Circ. Shock* 33: 222-227, 1991; Pittet et al., *Ann. Surg.* 213: 262-264, 1991), Cyclosporin-induced renal failure or hypertension (*Eur. J. Pharmacol.*, 180: 191-192, 1990, *Kidney Int.*, 37: 1487-1491, 1990) and endotoxin shock and other endotoxin induced diseases (*Biochem. Biophys. Res. Commun.*, 161: 1220-1227, 1989, *Acta Physiol. Scand.* 137: 317-318, 1989).

Endothelin has also been implicated in preclampsia of pregnancy. Clark et al., *Am. J. Obstet. Gynecol.* March 1992, p. 962-968; Kamor et al., *N. Eng. J. of Med.*, Nov. 22, 1990, p. 1486-1487; Dekker et al., *Eur. J. Ob. and Gyn. and Rep. Blo.* 40 (1991) 215-220; Schiff et al., *Am. J. Obst. Gynecol.* February 1992, p. 624-628; diabetes mellitus, Takahashi et al., *Diabetologia* (1990) 33: 306-310; and acute vascular rejection following kidney transplant, Watschinger et al., *Transplantation* Vol. 52, No. 4, pp. 743-746.

Endothelin stimulates both bone resorption and anabolism and may have a role in the coupling of bone remodeling. Tatrai et al. *Endocrinology*, 131, No. 2, p. 60-607.

Endothelin has been reported to stimulate the transport of sperm in the uterine cavity, Casey et al., *J. Clin. Endo and Metabolism*, Vol. 74, No. 1, p. 223-225, therefore endothelin antagonists may be useful as male contraceptives. Endothelin modulates the ovarian/menstrual cycle, Kenegberg, *J. of Clin. Endo. and Met.*, Vol. 74, No. 1, p. 12, and may also play a role in the regulation of penile vascular tone in man, Lau et al., *Asia Pacific J. of Pharm.*, 1991, 6: 287-292 and Tejada et al., *J. Amer. Physio. Soc.* 1991, H1078-H1085.

Thus, endothelin receptor antagonists would offer a unique approach toward the pharmacotherapy of hypertension, renal failure, cerebrovascular disease, myocardial ischemia, angina, heart failure, asthma, atherosclerosis, Raynaud's phenomenon, ulcers, sepsis, migraine, glaucoma, endotoxin shock, endotoxin induced multiple organ failure or disseminated intravascular coagulation, cyclosporin-induced renal failure and as an adjunct in angioplasty and prevention of restenosis, diabetes, preclampsia of pregnancy, bone remodeling, kidney transplant, male contraceptives, infertility and priapism.

SUMMARY OF THE INVENTION

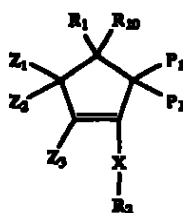
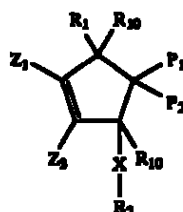
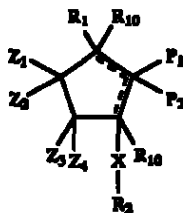
This invention comprises cyclopentane derivatives represented by Formulas (I), (II) and (III) and pharmaceutical compositions containing these compounds, and their use as endothelin receptor antagonists which are useful in the treatment of a variety of cardiovascular and renal diseases including but not limited to: hypertension, acute and chronic renal failure, cyclosporine induced nephrotoxicity, stroke, cerebrovascular vasospasm, myocardial ischemia, angina, heart failure, atherosclerosis and restenosis following balloon angioplasty.

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This invention further constitutes a method for antagonizing endothelin receptors in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I), (II) or (III).

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are represented by structural Formulas (I), (II) and (III):

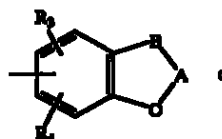
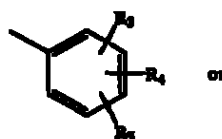


wherein:

- R_1 is $-X(CH_2)_nAr$;
- R_2 is Ar ;
- P_1 is $-X(CH_2)_mR_9$;
- P_2 is $-X(CH_2)_mR_9$, or $-XR_9Y$;
- R_3 and R_5 are independently hydrogen, R_{11} , OH, $C_{1-6}alkoxy$, $S(O)_qR_{11}$, $N(R_4)_2$, BR , F , I , Cl , CF_3 , $NHCOR_6$, $-R_{11}CO_2R_7$, $-XR_9Y$ or $-X(CH_2)_nR_9$ wherein each methylene group within $-X(CH_2)_nR_9$ may be unsubstituted or substituted by one or two $-(CH_2)_mAr$ groups;
- R_4 is hydrogen, R_{11} , OH, $C_{1-6}alkoxy$, $S(O)_qR_{11}$, $N(R_4)_2$, $-X(R_{11})$, Br , F , I , Cl or $NHCOR_6$ wherein the $C_{1-6}alkoxy$ may be unsubstituted or substituted by OH, methoxy or halogen;
- R_6 is independently hydrogen or $C_{1-4}alkyl$;
- R_7 is independently hydrogen, $C_{1-4}alkyl$ or $(CH_2)_nAr$;
- R_8 is hydrogen, R_{11} , CO_2R_7 , PO_3H_2 , $SO_2NR_7R_{11}$, $NR_7SO_2R_{11}$, $P(O)(OH)R_7$, CN , $-C(O)N(R_4)_2$, tetrazole or OR_4 ;
- R_9 is $C_{1-10}alkyl$, $C_{2-10}alkenyl$ or phenyl all of which may be unsubstituted or substituted by one or more OH, $N(R_4)_2$, $COOH$, $>C=O$, halogen, or $XC_{1-3}alkyl$;
- R_{10} is R_3 or R_4 ;
- R_{11} is $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$ all of which may be unsubstituted or substituted by one or more OH, CH_2OH , $N(R_4)_2$ or halogen;

4

X is $(CH_2)_n$, O , NR_4 or $S(O)_q$;
 Y is CH_3 or $X(CH_2)_nAr$;
 Ar is:



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(a)

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(b)

(I)

15

(II)

(III)

naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted by one or more R_3 or R_4 groups;

A is $>C=O$, or $[C(R_4)_2]_m$;

B is $-CH_2-$ or $-O-$;

Z_1 , Z_2 , Z_3 , and Z_4 are independently hydrogen, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, OH, $C_{1-6}alkoxy$, $S(O)_qC_{1-6}alkyl$, $N(R_4)_2$, Br , F , I , Cl , $NHCOR_6$, $-X(CH_2)_nR_9$, XR_9Y , phenyl, benzyl or $C_{2-6}cycloalkyl$ wherein the $C_{1-6}alkyl$, $C_{2-6}alkenyl$ or $C_{2-6}alkynyl$ may be optionally substituted by $COOH$, OH, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R_4)_2$ or halogen;

q is zero, one or two;

n is an integer from 0 to 6;

m is 1, 2 or 3;

and the dotted line in Formula (I) indicates the optional presence of a double bond; or a pharmaceutically acceptable salt thereof; provided that

when the optional double bond is present there is only one R_{10} and there is no P_1 and P_2 is not NR_4R_9Y ;

X is not NR_4 and Z_3 is not OH or $N(R_4)_2$ in Formula (III);

Z_1 and Z_2 are not OH, $N(R_4)_2$ or iodine in Formula (II);

when the optional double bond is present in Formula (I) and $X-R_2$ is attached to the double bond, X is not NR_4 ;

when the optional double bond is present in Formula (I) and R_1 is attached directly to the double bond, R_1 is not NR_4AR ;

when R_3 , R_4 , Z_1 , Z_2 , or Z_3 is $X(CH_2)_nR_9$ and n is not 0, X is oxygen or NR_4 when R_8 is OR_6 or CO_2H .

Also included in the invention are pharmaceutically acceptable salts of the active compounds.

All alkyl, alkenyl, alkynyl and alkoxy groups may be straight or branched. The term "halogen" is used to mean iodo, fluoro, chloro or bromo. Alkyl groups may be substituted by one or more halogens up to perhalogenation.

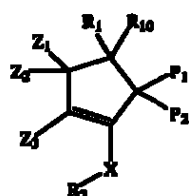
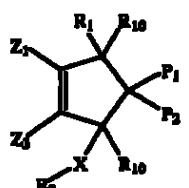
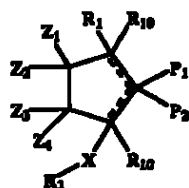
The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and diastereoisomers are contemplated to be within the scope of the present invention.

Preferred compounds are those wherein R_1 is $X(CH_2)_nAr$, Ar is (a) or (b), dihydrobenzofuranyl, benzodioxanyl, cyclohexyl, $C_{1-4}alkyl$; R_2 is (a), (b) or indolyl; R_3 and R_5 are independently hydrogen, OH, $C_{1-3}alkoxy$, halogen, $-OC_{1-4}alkyl$ phenyl, $R_{11}CO_2R_7$, $C_{1-4}alkyl$, $N(R_4)_2$, $NH(CO)CH_3$,

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$-\text{X}(\text{CH}_2)_n\text{R}_8$, $-\text{XR}_9$, pyridyl, $\text{SO}_2\text{NR}_9\text{R}_{11}$, $\text{NR}_9\text{SO}_2\text{R}_{11}$, phenyl or $\text{S}(\text{O})_2\text{C}_{1-3}\text{alkyl}$; R_4 is hydrogen, OH, $\text{C}_{1-3}\text{alkoxy}$, halogen, $\text{C}_{1-3}\text{alkyl}$, $\text{N}(\text{R}_8)_2$, $\text{NH}(\text{CO})\text{CH}_3$ or $\text{S}(\text{O})_2\text{C}_{1-3}\text{alkyl}$; Z_1 , Z_2 and Z_3 are independently XR_9Y , benzyl, hydrogen, OH, $\text{C}_{1-3}\text{alkoxy}$, $-\text{N}(\text{R}_8)_2$, $\text{S}(\text{O})_2\text{C}_{1-3}\text{alkyl}$, NHCOR_6 , $\text{X}(\text{CH}_2)_n\text{R}_8$ or halogen; P_1 and P_2 are independently hydrogen, CO_2H or tetrazole; Ar is (a), (b), phenyl, or pyridyl; X is $(\text{CH}_2)_n$ or oxygen.

The present invention provides compounds of Formula (I), (II) and (III) above.



which can be prepared by a process which comprises:

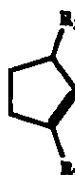
a) reacting cyclopentene with an equivalent amount of an aryl iodide (R_2I , wherein R_2 is as defined above) in a suitable solvent such as N,N -dimethylformamide containing potassium acetate and tetra- N -butylammonium chloride in the presence of a catalytic quantity of palladium acetate at $60-100^\circ\text{C}$. under an inert atmosphere such as argon to provide a compound of Formula (4).



Further treatment of compound (4) with an equivalent amount of an aryl iodide (R_1I , wherein R_1 is as defined above) in a suitable solvent such as N,N -dimethylformamide containing potassium acetate and tetra- N -butylammonium chloride in the presence of a catalytic quantity of palladium acetate at $60-100^\circ\text{C}$. under an inert atmosphere such as argon affords compounds of Formula (5).

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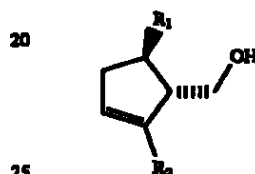
(5)



(I)

Reaction of compounds of Formula (5) with paraformaldehyde in the presence of diethylaluminum chloride in a solvent such as dichloromethane affords alcohols of structure (6).

(6)

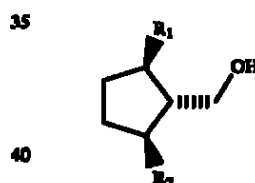


(II)

(III)

Reduction of compounds of structure (6) with hydrogen gas at atmospheric pressure in the presence of a suitable catalyst such as 5-10% palladium on charcoal in a solvent such as ethyl acetate affords cyclopentanes of Formula (7).

(7)



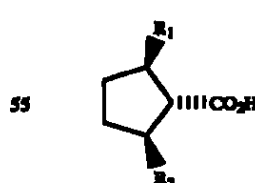
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Oxidation of alcohols of Formula (7) with Jones reagent in a suitable solvent such as acetone affords compounds of Formula (I), (II) and (III) wherein Z_1 , Z_2 , Z_3 , R_{10} and $\text{P}_2 = \text{H}$, $\text{P}_1 = \text{CO}_2\text{H}$ and $\text{X} = (\text{CH}_2)_n$, $n = 0$, and the optional double bond is not present, i.e., structures of Formula (8).

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(8)

(4)



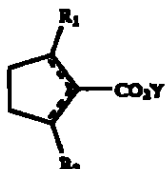
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b) Alternatively, oxidation of compounds of Formula (6) with an oxidant such as pyridinium dichromate in a suitable solvent such as N,N -dimethylformamide, followed by esterification with a suitable alcohol, YOH , wherein Y is $\text{C}_{1-3}\text{alkyl}$, in the presence of an acid such as sulfuric affords esters of Formula (9).

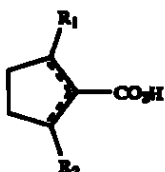
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(9)



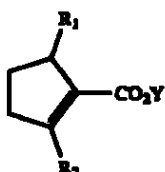
Saponification of esters of Formula (9) using aqueous sodium hydroxide solution in a suitable solvent such as methanol, followed by chromatographic separation of the double bond regioisomers affords compounds of Formula (I), (II) and (III) wherein $Z_1, Z_2, Z_3, Z_4 = H$, $P_1 = CO_2H$, the optional double bond is present, $X = (CH_2)_n$, $n = 0$, there is only one R_{10} and there is no P_1 , i.e., structures of Formula (10).

(10)



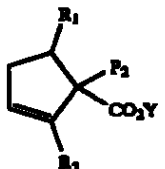
c) As a further alternative chromatographic separation of the double bond regioisomers of esters of Formula (9) affords compounds of Formula (11)

(11)



Deprotonation of esters of Formula (11) with a base such as lithium di-isopropylamide in a suitable solvent such as tetrahydrofuran under an inert atmosphere such as argon at low ($-40^\circ C.$ to $-78^\circ C.$) temperature followed by quenching with a suitable electrophile: $R_9(CH_2)_nX-Hal$ or YR_9X-Hal wherein $X = (CH_2)_n$ and Hal is a halogen, e.g., Br, I and R_9 and R_8 are as defined above, affords compounds of structure (12).

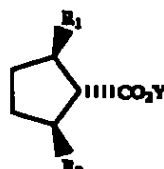
(12)



d) As a further alternative, esterification of acids of structure (8) with a suitable alcohol, YOH , wherein Y is $C_{1-3}alkyl$, in the presence of an acid such as sulfuric affords esters of Formula (13).

(13)

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Deprotonation of esters of Formula (13) with a base such as lithium di-isopropylamide in a suitable solvent such as tetrahydrofuran under an inert atmosphere such as argon at low ($-40^\circ C.$ to $-78^\circ C.$) temperature followed by quenching with phenylselenenyl chloride and subsequent oxidation with aqueous hydrogen peroxide affords esters of Formula (12) described above.

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With appropriate manipulation and protection of any chemical functionalities, synthesis of the remaining compounds of the Formulas (I), (II) and (III) is accomplished by methods analogous to those above and to those described in the Experimental section.

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In order to use a compound of the Formulas (I), (II) and (III) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

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Compounds of Formula (I), (II) and (III) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

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Compounds of Formula (I), (II) and (III) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

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Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

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Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorodifluoromethane.

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A typical suppository formulation comprises a compound of Formulas (I), (II) and (III) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example

polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I), (II) and (III) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formulas (I), (II) and (III).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formulas (I), (II) and (III) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formulas (I), (II) and (III) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formulas (I), (II) and (III) are demonstrated by the following tests:

I. Binding Assay

A) Membrane Preparation

Rat cerebellum or kidney cortex were rapidly dissected and frozen immediately in liquid nitrogen or used fresh. The tissues, 1-2 g for cerebellum or 3-5 g for kidney cortex, were homogenized in 15 mls of buffer containing 20 mM Tris HCl and 5 mM EDTA, pH 7.5 at 4° C. using a motor-driven homogenizer. The homogenates were filtered through cheesecloth and centrifuged at 20,000 x g for 10 minutes at 4° C. The supernatant was removed and centrifuged at 40,000 xg for 30 minutes at 4° C. The resulting pellet was resuspended in a small volume of buffer containing 50 mM Tris, 10 mM MgCl₂, pH 7.5; aliquotted with small vials and frozen in liquid nitrogen. The membranes were diluted to give 1 and 5 mg of protein for each tube for cerebellum and kidney cortex in the binding assay.

Freshly isolated rat mesenteric artery and collateral vascular bed were washed in ice cold saline (on ice) and lymph nodes were removed from along the major vessel. Then, the tissue was homogenized using a polytron in buffer containing 20 mM Tris and 5mM EDTA, pH 7.5 at 4° C. in 15 ml volume for ~6 gm of mesenteric artery bed. The homogenate was strained through cheesecloth and centrifuged at 2,000 xg for 10 min. at 4° C. The supernatant was removed and centrifuged at 40,000 xg for 30 min. at 4° C. The resulting pellet was resuspended as explained above for cerebellum and kidney cortex. Approximately 10 mg of membrane protein was used for each tube-in binding experiments.

B) [¹²⁵I]ET-1 Binding Protocol

[¹²⁵I]ET-1 binding to membranes from rat cerebellum (2-5 mg protein/assay tube) or kidney cortex (3-8 mg

protein/assay tube) were measured after 60 minutes incubation at 30° C. in 50 mM Tris HCl, 10 mM MgCl₂, 0.05% BSA, pH 7.5 buffer in a total volume of 100 ml. Membrane protein was added to tubes containing either buffer or indicated concentration of compounds. [¹²⁵I]ET-1 (2200 Ci/mmol) was diluted in the same buffer containing BSA to give a final concentration of 0.2-0.5 nM ET-1. Total and nonspecific binding were measured in the absence and presence of 100 nM unlabelled ET-1. After the incubation, the reactions were stopped with 3.0 ml cold buffer containing 50 mM Tris and 10 mM MgCl₂, pH 7.5. Membrane bound radioactivity was separated from free ligand by filtering through Whatman GF/C filter paper and washing the filters 5 times with 3 ml of cold buffer using a Brandel cell harvester. Filter papers were counted in a gamma counter with an efficiency of 75%. IC₅₀'s for the compounds of this invention range from 0.1 nM to 50 μM.

II. In Vitro Vascular Smooth Muscle Activity

Rat aorta are cleaned of connective tissue and adherent fat, and cut into ring segments approximately 3 to 4 mm in length. Vascular rings are suspended in organ bath chambers (10 ml) containing Krebs-bicarbonate solution of the following composition (millimolar): NaCl, 112.0; KCl, 4.7; KH₂PO₄, 1.2; MgSO₄, 1.2; CaCl₂, 2.5; NaHCO₃, 25.0; and dextrose, 11.0. Tissue bath solutions are maintained at 37° C. and aerated continuously with 95% O₂/5% CO₂. Resting tensions of aorta are maintained at 1 g and allowed to equilibrate for 2 hrs., during which time the bathing solution is changed every 15 to 20 min. Isometric tensions are recorded on Beckman R-611 dynographs with Grass FT03 force-displacement transducer. Cumulative concentration-response curves to ET-1 or other contractile agonists are constructed by the method of step-wise addition of the agonist. ET-1 concentrations are increased only after the previous concentration produces a steady-state contractile response. Only one concentration-response curve to ET-1 is generated in each tissue. ET receptor antagonists are added to paired tissues 30 min prior to the initiation of the concentration-response to contractile agonists.

ET-1 induced vascular contractions are expressed as a percentage of the response elicited by 60 mM KCl for each individual tissue which is determined at the beginning of each experiment. Data are expressed as the mean ± S.E.M. Dissociation constants (K_b) of competitive antagonists were determined by the standard method of Arunlakshana and Schild. The potency range for compounds of this invention range from 0.1 nM to 50 μM.

The following examples are illustrative and are not limiting of the compounds of this invention.

EXAMPLE 1

(1RS,2RS,3SR)-1,3 bis(4-methoxyphenyl) cyclopentane-2-carboxylic acid

a) 1,3-Bis(4-methoxyphenyl)cyclopent-1-ene

A mixture of cyclopentene (2.72 g, 40 mmol), p-iodoanisole (21.53 g, 92 mmol), palladium acetate (224.5 mg, 1 mmol), tetrabutylammonium chloride (25.57 g, 92 mmol), potassium acetate (27.10 g, 276 mmol) in DMF (140 ml) was stirred at room temperature for 1 hour, then the reaction was heated to 80° and stirred vigorously for 3 days. The reaction mixture was partitioned between hexane and H₂O, the aqueous layer separated and further extracted with hexane (3x) and the combined extracts were washed with 10% NH₄Cl, H₂O (2x), 1N HCl, 5% Na₂S₂O₃, 5% NaHCO₃, water and brine. After charcoal treatment, drying (MgSO₄), filtration, and evaporation gave a brown solid (13 g). The crude product was recrystallized from EtOH to give a first crop of (a) (6.87 g, 61%) contaminated only slightly with biphenyl.

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b) (3RS,4SR)-2,4-Bis(4-methoxyphenyl)-3-hydroxymethylcyclopent-1-ene

To a solution of 1,3-Bis(4-methoxyphenyl)-cyclopent-1-ene (280 mg, 1 mmol) and paraformaldehyde (120 mg, 4 mmol) in dry methylene chloride (2 ml) was added dropwise diethylaluminum chloride (3.6 ml of a 1M solution in hexanes, 3.6 mmol) at room temperature and the reaction stirred for 3 hrs. The temperature was lowered to -15° and the reaction quenched by addition of 6N HCl dropwise. The mixture was diluted with water and extracted with CH_2Cl_2 . The combined extracts were washed with 5% NaHCO_3 and brine, dried (MgSO_4), and filtered. Evaporation of the solvent under reduced pressure afforded crude purple oil (484 mg). Silica gel chromatography (eluant 30% EtOAc/hexanes) gave (b) as a colorless oil (188 mg, 60%).

c) (1RS,2RS,3SR)-1,3-bis(4-methoxyphenyl)-2-hydroxymethylcyclopentane

Crude (3RS,4RS)-2,4-bis(4-methoxyphenyl)-3-hydroxymethylcyclopent-1-ene was stirred under 1 atm of H_2 in EtOAc (3 ml) with 10% Pd/C catalyst (38 mg) for 4 hrs. The reaction mixture was diluted with EtOAc and filtered to remove the catalyst. The crude oil was chromatographed on silica gel to afford 300 mg of (c). (48% for 2 steps).

d) (1RS,2RS,3SR)-1,3-bis(4-methoxyphenyl)-cyclopentane-2-carboxylic acid

To a solution of (1RS,2RS,3SR)-1,3-bis(4-methoxyphenyl)-2-hydroxymethylcyclopentane (91 mg, 0.29 mmol) in acetone (3 ml) was added dropwise with vigorous stirring at room temperature Jones reagent until a persistent orange color remained. The reaction was quenched with addition of 1 to 2 drops of isopropanol and stirred until the solution turned green. The mixture was diluted with acetone and the salts removed by filtration. The solution was evaporated under reduced pressure and the residue taken up with EtOAc. After drying (MgSO_4 , anhyd.), filtration and evaporation afforded the title compound as a tan solid (76 mg, 80%). Recrystallization from EtOAc/hexanes gave white solid (22.7 mg). mp $153-155^{\circ}$

MS (DCI CH_4) m/e: 355 ($\text{M}+\text{C}_2\text{H}_5$) $^{+}$, 337.1 ($\text{M}+\text{C}_2\text{H}_5-\text{H}_2\text{O}$) $^{+}$, 327 ($\text{M}+\text{H}$) $^{+}$, 326.1 M^{+} , 309.1 ($\text{M}+\text{H}-\text{H}_2\text{O}$) $^{+}$

Anal. Calc. for $\text{C}_{20}\text{H}_{22}\text{O}_4$. 1/8 H_2O : C, 73.09; H, 6.80. Found: C, 73.03; H, 7.04.

EXAMPLE 2

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Inhalant Formulation

A compound of Formulas I, II, or III, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

Tablets/Ingredients	Per Tablet
1. Active ingredient (Cpd of Form. I, II or III)	40 mg
2. Corn Starch	20 mg
3. Alginate acid	20 mg
4. Sodium alginate	20 mg
5. Mg stearate	1.5 mg
	2.5 mg

Procedure for Tablets

Step 1 Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

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Step 2 Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3 The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4 The wet granules are then dried in an oven at 140°F . (60°C .) until dry.

Step 5 The dry granules are lubricated with ingredient No. 5.

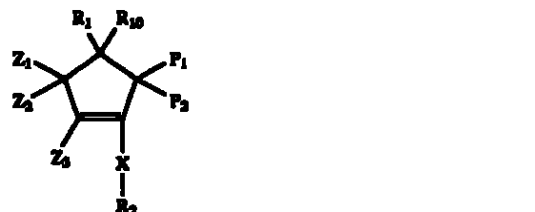
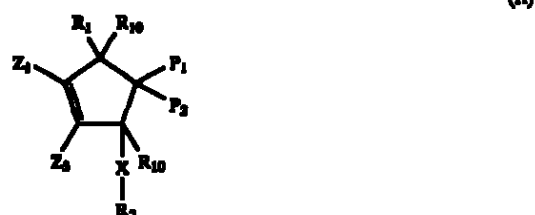
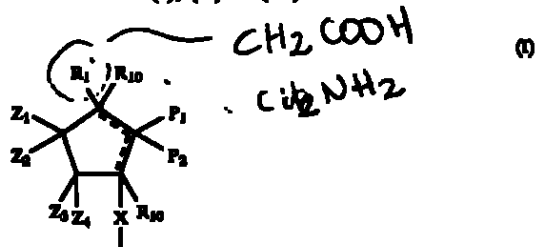
Step 6 The lubricated granules are compressed on a suitable tablet press.

Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of Formulas I, II or III in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

What is claimed is:

1. The compounds of this invention are represented by structural Formula (I), (II) or (III):



wherein:

R_1 is $-\text{X}(\text{CH}_2)_n\text{Ar}$;

R_2 is Ar;

P_1 is $-\text{X}(\text{CH}_2)_n\text{R}_6$;

P_2 is $-\text{X}(\text{CH}_2)_n\text{R}_6$, or $-\text{XR}_6\text{Y}$;

R_2 and R_6 are independently hydrogen, R_{11} , OH, C_{1-6} alkoxy, $\text{S}(\text{O})_2\text{R}_{11}$, $\text{N}(\text{R}_{11})_2$, BR, F, I, Cl, CF_3 , NHCOR_6 , $-\text{R}_{11}\text{CO}_2\text{R}_6$, $-\text{XR}_6\text{Y}$ or $-\text{X}(\text{CH}_2)_n\text{R}_6$ wherein each methylene group within $-\text{X}(\text{CH}_2)_n\text{R}_6$ may be unsubstituted or substituted by one or two $-(\text{CH}_2)_m\text{Ar}$ groups;

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R_4 is hydrogen, R_{11} , OH, C_{1-3} alkoxy, $S(O)_q R_{11}$, $N(R_4)_2$, $-X(R_{11})$, Br, F, I, Cl or $NHCO R_4$ wherein the C_{1-3} alkoxy may be unsubstituted or substituted by OH, methoxy or halogen;

R_5 is independently hydrogen or C_{1-4} alkyl;

R_7 is independently hydrogen, C_{1-4} alkyl or $(CH_2)_n Ar$;

R_8 is hydrogen, R_{11} , $CO_2 R_7$, $PO_3 H_2$, $SO_2 NR_7 R_{11}$, $NR_7 SO_2 R_{11}$, $P(O)(OH)R_7$, CN, $-C(O)N(R_4)_2$, tetrazole or OR_4 ;

R_9 is C_{1-10} alkyl, C_{2-10} alkenyl or phenyl all of which may be unsubstituted or substituted by one or more OH, $N(R_4)_2$, $COOH$, $>C=O$, halogen, or XC_{1-3} alkyl;

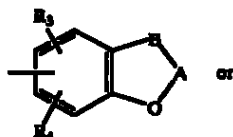
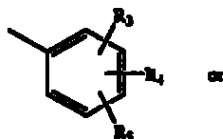
R_{10} is R_3 or R_4 ;

R_{11} is C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl all of which may be unsubstituted or substituted by one or more OH, CH_2OH , $N(R_4)_2$ or halogen;

X is $(CH_2)_n$, O, NR_4 or $S(O)_q$;

Y is CH_3 or $X(CH_2)_n Ar$;

Ar is:



naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted by one or more R_3 or R_4 groups;

A is $>C=O$, or $[C(R_4)_2]_q$;

B is $-CH_2-$ or $-O-$;

Z_1 , Z_2 , Z_3 , and Z_4 are independently hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, OH, C_{1-3} alkoxy, $S(O)_q C_{1-3}$ alkyl, $N(R_4)_2$, Br, F, I, Cl, $NHCO R_4$, $-X(CH_2)_n R_9$, $XR_9 Y$, phenyl, benzyl or C_{2-6} cycloalkyl wherein the

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C_{1-3} alkyl, C_{2-3} alkenyl or C_{2-3} alkynyl may be optionally substituted by $COOH$, OH, $CO(CH_2)_n CH_3$, $CO(CH_2)_n CH_2 N(R_4)_2$, or halogen;

q is zero, one or two;

n is an integer from 0 to 6;

m is 1, 2 or 3;

and the dotted line in Formula (I) indicates the optional presence of a double bond; or a pharmaceutically acceptable salt thereof; provided that

when the optional double bond is present there is only one R_{10} and there is no P_1 and P_2 is not $NR_9 R_9 Y$;

X is not NR_9 and Z_3 is not OH or $N(R_4)_2$ in Formula (III);

Z_1 and Z_2 are not OH, $N(R_4)_2$ or iodine in Formula (II);

when the optional double bond is present in Formula (I) and $X-R_2$ is attached to the double bond, X is not NR_9 ;

when the optional double bond is present in Formula (I) and R_1 is attached directly to the double bond, R_1 is not $NR_9 AR$;

when R_2 , R_3 , Z_1 , Z_2 , or Z_3 is $X(CH_2)_n R_9$ and n is not 0,

X is oxygen or NR_9 when R_9 is OR_9 or $CO_2 H$.

2. A compound of claim 1 wherein R_1 is $X(CH_2)_n Ar$, (Ar is (a) or (b)), dihydrobenzofuranyl, benzodioxanyl, cyclohexyl, C_{1-4} alkyl; R_2 is (a), (b) or indolyl; R_3 and R_4 are independently hydrogen, OH, C_{1-3} alkoxy, halogen, $-OC_{1-3}$ alkyl phenyl, $R_{11} CO_2 R_7$, C_{1-4} alkyl, $N(R_4)_2$, $NH(CO)CH_3$, $-(CH_2)_n R_9$, $-XR_9$, pyridyl, $SO_2 NR_7 R_{11}$, $NR_7 SO_2 R_{11}$, phenyl or $S(O)_q C_{1-3}$ alkyl; R_5 is hydrogen, OH, C_{1-3} alkoxy, halogen, C_{1-4} alkyl, $N(R_4)_2$, $NH(CO)CH_3$ or $S(O)_q C_{1-3}$ alkyl; Z_1 , Z_2 and Z_3 are independently $XR_9 Y$, benzyl, hydrogen, OH, C_{1-3} alkoxy, $-N(R_4)_2$, $S(O)_q C_{1-3}$ alkyl, $NHCO R_9$, $X(CH_2)_n R_9$ or halogen; P_1 and P_2 are independently hydrogen, $CO_2 H$ or tetrazole; Ar is (a), (b), phenyl, or pyridyl; X is $(CH_2)_n$ or oxygen.

3. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

4. A method of antagonizing endothelin receptors which comprises administering to a subject in need thereof, an effective amount to antagonize endothelin receptors of a compound of claim 1.

5. A method of treating hypertension, renal failure or cerebrovascular disease which comprises administering to a subject in need thereof, an effective amount of a compound of claim 1.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

2020

Bogotá, D.C., Abril 10 de 2006

Abogado

CARLOS MAYA RODRÍGUEZ

ASUNTO

Radicación No.

00 093 678

Trámite

002

Evento

001

Actuación

430

Oficio No.

458ⁿ

Folios

0

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

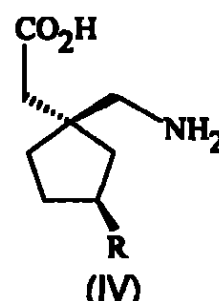
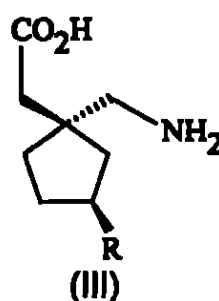
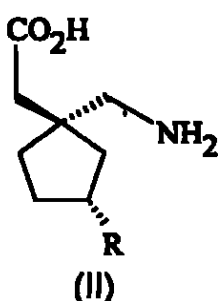
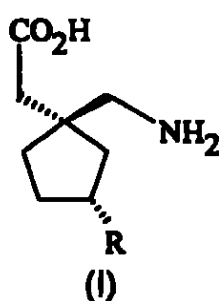
1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 7 - 182 y el capítulo reivindicatorio de los folios 183 - 286 de la solicitud en estudio.

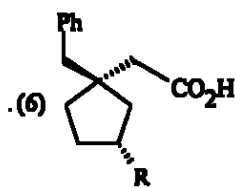
2. Objeto de la invención

El objeto de la presente solicitud de patente de invención consiste en:

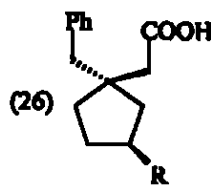
Las reivindicaciones 1 - 23 y 55 - 58 se refieren al proceso para preparar compuestos de las fórmulas:



Las reivindicaciones 24 - 49 se refieren a compuestos de fórmulas I, II, III, IV,

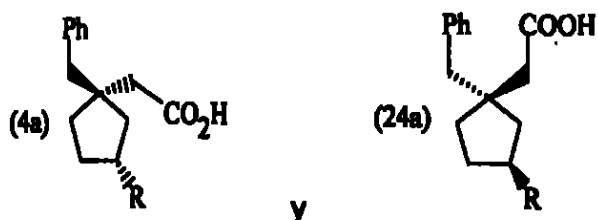


y



Las reivindicaciones 50 – 52 se refieren a compuestos.

Las reivindicaciones 53 – 54 se refieren a procesos para preparar compuestos de las fórmulas:



El problema planteado en esta solicitud es la necesidad de proporcionar compuestos para tratamiento de epilepsia, ataques de desvanecimiento, hipoquinesia, desórdenes neurodegenerativos, depresión, pánico, ansiedad, artritis, colon irritable.

Para resolver este problema técnico la solicitud en estudio proporciona aminoácidos cíclicos y proceso para su preparación.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 31/197; C 07 C 65/00.

También se reivindica prioridad de la Solicitud de Patente de los Estados Unidos US 60 169 602 de diciembre 8 de 1999, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Claridad de la Solicitud

La descripción divulga la invención de manera suficientemente clara y completa para su comprensión, tal como lo establece el Art 28 de la decisión 486 de la Comisión Andina. Menciona el sector tecnológico al que pertenece, los antecedentes de la técnica, la divulgación del problema técnico, la solución propuesta y la ventaja frente a la tecnología anterior.

Pero en cuanto a las reivindicaciones 50 - 52 se observa que no mantienen una relación clara con los compuestos y los procedimientos de reivindicaciones anteriores. Debe hacerse claridad al respecto.

4. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."*

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es diciembre 8 de 1999, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan

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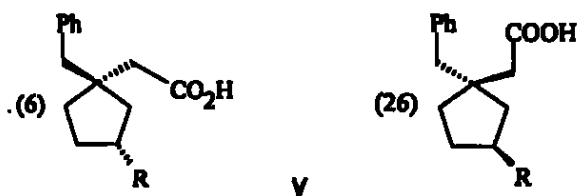
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Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*

Las reivindicaciones 24 - 49 se refieren a compuestos de fórmulas I, II, III, IV,



Las reivindicaciones 50 – 52 se refieren a compuestos.

D1 enseña (folios 870, 872, 873, 875) compuestos aminoácidos cíclicos como los de esta solicitud.

D2 enseña (folio 894) compuestos aminoácidos cíclicos como los de esta solicitud.

D3 enseña (folio 899) compuestos aminoácidos cíclicos como los de esta solicitud.

D4 enseña (folio 907) compuestos aminoácidos cíclicos como los de esta solicitud.

Se observa que:

- la estructura de los compuestos reivindicados caracterizada porque tiene el grupo aminoácido cíclico, era evidente para una persona conocedora de la materia; considerando que los compuestos de las anterioridades D1 – D4 ya incluían el grupo aminoácido cíclico, era obvio el elaborar estos compuestos de manera similar, teniendo en cuenta los compuestos de las anterioridades. El hecho de mencionan ahora los enantiómeros de un compuesto conocido, no le concede el carácter de nivel inventivo;
- las reivindicaciones de esta solicitud no mencionan una característica que conceda un efecto diferente o especial a los compuestos aminoácidos cíclicos, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia y
- el problema planteado en esta solicitud que era la necesidad de compuestos para tratamiento de epilepsia, ataques de desvanecimiento, hipoquinesia, desórdenes neurodegenerativos, depresión, pánico, ansiedad, artritis, colon irritable se resuelve proporcionando aminoácidos cíclicos, es decir de manera similar a como se resolvía en las anterioridades; las reivindicaciones son obvias y evidentes para una persona versada en la materia.
- el resultado obtenido: los aminoácidos cíclicos no es inesperado.
- no parece haberse superado un prejuicio técnico anterior, con los compuestos propuestos

Por todo lo anterior se observa que los compuestos reivindicados no tienen nivel inventivo.

6. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están

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afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO 97 21824	24 - 49 y 50 - 52	Novedad y Nivel inventivo
D2	US 4 024 175	24 - 49 y 50 - 52	Novedad y Nivel inventivo
D3	US 4 087 544	24 - 49 y 50 - 52	Novedad y Nivel inventivo
D4	US 5 929 116	24 - 49 y 50 - 52	Novedad y Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

~

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No. 10 de 2001.



ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha
27 ABR. 2006

CONCEPTO TÉCNICO No. 615	EXAMINADOR TÉCNICO Código 202007
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EXAMEN TÉCNICO DE FONDO			
N° Radicación	00/093 678	Fecha de presentación	07-12-2000
N° Prioridad	US 60 169 602	Fecha de Prioridad	08-12-1999

Palabras clave	síntesis	Esteroselectiva
	aminoácidos	Cíclicos

CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA			
A 61 K 31/197	C 07 C 65/00		

DOCUMENTOS CORRESPONDIENTES EN OTROS PAÍSES	
Patente Original	WO 01 42190
Otros	MXPA02004829 (A), CN1607201 (A), CA2392761 (A1)

BASES DE DATOS CONSULTADAS			
OEPM	Epoline	Espacenet	Oficina US

INFORMES DE EXÁMENES EN OTRAS OFICINAS		
Documento	Fecha	Relv. Afectadas
WO 01 42190	14 Jun 2001	1 - 55

ANTERIORIDADES ENCONTRADAS		
Documento de Patentes	Relv. Afectadas	Relevancia
WO 97 21824	1 - 55	Novedad y Nivel inventivo
US 4 024 175	1 - 55	Novedad y Nivel Inventivo
US 4 087 544	1 - 55	Novedad y Nivel Inventivo
US 5 929 116	1 - 55	Novedad y Nivel Inventivo

LITERATURA NO PATENTES		
Documento no Patentes	Relv. Afectadas	Relevancia

Observaciones	

Fecha del examen	Abril 10 de 2006
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No hay Rtas. + 45
 Al 10/08/06