



Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

P-C-T Sin

SOLICITUD

imagenes

PATENTE DE INVENCION

- ENTRADA EN FASE NACIONAL -

21. EXPEDIENTE No.

05-96675

54. TÍTULO DERIVADOS DE PIRROLOIMIDA ZOLE, SU
PREPARACION, COMPOSICION FARMACEUTICA QUE LOS
CONTIENE Y SU UTILIZACION COMO AGENTES
NOOTROPICOS. AG. P25/02

51. CLASIFICACION INTERNACIONAL C07D487/04 // A61K31/4188.

71. SOLICITANTE NIKEM RESEARCH S.R.L.

DOMICILIO VIA ZAMBELETTI 25, I-20021 BARANZATE DI
BOLLATE ITALIA.

74. APODERADO DRA. DORA MARIA GOMEZ DIAZ

22. BOGOTÁ, D. C.,

PETITORIO



SUPERINDUSTRIA Y COMERCIO

Radicación : 05096675 00000000

Folios: 140

Fecha (ARD): 2005-09-23 16:37:33

Trámite : 011 PCT-PATENT 379 FASE HACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

24-10-05

1

SOLICITUD DE :

☒

Patente de Invención

☐ Patente de Modelo de Utilidad

☒

Capítulo I.

☐ Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: NIKEM RESEARCH S.R.L.
Dirección: Vía Zambeletti 25, I-20021
BARANZATE DI BOLLATE - ITALIA
Nacionalidad o Domicilio: ITALIA
Lugar de Constitución: ITALIA
Teléfono:
Fax: E-mail:

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ OTRO ☐

Cual:
Número:

3

**REPRESENTANTE
O
APODERADO**

Nombre: DORA MARIA GOMEZ DIAZ
Dirección: CARRERA 7 No. 32 - 85 OFICINA 501
Teléfono: 2859058 - 2452462
Fax: 2859919
E-mail: gerencia@gomezydiaz.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ OTRO ☐

Cual:
Número: 52.145.354 Bogotá
T.P.: 95.718 C.S. de la J.

4

**INVENTOR (ES)
(72)**

Nombre: Carlo FARINA, Stefania GAGLIARDI, Carlo PARINI, Marisa MARTINELLI, Carla GHELARDINI
Dirección: Vía Zambeletti 25, I-20021 BARANZATE DI BOLLATE-ITALIA, Vía Zambeletti 25, I-20021 BARANZATE DI BOLLATE-ITALIA, Vía Zambeletti 25, I-20021 BARANZATE DI BOLLATE - ITALIA, Vía Zambeletti 25, I-20021 BARANZATE DI BOLLATE - ITALIA, Dipartimento di Farmacologia Preclínica e Clínica "M. Aiazzi Manzini" Università di Firenze, Viale G. Pieraccini 6, I-50139 FIRENZE-ITALIA. (RESPECTIVAMENTE)
Nacionalidad o Domicilio: ITALIA

5

PCT (86)

Solicitud Internacional No. PCT/EP2004/050339
Publicación Internacional No. WO 2004/085438 A3

Fecha: 22 MARZO 2004
Fecha: 7 OCTUBRE DE 2004

6

Título (54)

**DERIVADOS DE PIRROLOIMIDAZOLE, SU PREPARACIÓN,
COMPOSICIÓN FARMACEUTICA QUE LOS CONTIENE Y SU
UTILIZACIÓN COMO AGENTES NOOTROPICOS**

7

Clasificación Internacional (51): C07D 487/04

8

Prioridad

SI

☒

NO

☐

(33) País de Origen

(32) Fecha

(31) Número de Solicitud

-----ITALIA-----

-----24/03/03-----

-----MI2003A000573-----

9

Comprobante de pago No. 05-61,690 Y 05-61,694

Fecha: AGOSTO 17/2005

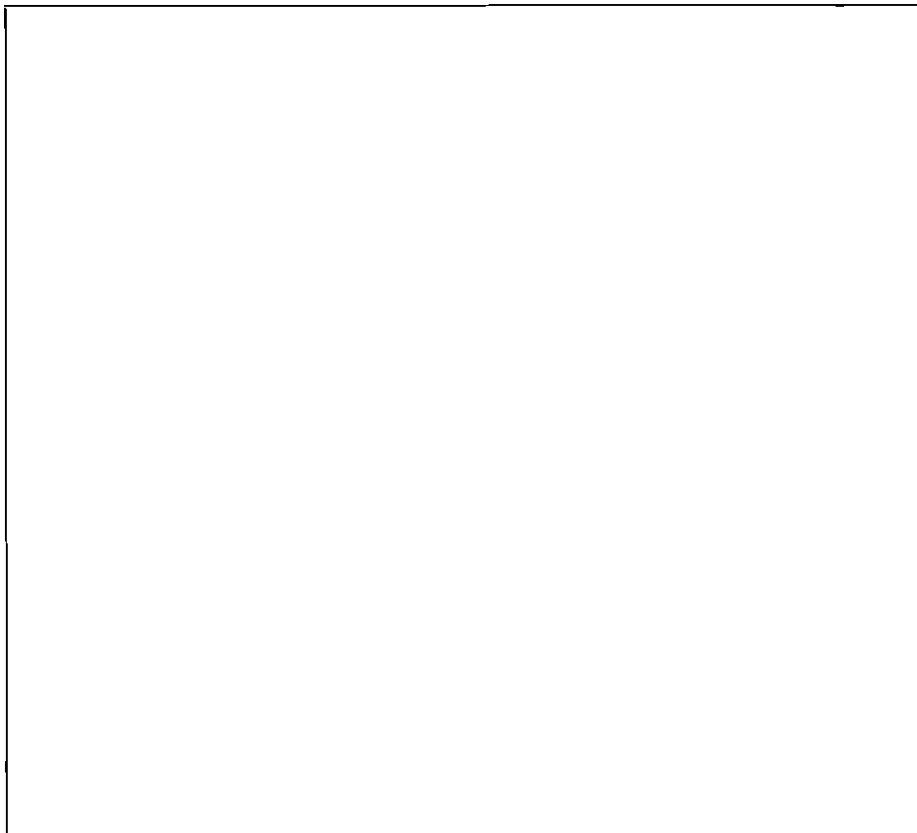
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2
10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud \$443.000.00
- ☒ Comprobante de pago por reivindicación de prioridad \$124.000.00
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes, si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud Internacional
- ☐ Otros

11

FIGURA CARACTERÍSTICA:



12

Solicito la concesión de la patente,

NOMBRE: DORA MARIA GOMEZ DIAZ

FIRMA:

C.C.: 521145354 Bogotá E.P.: 95.718 C.S.J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 80017608

Radicación : 05036675 00000000

Fecha (AMD): 2005-09-23 16:37:33

Folios: 140

Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 05 - 61,690
FECHA : AGOSTO 17 DE 2005

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
DORA M GOMEZ D	CONSIGNACION	BANCO POPULAR	050-00110-6	31558910	17/08/2005	443,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL :	\$ 443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

4

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05096675 00000000
Fecha (AND): 2005-09-23 16:37:33
Tramite : 011 PCI-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 140

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 61,694
FECHA : AGOSTO 17 DE 2005

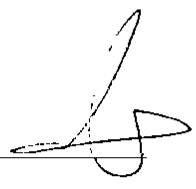
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
DORA MARIA GOMEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	31558824	17/08/2005	124,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	82 INVOCACION DE UNA PRIORIDAD EN NU	124,000.00
TOTAL :			\$ 124,000.00

SON: CIENTO VEINTICUATRO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No

From the INTERNATIONAL BUREAU

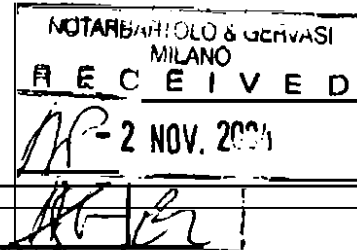
PCT

FIRST NOTICE INFORMING THE APPLICANT OF
THE COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES WHICH
DO NOT APPLY THE 30 MONTH TIME LIMIT
UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To

GERVASI, Gemma
NOTARBARTOLO & GERVASI S.p.A.
Corso di Porta Vittoria 9
I-20122 MILAN
ITALIE



IMPORTANT NOTICE

Date of mailing (day/month/year) 28 October 2004 (28.10.2004)		
Applicant's or agent's file reference 4050PTWO/er		
International application No PCT/EP2004/050339	International filing date (day/month/year) 22 March 2004 (22.03.2004)	Priority date (day/month/year) 24 March 2003 (24.03.2003)
Applicant NIKEM RESEARCH S.R.L et al		

1. **ATTENTION** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does apply**, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).
2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
07 October 2004 (07.10.2004)

CH

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1

FI, LU, SE, TZ, UG, ZM

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of **19 months** from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph**, be **20 MONTHS** from the priority date.

In practice, **time limits other than the 20-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For **regular updates on the applicable time limits** (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>

It is the applicant's **sole responsibility** to monitor all these time limits

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Agnes Wittmann-Regis
Facsimile No. +41 22 740 14 35	Facsimile No. +41 22 338 89 70

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

GERVASI, Gemma
NOTARBARTOLO & GERVASI S.p.A.
Corso di Porta Vittoria 9
I-20122 MILAN
Italy

Date of mailing (day/month/year) 20 July 2004 (20.07.2004)	
Applicant's or agent's file reference 4050PTWO/er	IMPORTANT NOTIFICATION
International application No. PCT/EP2004/050339	International filing date (day/month/year) 22 March 2004 (22.03.2004)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 24 March 2003 (24.03.2003)
Applicant NIKEM RESEARCH S.R.L. et al	

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- (If applicable) The letters "NR" appearing in the right-hand column denote a **priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- (If applicable) An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a **priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
24 Marc 2003 (24.03.2003)	MI2003A000573	IT	09 June 2004 (09.06.2004)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.89.70	Authorized officer L.H. HERNANDEZ (fax 338-8970) Telephone No. (41-22) 338 8292
--	---

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
7 October 2004 (07.10.2004)

PCT

(10) International Publication Number
WO 2004/085438 A3

(51) International Patent Classification⁷: C07D 487/04,
A61K 31/4188

(21) International Application Number:
PCT/EP2004/050339

(22) International Filing Date: 22 March 2004 (22.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2003A000573 24 March 2003 (24.03.2003) IT

(71) Applicant (for all designated States except US): NIKEM
RESEARCH S.R.L. [IT/IT]; Via Zambeletti 25, I-20021
BARANZATE DI BOLLATE (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): FARINA, Carlo
[IT/IT]; c/o NIKEM RESEARCH S.R.L., Via Zam-
beletti 25, I-20021 BARANZATE DI BOLLATE (IT).
GAGLIARDI, Stefania [IT/IT]; c/o NIKEM RESEARCH
S.R.L., Via Zambeletti 25, I-20021 BARANZATE DI
BOLLATE (IT). PARINI, Carlo [IT/IT]; c/o NIKEM
RESEARCH S.R.L., Via Zambeletti 25, I-20021 BARAN-
ZATE DI BOLLATE (IT). MARTINELLI, Marisa
[IT/IT]; c/o NIKEM RESEARCH S.R.L., Via Zam-
beletti 25, I-20021 BARANZATE DI BOLLATE (IT).
GHELARDINI, Carla [IT/IT]; c/o Dipartimento di
Farmacologia Preclinica e Clinica "M. Aiazzi Mancini"
Università di Firenze, Viale G. Pieraccini 6, I-50139
FIRENZE (IT).

(74) Agent: GERVASI, Gemma; NOTARBARTOLO & GER-
VASI S.p.A., Corso di Porta Vittoria 9, I-20122 MILAN
(IT).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Euro-
pean (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR,
GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

Published:

— with international search report
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(88) Date of publication of the international search report:
25 November 2004

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PYRROLOIMIDAZOLE DERIVATIVES, THEIR PREPARATION, PHARMACEUTICAL COMPOSITION
CONTAINING THEM, AND THEIR USE AS NOOTROPIC AGENTS

(57) Abstract: Described herein are new bicyclic arylimidazolones having nootropic action (i.e., protecting and stimulating cere-
bral functions), analgesic action and anti hyperalgesic action, also described is the process for their preparation and pharmaceutical
compositions comprising them, useful for the treatment of cognitive deficits, and of various types of pain.

WO 2004/085438 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/050339

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/4188

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

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

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

CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	WO 93/09120 A (SMITHKLINE BEECHAM FARMA) 13 May 1993 (1993-05-13) cited in the application page 31 -page 33; claims 1-12	8-20
Y	EP 0 335 483 A (ISF SPA) 4 October 1989 (1989-10-04) cited in the application page 3	1-26
Y	EP 0 174 136 A (WARNER LAMBERT CO) 12 March 1986 (1986-03-12) page 1 -page 5	1-26
	--- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

10 September 2004

Date of mailing of the international search report

11/10/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 epo nl
Fax (+31-70) 340-3016

Authorized officer

Kyriakakou, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/050339

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MARIO PINZA ET AL.: "Synthesis and Pharmacological Activity of a Series of Dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H, 6H)-diones, a Novel Class of Potent Cognition Enhancers" JOURNAL OF MEDICINAL CHEMISTRY., vol. 36, no. 26, 24 December 1993 (1993-12-24), pages 4214-4220, XP002295812 USAMERICAN CHEMICAL SOCIETY. the whole document -----	1-26

INTERNATIONAL SEARCH REPORT

 International Application No.
 PCT/EP2004/050339

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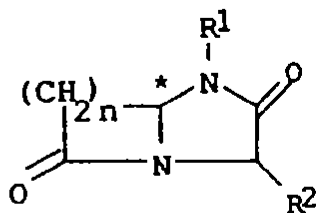
Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9309120	A	13-05-1993	AU 2894392 A	07-06-1993
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			AU 2969289 A	10-08-1989
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			CA 1324378 C	16-11-1993
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			DD 283393 A5	10-10-1990
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			EP 0335483 A2	04-10-1989
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			HU 53363 A2	28-10-1990
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			JP 1246281 A	02-10-1989
			NO 890515 A ,B,	09-08-1989
			NO 911566 A	09-08-1989
			NZ 227833 A	25-09-1991
			PL 158198 B1	31-08-1992
			PT 89657 A ,B	04-10-1989
			RO 104070 B1	20-07-1993
			RO 105963 B1	30-01-1993
			RO 105964 B1	30-01-1993
			RO 105965 B1	30-01-1993
			SU 1799383 A3	28-02-1993
			US 5053422 A	01-10-1991
			US 5130319 A	14-07-1992
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			ZA 8900894 A	30-10-1991
			ZW 1489 A1	02-08-1989
EP 0174136	A	12-03-1986	US 4582838 A	15-04-1986
			AT 41662 T	15-04-1989
			DE 3568987 D1	27-04-1989
			EP 0174136 A1	12-03-1986
			JP 61057586 A	24-03-1986



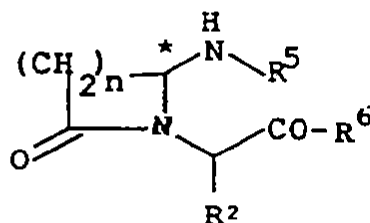
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP92/02560 (22) International Filing Date: 3 November 1992 (03.11.92) (30) Priority data: 9123641.4 7 November 1991 (07.11.91) GB (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM FARMACEUTICI S.P.A. [IT/IT]; Via Zambelletti, I-20021 Baranzate di Bollate (IT). (72) Inventors; and (75) Inventors/Applicants (for US only) : POZZI, Ottorino [IT/IT]; SmithKline Beecham Farmaceutici, Via Zambelletti, I-20021 Baranzate di Bollate (IT). PINZA, Mario [IT/IT]; Via per Cesano Boscone, 24, I-20094 Corsico (IT). FARINA, Carlo [IT/IT]; PARINI, Carlo [IT/IT]; SmithKline Beecham Farmaceutici, Via Zambelletti, I-20021 Baranzate di Bollate (IT). CORNAGGIA, Nicoletta [IT/IT]; Via Val d'Ossola, 7, I-20086 Motta Visconti (IT). PFEIFFER, Ugo, Claudio [IT/IT]; Via Raffaello Sanzio, 31, I-20149 Milan (IT).		(74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). (81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE). Published With international search report.

(54) Title: PROCESS FOR THE PREPARATION OF CONDENSED IMIDAZOLES



(I)



(II)

(57) Abstract

A process for the preparation of compounds of formula (I), wherein R¹ represents hydrogen, C₁₋₄ alkyl, CHR³CONHR⁴ or CHR³COOR⁴ in which R³ and R⁴ each independently represent hydrogen or C₁₋₄alkyl; R² represents hydrogen or C₁₋₅ alkyl; and n is an integer 2, 3 or 4; which process comprises cyclising a compound of formula (II), wherein R² and n are as defined in relation to formula (I); R⁵ represents hydrogen or a group COOR⁷ wherein R⁷ is a C₁₋₄ alkyl group or a benzyl group; and R⁶ represents a hydroxy group or a group OR⁸ wherein R⁸ represents C₁₋₄ alkyl or a benzyl group; and thereafter, as necessary, carrying out one more of the following steps: i) removing any protecting group; and ii) converting a compound of formula (I) into another compound of formula (I).

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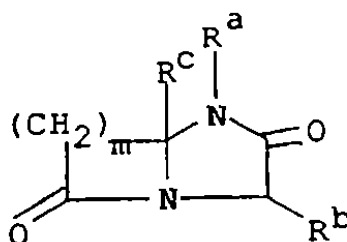
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Process for the preparation of condensed imidazoles

The invention relates to a process for preparing certain fused imidazole derivatives and in particular for preparing chiral fused imidazole derivatives.

European Patent Application, Publication No. 0,335,483 discloses certain fused imidazole derivatives of formula (A):



wherein,

R^a is hydrogen, C_{1-4} alkyl, $CH(R^d)CONH(R^e)$ or $CH(R^d)COO(R^e)$ in which R^d and R^e are each hydrogen or C_{1-4} alkyl;

R^b is hydrogen, C_{1-5} alkyl or any residue R^b of an amino acid $R^bCH(NH_2)COOH$

R^c is hydrogen, C_{1-4} alkyl, $CONH_2$ or CO_2R^f in which R^f is hydrogen or C_{1-4} alkyl; and

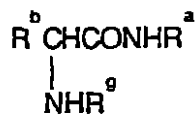
m is 2, 3 or 4.

EP 0,335,483 also discloses a process for preparing the compounds of formula (A) which involves either:

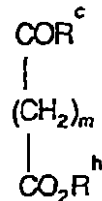
a) reacting a compound of formula (B) with a compound of formula (C):

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(B)

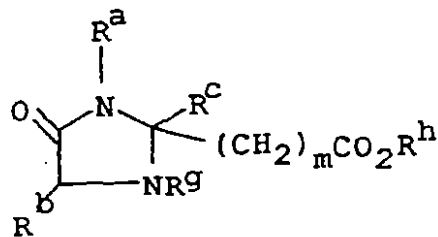


(C)

- 5 wherein R^a , R^b , R^c , and m are as defined in relation to formula (A), R^g is hydrogen and R^h is hydrogen, C_{1-4} alkyl or benzyl; or

b) cyclising a compound of formula (D):

10



(D)

- 15 where in R^a , R^b , R^c and m are as defined in relation to formula (A) and R^g and R^h are as defined in relation to formulae (B) and (C).

The compounds of formula (A) are disclosed in EP 0,335,483 as having activity as nootropic reagents.

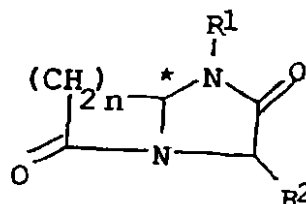
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EP 0,335,483 also discloses that the compounds of formula (A) can contain one or more chiral carbons. In particular it is to be noted that the bridgehead carbon of formula (A) is always a chiral carbon.

- 25 A process has now been discovered which facilitates the preparation of certain compounds of formula (A) and in particular facilitates the preparation of individual optical isomers of such compounds in which the chiral carbon is the bridgehead carbon.

- 30 Accordingly, the present invention provides a process for the preparation of compounds of formula (I):

35



(I)

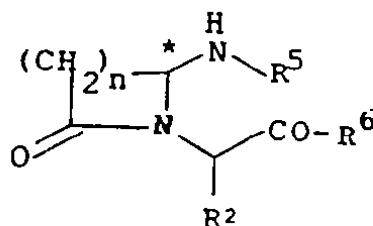
wherein

R^1 represents hydrogen, C_{1-4} alkyl, CHR^3CONHR^4 or CHR^3COOR^4 in which R^3 and R^4 each independently represent hydrogen or C_{1-4} alkyl;

5 R^2 represents hydrogen or C_{1-5} alkyl; and n is an integer 2, 3 or 4;

which process comprises cyclising a compound of formula (II):

10



(II)

15

wherein R^2 and n are as defined in relation to formula (I);

R^5 represents hydrogen or a group $COOR^7$ wherein R^7 is a C_{1-4} alkyl group or a benzyl group; and R^6 represents a hydroxy group or a group OR^8 wherein R^8 represents C_{1-6} alkyl or a benzyl group; and thereafter,

20

as necessary, carrying out one or more of the following steps:

i) removing any protecting group; and

ii) converting a compound of formula (I) into another compound of

25

formula (I).

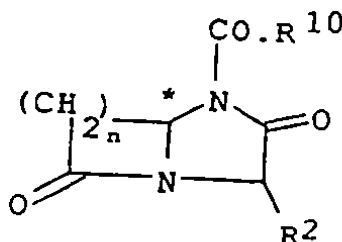
Suitably the cyclisation is effected by a cyclising reagent.

In certain circumstances, the cyclisation of the compound of formula (II)

30

may provide a compound of formula (III):

35



(III)

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wherein R^2 and n are as defined in relation to formula (I) and R^{10} is a C_{1-6} alkyl group or a group OR^7 wherein R^7 is as defined in relation to formula (II); the compound of formula (III) may then be converted into a compound of formula (I), wherein R^1 is H, by hydrogenolysis or
5 hydrolysis, the resulting compound of formula (I) may subsequently be converted into other compounds of formula (I) as desired.

Compound (III) is generally provided when the cyclising reagent is a carboxylic anhydride.

10

Accordingly, the present invention, in a further particular aspect provides a process for preparing a compound of formula (I), which process comprises hydrogenolysing or hydrolysing a compound of the above defined formula (III); and thereafter, as necessary converting the resulting
15 compound of formula (I), wherein R^1 is H, into a further compound of formula (I).

When R^6 is OH, the cyclisation of a compound of formula (II) is conveniently effected under dehydration cyclisation conditions, preferably
20 in the presence of a dehydration cyclisation reagent.

Suitable dehydration cyclisation reagents include dicyclohexylcarbodiimide or carboxylic anhydrides such as acetic anhydride.

25

When the reagent is dicyclohexylcarbodiimide, the reaction is preferably carried out in the presence of an organic base such as triethylamine, in any suitable solvent, such as acetonitrile, at any convenient temperature providing a suitable rate of formation of the required product, aptly at
30 ambient temperature.

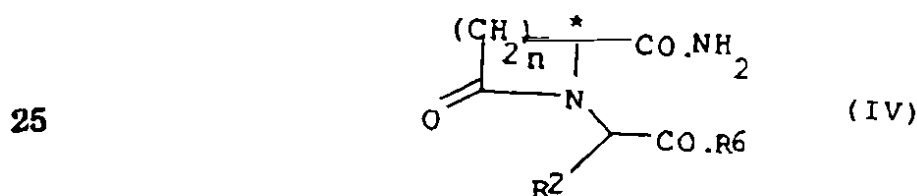
When the reagent is a carboxylic anhydride such as acetic anhydride, the reaction may be carried out in any suitable solvent, but conveniently using acetic anhydride itself as solvent, and at any convenient
35 temperature providing a suitable rate of formation of the product, suitably at the reflux temperature of the solvent and preferably in the presence of anhydrous sodium acetate.

Suitable means for hydrogenolysing any compound of formula (III) include conventional catalytic hydrogenolysis techniques. Suitable means for hydrolysing any compound include conventional hydrolysis techniques, such as mild acid hydrolysis, for example by using an acidic resin such as
 5 Amberlite IR 120.

When R_6 is a group OR_8 , the cyclisation is preferably effected by use of a strong base such as n-butyl lithium or potassium t-butoxide.

10 The cyclisation of a compound of formula (II), wherein R_6 is a group OR_8 , may be suitably carried out in an aprotic solvent, such as tetrahydrofuran or toluene: for example when potassium t-butoxide is the strong base the reaction is conveniently carried out in toluene, at ambient temperatures: when n-butyl lithium is the strong base the reaction is conveniently
 15 carried out in tetrahydrofuran at low to ambient temperature, generally at a temperature within the range of from -80°C to -30°C , for example in the range of from -70 to -65°C .

A compound of the abovedefined formula (II), may be prepared by reacting
 20 a compound of formula (IV):



wherein R^2 , R^6 and n are as defined in relation to formula (II), with a
 30 reagent capable of converting a -CO.NH_2 group into an -NH_2 group, and thereafter, if required, carrying out one or more of the following optional steps:

- 35
- i) protecting and thereafter, as necessary, de-protecting any group;
 - ii) converting a compound wherein R^5 is H into a compound wherein R^5 is COOR^7 , wherein R^7 is as defined in relation to formula (II); and

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iii) converting any group R^6 which represents OR^8 into a group R^6 which represents hydroxy.

Suitable reagents capable of converting a $-CO.NH_2$ group into an $-NH_2$ group include bis(trifluoroacetoxy)iodosobenzene or a source of hypochlorite ion, such as sodium hypochlorite.

The conditions for the reaction between the compound of formula (IV) and the reagent capable of converting a $-CO.NH_2$ group into an $-NH_2$ group will of course depend upon the particular reagent used, but generally the appropriate conventional conditions for the particular reagent chosen will be used: when the reagent is bis(trifluoro- acetoxy)iodosobenzene the reaction is carried out in any suitable solvent, such as aqueous acetonitrile, preferably in an inert atmosphere such as nitrogen, at any convenient temperature which provides a suitable rate of formation of the desired product, conveniently at a low to ambient temperature, for example in the range of from $0^\circ-5^\circ C$: when the reagent is a source of hypochlorite ions, such as sodium hypochlorite, the reaction is carried out in any suitable solvent, generally an aqueous solvent, conveniently water, at any convenient temperature providing a suitable rate of formation of the required product, such as in the range of $0^\circ C$ to $100^\circ C$, generally in the range of from $0^\circ C$ to room temperature, for example $0^\circ C$ to $5^\circ C$; preferably the sodium hypochlorite reaction is carried out in the presence of sodium hydroxide.

The conversion of a compound wherein R^5 is H into a compound wherein R^5 is $COOR^7$ may be carried out using a conventional chemical procedures, for example the conversion of a compound wherein R^5 is H into a compound wherein R^5 is $COOR^7$ is provided by treating the appropriate compound with a compound of formula (V):



wherein R^7 is as defined in relation to formula (II) and X represents a leaving group, such as a halogen atom, for example a chlorine atom. Usually, the appropriate compound is present in salted form, for example alkali metal salted form, such as a sodium salted form, prepared by treating the appropriate compound with a base, for example an alkali

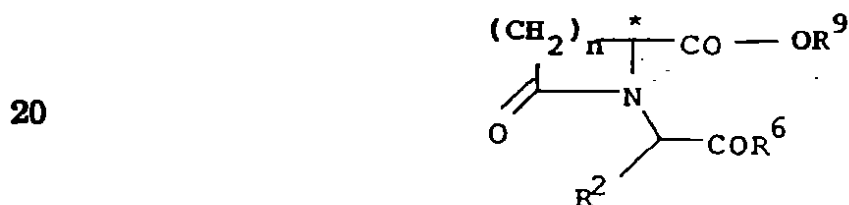
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metal hydroxide, such as sodium hydroxide.

- The reaction between the appropriate compound and the compound of formula (V) may be carried out in any suitable solvent, generally an aqueous solvent, conveniently water, at low to medium temperature, generally in the range of 0°C to + 40°C, suitable from 0°C to 5° or from 5°C to ambient temperature.

- The conversion of any group R⁶ which represents OR⁸ into a group R⁶ which represents hydroxy may be carried out using the appropriate conventional procedure, for example by using conventional hydrolysis methods, for example treatment with an alkali metal hydroxide, such as sodium hydroxide.

- A compound of formula (IV) may be prepared by aminating a compound of formula (VI):



(VI)

- wherein R², R⁶ and n are as defined in relation to formula (II) and R⁹ is a C₁₋₆ alkyl group; and thereafter, if required,

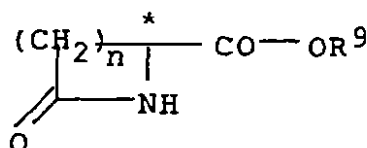
- i) protecting and thereafter, as necessary, deprotecting any group;
- ii) converting any group R⁶ which represents OR⁸ into a group R⁶ which represents hydroxy.

- The amination of compound (VI) may be effected using conventional amination conditions, for example by using concentrated aqueous ammonia at any temperature providing a convenient rate of formation of the required product, conveniently at ambient temperature.

A compound of formula (VI) may be prepared by reacting a compound of

formula (VII):

5



(VII)

- 10 wherein R^9 and n are as defined in relation to formula (VI), with a compound of formula (VIII):



- 15 wherein R^2 and R^6 are as defined in relation of formula (II) and X is a leaving group such as halide; and thereafter, if required carrying out one or more of the following optional steps:

- 20 i) protecting and thereafter, as necessary, de-protecting any group;
 ii) converting any group R^6 which represents OR^8 into a group R^6 which represents hydroxy.

- 25 Suitably the compound of formula (VII) is present in an activated form, for example a salted form such as a sodium salted form, provided by treating the compound of formula (VII) with a salting agent such as sodium hydride.

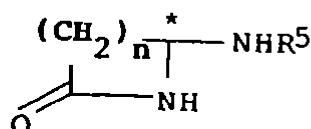
- 30 The reaction between a compound of formula (VII) and a compound of formula (VIII) may be carried out using analogous conditions to those described in *Berichte*, 44, 1333 (1911).

- 35 The compounds of formula (VII) are known compounds or they may be prepared by analogous procedures to those used to prepare known compounds, for example the compounds of formula (VII) wherein n is 2 are known, commercially available compounds.

A compound of formula (II) may also be prepared by reacting a compound

of formula (IX):

5



(IX)

10 wherein R^5 and n are as defined in relation to formula (II), with a compound of the hereinbefore defined formula (VIII); and thereafter, if required, carrying out one or more of the following optional steps:

- 15 i) protecting and thereafter, as necessary, de-protecting any group;
- ii) converting one group R^5 into another group R^5 .

The reaction between the compounds of formulae (VIII) and (IX) may be carried out using conditions analogous to those used in the reaction

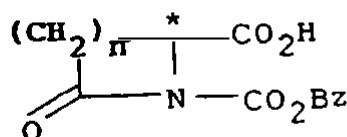
20 between compounds of formulae (VII) and (VIII).

The compounds of formula (IX) are known compounds or they may be prepared using methods analogous to those used to prepared known compounds, for example the methods disclosed in Heterocycles, 14, 1245

25 (1980).

Alternatively, a compound of formula (IX) may be prepared by reacting a compound of formula (X):

30



35

(X)

wherein n is as defined in relation to formula (I), with a reagent capable of

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converting a carboxyl group into a group -NHR^5 and thereafter, as required, carry out one or more of the following optional steps:

- i) removing any protecting group, in particular any
5 benzylcarboxylate group;
- ii) converting one group R^5 into another group R^5 .

10 A suitable reagent capable of converting a carboxyl group into a group -NHR^5 is diphenylphosphorylazide in the presence of triethylamine and, as required, an appropriate alcohol. The reaction conditions for the reaction between the compound of formula (X) and the reagent capable of converting a carboxyl group into a group -NHR^5 will in general be the appropriate conventional conditions for the particular reagent chosen; for
15 example when the reagent is a Curtius reagent such as diphenylphosphorylazide the reaction is suitably effected under the Curtius reaction conditions such as those disclosed in Synthesis, 294 (1985).

20 An alcohol is generally required when R^5 represents a group -COOR^7 : the particular alcohol required is that dictated by the value of R^7 in the required compound of formula (IX); thus the alcohol is an alcohol of formula R^7OH .

25 Protecting groups may be removed using the appropriate conventional procedure, for example a benzyl carboxylate group may be removed using conventional catalytic hydrogenolysis using hydrogen and a Pd/C catalyst.

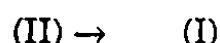
30 Suitable conversions of one group R^5 into another group R^5 include those mentioned hereinbefore.

The compounds of formula (X) are known compounds or they may be prepared in accordance with procedures used to prepare known compounds, for example those disclosed in Synthesis, 294 (1985). In
35 particular it is to be noted that the compounds of formula (X) wherein n is 2 may be prepared by conventional benzylation of the naturally occurring amino acid pyroglutamic acid. The R and S isomers of pyroglutamic acid are readily available in resolved form.

Suitable protecting groups for any of the groups mentioned herein and methods for removing such protecting groups are those used conventionally in the art, for example a suitable amino protecting group is the group COR¹⁰ as defined above.

The preparation of a resolved form ((R) or (S)) isomer of a compound of formula (I) may suitably be obtained by the sequence of reactions summarised below in Schemes 1 to 5:

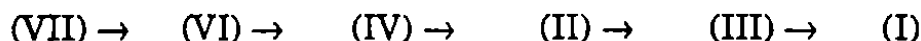
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Scheme (1)15 **Scheme (2):****Scheme (3):**

20

**Scheme (4):**

25

**Scheme (5):**

30

In the abovementioned schemes the compounds of formulae (I), (II), (III), (IV), (VI), (VII), (IX) and (X) are as defined above and the reaction conditions for each reaction are as defined hereinbefore.

Each of the abovementioned Schemes (1), (2), (3), (4) and (5) form a further specific aspect of the present invention.

In Schemes (1) and (3) it is particularly advantageous if the cyclisation of

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(II) to (I) is effected using dicyclohexylcarbodiimide.

In Schemes (2), (4) and (5) it is particularly advantageous if the cyclisation of (II) to (III) is effected using a carboxylic anhydride.

5

In Scheme (4) it is particularly advantageous if variable R^6 in the compounds of formulae (VI) and (IV) is -O-t-butyl.

10 The following Examples illustrate the present invention but do not limit it in any way.

Example 1**(R,S)-5-Benzylloxycarbonylamino-2-pyrrolidinone**

- 5 A mixture of 5-ethoxy-2-pyrrolidinone (20 g) and benzyl carbamate (25.8 g) were stirred at 85°C until fusion. A catalytic amount of 4-toluenesulfonic acid was added and stirring at 85°C was continued for six hours, while distilling off the ethanol formed.
- 10 After cooling, the reaction mixture was chromatographed over silica gel (dichloromethane - methanol 95:5) to yield 26.7 g of the title compound, as a white solid melting at 90-92°C.

¹H-NMR (DMSO-d₆ delta: 8.10 (bs; 1H; CONH); 7.90 (bd; J = 9Hz, 1H, CHNHCO); 7.35 (s; 5H, Ph); 5.20 (c.a.; 1H, CH); 5.05 (s; 2H, CH₂Ph); 2.50 - 1.50 (c.a.; 4H, CH₂CH₂).

MS (E.L., 70 eV), m/z: 234 (M+.), 190 (M-CO₂), 150 (M-C₄H₆NO), 143 (M-C₇H₇), 128 (M-C₇H₆O), 108 (C₇H₈O), 91 (C₇H₇), 84 (C₄H₆NO).

20

Example 2**Ethyl (R,S)-5-benzylloxycarbonylamino-2-oxo-1-pyrrolidine-acetate**

- To an ice cold solution of (R,S)-5-benzylloxycarbonylamino-2-pyrrolidinone (8 g) in acetonitrile (400 ml), sodium hydride (55-60% oil dispersion) (1.5 g) was added portionwise. Stirring was continued for 1 hour, then a
- 30 solution of ethyl bromoacetate (6.3 g) in acetonitrile was added dropwise, keeping the internal temperature between 0 and 5°C.

- After stirring for 4 hours at room temperature, the reaction mixture was heated at 50°C for 1 hour. The solvent was removed under vacuum and
- 35 the residue was partitioned between ethyl acetate and water. The organic layer was washed with a saturated solution of sodium hydrogen carbonate and water, dried (Na₂SO₄) and evaporated under vacuum to give 9 g of the title compound, as an oil, R_f = 0.33 (silica gel plates, dichloromethane -

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methanol 95:5).

¹H-NMR (CDCl₃), delta: 7.35 (s, 5H, Ph); 5.85 (bd, J = 8.5Hz, 1H, NH); 5.50 (c.a., 1H, CH); 5.10 (s, 2H, CH₂Ph); 4.15 (q, J = 7.5Hz, 2H, CH₂CH₃);
5 4.10 and 3.95 (ABq, J = 14Hz, 2H, NHCH₂CO); 2.75-1.75 (c.a., 4H, CH₂CH₂); 1.22 (t, J = 7.5Hz, 3H, CH₂CH₃).

MS (E.I., 70 eV), m/z: 275 (M-C₂H₅O), 247 (M-C₃H₅O₂), 228 (M-C₇H₇), 185 (M-C₈H₇O₂), 170 (M-C₈H₈NO₂), 96 (C₅H₆NO), 91 (C₇H₇).

10

Example 3

(R,S)-5-Benzylloxycarbonylamino-2-oxo-1-pyrrolidineacetic acid

15

To an ice cold solution of ethyl (R,S)-5-benzylloxycarbonyl-amino-2-oxo-1-pyrrolidineacetate (8.5 g) in methanol (64 ml), a solution of potassium hydroxide 85% (2 g) in methanol (43 ml), was added dropwise. The solution was stirred at room temperature for six hours, the solvent
20 was removed under vacuum, the residue was dissolved in water and adjusted to pH 1 with 20% hydrochloric acid.

The precipitate was collected and dried to give 6.4 g of the title compound, as a white powder melting at 139-141°C.

25

¹H-NMR (DMSO-d₆), delta: 7.98 (bd, J = 9Hz, 1H, NH); 7.35 (s, 1H, Ph); 5.28 (c.a., 1H, CH); 5.06 (s, 2H, CH₂Ph); 4.06 and 3.56 (ABq, J = 17Hz, 2H, NHCH₂O); 2.50-1.80 (c.a., 4H, CH₂CH₂).

30 **MS** (E.I., 70 eV), m/z: 201 (M-C₇H₇), 157 (M-C₈H₇O₂), 151 (C₈H₉NO), 141 (M-C₈H₉NO), 108 (C₇H₈O), 96 (C₅H₆NO), 91 (C₇H₇).

Example 4

35

Ethyl (R,S)-5-amino-2-oxo-1-pyrrolidineacetate

A mixture of ethyl (R,S)-5-benzylloxycarbonylamino-2-oxo-

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1-pyrrolidineacetate (3 g), ethanol (60 ml) and 10% palladium on carbon (0.3 g) was hydrogenated (20°C, ambient pressure) for one hour. The catalyst was filtered off and the solvent was evaporated to yield 1.4 g of the title compound as an oil, R_f = 0.25 (silica gel plates, ethyl acetate-acetone-methanol 6:3:1).

¹H-NMR (CDCl₃), delta: 4.60 (c.a., 1H, CH); 4.15 (q, J = 7Hz, 2H, CH₂CH₃); 4.13 - 3.95 (ABq, J = 20Hz, 2H, NCH₂CO); 2.50-1.50 (c.a., 4H, CH₂CH₂); 1.80 (s, 2H, NH₂); 1.22 (t, J = 7Hz, 3H, CH₂CH₃).

MS (E.I., 70 eV), m/z: 185 (M-H)⁺, 170 (M-NH₂), 141 (M-C₂H₅O), 113 (M-C₃H₅O₂), 99 (M-C₄H₇O₂), 84 (C₄H₆NO).

Example 5

(R,S)-5-Amino-2-oxo-1-pyrrolidineacetic acid hydrochloride

A mixture of (R,S)-5-benzyloxycarbonylamino-2-oxo-1-pyrrolidine acetic acid (2.6 g), methanol (78 ml), 2N hydrochloric acid (4.5 ml) and 10% palladium on carbon (0.3 g) was hydrogenated (20°C, ambient pressure) for 30 minutes.

The catalyst was filtered off, the solvent was evaporated and the solid residue was triturated with diisopropyl ether to yield 1,3 g of the title compound as a white solid melting at 140-141°C.

¹H-NMR (DMSO-d₆), delta: 9.00 (bs, 4H, NH₃+COOH); 5.00 (c.a., 1H, CH); 4.15 (s, 2H, NCH₂CO); 2.90-2.00 (c.a., 4H, CH₂CH₂).

MS (E.I., 70 eV), m/z: 141 (M-NH₃), 123 (M-H₂O, NH₃), 96 (C₅H₆NO).

Example 6**(R,S)-Dihydro-1-benzyloxycarbonyl-1H-pyrrolo[1,2-a]-imidazole-2,5(3H,6H)-dione**

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A mixture of (R,S)-5-benzyloxycarbonylamino-2-oxo-1-pyrrolidineacetic acid (6.1 g), acetic anhydride (61 ml) and anhydrous sodium acetate (1.7 g) was refluxed for one hour. The solvent was evaporated under vacuum, the residue was triturated with water (50 ml) and collected, to give 4.4 g of the
10 title compound melting at 110-111°C.

¹H-NMR (CDCl₃), delta: 7.40 (s, 5H, Ph); 5.60 (t; J = 6Hz, 1H, CH); 5.33 (s, 2H, CH₂Ph); 4.35 and 3.66 (ABq, J = 17Hz, 2H, NCH₂CO); 3.00-1.90 (c.a., 4H, CH₂CH₂).

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MS (E.I., 70 eV), m/z: 274 (M+.), 167 (M-C₇H₆O), 139 (M-C₈H₇O₂), 91 (C₇H₇), 84 (C₄H₆NO).

20 **Example 7****(R,S)-Dihydro-1H-pyrrolo[1,2-a]imidazole-2,5-(3H,6H)-dione**

A mixture of (R,S)-dihydro-1-carbobenzyloxy-1H-pyrrolo[1,2-a]imidazole-
25 2,5(3H,6H)-dione (4 g), methanol (120 ml) and 10% palladium on carbon (0.4 g), was hydrogenated (20°C, ambient pressure) for one hour. The catalyst was filtered off and the solvent was evaporated under vacuum, to give the crude title compound as a solid, melting at 130-133°C. Crystallization from isopropyl alcohol gave 1.2 g of the pure title
30 compound as a white powder, melting at 152-154°C.

Example 835 **(R,S)-Dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione**

To a mixture of (R,S)-5-amino-2-oxo-1-pyrrolidineacetic acid hydrochloride (0.2 g), acetonitrile (60 ml) and triethylamine (0.1 g), a solution of

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dicyclohexylcarbodiimide (0.2 g) in acetonitrile (8 ml) was added dropwise. The solution was stirred for 24 hours, the precipitate was filtered off and the solvent evaporated under vacuum. The solid residue was chromatographed over silica gel (ethyl acetate-acetone-methanol 6:3:1) to yield 80 mg of the title compound as a white solid, melting at 151-153°C.

Example 9

10 (R,S)-Dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione

To a solution of ethyl (R,S)-5-amino-2-oxo-1-pyrrolidineacetate (0.5 g) in anhydrous toluene (10 ml), potassium tert-butoxide (0.3 g) was added and stirring was continued for three hours. Then more potassium tert-butoxide (0.3 g) was added and after 1.5 hours the mixture was neutralized with 1N hydrochloric acid. The separated aqueous layer was passed through a column of cation exchanger Amberlite IR 120 (4 g) and evaporated. The residue was chromatographed over silica gel (ethyl acetate - acetone - methanol 6:3:1) to yield 80 mg of the title compound as a white solid, melting at 149-151°C.

Example 10

25 (R,S)-Dihydro-1-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione

To a solution of ethyl (R,S)-5-amino-2-oxo-1-pyrrolidineacetate (1 g) in anhydrous tetrahydrofuran (20 ml), 1.6 M butyllithium in n-hexane (3.4 ml) was added dropwise, keeping the temperature between -70 and -65°C. After one hour the temperature was allowed to rise to 0°C and the reaction mixture was neutralized with 1N hydrochloric acid. The mixture was evaporated under vacuum and the residue was chromatographed over silica gel (ethyl acetate - acetone - methanol 6:3:1) to yield 0.2 g of the title compound.

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Example 11**(R)-1-Benzylloxycarbonyl-5-benzylloxycarbonylamino-2-pyrrolidinone**

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A stirred suspension of N-benzylloxycarbonyl-D-pyroglutamic acid (25 g) in freshly distilled dry toluene (125 ml) was flushed with nitrogen and treated with diphenylphosphoryl azide (20.5 ml). The mixture was heated to 80°C, and keeping this temperature, a solution of triethylamine (13.1 ml) in toluene (62.5 ml) was added dropwise during 3 h. To the clear solution, benzyl alcohol (10.7 ml) in toluene (62.5 ml) was added quickly and the mixture was allowed to reach room temperature. The crystalline product precipitated on standing. After filtration it was washed thoroughly with cold toluene and dried under vacuum, affording the title compound (18.61 g) as a white solid, m.p. 149-152°C; $[\alpha]_D^{20} = +31.2$ (c=1, DMF).

¹H-NMR (CDCl₃), delta: 7.35 (s, 10H, Ph); 5.72 (c.a., 2H, CH-NH); 5.25 (s, 2H, COOCH₂); 5.07 (s, 2H, NHCOOCH₂); 2.00-3.10 (c.a., 4H, CH₂CH₂).

MS (E.I., 70 eV), m/z: 368 (M+.), 277 (M-C₇H₇), 260 (M-C₇H₈O), 217 (M-C₈H₉NO₂), 127 (C₁₅H₁₅NO₂), 107 (C₇H₇O), 91 (C₇H₇), 84 (C₄H₆NO).

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Example 12**(R)-5-Amino-2-pyrrolidinone hydrochloride**

A solution of (R)-1-benzylloxycarbonyl-5-benzylloxycarbonylamino-2-pyrrolidinone (18.61 g) in methanol/dioxane (4/1) (2.5 l) and 10% hydrochloric acid (22.3 ml) was hydrogenated (20°C, ambient pressure) over 10% Pd/C (2.05 g). The reaction was allowed to proceed for 0.5 h, then the catalyst was removed by suction filtration through a Celite pad. Evaporation of the filtrate afforded the title compound (6.8 g) as a yellow solid, $[\alpha]_D^{20} = +11.8^\circ$ (c=0.17, H₂O/dioxane = 1/1).

¹H-NMR (DMSO-d₆), delta: 8.70 (bs, 3H, NH₃⁺); 8.33 (bs, 1H, CONH);

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4.88 (bs, 1H, CH); 2.80-1.80 (c.a., 4H, CH₂CH₂).MS (E.I., 70 eV), m/z: 100 (M⁺), 84 (M-NH₂).

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Example 13**(S)-5-Benzylloxycarbonylamino-2-pyrrolidinone**

- 10 To an ice cold solution of (R)-5-amino-2-pyrrolidinone hydrochloride (6.7 g) in water (1.4 l), benzyl chloroformate (12 ml) and 0.5 N NaOH (82 ml) were added. The reaction mixture was stirred at 2-7°C for 1.5 h. Then, 0.5 N sodium hydroxide was added portionwise to maintain the pH between 7 and 9 while the mixture was allowed to warm to room temperature. After
15 2.5 h, more benzyl chloroformate (12 ml) was added quickly and stirring was continued for 2 hours at room temperature. The mixture was extracted with dichloromethane (500 ml x 3). The organic layer was dried (Na₂SO₄) and evaporated under reduced pressure. The oily residue was triturated with diisopropyl ether to afford 8.5 g of the title compound as a
20 white solid, m.p. 127-129°C; [α]_D²⁰ = -79.6 (c=1, MeOH).

¹H-NMR (CDCl₃), delta: 7.35 (s, 5H, Ph); 6.50 (bs, 1H, CONH); 5.70 (bd, J = 7Hz, 1H, CHNHCO); 5.40 (c.a., 1H, CH); 5.15 (s, 2H, CH₂Ph); 2.75-1.75 (c.a., 4H, CH₂CH₂).

25

MS (E.I., 70 eV), m/z: 234 (M⁺), 190 (M-CO₂), 143 (M-C₇H₇), 126 (M-C₇H₈O), 108 (C₇H₈O), 91 (C₇H₇), 84 (C₄H₆NO).

Example 14

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Ethyl (R)-5-benzylloxycarbonylamino-2-oxo-1-pyrrolidineacetate

- The procedure of example 2 was repeated starting from (R)-5-benzyloxy-carbonylamino-2-pyrrolidinone (9.24 g) to afford the title
35 compound (11.8 g) as an oil. Rf: 0.33 (silica gel plates, dichloromethane-methanol 95:5).

¹H-NMR (CDCl₃), delta: 7.35 (s, 5H, Ph); 5.85 (bd, J = 8.5HZ, 1H, NH);

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5.50 (c.a., 1H, CH); 5.10 (2H, CH_2Ph); 5.15 (q, $J = 7.5\text{Hz}$, 2H, CH_2CH_3); 4.10 and 3.95 (ABq, $J = 14\text{Hz}$, 2H, NCH_2CO); 2.75-1.75 (c.a., 4H, CH_2CH_2); 1.22 (t, $J = 7.5\text{Hz}$, 3H, CH_2CH_3).

5 MS (E.I., 70 eV), m/z : 320 (M^+), 275 ($\text{M}-\text{C}_2\text{H}_5\text{O}$), 247 ($\text{M}-\text{C}_3\text{H}_5\text{O}_2$), 185 ($\text{M}-\text{C}_8\text{H}_7\text{O}_2$); 170 ($\text{M}-\text{C}_8\text{H}_8\text{NO}_2$), 91 (C_7H_7).

Example 15

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(R)-5-Benzyloxycarbonylamino-2-oxo-1-pyrrolidineacetic acid

The procedure of example 3 was repeated starting from ethyl (R)-5-benzyloxycarbonylamino-2-oxo-1-pyrrolidineacetate (11.5 g) to afford the title compound (7.44 g) as a solid foam. Rf: 0.59, silica gel plates, butanol - acetic acid - water 4:1:1).

$^1\text{H-NMR}$ (DMSO-d_6), δ : 7.95 (bd, $J = 9\text{Hz}$, 1H, NH); 7.35 (s, 5H, Ph); 5.28 (c.a., 1H, CH); 5.06 (s, 2H, CH_2Ph); 4.06 and 3.56 (ABq, $J = 17\text{Hz}$, 2H, NCH_2CO); 2.50-1.80 (c.a., 4H, CH_2CH_2).

MS (E.I., 70 eV), m/z : 201 ($\text{M}-\text{C}_7\text{H}_7$), 151 ($\text{C}_8\text{H}_9\text{NO}_2$), 142 ($\text{M}-\text{C}_9\text{H}_{10}\text{O}_2$), 108 ($\text{C}_7\text{H}_8\text{O}$), 91 (C_7H_7).

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Example 16

(S)-Dihydro-1-benzyloxycarbonyl-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione

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The procedure of example 6, was repeated starting from (R)-5-benzyloxycarbonylamino-2-oxo-1-pyrrolidineacetic acid (7.33 g) to afford 4 g of the title compound as a brown solid, m.p. = 123-127°; $[\alpha]_D^{20} = +53.8^\circ$, ($c=1$, DMF).

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$^1\text{H-NMR}$ (CDCl_3), δ : 7.40 (s, 5H, Ph); 5.60 (t; $J = 6\text{Hz}$, 1H, CH); 5.33 (s, 2H, CH_2Ph); 4.40 and 3.70 (ABq, $J = 17\text{Hz}$, 2H, NCH_2CO); 3.00-1.90 (c.a., 4H, CH_2CH_2).

MS (E.I., 70 eV), m/z: 274 (M+.), 168 (M-C₇H₆O), 139 (M-C₈H₇O₂), 91 (C₇H₇), 84 (C₄H₆NO).

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Example 17**(R)-Dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione**

- 10 The procedure of example 7, was repeated starting from (R)-dihydro-1-benzyloxycarbonyl-1H-pyrrolo[1,2-a]-imidazole-2,5[3H,6H]-dione (4 g) to afford the title compound (1.15 g) as a white solid, m.p. 197-200°; [α]_D²⁰ = -39.8°, (c=0.43, MeOH).

- 15 ¹H-NMR (DMSO-d₆), delta: 8.68 (bs; 1H, NH); 5.25 (t, J = 4Hz, 1H, CH); 3.80 and 3.40 (ABq, J = 15Hz, 2H, NCH₂CO); 2.90-1.55 (c.a.; 4H, CH₂CH₂).

- MS (E.I., 70 eV), m/z: 140 (M+.), 111 (M-CHO), 97 (M-CHNO); 84
20 (C₃H₄N₂O).

Example 18**25 Benzyl (S)-5-carbethoxy-2-oxo-1-pyrrolidineacetate**

A mixture of ethyl L-pyroglutamate [E. Fischer et al., Berichte 44, 1333 (1911)] (13.1 g), tetrabutylammonium bromide (10.36 g) and potassium carbonate (45 g) in acetonitrile (100 ml) was stirred at 20°C for 1 hour.

- 30 Benzyl 2-bromoacetate (25 ml) was added and the temperature was raised to 60°C. Stirring was continued for 2.5 hours, maintaining the temperature at 60-65°C. After cooling the insoluble material was filtered off and washed with diethyl ether.

- 35 The combined filtrates were evaporated under reduced pressure. The oily residue was dissolved in ethyl acetate (100 ml) and washed with 10% hydrochloric acid, a saturated solution of sodium hydrogen carbonate and water. The organic layer was dried and evaporated, the oily residue was

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chromatographed over silica gel (eluting first with dichloromethane then with dichloromethane/methanol 8:2). The appropriate fractions were collected and evaporated to give 18.5 g of title compound as a brown oil; b.p. 240-250°C at 0.6 mmHg (partial decomposition); $[\alpha]^{20}_D = -36.1^\circ$,
5 (c=5; CH₂Cl₂).

¹H-NMR (CDCl₃), delta: 7.37 (s, 5H, Ph); 5.18 (s, 2H, CH₂Ph); 4.70 and 3.84 (ABq, J = 17Hz, 2H, NCH₂COO); 4.45 (c.a., 1H, CH); 4.22 (q, J = 6Hz, 2H, CH₂CH₃); 2.75-2.00 (c.a., 4H, CH₂CH₂); 1.28 (t, J = 6Hz, 3H, CH₂CH₃).
10 CH₂CH₃).

MS (E.I., 70 eV), m/z: 305 (M+.), 232 (M-C₃H₅O₂), 214 (M-C₇H₇), 170 (M-C₈H₇O₂), 156 (M-C₉H₉O₂), 142 (C₆H₈NO₃), 98 (C₅H₈NO), 96 (C₅H₆NO), 91 (C₇H₇).
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Example 19

(S)-5-Carboethoxy-2-oxo-1-pyrrolidineacetic acid 20

A mixture of benzyl (S)-5-carbethoxy-2-oxo-1-pyrrolidine-acetate (6.5 g, 21 mmol) and 10% Pd on charcoal (0.65 g) in ethyl acetate (65 ml) was hydrogenated at room temperature and ambient pressure. After 6 hours the catalyst was filtered off and the solvent was evaporated under
25 vacuum, affording 4.6 g of the title compound as a yellowish oil, $[\alpha]^{20}_D -36.1^\circ$, (c=5, CH₂Cl₂).
Dicyclohexylammonium salt: m.p.115°C.

¹H-NMR (CDCl₃), delta: 8.43 (bs, 1H, COOH); 4.65 and 3.87 (ABq, J = 18Hz, 2H, NCH₂COO); 4.48 (c.a., 1H, CH); 4.25 (q, J = 6Hz, 2H, CH₂CH₃), 2.70-2.00 (c.a., 4H, CH₂CH₂); 1.30 (t, J = 6Hz, 3H, CH₂CH₃).
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MS (E.I., 70 eV), m/z: 215 (M+.), 197 (M-H₂O), 169 (M-C₂H₆O), 156 (M-C₂H₃O₂), 142 (M-C₃H₅O₂), 96 (C₅H₆NO).
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Example 20**(S)-5-Carbamoyl-2-oxo-1-pyrrolidineacetic acid**

- 5 A solution of (S)-5-carbethoxy-2-oxo-1-pyrrolidineacetic acid (22.1 g) in concentrated ammonia solution (170 ml) was stirred at room temperature for 3 h. After evaporation under vacuum, the oily residue was dissolved in water (150 ml) and stirred with cation exchange resin Amberlite IRA 120 (30 ml) for 2 hours. The resin was filtered off and the solution was
10 evaporated under reduced pressure, affording the title compound (17.5 g) as a deiquescent amorphous solid, $[\alpha]^{20}_D = -14.5^\circ$, (c=5, H₂O).
Dicyclohexylammonium salt: m.p. 187-190°C.

- ¹H-NMR (DMSO-d₆), delta: 8.27 (bs, 1H, COOH); 7.92 and 7.15 (bs, 2H, CONH₂); 4.20 (c.a., 1H, CH); 4.10 and 3.35 (ABq, J = 17Hz, 2H, NCH₂CO); 2.40-1.70 (c.a., 4H, CH₂CH₂).

- MS (E.I., 70 eV), m/z: 185 (M-H)⁺, 168 (M-H₂O), 142 (M-CH₂NO), 126 (M-C₂H₄O₂), 96 (C₅H₆NO), 84 (C₄H₆NO).

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Example 21**(S)-5-Amino-2-oxo-1-pyrrolidineacetic acid hydrochloride**

- 25 A solution of (S)-5-carbamoyl-2-oxo-1-pyrrolidineacetic acid (14.7 g) and [bis(trifluoroacetoxy)iodo]benzene (34.5 g) in water (100 ml) and acetonitrile (200 ml) was stirred at room temperature, under nitrogen, for 4 hours. Acetonitrile was removed under reduced pressure, the aqueous
30 layer was washed with diethyl ether (2 x 50 ml) and evaporated under reduced pressure. The residue was dissolved in 10% hydrochloric acid (50 ml) and evaporated. The residue was triturated with acetone to afford the title compound (7.5 g) as a white solid, m.p. > 250°C; $[\alpha]^{20}_D = +2.5^\circ$, (c=1, water).

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- ¹H-NMR (DMSO-d₆), delta: 9.75 (bs, 4H, NH₃⁺ COOH); 5.00 (c.a., 1H, CH); 4.15 (s, 2H, NCH₂CO); 2.90-2.00 (c.a., 4H, CH₂CH₂).

Example 22**(R)-Dihydro-1-benzyloxycarbonyl-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione**

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A solution of (S)-5-carbamoyl-2-oxo-1-pyrrolidineacetic acid (1 g, 5.4 mmol) and [bis(trifluoroacetoxy)iodo]benzene (2.72 g, 6.2 mmol) in acetonitrile/water 1:1 (26 ml) was stirred at room temperature for 2.5 hours. Acetonitrile was added to obtain a clear solution and stirring was continued for 1.5 hours. The solution was evaporated, the residue was dissolved in water (20 ml) and washed with diethyl ether (2 x 15 ml). To the aqueous solution, sodium hydrogen carbonate (2.25 g) and benzyl chloroformate (1.9 ml) were added and the mixture was stirred at room temperature overnight. The solution was washed with dichloromethane (2 x 25 ml), acidified, and extracted with dichloromethane (2 x 25 ml). Drying (Na₂SO₄) and evaporation of the organic solution afforded crude (S)-5-benzyloxycarbonylamino-2-oxo-1-pyrrolidineacetic acid (0.4 g). This compound was dissolved in acetic anhydride (5 ml) containing sodium acetate (150 mg) and the mixture refluxed for 1 hour. After evaporation the residue was triturated with water to yield 0.14 g of the title compound as a brown solid, m.p. 118-128°C [α]_D = -52.2° (c=1, DMF).

Example 23

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(S)-Dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione

A mixture of (S)-5-amino-2-oxo-1-pyrrolidineacetic acid hydrochloride (7 g), triethylamine (5.05 ml) and dicyclohexylcarbodiimide (7.4 g) in acetonitrile (1 l) was stirred under nitrogen for 24 hours. The mixture was evaporated under reduced pressure, the residue was dissolved in water (50 ml), and the insoluble material filtered off. The aqueous filtrate was treated with cation exchanger Amberlite IRA 120 (40 ml) and anion exchanger Amberlite IR 68 (40 ml) under stirring for 1.5 hours. The resin was filtered off, the aqueous solution was evaporated under reduced pressure and the residue was triturated from isopropanol and recrystallized from isopropanol, to yield 1.5 g of the title compound as a white crystalline solid m.p. 197-202°C [α]_D²⁰ = +41.6°, (c=0.38,

MeOH).

Example 24

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(S)-Dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione

The procedure of example 7 was reported starting from (S)-dihydro-1-benzyloxycarbonyl-1H-pyrrolo[1,2-a]imidazole-2, 5(3H,6H)-dione (0.14 g)
10 to afford the title compound (0.03 g) as a white solid, m.p. 198-202°C; $[\alpha]^{20}_D = +42.8^\circ$, (c=0.26, MeOH).

Example 25

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(R)-t-Butyl-5-carbomethoxy-2-oxo-1-pyrrolidineacetate

A solution of (5-R)-methyl pyroglutamate (122g) in 1.75l of acetonitrile was cooled to 0°-5°C and 55-60% sodium hydride (34.1g) was added
20 portionwise. Stirring was continued for 1.5 hours and t-butyl bromoacetate (175.5g) was added dropwise. The ice bath was removed and stirring continued for 1.5 hours. After evaporation of the solvent, the residue was dissolved in ethyl acetate, the organic phase was washed with a saturated solution of NaHCO₃, dried, and evaporated to dryness, to give
25 the title compound (182.1g, 83%) as a yellow oil; $[\alpha]^{20}_D = +42.3^\circ$ (c = 5, CH₂Cl₂).

¹H-NMR (CDCl₃), δ_{H} : 4.53 - 3.60 (ABq, J = 17.5Hz, 2H, NCH₂O); 4.45 (m, 1H, NCHCO); 2.6 - 2.0 (m, 4H, CH₂CH₂); 1.45 (s, 9H, t-butyl).

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MS (E.I., 70 eV, 1.5 mA): m/z 201(M-C₄H₈), 156 (M-C₅H₉O₂), 184 (C₄H₉O).

Example 26**(S)-t-Butyl-5-carbomethoxy-2-oxo-1-pyrrolidineacetate**

- 5 The title compound was prepared using the same procedure described in Example 25 starting from (5-S)-methyl pyroglutamate; $[\alpha]^{20}_D = -38.9$ (c=5, CH₂Cl₂).

10 ¹H-NMR (CDCl₃), δ_{H} : 4.53 - 3.50 (ABq, J = 17.5Hz, 2H, NCH₂O); 4.45 (m, 1H, NCHCO); 2.6 - 2.0 (m, 4H, CH₂CH₂); 1.45 (s, 9H, t-butyl)

MS (E.I., 70 eV, 1.5 mA): m/z 201 (M - C₄H₈), 156 (M - C₅H₉O₂), 184 (C₄H₉O).

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Example 27**(R)-t-Butyl-5-carbamoyl-2-oxo-1-pyrrolidineacetate**

- 20 A mixture of (5-R)-t-butyl-5-carbomethoxy-2-oxo-1-pyrrolidinacetate (182.1g) and 32% ammonium hydroxide (900 ml) was stirred at room temperature for 1.5 hours.

25 The excess of ammonia was removed under vacuum, the solution neutralised with 37% hydrochloric acid, and extracted with ethyl acetate. The organic phase was dried over sodium sulphate and evaporated to dryness to give the title compound 104.7 g (61.1%) as a white powder, m.p. 132-135°C; $[\alpha]^{20}_D = +32.4^\circ$ (c = 5, CH₂Cl₂).

30 ¹H-NMR (DMSO - d₆), δ_{H} : 7.55 - 7.12 (bs, 2H, CONH₂); 4.25 - 3.40 (ABq, J = 17.5Hz, 2H, NCH₂CO); 4.15 (m, 1H, NHCO); 2.40 - 1.75 (m, 4H, CH₂CH₂); 1.45 (s, 9H, t-butyl).

35 MS (E.I., 70 eV, 1.5 mA): m/z = 198 (M - CNH₂O), 185 (M - C₄H₉), 142 (M - CNH₂O - C₄H₈).

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Example 28**(S)-t-Butyl-5-carbamoyl-2-oxo-1-pyrrolidineacetate**

- 5 The title compound was prepared using the same procedure described in Example 27 starting from (5-S)-t-butyl-5-carbomethoxy-2-oxo-1-pyrrolidinacetate; m.p. 128-129°C; $[\alpha]^{20}_D = -31.3^\circ$ (c = 5, CH₂Cl₂).
- 10 ¹H-NMR (DMSO - d₆), δ_{H} : 7.60 - 7.17 (bs, 2H, CONH₂); 4.25 - 3.40 (ABq, J = 17.5, 2H, NCH₂CO); 4.15 (m, 1H, NHCO); 2.40 - 1.75 (m, 4H, CH₂CH₂); 1.45 (s, 9H, t-butyl).
- MS (E.I., 70 eV, 1.5 mA): m/z = 198 (M - CNH₂O), 185 (M - C₄H₉), 142 (M - CNH₂O - C₉H₈).
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Example 29**(R)-5-Amino-2-oxo-1-pyrrolidineacetic acid, hydrochloride**

- 20 A solution of 5.7% sodium hypochlorite (570 ml) was added dropwise to a solution of sodium hydroxide pellets (51.9 g) in water (1.05 l), maintaining the temperature at 0 - 5°C. To this solution, (5-R)-t-butyl-5-carbamoyl-2-oxo-1-pyrrolidinacetate (104.7g), was added portionwise maintaining the
- 25 same temperature, and then for 15 minutes at 55-60°C. After cooling to 0-5°C, 37% of hydrochloric acid (145 ml) was added to pH2. The solution was evaporated under vacuum and the residue triturated with methanol.
- The solvent was removed to give the title compound (69.8 g, 83%) as a
- 30 white solid; $[\alpha]^{20}_D = -2.3^\circ$ (c=1, H₂O)
- ¹H-NMR (DMSO - d₆), δ_{H} : 9.5 (bs, 1H, COOH); 4.95 (m, 1H, NHCO); 4.15 (s, 2H, NCH₂CO); 2.85 - 2.0 (m, 4H, CH₂CH₂).
- 35 MS (E.I., 70 eV, 1.5 mA): m/z 141 (M - NH₃), 123 (M - H₂O, NH₃).

Example 30**(S)-5-Amino-2-oxo-1-pyrrolidineacetic acid, hydrochloride**

- 5 The title compound was prepared using the same procedure described in Example 29, starting from (5-S)-t-butyl-5-carbamoyl-2-oxo-1-pyrrolidinacetate.

10 **Example 31**

(S)-Dihydro-1-acetyl-1H-pyrrolo[1,2a]imidazole-2,5(3H, 6H)-dione

- 15 A mixture of (5-R)-5-amino-2-oxo-1-pyrrolidinacetic acid hydrochloride (69.8g), anhydrous sodium acetate (29.4 g) and acetic anhydride (700 ml), was refluxed for 1.5 hours. The brown mixture was allowed to cool to room temperature and then evaporated to dryness.

- 20 The residue was treated under stirring with ethyl acetate and a saturated solution of ammonium sulphate.

- The organic layer was dried over sodium sulphate and evaporated under vacuum to give the title compound (54g, 82.5%) as an oil; m.p. 82-83°C; $[\alpha]_D^{20} = +159^\circ$ (c = 0.1, MeOH)

- 25 $^1\text{H-NMR}$ (CDCl_3), δ_{H} : = 5.65 (m, 1H, NCHN); 4.45 - 3.75 (ABq, J = 17.5Hz, 2H, NCH₂CO); 3.1 - 2.0 (m, 4H, CH₂CH₂); 2.50 (s, 3H, COCH₃).

- 30 MS (E.I., 70 eV, 1.5 mA): m/z = 154 (H - CO), 139 (H - C₂H₃O).

Example 32**(R)-Dihydro-1-acetyl-1H-pyrrolo[1,2a]imidazole-2,5(3H,6H)-dione**

- 35 The title compound was prepared using the same procedure described in Example 31, starting from (5-S)-5-amino-2-oxo-1-pyrrolidinacetic acid hydrochloride; m.p. 81-82°C, $[\alpha]_D^{20} = -153.9^\circ$ (c = 0.1, MeOH).

¹H-NMR (CDCl₃), δ _H: 5.65 (m, 1H, NCHN); 4.615 - 3.75 (ABq, J = 17.5Hz, 2H, NCH₂CO); 3.1 - 2.0 (m, 4H, CH₂CH₂); 2.50 (s, 3H, COCH₃).

5 **MS (E.I., 70 eV, 1.5 mA):** m/z = 154 (H - CO), 139 (H - C₂H₃O).

Example 33

10 **(R)-Dihydro-1H-pyrrolo[1,2a]imidazole-2,5(3H,6H)-dione**

A mixture of (7a-S)-dihydro-1-acetyl-1H-pyrrolo[1,2a]imidazole-2,5-(3H, 6H)-dione (54 g), Amberlite IR 120 (54 g) in water (540 ml), was stirred at room temperature for 24 hours. The resin was collected on a Buckner
15 funnel and the dark filtrate was evaporated under vacuum, the residue was triturated with isopropanol to give the title compound.

Crystallisation from isopropanol gave the pure compound (15.5 g) as a white crystalline solid, m.p. 197-199°C, $[\alpha]^{20}_D = -39.2^\circ$ (c = 1, MeOH).
20

¹H-NMR (DMSO-d₆) δ _H: 8.63 (bs, 1H, NH); 5.23 (t, J = 5Hz, 1H, CH₂CH); 3.8 - 3.45 (ABq, J = 17 Hz, 2H, NCH₂CO); 2.90 - 1.60 (m, 4H, CH₂CH₂).

25 **MS (E.I., 70 eV, 1.5 mA):** m/z = 140 (M⁺), 97 (M - CONH).

Example 34

30 **(S)-Dihydro-1H-pyrrolo[1,2a]imidazole-2,5(3H,6H)-dione**

The title compound was prepared using the same procedure described in Example 33 starting from (R)-dihydro-1-acetyl-1H-pyrrolo[1,2a]imidazole-
35 2,5-(3H,6H)-dione; m.p. 197-199°C, $[\alpha]^{20}_D = +39.9^\circ$ (c = 1, MeOH)

¹H-NMR (DMSO-d₆) δ _H: 8.63 (bs, 1H, NH); 5.23 (t, J = 5Hz, 1H, CH₂CH); 3.8 - 3.45 (ABq, J = 17Hz, 2H, NCH₂CO); 2.90 - 1.60 (m, 4H,

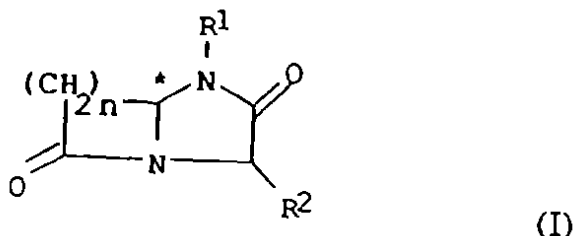
-30-

 CH_2CH_2).**MS (E.I., 70 eV, 1.5 mA): m/z = 140 (M+), 97 (M - CONH).**

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Claims

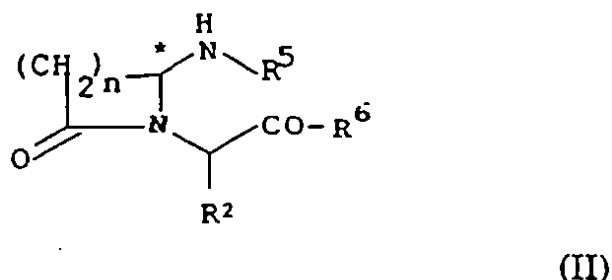
1. A process for the preparation of compounds of formula (I):



10 wherein

R^1 represents hydrogen, C_{1-4} alkyl, CHR^3CONHR^4 or CHR^3COOR^4 in which R^3 and R^4 each independently represent hydrogen or C_{1-4} alkyl; R^2 represents hydrogen or C_{1-5} alkyl; and n is an integer 2, 3 or 4;

15 which process comprises cyclising a compound of formula (II):



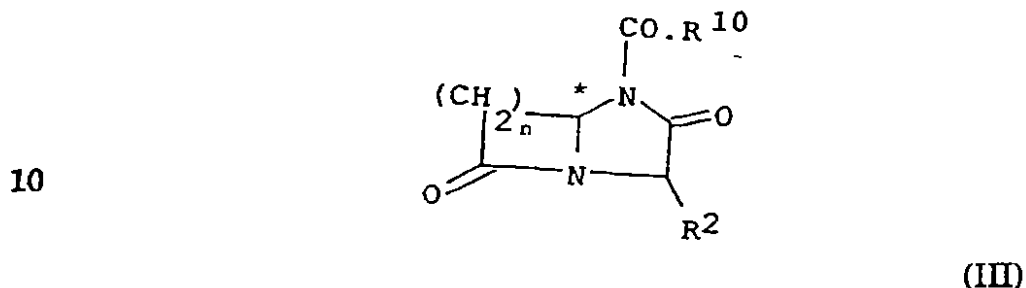
- 25 wherein R^2 and n are as defined in relation to formula (I); R^5 represents hydrogen or a group $COOR^7$ wherein R^7 is a C_{1-4} alkyl group or a benzyl group; and R^6 represents a hydroxy group or a group OR^8 wherein R^8 represents C_{1-6} alkyl or a benzyl group; and thereafter, as necessary, carrying out one or more of the following steps:

- 30 i) removing any protecting group; and
- ii) converting a compound of formula (I) into another compound of formula (I).

- 35 2. A process according to claim 1, wherein the cyclisation is effected by a cyclising reagent.

-32-

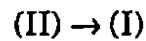
3. A process according to claim 1 or claim 2, wherein the cyclising reagent is a carboxylic anhydride.
4. A process according to claim 3, wherein the cyclisation of the compound of formula (II) provides a compound of formula (III):



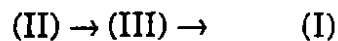
- 15 wherein R^2 and n are as defined in relation to formula (I) and R^{10} is a C_{1-6} alkyl group or a group OR^7 wherein R^7 is as defined in relation to formula (II); and wherein the compound of formula (III) is converted into a compound of formula (I), wherein R^1 is H, by hydrogenolysis or hydrolysis, the resulting compound of formula (I) subsequently being converted into other compounds of formula (I) as desired.

20

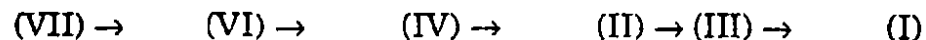
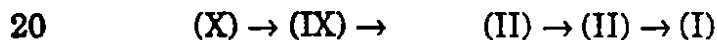
5. A process according to claim 1, wherein R^6 is OH and the cyclisation of a compound of formula (II) is effected under dehydration cyclisation conditions in the presence of a dehydration cyclisation reagent.
- 25 6. A process according to claim 5, wherein the dehydration cyclisation reagents include dicyclohexylcarbodiimide or carboxylic anhydrides such as acetic anhydride.
7. A process according to claim 1, wherein R_6 is a group OR_6 and the cyclisation is effected by use of a strong base such as n-butyl lithium or potassium t-butoxide.
- 30 8. A process according to claim 1, for the preparation of a resolved form ((R) or (S)) isomer of a compound of formula (I) which process comprises the sequence of reactions summarised below in Schemes 1 to 5:
- 35

Scheme (1):

5

Scheme (2):10 **Scheme (3):****Scheme (4):**

15

**Scheme (5):**

and wherein the compounds of formulae (I), (II), (III), (IV), (VI), (VII), (IX) and (X) are as defined above and the reaction conditions for each reaction are as defined hereinbefore.

25

9. A process according to schemes (1) and (3) of claim 8, wherein the cyclisation of (II) to (I) is effected using dicyclohexylcarbodiimide.

10. A process according to schemes (2), (4) and (5) of claim 8, wherein
30 the cyclisation of (II) to (III) is effected using a carboxylic anhydride.

11. A process according to scheme (4) of claim 8, wherein variable R⁶ in the compounds of formulae (VI) and (IV) is -O-t-butyl.

35 12. A process according to claim 1, for the preparation of a compound selected from the list consisting of:

(R,S)-dihydro-1H-pyrrolo[1,2-a]imidazole-2,5-(3H,6H)-dione;

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(R)-dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione; and

(S)-dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione.

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I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D487/04; C07D471/04; //(C07D487/04,235:00,209:00)
(C07D471/04,235:00,221:00)(C07D487/04,235:00,223:00)**II. FIELDS SEARCHED****Minimum Documentation Searched⁷**

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation
to the extent that such Documents are included in the Fields Searched⁸**III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹**

Category ^a	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 335 483 (ISF) 4 October 1989 cited in the application see claim 4 -----	1

^a Special categories of cited documents: ¹⁰

- ^{"A"} document defining the general state of the art which is not considered to be of particular relevance
- ^{"E"} earlier document but published on or after the international filing date
- ^{"L"} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- ^{"O"} document referring to an oral disclosure, use, exhibition or other means
- ^{"P"} document published prior to the international filing date but later than the priority date claimed

^{"T"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention^{"X"} document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step^{"Y"} document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.^{"A"} document member of the same patent family**IV. CERTIFICATION**

Date of the Actual Completion of the International Search 11 FEBRUARY 1993	Date of Mailing of this International Search Report 26. 02. 93
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer ALFARO FAUS I.

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

EP 9202560
SA 66848

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0335483	04-10-89	AU-A- 2969289	10-08-89
		AU-A- 7947991	12-09-91
		JP-A- 1246281	02-10-89
		US-A- 5053422	01-10-91
		US-A- 5130319	14-07-92

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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(11) Publication number:

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A61K 31/415 , A61K 31/435 ,
A61K 31/55 , C07D 233/32 ,
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(C07D471/04,235:00,221:00)

The title of the invention has been amended
(Guidelines for Examination in the EPO, A-III,
7.3).

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AT BE CH DE ES FR GB GR IT LI LU NL SE

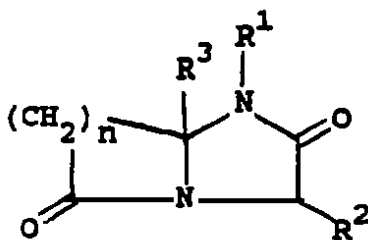
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(84) Condensed imidazole derivatives, process and intermediates for their preparation and
pharmaceutical compositions containing them.

(87) Compounds of structure (I)



(1)

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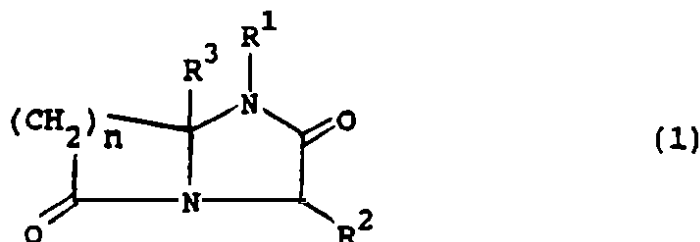
in which, R^1 is hydrogen, C_{1-4} alkyl, CHR^6CONHR^7 or CHR^6COOR^7 in which R^6 and R^7 are each hydrogen or C_{1-4} alkyl; R^2 is hydrogen, C_{1-5} alkyl or a residue R^2 of an amino acid $R^2 CH(NH_2)COOH$; R^3 is hydrogen, C_{1-4} alkyl, $CONH_2$ or CO_2R^8 in which R^8 is hydrogen or C_{1-4} alkyl; and n is 2, 3 or 4, processes for their preparation, intermediates useful in their preparation, pharmaceutical composition containing them and their use in therapy as nootropic agents.

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy, in particular as nootropic agents.

Compounds having nootropic activity are known in the art. In particular, 4-substituted derivatives of 2-oxo-1-pyrrolidineacetamide are valued psychotropic agents that restore cognitive function that has been damaged as a result of various pathologies. These drugs are described for example in Pharm. Res. Commun., 16, 67, (1984) by Banfi et al and in Drug Development Res.; 2, 447 (1982) by Itil et al. A particularly well known member of the above-noted class is 4-hydroxy-2-oxo-1-pyrrolidine acetamide (oxiracetam).

It has now been found that certain perhydroazacycloalka[1,2-a]imidazole derivatives also demonstrate psychotropic properties and are expected to be of use as nootropic agents.

The present invention therefore provides, in a first aspect, compounds of structure (1)



in which,

R¹ is hydrogen, C₁₋₄alkyl, CHR⁶CONHR⁷ or CHR⁶COOR⁷ in which R⁶ and R⁷ are each hydrogen or C₁₋₄alkyl;

R² is hydrogen, C₁₋₅alkyl or any residue R² of an amino acid R²CH(NH₂)COOH

R³ is hydrogen, C₁₋₄alkyl, CONH₂ or CO₂R⁸ in which R⁸ is hydrogen or C₁₋₄alkyl; and

n is 2, 3 or 4.

Suitably R¹ and R³ are each C₁₋₄alkyl and R² is C₁₋₅alkyl. More suitably two of R¹ to R³ are hydrogen and the third is other than hydrogen. Preferably R¹ to R³ are each hydrogen. Preferably n is 2. Suitable groups R² which are any residue R² of an amino acid R²CH(NH₂)CO₂H, include for example CH₃, (CH₃)₂CH, PhCH₂, CH₂OH, CH₂CH₂CONH₂ and CH₂COOH.

C₁₋₄ and C₁₋₅alkyl groups can be straight or branched, in particular methyl, ethyl or isobutyl.

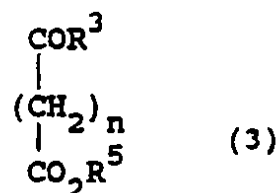
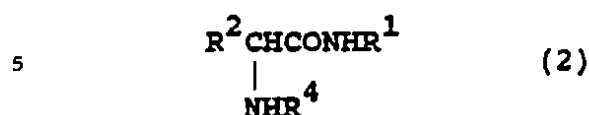
Particular compounds of the present invention include, for example,

- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole;
- 2,5-dioxo-7a-methylhexahydro-1H-pyrrolo[1,2-a]imidazole;
- 2,5-dioxo-3-methylhexahydro-1H-pyrrolo[1,2-a]imidazole;
- 2,5-dioxo-3-isobutylhexahydro-1H-pyrrolo[1,2-a]imidazole;
- 2,5-dioxo-1-ethylhexahydro-1H-pyrrolo[1,2-a]imidazole;
- 2,5-dioxo-3,7a-dimethylhexahydro-1H-pyrrolo[1,2-a]imidazole;
- ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetate;
- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetamide;
- (3-L)-3-benzyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole;
- (3-L)-3-hydroxymethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole;
- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylic acid;
- ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylate;
- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxamide;
- 2,5-dioxooctahydro-1H-imidazo[1,2-a]pyridine;
- 2,5-dioxooctahydro-1H-imidazo[1,2-a]azepine.

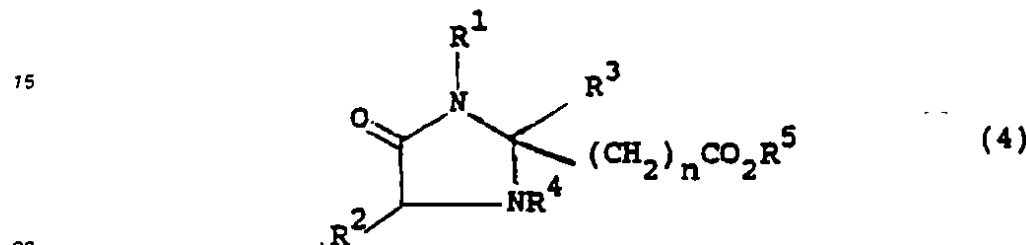
It will be appreciated that certain of the compounds of structure (1) can contain one or more chiral centres. The present invention covers all optical isomers of these compounds in their fully and partially resolved forms and in the form of racemic mixtures.

The present invention therefore provides in a further aspect, a process for the preparation of compounds of structure (1) which comprises:

- a) reaction of a compound of structure (2) with a compound of structure (3) :



in which R¹ to R³ and n are as described for structure (1), R⁴ is hydrogen and R⁵ is hydrogen, C₁₋₄ alkyl or benzyl; or
b) cyclization of a compound of structure (4)



in which R¹ to R³ and n are as described for structure (1), R⁴ is hydrogen and R⁵ is hydrogen, C₁₋₄ alkyl or benzyl.

Suitably the reaction between compounds of structure (2) and (3) is carried out by heating in a suitable solvent and in the presence of a base, such as an alkali metal alkoxide, when compound (2) is employed in the form of an acid addition salt (e.g. hydrochloride). Preferably the reaction is carried out at reflux in water as a solvent.

Suitably, the cyclization of a compound of structure (4) when R⁴ is hydrogen and R⁵ is alkyl or benzyl is carried out by heating the compound, optionally under reduced pressure, in the presence or absence of solvent. Preferably, the cyclization is effected by heating the compound of structure (4) in water at reflux temperature. When R⁵ is hydrogen, cyclization will require activation of the carboxyl group or the use of a peptide coupling reagent in a dipolar aprotic solvent.

Suitable methods for activating carboxyl groups and suitable peptide coupling reagents are all well known to the art and are described for example in "Peptide Synthesis" by M. Bodansky, Y. Klausner and M. Ondetti (Wiley 1976) and in "Protective Groups in Organic Synthesis" by T.W. Greene (Wiley, 1981). Examples of activated derivatives of carboxyl groups are acyl chlorides, acyl azides, mixed anhydrides (e.g. formed with an alkyl chloroformate or pivaloyl chloride) and activated esters (e.g. trichlorophenyl, N-hydroxysuccinimide and 1-hydroxybenzotriazole esters). Examples of peptide coupling reagents are carbodiimides and Woodward's Reagent K (N-ethyl-5-phenylisoxazolium-3'-sulphonate).

Suitable dipolar aprotic solvents are tetrahydrofuran, acetonitrile, dimethylformamide or dimethylsulfoxide.

Preferably the cyclization of a compound of structure (4) in which R⁴ is hydrogen and R⁵ is C₁₋₄ alkyl or benzyl is carried out in a suitable solvent, such as methanol, in the presence of ammonium hydroxide at moderate temperatures of about 50°C and for short reaction times of about 1 hour, or until reaction is complete. Such cyclization produces the compounds of structure (1) in high yields, is novel, and forms a further aspect of the invention.

The starting compounds (2), (3) and (4) can be prepared by methods known to those skilled in the art or analogous to those known in the art; for example, compounds of structure (2) in which R¹ and R⁴ are hydrogen and R² is methyl or isobutyl can be prepared by procedures described in J. Am. Chem. Soc., 53, 3183 [1931] and 79, 4686, [1957]; compounds of structure (2) in which R¹ and R⁴ are hydrogen and R² is CH₂OH can be prepared by procedures described in J. Biol. Chem., 212, 271 [1955]; compounds of structure (2) in which R¹ is ethyl and R² and R⁴ are hydrogen can be prepared by the method described in Chem. Ber., 89, 1363, [1956]; for example compounds of structure (3) in which R³ is methyl, R⁵ is ethyl and n is 2 can be prepared by the procedure described in J. Prakt. Chem. 1 (4), 153 [1955]; compounds of structure (3) in which R³ is hydrogen, R⁵ is ethyl and n is 2 can be prepared by the procedure described in J. Pharm. Soc. Japan, 75, 622 [1955]; compounds of structure (3) in which R³ is hydrogen, R⁵ is methyl and n is 3 can be prepared by the procedure described in Synthesis, 1982, 881; compounds of structure (3) in

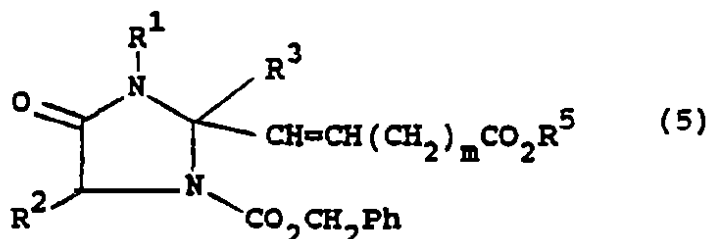
which R^3 is hydrogen, R^5 is methyl and n is 4 can be prepared by the procedure described in J. Org. Chem., 53, 1064 [1988].

Compounds of structure (3) in which R^3 is hydrogen R^5 is isobutyl and n is 2 can be prepared by reduction of a compound of structure $HCOCH=CHCO_2iBu$. This process is new and forms a further aspect of the present invention. Suitably the reaction is carried out in a C_{1-4} alkanol, in the presence of a noble metal catalyst at atmospheric pressure; preferably the reaction is carried out in 96% ethanol in the presence of a 5% palladium on charcoal catalyst.

Compounds of the structure (4) in which R^4 is hydrogen can be prepared by hydrogenation of compounds of structure (5)

10

15



in which R^1 to R^3 are as described for structure (1) m is 0, 1 or 2 and R^5 is hydrogen or C_{1-4} alkyl or benzyl; or directly from the appropriate compounds of structure (2) in which R^4 is hydrogen and (3). Alternatively, compounds of structure (4) in which R^4 is hydrogen can be obtained by catalytic hydrogenation of compounds of structure (4) in which R^4 is benzyl, which, in turn, can be prepared from the appropriate compounds of structure (2), in which R^4 is benzyl, and (3). Suitably the hydrogenations are carried out under conditions which remove the N-protecting groups and also reduce the side-chain double bond, when present, for example by using a noble metal catalyst, such as palladium on charcoal in a suitable solvent, such as ethanol. When R^5 is benzyl, compound (4) in which R^5 is hydrogen is directly obtained.

Compounds of structure (5) can themselves be prepared by reaction between compound of structure (2) in which R^4 is $PhCH_2OCO$ and an appropriate carbonyl compound of structure (6)

$$R^3COCH=CH(CH_2)_mCO_2R^5 \quad (6)$$

in which R^3 , R^5 and m are as hereinbefore described.

The reaction is carried out in a suitable solvent at elevated temperature, optionally in the presence of a suitable catalyst. Preferably the reaction is carried out in toluene at elevated temperature, in the presence of p-toluenesulphonic acid monohydrate as described in, Tetrahedron, 41, 611, 1985.

The starting compounds (2) in which R^4 is $PhCH_2$ or $PhCH_2OCO$ and (6) can be prepared by methods known to those skilled in the art or analogous to those known in the art; for example compounds of structure (2) in which R^1 and R^2 are hydrogen and R^4 is $PhCH_2OCO$ can be prepared by procedures described in J. Am. Chem. Soc., 73, 2936 [1951], compounds of structure (2) in which R^1 and R^2 are hydrogen and R^4 is benzyl can be prepared by procedures described in Synthesis, 1983, 329; and, for example, compounds of structure (6) in which R^3 is hydrogen, R^5 is ethyl and m is 2 can be prepared by procedures described in J. Pharm. Soc. Japan, 75, 622 [1955]; compounds of structure (6) in which R^3 is methyl, R^5 is methyl and m is 0 can be prepared by the procedure described in J. Am. Chem. Soc., 68, 2510 [1946]; compounds of structure (6) in which R^3 is methyl, R^5 is ethyl and m is 0 can be prepared by procedures described in Annalen der Chemie, 264, 248 [1891]. In particular compound (6) in which R^3 is hydrogen, R^5 is isobutyl and m is 0 can be prepared by base catalyzed rearrangement of isobutyl 3,4-epoxybutanoate (whose preparation is described in E.P. Appl. 154,490) and subsequent oxidation with methods known to those skilled in the art or analogous to those known in the art; for example with a transition metal compound as described in "Oxidation" Vol.1, by D.G.Lee; R.L. Augustine Ed., (Dekker 1969).

The compounds of structure (1) are of use as therapeutic agents and in particular have nootropic activity, that is to say they help restore learning and memory difficulties associated with ageing and various pathologies including for example Alzheimer's disease.

The present invention therefore provides, in a further aspect a method of restoring learning and treating memory difficulties which comprises administering to a mammal in need thereof a non-toxic effective amount of a compound of structure (1). The cognitive disorders occurring in such pathologies are known to be related to deficits in the brain cholinergic system as shown both by morphological (B.E. Tomlinson in "Biochemistry of Dementias"; P.J. Roberts Ed.; John Wiley & Sons, New York, N.Y. p.15-22, 1980) and neurochemical findings (R.T. Bartus et al., Science, 217, 408, 1982). It is also well known that significant

impairments of cognitive functions are the more evident and debilitating symptoms observed in patients with Alzheimer's disease, senile dementia of the Alzheimer type and multiinfarctual dementia. On the other hand, the anticholinergic drug scopolamine, produces in humans (D.A. Drachman, Archs. Neurol., Chicago, 30, 113, 1974) as well as in animals (D.A. Eckerman, Pharmacol. Biochem. Behav., 12, 595, 1980) a
5 significant memory loss, which is directly related to a decrease of acetylcholine concentration in specific cerebral areas such as the cerebral cortex and the hippocampus. On the basis of these premises, compounds of structure 1 have been specifically tested in rats against both the disruptive action of scopolamine on mnestic trace and on the reduction of acetylcholine levels in hippocampus. To evaluate the effect on memory and learning, one trial-step through-passive avoidance test in male Wistar rats (150-160
10 g) was used. The equipment was essentially the same described by Essman (Pharmacol.Res.Comm., 5, 295, 1973).

The passage from a light box into a dark one was punished by unavoidable electric foot shocks. The animals must learn to avoid, after a single learning session, the crossing from the light to the dark box. Thirty minutes after the first session (learning session), the learning effect was quantified (retest session) by
15 means of the latencies (in seconds) between the admission of animals into the light box and the entering into the dark one. The learning effect is substantially impaired by a treatment with scopolamine (0.63 mg/kg s.c.) sixty minutes before the learning session. Saline or the test compounds were administered i.p. thirty minutes before scopolamine. The control group was treated in the same way but with saline only. For example, results on compounds A (1, $R^1 = R^2 = R^3 = H$ and $n = 2$), B (1, $R^1 = R^2 = H$, $R^3 = Me$ and $n = 2$) and C
20 (1, $R^1 = H$, $R^2 = R^3 = Me$, $n = 2$ and the configuration at carbon in 3 position is S) in comparison with oxiracetam are given in Table 1.

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TABLE 1

One-trial step through passive avoidance test in rats:
activity of compound A and oxiracetam against amnesia
induced by scopolamine (0.63 mg/kg s.c.)

a	Dose mg/kg i.p.	Latencies		b
		Learning session	Retest session	
Treatment				Difference
SALINE	---	21.3	118.3	97.0 **
SCOPOLAMINE	---	20.3	72.5	52.2
A + SCOPOLAMINE	0.1	20.9	100.5	79.6 *
" + "	0.3	19.7	103.6	83.9 *
" + "	1	19.7	120.0	100.3 **
B + SCOPOLAMINE	0.1	20.4	98.4	78.0 *
" + "	0.3	18.6	102.3	83.7 *
" + "	1	21.1	119.0	97.9 **
C + SCOPOLAMINE	0.1	20.3	96.4	76.1 *
" + "	0.3	21.3	107.5	86.2 *
" + "	1	19.5	120.0	100.5 **
OXIRACETAM + SCOP.	3	21.5	78.0	56.5 n.s.
" + "	10	19.7	115.0	95.3 **
" + "	30	19.1	120.0	100.9 **

a) Twenty rats were used for each experimental group

b) cut-off time = 120 sec.

* Dunnett's test less than 0.05 versus scopolamine

** Dunnett's test less than 0.01 versus scopolamine

When used in the therapeutic treatment of humans and animals, the compounds of structure (1) are normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Therefore in another aspect the present invention there is provided a pharmaceutical composition which comprises a compound of structure (1) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of the structure (1) may be administered in standard manner for the treatment of the indicated diseases, for example orally, parenterally, rectally, transdermally or by transmucosal (for example sub-lingual, or buccal or insufflatory) administration.

The compounds of the structure (1) which are active when given orally or via sub-lingual or buccal administration 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, 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, 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 utilised, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound of the structure (1) 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.

A typical suppository formulation comprises a compound of structure (1) 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.

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

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

Oxiracetam is a compound which is used in the treatment of senile dementia and related disease conditions. The compounds of structure (1) can be administered in similar regimes to those established for oxiracetam with any appropriate adjustment in dose levels or frequency of dosing having regard to the greater activity and better pharmacological profile of the compounds of structure (1).

Each dosage unit for oral administration contains suitably from 0.05 mg/Kg to 20 mg/Kg, and preferably from 0.1 mg/Kg to 5 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.05 mg/Kg to 10 mg/Kg, of a compound of structure (1).

The daily dosage regimen for oral administration is suitably about 0.05 mg/Kg to 50 mg/Kg, more suitably about 0.1 mg/Kg to 20 mg/Kg of a compound of structure (1). The active ingredient may be administered from 1 to 6 times daily. The compounds of structure (1) may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially, particularly with other compounds used in the treatment of elderly patients e.g. tranquillisers, diuretics, antihypertensives, vasodilators and inotropic agents.

The invention is illustrated by the following Examples.

Preparation 1

A) Isobutyl (E)-4-hydroxy-2-butenate

To an ice cold solution of Isobutyl 3,4-epoxybutanoate (300 g, 1.9 mol) in toluene (2.5 l), sodium hydride (55% suspension in oil, 3 g, 0.07 mol) was added portionwise. The solution was stirred at 0-5 °C for 1 hour, then 55% sodium hydride (3 g, 0.07 mol) was added again. After stirring at room temperature for 1 hour the solution was washed with brine (0.4 l) containing 10% hydrochloric acid (60 ml), then twice with brine (300 ml each). The organic solution was dried over anhydrous sodium sulfate and evaporated to dryness. Distillation of the residue afforded 175 g (58.3%) of the title compound as a colourless oil, b.p. 89-90 °C (0.5 mmHg).

NMR (CDCl₃): δ_{H} = 7.05 (dt, J = 15 and 4 Hz, 1H, CH=CH-CO), 6.12 (dt, J = 15 and 2 Hz, 1H, CH=CH-CO), 4.40 (c.a. 2H, CH₂OH). MS (E.I., 70 eV, 1.5 mA) m/z = 127 (M-CH₂OH)⁺, 85 (M-C₃H₅O₂)⁺.

B) Isobutyl (E)-4-oxo-2-butenate

To a suspension of pyridinium, chlorochromate (100 g, 0.463 mol) in dichloromethane (350 ml), a solution of isobutyl (E)-4-hydroxycrotonate (50 g, 0.316 mol) in dichloromethane (150 ml) was added. The internal temperature gradually rose to 40 °C and stirring was continued for 2 hours without cooling. Diethyl

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ether (0.9 l) was added and the supernatant was decanted from the black gum. The insoluble residue was washed twice with 300 ml portions of diethyl ether. The combined organic solutions were passed through a short pad of Florisil and the solvent was removed by distillation, to yield 45.3 g (91.6%) of the title compound, as a pale yellow oil, $R_f = 0.5$ (silica gel plates, cyclohexane-ethyl acetate 6:4). NMR (CDCl_3): δ_{H} = 9.80 (ABX, 1H, CHO), 6.98 and 6.75 (ABX, $J_{\text{AB}} = 15$ Hz, 2H, $\text{CH}=\text{CH}$). MS (E.I., 70 eV, 1.5 mA) m/z = 155 ($\text{M}-\text{H}$)⁺, 85 ($\text{M}-\text{C}_3\text{H}_3\text{O}_2$)⁺.

C) Isobutyl 4-oxobutanoate

To a solution of isobutyl (E) 4-oxo-2-butenate (97 g, 0.62 mol) in 96% ethanol (800 ml), 5% palladium on charcoal (9.7 g) was added and hydrogen was bubbled at 5-10 °C and at atmospheric pressure for 20 hours. Removal of the catalyst and evaporation of the solvent gave 97.6 g (99%) of the title compound; $R_f = 0.41$ (silica gel plates, eluent: cyclohexane-ethyl acetate 6:4). NMR (CDCl_3): δ_{H} = 12.5 (d, $J = 1$ Hz, 1H, CHO); 3.85 (d, $J = 6$ Hz, 2H, COOCH_2); 2.80-2.40 (c.a., 4H, $\text{CH}_2\text{CH}_2\text{CO}$); 2.10-1.70 (c.a., 1H, CH_2CHMe_2); 0.90 (d, $J = 6$ Hz, 6H, CH_3). MS (E.I., 70 eV, 1.5 mA) m/z = 103 ($\text{M}-\text{C}_3\text{H}_3\text{O}$)⁺, 85 ($\text{M}-\text{C}_3\text{H}_3\text{O}_2$)⁺, 57 ($\text{M}-\text{C}_4\text{H}_5\text{O}_3$)⁺.

EXAMPLE 1

A) Isobutyl (E)-1-benzyloxycarbonyl-4-oxo-2-imidazolidineacrylate

To a solution of isobutyl (E)-4-oxo-2-butenate (11 g, 70.43 mmol) in toluene (170 ml) benzyloxycarbonylglycinamide (14.87 g, 70.43 mmol) and p-toluensulfonic acid monohydrate (0.67 g, 3.5 mmol) were added. The mixture was refluxed for 4 hours in a Dean-Stark apparatus. The obtained solution was cooled, the precipitate matter was filtered off and the filtrate was washed with a saturated solution of sodium hydrogen carbonate (50 ml) and brine (50 ml). The organic phase, dried over anhydrous sodium sulfate, was evaporated to dryness. The residue was chromatographed over silica gel (ethyl acetate-cyclohexane 1:1). The collected fractions were evaporated and the residue, triturated with diisopropyl ether, afforded 7.72 g (31.6%) of the title compound as a white solid, m.p. 97-100 °C. NMR (CDCl_3): δ_{H} = 6.80 (ABX, $J_{\text{AB}} = 15$ Hz, $J_{\text{AX}} = 7$ Hz, 1H, $\text{CH}=\text{CH}-\text{CO}$), 6.15 (c.a., 1H, $\text{CH}=\text{CH}-\text{CO}$), 5.70 (ABX, $J_{\text{AB}} = 7$ Hz, $\text{CH}=\text{CH}-\text{CH}$), 4.10 and 3.87 (ABq, $J = 16$ Hz, 2H, COCH_2N). MS (E.I., 70 eV, 1.5 mA) m/z = 346 (M)⁺, 239 ($\text{M}-\text{C}_7\text{H}_7\text{O}$)⁺, 91 (C_7H_7)⁺.

B) Isobutyl 4-oxo-2-imidazolidinepropanoate

To a solution of isobutyl (E)-1-benzyloxycarbonyl-4-oxo-2-imidazolidineacrylate (7.7 g, 22.2 mmol) in 96% ethanol (200 ml), 5% palladium on charcoal (0.5 g) was added and hydrogen was bubbled at 20 °C and at atmospheric pressure for 2 hours. Removal of the catalyst and evaporation of the solvent gave a residue which was triturated with diisopropyl ether to give 4.1 g (88%) of the title compound, m.p. 50-52 °C. NMR (CDCl_3): δ_{H} = 4.45 (t, $J = 6$ Hz, 1H, N-CH-N), 3.10 (s, 2H, N-CH₂-CO). MS (E.I., 70 eV, 1.5 mA) m/z = 214 (M)⁺, 157 ($\text{M}-\text{C}_4\text{H}_9$)⁺, 85 ($\text{M}-\text{C}_7\text{H}_{13}\text{O}_2$)⁺.

C) 2,5-Dioxohexahydro-1H-pyrrolo[1,2-a]imidazole

Isobutyl 4-oxo-2-imidazolidinepropanoate (4 g, 18.7 mmol) was stirred at 120-130 °C (external temperature) under vacuum for 3-5 hours. The residue was triturated with ethyl acetate to yield 0.75 g (28.6%) of the title compound, m.p. 155-157 °C. NMR (CDCl_3): δ_{H} = 5.45 (t, $J = 6$ Hz, 1H, CH), 4.23 and 3.80 (ABq, $J = 16$ Hz 2H, COCH_2N). MS (E.I., 70 eV, 1.5 mA) m/z = 140 (M)⁺, 97 ($\text{M}-\text{CONH}$)⁺.

EXAMPLE 2

2,5-Dioxo-7a-methylhexahydro-1H-pyrrolo[1,2-a]imidazole

To a solution of glycineamide hydrochloride (18.4 g, 0.166 mol) in water (200 ml), adjusted to pH 9.5 with 10% sodium hydroxide (about 60 ml), ethyl 4-oxopentanoate (20 g, 0.139 mol) was added. The solution was refluxed for 24 hours. After cooling the solvent was evaporated under vacuum and the residue was chromatographed over silica gel (dichloromethane-methanol 9:1) to afford 4.5 g (21%) of the title compound, m.p. 187-189 °C. NMR (CDCl₃): δ_{H} = 4.17 and 3.53 (ABq, J = 18 Hz, 2H, NCH₂CO), 1.5 (s, 3H, CH₃). MS (E.I., 70 eV, 1.5 mA) m/z = 154 (M⁺), 139 (M-CH₃)⁺, 111 (M-CONH)⁺.

EXAMPLE 3(3S)-3,7a-Dimethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole

L-Alaninamide hydrochloride (20.7 g, 0.166 mol) and ethyl 4-oxopentanoate (20 g, 0.13 mol) were reacted together according to the procedure of Example 2 to give the title compound, 4.5 g (19.1%), m.p. 228-230 ° (with decomposition), $[\alpha]_{\text{D}}^{20}$ = + 50.7° (c=3, H₂O).

NMR (CDCl₃): δ_{H} = 7.95 (bs, 1H, NH); 4.30 (q, J = 8 Hz, 1H, CHCH₃); 3.00-2.10 (c.a., 4H, CH₂CH₂); 1.60 (s, 3H, C-CH₃); 1.45 (d, J = 8 Hz, 3H, CH₃CH).

MS (E.I., 70 eV, 1.5 mA) m/z = 168 (M⁺), 153 (M-CH₃)⁺, 125 (M-CHNO)⁺, 112 (M-C₃H₄O)⁺.

EXAMPLE 4(3R,S)-3,7a-Dimethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole

DL-Alaninamide hydrochloride (6.9 g), 0.055 mol) and ethyl 4-oxopentanoate (6.7 g, 0.043 mol) were reacted together according to the procedure of Example 2 to give the title compound, 1.65 g (22.8%), m.p. 184-192 °.

NMR (DMSO-d₆): δ_{H} = 8.80 (bs, 1H, NH); 3.90 (q, J = 7.5 Hz, 1H, CHCH₃); 3.00-2.00 (c.a., 4H, CH₂CH₂); 1.42 (s, 3H, C-CH₃); 1.22 (d, J = 7.5 Hz, 1H, CHCH₃).

EXAMPLE 5A) Isobutyl (4S)-4-methyl-5-oxo-2-imidazolidinepropanoate

To a suspension of L-alaninamide hydrochloride (2.4 g, 19.3 mmol) in butanol (20 ml) isobutyl 4-oxobutanoate (3 g, 18.96 mmol) and sodium carbonate (1 g, 9.4 mmol) were added and the mixture was refluxed for 7 hours. After cooling the precipitate was filtered off and the filtrate was evaporated to dryness. The residue was chromatographed over silica gel (dichloromethane-methanol 9:1) to afford 0.87 g (20%) of the title compound.

Hydrochloride salt: m.p. 146-148 °C (with decomposition).

NMR (DMSO-d₆): δ_{H} = 9.20 (bs, 1H, CONH); 4.80 (t, J = 6 Hz, 1H, HN-CH-NH); 4.00 (q, J = 8 Hz, 1H, CHCH₃); 3.83 (d, J = 6 Hz, 2H, COOCH₂); 3.40 (bs, 1H, CHNHCH); 2.90-2.65 (c.a., 2H, CH₂CO); 2.25-1.75 (c.a., 3H, CH₂CH₂CO and CH(CH₃)₂); 1.37 (d, J = 6 Hz, 3H, CH₃CHNH); 0.87 (d, J = 6 Hz, 6H, CH(CH₃)₂).

MS (E.I., 70 eV, 1.5 mA) m/z = 228 (M⁺), 171 (M-C₄H₉)⁺, 155 (M-C₄H₉O)⁺, 99 (M-C₇H₁₃O₂)⁺.

B) (3S)-2,5-Dioxo-3-methylhexahydro-1H-pyrrolo[1,2-a]imidazole

Isobutyl (4S)-4-methyl-5-oxo-2-imidazolidinepropanoate (0.870 g, 3.8 mmol) was stirred without solvent

at 110-120 °C (external temperature) for 5 hours. The residue was chromatographed over silica gel (dichloromethane-methanol 9:1). The collected fractions were evaporated and the residue was triturated with diethyl ether, to afford 0.4 g (68.2%) of the title compound, m.p. 126-129 °C.

NMR (CDCl₃): δ_{H} = 8.02 (bs, 1H, CONH); 5.35 (t, J = 5 Hz, 1H, NCHNH); 4.30 (q, J = 8 Hz, 1H, NCHCH₃); 2.90-1.80 (c.a., 4H, COCH₂CH₂); 1.38 (d, J = 8 Hz, 3H, CH₃CH). MS (E.I., 70 eV, 1.5 mA) m/z = 154 (M⁺), 139 (M-CH₃)⁺, 111 (M-CH₂NO)⁺, 98 (M-C₃H₄O)⁺.

EXAMPLE 6

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(3R,S)-2,5-Dioxo-3-methylhexahydro-1H-pyrrolo[1,2-a]imidazole.

15 DL-Alaninamide hydrochloride (6.9 g, 0.055 mol) and isobutyl 4-oxobutanoate (7.3 g, 0.046 mol) were reacted together according the procedure of Example 2 to give the title compound, 1.7 g (24%), m.p. 84-86 °C.

NMR (DMSO-d₆): δ_{H} = 8.55 (bs, 1H, NH); 5.20 (t, J = 5 Hz, NCHNH); 3.92 (q, J = 6.5 Hz, 1H, CHCH₃); 2.82-1.50 (c.a., 4H, CH₂CH₂); 1.17 (d, J = 6.5 Hz, 3H, CHCH₃).

20 MS (E.I., 70 eV, 1.5 mA) m/z = 154 (M⁺), 111 (M-CHNO)⁺, 98 (M-C₃H₄O)⁺.

EXAMPLE 7

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A) Isobutyl (4S)-4-isobutyl-5-oxo-2-imidazolidinepropanoate

30 L-Leucinamide hydrochloride (3.2 g, 19.2 mmol) and isobutyl 4-oxobutanoate (3 g, 18.96 mmol) were reacted together according to the procedure of example 5A to give the title compound, 1.7 g (33%).

Hydrochloride salt: m.p. 187-188 °C (with decomposition).

NMR (DMSO-d₆): δ_{H} = 9.23 and 9.18 (bs, 1H, CONH); 4.92 and 4.85 (t, J = 6 Hz, 1H, NHCHNH); 4.10-3.80 (c.a., 1H, COCHNH); 3.82 (d, J = 6 Hz, 2H, COOCH₂); 2.70-2.40 (c.a., 2H, CH₂CO); 2.20-1.55 (c.a., 6H, CHCH₂CH(CH₃)₂, NHCHCH₂CH₂ and COCH₂CH(CH₃)₂); 0.92 and 0.87 (d, J = 6 Hz, 12H, CH(CH₃)₂). MS

35 (E.I., 70 eV, 1.5 mA) m/z = 270 (M⁺), 213 (M-C₄H₉)⁺, 141 (M-C₇H₁₃O₂)⁺.

B) (3S)-2,5-Dioxo-3-isobutylhexahydro-1H-pyrrolo[1,2-a]imidazole.

40 Isobutyl (4S)-4-isobutyl-5-oxo-2-imidazolidine propanoate (1.4 g, 5.4 mmol) was heated at 130-140 °C (external temperature) for 5 hours. Chromatography of the residue over silica gel (dichloromethane-methanol 9:1) gave the title compound, 0.45 g (45%) m.p. 156-157 °C.

NMR (CDCl₃): δ_{H} = 7.35 (bs, 1H, CONH); 5.30 (t, J = 6 Hz, 1H, NCHNH); 4.22 (c.a., 1H, NCHCO); 2.75-1.40 (c.a., 7H, CH₂CH₂ and CHCH₂CH); 1.03 and 0.90 (d, J = 6 Hz, 6H, CH₃). MS (E.I., 70 eV, 1.5 mA)

45 m/z = 196 (M⁺), 140 (M-C₃H₄O)⁺, 84 (M-C₆H₁₀NO)⁺.

EXAMPLE 8

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2,5-Dioxo-1-ethylhexahydro-1H-pyrrolo[1,2-a]imidazole.

55 Glycine ethylamide hydrochloride (2.1 g, 15.1 mmol) and isobutyl 4-oxobutanoate (2 g, 12.6 mmol) were reacted together according the procedure of Example 2 to give the title compound, 0.5 g (23.5%) as a viscous oil. R_f = 0.51 (silica gel plates, eluent dichloromethane-methanol 9:1).

NMR (CDCl₃): δ_{H} = 5.27 (t, J = 6 Hz, 1H, N-CH-N); 4.20 and 3.45 (ABq, J = 17 Hz, 2H, N-CH₂-CO); 3.25 (q, J = 7 Hz, 2H, NCH₂CH₃); 2.70-1.75 (c.a., 4H, COCH₂CH₂CH); 1.12 (t, J = 7 Hz, 3H, CH₃). MS (E.I., 70

eV, 1.5 mA) m/z = 168 (M^+), 112 ($M-C_3H_4O$) $^+$, 97 ($M-C_4H_7O$) $^+$.

EXAMPLE 9

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2,5-Dioxohexahydro-1H-pyrrolo[1,2-a]imidazole

10 Glycinamide hydrochloride (4.2 g, 38 mmol) and isobutyl 4-oxobutanoate (5 g, 31.6 mmol) were reacted together according to the procedure of example 2, to give the title compound 1 g (22.6%), m.p. 154-157°C.

EXAMPLE 10

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Ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetate

20 A mixture of 2,5-dioxohexahydropyrrolo-1H-[1,2-a]imidazole (0.5 g, 3.57 mmol), tetrabutylammonium bromide (0.57 g, 1.78 mmol) and potassium carbonate (2.5 g, 17.8 mmol) in dry acetonitrile (6 ml) was stirred at room temperature for 1 hour. Ethyl bromoacetate (0.5 ml, 4.53 mmol) was added and the suspension was heated at 60°C for 2.5 hours. The precipitate was filtered off, the filtrate was evaporated under vacuum and the residue was chromatographed over silica gel (ethyl acetate-acetone-methanol 6:3:1) to afford 0.7 g (92%) of the title compound, m.p. 75-80°C.

25 NMR ($CDCl_3$): δ_{H} = 5.40 (c.a., 1H, N-CH-N); 4.21 (q, J = 7.2 Hz, 2H, $COOCH_2CH_3$); 4.32 e 3.68 (ABq, J = 15.9 Hz, 2H, NCH_2CO); 4.30 and 3.80 (ABq, J = 17.8 Hz, 2H, $-CH_2COOEt$); 2.80-1.70 (c.a., 4H, CH_2CH_2) 1.28 (t, J = 7.2 Hz, 3H, $COOCH_2CH_3$). MS (E.I., 70 eV, 1.5 mA) m/z = 228 (M^+), 153 ($M-CO_2Et$) $^+$; 140 ($M-CH_2CO_2Et$) $^+$.

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EXAMPLE 11

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2,5-Dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetamide

A solution of ethyl 2,5-dioxohexahydropyrrolo[1,2-a]imidazole-1-acetate (1.4 g, 6.18 mmol), in methanol (25 ml) was saturated with ammonia at 0°C. After stirring at room temperature for 16 hours the precipitate 40 was collected, washed with methanol and dried to yield 0.9 g (75%) of the title compound, m.p. 182-185°C. NMR ($DMSO-d_6$): δ_{H} = 7.50 and 7.10 (2s, 2H, $CONH_2$); 5.25 (c.a. 1H, N-CH-N); 3.94 and 3.55 (ABq, J = 16 Hz, 2H, $N-CH_2CO$); 3.85 and 3.70 (ABq, J = 16.5 Hz, 2H, $N-CH_2CONH_2$); 2.90 and 1.90 (c.a., 4H, CH_2CH_2).

MS (E.I., 70 eV, 1.5 mA) m/z = 139 ($M-CH_2CONH_2$) $^+$.

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EXAMPLE 12

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A) Isobutyl (4S)-4-benzyl-5-oxo-2-imidazolidinepropanoate

To a solution of L-phenylalaninamide hydrochloride (20 g, 0.1 mol) in water (200 ml), adjusted to pH 8.2 with 10% sodium hydroxide (about 35 ml), was added isobutyl 4-oxobutanoate (16 g, 0.1 mol). The solution 55 was refluxed for 24 hours. After cooling, the solution was extracted with dichloromethane (4 x 200 ml). The organic phase was dried and evaporated to dryness under vacuum. The residue was chromatographed over silica gel (dichloromethanemethanol 9:1) to afford 6 g (20%) of the title compound, as an oil, which was characterized as the hydrochloride, m.p. 152-155°C (with decomposition) (after crystallization from ethanol-

diethyl ether).

NMR (DMSO- d_6 , $CDCl_3$): $\delta_{H1} = 9.25$ (b.s., 1H, CONH); 7.6-7.1 (c.a., 5H, PhH); 4.90 (t, J = 6.1 Hz, 1H, NHCHNH); 4.17 (t, J = 6.1 Hz, 1H, CHCH₂Ph); 3.84 (d, J = 6.9 Hz, 2H, COOCH₂CH); 3.35 (c.a., 2H, CH₂Ph); 2.50-1.60 (c.a., 5H, CH₂CH₂COO, CH₂CH(CH₃)₂). MS (E.I., 70 eV, 1.5 mA) $m/z = 304$ (M^+), 213 ($M-C_7H_7$), 84 ($C_3H_4N_2O$).

B) (3S)-3-Benzyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole

A solution of isobutyl (4S)-4-benzyl-5-oxo-2-imidazolidinepropanoate (2.3 g, 7.33 mmol) in toluene (100 ml) was refluxed for 8 days. After evaporation of the solvent, the residue was chromatographed over silica gel (dichloromethane-methanol 9:1). The appropriate fractions were collected and evaporated; the residue was triturated with diethyl ether to afford 850 mg (50%) of the title compound, m.p. 141-145 °C. NMR ($CDCl_3$): $\delta_{H1} = 7.25$ (s, 5H, PhH); 7.02 (b.s., 1H, NH); 4.52 (t, J = 4.5 Hz, 1H, PhCH₂CH); 4.37 (t, J = 5 Hz, 1H, NCHNH); 3.13 (d, J = 4.5 Hz, 2H, PhCH₂); 2.80-1.6 (c.a., 4H, CH₂CH₂). MS (E.I., 70 eV, 1.5 mA) $m/z = 230$ (M^+), 139 ($M-C_7H_7$), 91 (C_7H_7), 84 (C_4H_6NO).

EXAMPLE 13

(3S)-3-Hydroxymethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole

L-Serine hydrochloride (10 g, 0.071 mol) and isobutyl 4-oxo-butanoate (11.25 g, 0.071 mol) were reacted together according to the procedure of Example 2 to afford, after chromatography over silica gel (dichloromethane-methanol 8:2), 2.3 g (19%) of the title compound, m.p. 150-162 °C. NMR (DMSO- d_6): $\delta_{H1} = 8.57$ (b.s., 1H, NH); 5.15 (t, J = 5 Hz, 1H, N-CH-NH); 4.97 (ABCX System, 1H, CH₂OH); 3.88-3.81 (ABCX System, 1H, CHCH₂OH); 3.87-3.40 (ABCX System, 2H, CH₂OH); 2.85-1.52 (c.a., 4H, CH₂-CH₂). MS (E.I., 70 eV, 1.5 mA) $m/z = 140$ ($M-CH_2O$), 84 ($C_3H_4N_2O$) and, as a by-product, 0.25 g of isobutyl (4S)-4-hydroxymethyl-5-oxo-2-imidazolidinepropanoate, m.p. 61-75 °C. NMR (DMSO- d_6): $\delta_{H1} = 8.1$ (b.s., 1H, CONH); (c.a., 2H, NHCHNH, CH); 3.75 (d, J = 6.1, 2H, COOCH₂CH); 3.55-2.90 (c.a., 4H, NH, CH-CH₂-OH); 2.50-2.30 (c.a., 2H, CH₂COO); 2.00-1.40 (c.a., 3H, CH(CH₃)₂, CH₂CH₂COO); 0.84 (d, J = 6.1 Hz, 6H, CH(CH₃)₂). MS (E.I., 70 eV, 1.5 mA) $m/z = 213$ ($M-CH_2OH$), 115 ($C_6H_{11}O_2$), 85 ($C_3H_5N_2O$).

EXAMPLE 14

A) 2-Carboxy-4-oxo-2-imidazolidinepropanoic acid

A solution of 2-oxoglutaric acid (10 g, 0.068 mol), glycineamide hydrochloride (8.3 g, 0.075 mol) and sodium hydroxide (8.2 g, 0.205 mol) in water (120 ml) was refluxed for 4 hours. After cooling the solution was adjusted to pH 2.5 and the resulting precipitate was collected and dried under vacuum at 60 °C to afford 5.9 g (43%) of the title compound, m.p. 202-205 °C. NMR (DMSO- d_6): $\delta_{H1} = 8.5$ (s, 1H, CONH); 7.00-4.00 (b.s., 3H, NH, COOH); 3.22 and 3.18 (ABq, J = 18 Hz, 2H, NHCH₂CO); 2.40-1.75 (c.a., 4H, CH₂CH₂COOH). MS (E.I., 70 eV, 1.5 mA) $m/z = 140$ ($M-H_2O-COOH$), 84 ($C_3H_4N_2O$).

B) 2,5-Dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylic acid

A mixture of 2-carboxy-4-oxo-2-imidazolidinepropanoic acid (2 g, 9.89 mmol), hexamethyldisilazane (20 ml) and trimethylchlorosilane (10 ml) in dry acetonitrile (50 ml) was refluxed under nitrogen for 4 hours. After cooling, the precipitate was filtered off and the filtrate was evaporated under vacuum. The residue was dissolved in methanol (20 ml) containing some drops of concentrated hydrochloric acid and stirred for 10 minutes. The insoluble material was filtered off and the filtrate was evaporated to dryness. The residue was

trituated with acetonitrile and crystallized with tetrahydrofuran (250 ml) to yield 0.9 g (50%) of the title compound, m.p. 207 °C (with decomposition). NMR (DMSO-d₆): δ_{H} : 9.20 (b.s., 1H, NH); 3.82 and 3.46 (ABq, J = 16.8 Hz, 2H, NCH₂CO); 2.90-1.80 (c.a., 4H, CH₂-CH₂). MS (E.I., 70 eV, 1.5 mA) m/z = 184 (M⁺), 139 (M-COOH)⁺, 83 (C₃H₃N₂O)⁺.

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EXAMPLE 15

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Ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylate

A solution of 2,5-dioxohexahydropyrrolo-1H-[1,2-a]imidazole-7a-carboxylic acid (0.8 g, 4.34 mmol) in dry tetrahydrofuran (100 ml), was cooled to 0 °C, treated with oxalyl chloride (0.56 g, 4.34 mmol) and a drop of dimethylformamide and stirred for 2 hours at 0 °C. The solution was stirred under vacuum at room temperature for 10 minutes. After cooling to 0 °C, 4-dimethylaminopyridine (0.53 g, 4.34 mmol) and dry ethanol (2 ml) were added. The suspension was stirred at 0 °C for 30 minutes and at room temperature for 30 minutes. The precipitate was filtered off and the filtrate was evaporated under vacuum. The residue was chromatographed over silica gel (ethyl acetate-methanol 95:5) to afford 0.45 g (49%) of the title compound, m.p. 116 °C. NMR (DMSO-d₆): δ_{H} = 9.22 (b.s., 1H, NH); 4.16 (q, J = 7.4 Hz, 2H, COOCH₂CH₃); 3.85 and 3.48 (ABq, J = 14.8, 2H, NCH₂CO); 2.95-2.05 (c.a., 4H, CH₂CH₂); 1.2 (t, J = 7.4 Hz, 3H, COOCH₂CH₃). MS (E.I., 70 eV, 1.5 mA) m/z = 183 (M-C₂H₅)⁺, 139 (M-COOC₂H₅)⁺, 83 (C₃H₃N₂O)⁺.

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EXAMPLE 16

2,5-Dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxamide

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An ice cold solution of ethyl 2,5-dioxo-1H-hexahydropyrrolo [1,2-a]imidazole-7a-carboxylate (2.55 g, 12 mmol) in dry methanol (20 ml) was treated with a saturated solution of ammonia in methanol (40 ml) and stirred for 1 hour at 0 °C. The precipitate was collected, washed with acetone and dried to afford 1.7 g (77%) of the title compound m.p. 295 °C (with decomposition). NMR (DMSO-d₆): δ_{H} = 9.05 (b.s., 1H, NH); 7.50 (b.s., 2H, CONH₂); 3.80 and 3.50 (ABq, J = 14.8 Hz, 2H, NCH₂CO); 2.85-1.95 (c.a., 4H, CH₂CH₂). MS (E.I., 70 eV, 1.5 mA) m/z = 139 (M-CONH₂)⁺, 83 (C₃H₃N₂O)⁺.

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EXAMPLE 17

2,5-Dioxo-1H-octahydroimidazo[1,2-a]pyridine

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Glycinamide hydrochloride (4.24 g, 38.4 mmol) and methyl 5-oxopentanoate (5 ml, 38.4 mmol) were reacted together according to the procedure of example 2, to give 1.8 g (30%) of the title compound, m.p. 170-174 °C. NMR (DMSO-d₆): δ_{H} = 8.65 (b.s., 1H, CONH); 5.10-4.85 (c.a., 1H, NCHNH); 3.90 and 3.55 (ABq, J = 14.8 Hz, 2H, N-CH₂-CO); 2.40-1.10 (c.a., 6H, (CH₂CH₂CH₂)). MS (E.I., 70 eV, 1.5 mA) m/z = 153 (M-H)⁺, 111 (M-CONH)⁺, 84 (C₃H₄N₂O)⁺.

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EXAMPLE 18

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A) Methyl 4-oxo-2-imidazolidinepentanoate

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Glycinamide hydrochloride (6.73 g, 0.061 mol) and methyl 6-oxohexanoate (8.8 ml, 0.061 mol) were reacted together according to the procedure of example 2, to give 0.93 (7.6%) of the title compound, m.p. 58-60 °C (with decomposition). NMR (DMSO-d₆): δ_{H} = 8.10 (b.s., 1H, CONH); 4.50-4.15 (c.a., 1H, NHCHNH); 3.55 (s, 3H, COOCH₃); 3.20 (b.s., 1H, CH₂NHCH); 3.05 (s, 2H, NHCH₂CO); 2.45-2.10 (c.a., 2H, CH₂COO); 1.80-1.10 (c.a., 6H, CH₂CH₂CH₂CH₂COO). MS (E.I., 70 eV, 1.5 mA) m/z = 200 (M^+), 169 (M -OCH₃), 85 (C₃H₅N₂O).

B) 2,5-Dioxo-1H-octahydroimidazo[1,2-a]azepine

A solution of methyl 4-oxo-2-imidazolidinepentanoate (1 g, 5 mmol) in toluene (300 ml) was refluxed for 80 hours. After cooling the solution was evaporated and the residue was chromatographed over silica gel (dichloromethane-methanol 9:1) to afford 0.2 g (23%) of the title compound, m.p. 175-176 °C. NMR (DMSO-d₆) δ_{H} = 8.60 (b.s., 1H, CONH); 5.35-5.10 (c.a., 1H, NCHNH); 3.70 (s, 2H, NCH₂CO); 2.60-2.10 (c.a., 2H, CH₂CH₂CON); 2.10-1.10 (c.a., 6H, CH₂CH₂CH₂). MS (E.I., 70 eV, 1.5 mA) m/z = 168 (M^+), 85 (C₃H₅N₂O).

EXAMPLE 19

A) Isobutyl 3-benzyl-5-oxo-2-imidazolidinepropanoate hydrochloride

A solution of N-benzylglycinamide (3.7 g, 0.022 mol) and isobutyl 4-oxobutanoate (4 g, 0.023 mol) in dioxane (40 ml) and water (10 ml) was heated at 100 °C for 10 hours. After cooling, the solvent was removed under vacuum and the residue was treated with 10% hydrochloric acid (8 ml) to give a precipitate which was collected and triturated with acetone to afford 3.6 g (47%) of the title compound, m.p. 177 °C (with decomposition). NMR (DMSO-d₆): δ_{H} = 9.2 (b.s., 1H, NH); 7.80-7.30 (c.a., 5H, PhH); 4.90 (t, J = 5 Hz, 1H, N-CH-NH); 4.50 and 4.30 (ABq, J = 13.6 Hz, 2H, CH₂Ph); 3.80 (d, J = 6.1 Hz, 2H, COOCH₂CH); 3.68 (s, 2H, CONH₂N); 2.65-2.35 (c.a., 2H, CH₂CH₂COO); 2.20 - 1.50 (c.a., 3H, CH(CH₃)₂ and CH₂CH₂COO); 0.88 (d, J = 6.1 Hz, 6H, CH(CH₃)₂). MS (E.I., 70 eV, 1.5 mA) m/z = 304 (M^+), 175 (M -C₇H₁₃O₂), 91 (C₇H₇).

B) Isobutyl 5-oxo-2-imidazolidinepropanoate hydrochloride

To a mixture of 10% palladium on charcoal (1 g) and 99% formic acid (1 ml) in methanol (25 ml), under nitrogen, was added a solution of isobutyl 3-benzyl-5-oxo-2-imidazolidinepropanoate hydrochloride (1 g, 2.93 mmol) and 99% formic acid (1.25 ml) in methanol (25 ml). The mixture was stirred under nitrogen for 6 hours. After addition of water (15 ml) and removal of the catalyst, the solvent was evaporated and the residue was triturated with ethanol to give 0.3 g (41%) of the title compound, m.p. 136-140 °C. The same compound was obtained also by the following procedure: into a mixture of isobutyl 3-benzyl-5-oxo-2-imidazolidinepropanoate hydrochloride (2.2 g, 6.4 mmol), and 10% palladium on charcoal (1.1 g) in water-methanol 2:1 (150 ml) hydrogen was bubbled at room temperature and at atmospheric pressure for 2 hours. Removal of the catalyst and evaporation of the solvent under reduced pressure gave a residue which was triturated with ethanol to afford 1.4 g (90%) of the title compound, m.p. 136-140 °C. NMR (DMSO-d₆): δ_{H} = 11.1-9.50 (b.s., 2H, NH₂); 9.20 (b.s., 1H, CONH); 4.95 (t, J = 6.2 Hz, 1H, NHCHNH); 3.84 (d, J = 6.7 Hz, 2H, COOCH₂); 3.65 (s, 2H, NCH₂CO); 2.70-2.30 (c.a., 2H, CH₂CH₂COO); 2.25-1.60 (c.a., 3H, CH₂CH₂COO, CH(CH₃)₂); 0.87 (d, J = 6.7 Hz, 6H, CH(CH₃)₂). MS (E.I., 70 eV, 1.5 mA) m/z = 214 (M^+), 141 (M -OC₄H₉), 85 (C₃H₅N₂O).

C) 2,5-Dioxohexahydro-1H-pyrrolo[1,2-a]imidazole

A solution of isobutyl 5-oxo-2-imidazolidinepropanoate hydrochloride (1.4 g, 5.76 mmol) in water (100 ml) was treated with sodium hydrogen carbonate (0.54 g, 6.4 mmol) and heated at 100 °C for 20 hours. The solution was evaporated and the residue was chromatographed over silica gel (ethyl acetate-acetone-methanol 6:3:1) to afford 300 mg (37%) of the title compound, m.p. 155-157 °C.

EXAMPLE 205 A) Ethyl 1-benzyl-4-oxo-2-imidazolidinepropanoate

A suspension of N-benzylglycinamide (35.5 g, 0.22 mol) and ethyl 4-oxobutanoate (31 g, 0.24 mol) in toluene (370 ml) was refluxed for 6 hours in a Dean-Stark apparatus. After cooling, the mixture was extracted twice with 10% sulphuric acid (200 + 100 ml); the aqueous extracts were neutralized with sodium hydrogen carbonate and extracted twice with toluene (250 ml each time). The organic solution was washed with water (100 ml), dried (MgSO₄) and evaporated under vacuum to afford an oil which was triturated with a mixture of diethyl ether -light petroleum (1:2) to give 45 g (75%), of the title compound as a yellow solid, m.p. 60-62 °C.

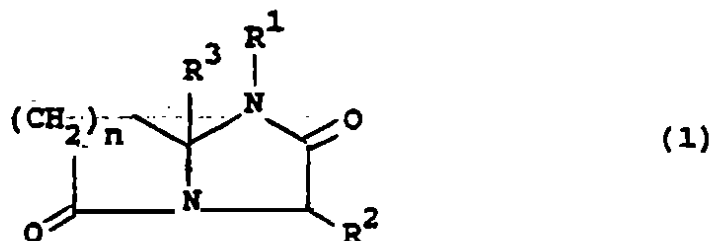
NMR (CDCl₃): δ = 7.5 (bs, 1H, NH); 7.30 (bs, 5H, PhH); 4.5-4.25 (ABX, 1H, CH-M); 4.13 (q, J = 6.9 Hz, 2H, OCH₂); 4.00 and 3.53 (ABq, J = 12.4 Hz, 2H, PhCH₂); 3.37 and 3.02 (ABX, J = 14.9 Hz, 2H, NCH₂CO); 2.65-2.30 (c.a., 2H, CH₂CH₂CO); 2.20-1.15 (c.a., 2H, CH₂CH₂CO); 1.24 (t, J = 6.9 Hz, 3H, CH₃). MS (E.I., 70 eV, 1.5 mA) m/z = 276 (M⁺), 231 (M-OEt), 185 (M-PhCH₂), 175 (M-C₅H₅O₂), 91 (PhCH₂)⁺.

20 B) 2,5-Dioxohexahydro-1H-pyrrolo[1,2-a]imidazole

To a suspension of 10% palladium on charcoal (11.6 g) in water (60 ml), a solution of ethyl 3-benzyl-5-oxo-2-imidazolidinepropanoate (58 g, 0.21 mol) and ammonium formate (52.9 g, 0.84 mol) in methanol (580 ml) were added. The mixture was refluxed under nitrogen for 1 hour. After cooling to 40 °C, 32% ammonia (145 ml) was added and the temperature was maintained between 40 and 50 °C for 1.5 hours. After cooling to room temperature, the catalyst was removed by filtration and the solution was evaporated to dryness. The residue was diluted with water (700 ml) and stirred in the presence of ion exchange resins Amberlite IR 120 H (200 ml) and Amberlite IRA 68 (200 ml) for 1.5 hours. The resins were filtered off and washed with water (600 ml). The clear solution was evaporated under vacuum at 60 °C to afford an oil which was dried by azeotropic distillation with ethanol. The resulting residue was triturated with acetone (75 ml) to afford 19.7 g (67%) of the title compound as a white solid, m.p. 154-157 °C.

Claims

1. A compound of structure (1)



in which,

R¹ is hydrogen, C₁₋₄alkyl, CHR⁶CONHR⁷ or CHR⁶COOR⁷ in which R⁶ and R⁷ are each hydrogen or C₁₋₄alkyl;

R² is hydrogen, C₁₋₅alkyl or a residue R² of an amino acid R² CH(NH₂)COOH

R³ is hydrogen, C₁₋₄alkyl, CONH₂ or CO₂R⁸ in which R⁸ is hydrogen or C₁₋₄alkyl, and n is 2, 3 or 4.

2. A compound of structure (1) as claimed in claim 1 in which R¹ to R³ are each hydrogen.

3. A compound of structure (1) as claimed in claim 1 which is :

2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole

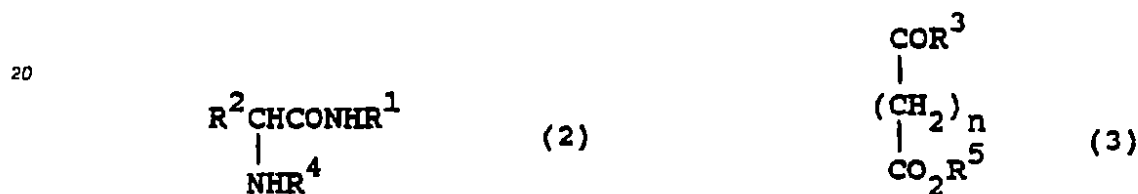
2,5-dioxo-7a-methylhexahydro-1H-pyrrolo[1,2-a]imidazole

(3S)-3,7a-dimethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole

(3R,S)-3,7a-dimethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole

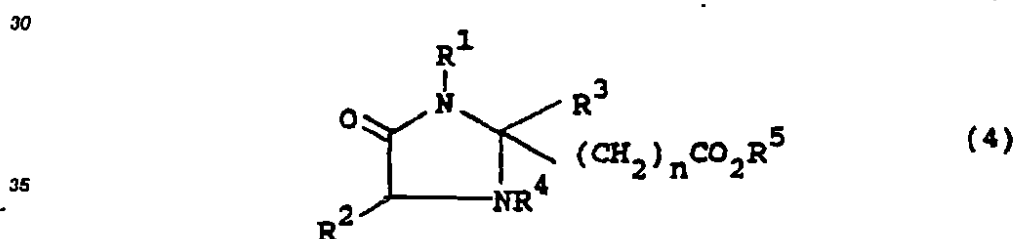
37

- (3S)-2,5-dioxo-3-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
 (3R,S)-2,5-dioxo-3-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
 (3S)-2,5-dioxo-3-isobutylhexahydro-1H-pyrrolo[1,2-a]imidazole
 2,5-dioxo-1-ethylhexahydro-1H-pyrrolo[1,2-a]imidazole
 5 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetate
 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetamide
 (3S)-3-benzyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 (3S)-3-hydroxymethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 10 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylic acid
 ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylate
 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxamide
 2,5-dioxo-1H-octahydroimidazo[1,2-a]pyridine, or
 2,5-dioxo-1H-octahydroimidazo[1,2-a]azepine.
 15 4. A process for the preparation of a compound of structure (1) as claimed in claim 1 which comprises :
 a) reaction of a compound of structure (2) with a compound of structure (3) :



in which R¹ to R³ and n are as described for structure (1), R⁴ is hydrogen and R⁵ is hydrogen, C₁₋₄ alkyl or benzyl; or

b) cyclization of a compound of structure (4)



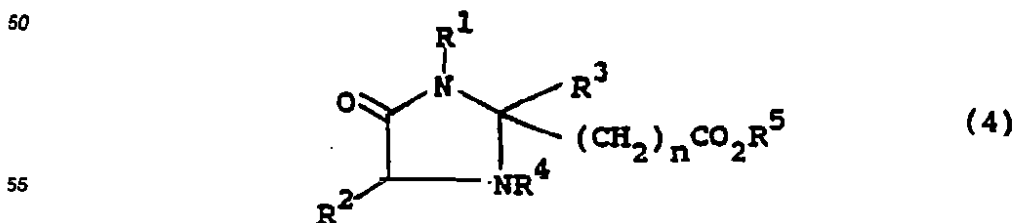
in which R¹ to R³ and n are as described for structure (1), R⁴ is hydrogen and R⁵ is hydrogen, C₁₋₄ alkyl or benzyl.

5. A process according to claim 4(b) in which the cyclization of the compound of structure (4) is carried out in the presence of ammonium hydroxide.

6. A process for the preparation of a compound of structure (3) in which R³ is hydrogen, R⁵ is isobutyl and n is 2, which comprises reduction of a compound of structure :

HCOCH = CHCO₂iBu

7. A compound of structure (4)



in which R^1 to R^3 and n are as described for structure (1) in claim 1, R^4 is hydrogen and R^5 is hydrogen, C_1 - ∞ alkyl or benzyl.

8. A pharmaceutical composition comprising a compound of structure (1) as claimed in claim 1 and a pharmaceutically acceptable carrier.

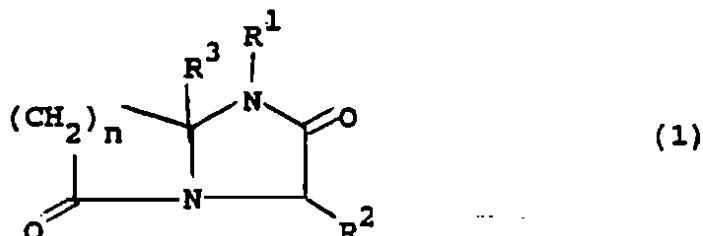
9. A pharmaceutical composition according to claim 8 in which the compound of structure (1) is 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole.

10. A compound of structure (1) as claimed in claim 1 for use as a therapeutic agent.

11. A compound of structure (1) as claimed in claim 1 for use as a nootropic agent.

Claims for the following Contracting State: ES

1. A process for the preparation of a compound of structure (1)



in which,

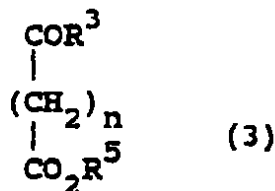
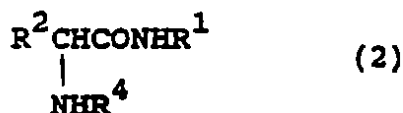
R^1 is hydrogen, C_1 - ∞ alkyl, CHR^6CONHR^7 or CHR^6COOR^7 in which R^6 and R^7 are each hydrogen or C_1 - ∞ alkyl;

R^2 is hydrogen, C_1 - ∞ alkyl or a residue R^2 of an amino acid $R^2 CH(NH_2)COOH$

R^3 is hydrogen, C_1 - ∞ alkyl, $CONH_2$ or CO_2R^8 in which R^8 is hydrogen or C_1 - ∞ alkyl, and n is 2, 3 or 4.

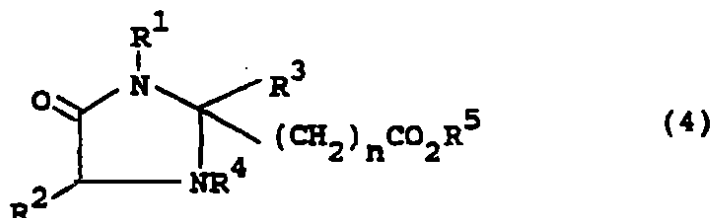
which comprises :

a) reaction of a compound of structure (2) with a compound of structure (3) :



in which R^1 to R^3 and n are as described for structure (1), R^4 is hydrogen and R^5 is hydrogen, C_1 - ∞ alkyl or benzyl; or

b) cyclization of a compound of structure (4)



in which R^1 to R^3 and n are as described for structure (1), R^4 is hydrogen and R^5 is hydrogen, C_1 - ∞ alkyl or benzyl.

2. A process according to claim 1(a) in which the reaction is carried out in the presence of a base.

3. A process according to claim 2 in which the base is selected from sodium hydroxide or sodium carbonate.

4. A process according to claim 1(b) in which the cyclization is carried out in the presence of ammonium hydroxide.

5. A process according to any one of claims 1 to 4 in which in the compound of structure (1) R¹ to R³ are each hydrogen.

6. A process according to any one of claims 1 to 4 in which the compound of structure (1) so prepared is selected from

- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
- 2,5-dioxo-7a-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
- (3S)-3,7a-Dimethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
- (3R,S)-3,7a-dimethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
- (3S)-2,5-dioxo-3-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
- (3R,S)-2,5-dioxo-3-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
- (3S)-2,5-dioxo-3-isobutylhexahydro-1H-pyrrolo[1,2-a]imidazole
- 2,5-dioxo-1-ethylhexahydro-1H-pyrrolo[1,2-a]imidazole
- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
- Ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetate
- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetamide
- (3S)-3-benzyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
- (3S)-3-hydroxymethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylic acid
- ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylate
- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxamide
- 2,5-dioxo-1H-octahydroimidazo[1,2-a]pyridine, or
- 2,5-dioxo-1H-octahydroimidazo[1,2-a]azepine.

7. A process for preparing a pharmaceutical composition which comprises bringing into association a compound of structure (1) as described in claim 1 and a pharmaceutically acceptable carrier.

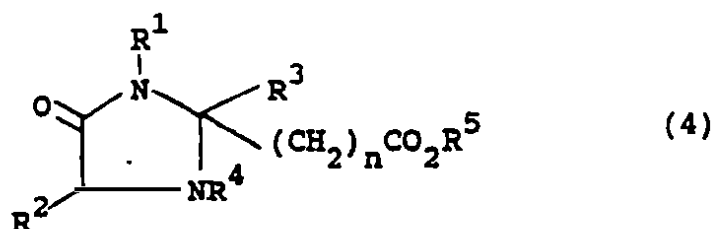
8. A process according to claim 7 in which the compound of structure (1) is selected from :

- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
- 2,5-dioxo-7a-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
- (3S)-3,7a-dimethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
- (3R,S)-3,7a-dimethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
- (3S)-2,5-dioxo-3-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
- (3R,S)-2,5-dioxo-3-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
- (3S)-2,5-dioxo-3-isobutylhexahydro-1H-pyrrolo[1,2-a]imidazole
- 2,5-dioxo-1-ethylhexahydro-1H-pyrrolo[1,2-a]imidazole
- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
- ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetate
- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetamide
- (3S)-3-benzyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
- (3S)-3-hydroxymethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylic acid
- ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylate
- 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxamide
- 2,5-dioxo-1H-octahydroimidazo[1,2-a]pyridine, or
- 2,5-dioxo-1H-octahydroimidazo[1,2-a]azepine.

9. A process for the preparation of a compound of structure (3) as described in claim 1 in which R³ is hydrogen, R⁵ is isobutyl and n is 2 which comprises reduction of a compound of structure

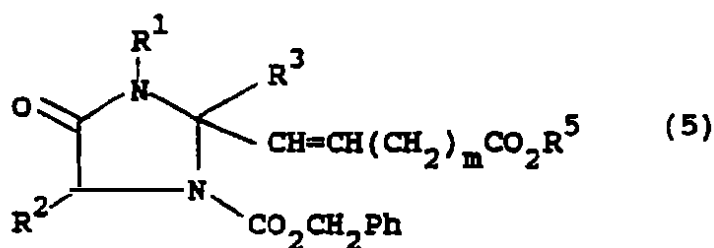
HCOCH = CHCO₂iBu

10. A process for preparing a compound of structure (4) :



10 in which R¹ to R³ and n are as described for structure (1) as claimed in claim 1, R⁴ is hydrogen and R⁵ is hydrogen, C₁-4alkyl or benzyl, which comprises :

a) hydrogenation of compounds of structure (5)

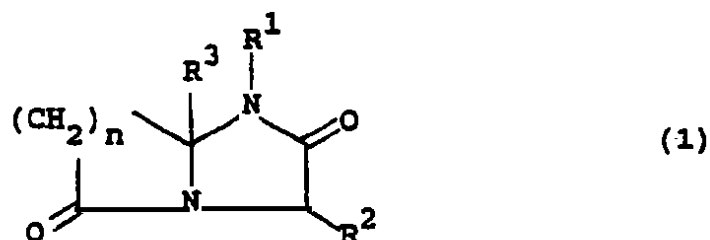


in which R¹ to R³ are as described for structure (1) in claim 1, m is 0 to 2 and R⁵ is hydrogen or C₁-4alkyl or benzyl; or

25 b) hydrogenation of compounds of structure (4), in which R⁴ is benzyl and R¹ to R³ and R⁵ are as described above.

30 Claims for the following Contracting State: GR

1. A process for the preparation of a compound of structure (1)



in which,

45 R¹ is hydrogen, C₁-4alkyl, CHR⁶CONHR⁷ or CHR⁶COOR⁷ in which R⁶ and R⁷ are each hydrogen or C₁-4alkyl;

R² is hydrogen, C₁-5alkyl or a residue R² of an amino acid R² CH(NH₂)COOH

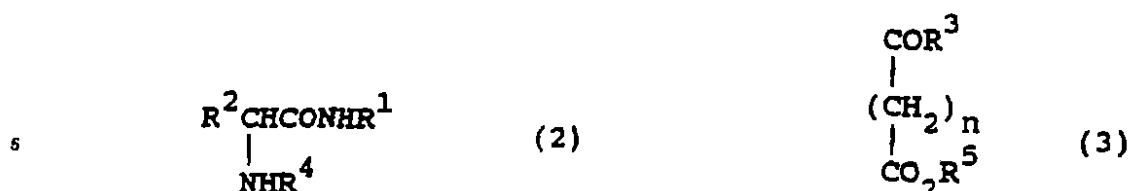
R³ is hydrogen, C₁-4alkyl, CONH₂ or CO₂R⁸ in which R⁸ is hydrogen or C₁-4alkyl, and n is 2, 3 or 4.

50 which comprises :

a) reaction of a compound of structure (2) with a compound of structure (3) :

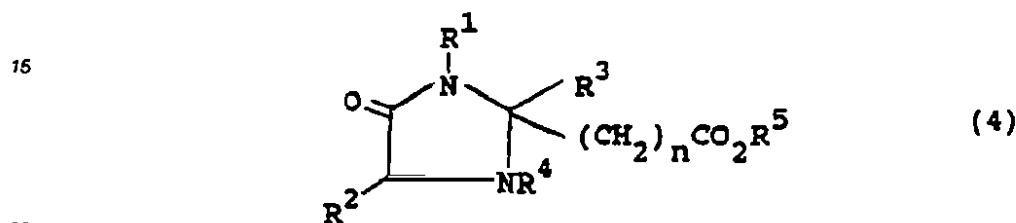
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in which R¹ to R³ and n are as described for structure (1), R⁴ is hydrogen and R⁵ is hydrogen, C₁₋₄ alkyl or benzyl; or

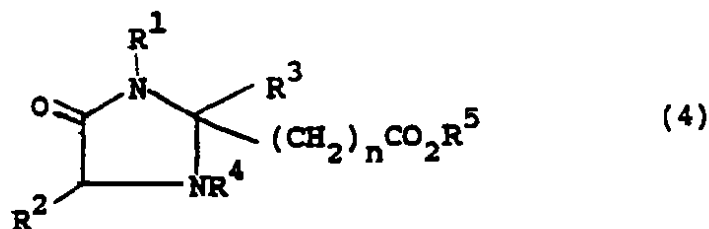
b) cyclization of a compound of structure (4)



in which R¹ to R³ and n are as described for structure (1), R⁴ is hydrogen and R⁵ is hydrogen, C₁₋₄ alkyl or benzyl.

2. A process according to claim 1(a) in which the reaction is carried out in the presence of a base.
3. A process according to claim 2 in which the base is selected from sodium hydroxide or sodium carbonate.
4. A process according to claim 1(b) in which the cyclization is carried out in the presence of ammonium hydroxide.
5. A process according to any one of claims 1 to 4 in which in the compound of structure (1) R¹ to R³ are each hydrogen.
6. A process according to any one of claims 1 to 4 in which the compound of structure (1) so prepared is selected from
 - 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 - 2,5-dioxo-7a-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
 - (3S)-3,7a-dimethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 - (3R,S)-3,7a-dimethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 - (3S)-2,5-dioxo-3-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
 - (3R,S)-2,5-dioxo-3-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
 - (3S)-2,5-dioxo-3-isobutylhexahydro-1H-pyrrolo[1,2-a]imidazole
 - 2,5-dioxo-1-ethylhexahydro-1H-pyrrolo[1,2-a]imidazole
 - 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 - ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetate
 - 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetamide
 - (3S)-3-benzyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 - (3S)-3-hydroxymethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 - 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylic acid
 - ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylate
 - 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxamide
 - 2,5-dioxo-1H-octahydroimidazo[1,2-a]pyridine, or
 - 2,5-dioxo-1H-octahydroimidazo[1,2-a]azepine.
7. A process for preparing a pharmaceutical composition which comprises bringing into association a compound of structure (1) as described in claim 1 and a pharmaceutically acceptable carrier.
8. A process according to claim 7 in which the compound of structure (1) is selected from
 - 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 - 2,5-dioxo-7a-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
 - (3S)-3,7a-dimethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 - (3R,S)-3,7a-dimethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole

- (3S)-2,5-dioxo-3-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
 (3R,S)-2,5-dioxo-3-methylhexahydro-1H-pyrrolo[1,2-a]imidazole
 (3S)-2,5-dioxo-3-isobutylhexahydro-1H-pyrrolo[1,2-a]imidazole
 2,5-dioxo-1-ethylhexahydro-1H-pyrrolo[1,2-a]imidazole
 5 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetate
 2,5-Dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-acetamide
 (3S)-3-benzyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 (3S)-3-hydroxymethyl-2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole
 10 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylic acid
 ethyl 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxylate
 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole-7a-carboxamide
 2,5-dioxo-1H-octahydroimidazo[1,2-a]pyridine, or
 2,5-dioxo-1H-octahydroimidazo[1,2-a]azepine.
 15 9. A process for the preparation of a compound of structure (3) as described in claim 1 in which R³ is hydrogen, R⁵ is isobutyl and n is 2 which comprises reduction of a compound of structure
 $\text{HCOCH} = \text{CHCO}_2\text{iBu}$
 10. A compound of structure (4)



- 30 in which R¹ to R³ and n are as described for structure (1) in claim 1, R⁴ is hydrogen and R⁵ is hydrogen, C₁₋₄ alkyl or benzyl.

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Publication number: **0 335 483 A3**

EUROPEAN PATENT APPLICATION

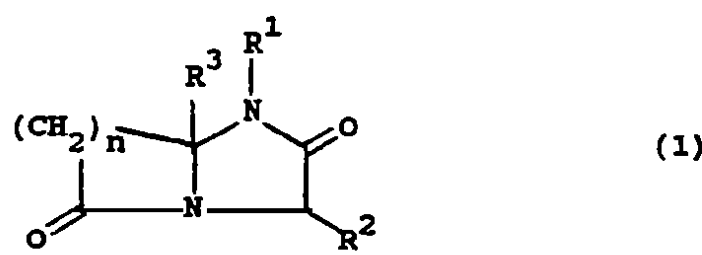
Application number: **89301123.9**
Date of filing: **06.02.89**
Int. Cl.⁵: **C07D 487/04, C07D 471/04, A61K 31/415, A61K 31/435, A61K 31/55, C07D 233/32, //(C07D487/04,235:00,209:00), (C07D487/04,235:00,223:00), (C07D471/04,235:00,221:00)**

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Condensed imidazole derivatives, process and intermediates for their preparation and pharmaceutical compositions containing them.

Compounds of structure (I)



in which, R¹ is hydrogen, C₁₋₄alkyl, CHR⁶CONHR⁷ or CHR⁶COOR⁷ in which R⁶ and R⁷ are each hydrogen or C₁₋₄alkyl; R² is hydrogen, C₁₋₃alkyl or a residue R² of an amino acid R² CH(NH₂)COOH; R³ is hydrogen, C₁₋₄alkyl, CONH₂ or CO₂R⁸ in which R⁸ is hydrogen or C₁₋₄alkyl; and n is 2, 3 or 4, processes for their preparation, intermediates useful in their preparation, pharmaceutical composition containing them and their use in therapy as nootropic agents.

Rank Xerox (UK) Business Services

EP 0 335 483 A3



DOCUMENTS CONSIDERED TO BE RELEVANT			EP 89301123.9
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	US - A - 4 251 533 (K. KUBO et al.) * Abstract; claim 1 * --	1, 8, 10	C 07 D 487/04 C 07 D 471/04 A 61 K 31/415 A 61 K 31/435
A	PATENT ABSTRACTS OF JAPAN, unexamined applications, C field, vol. 12, No. 186, May 31, 1988 THE PATENT OFFICE JAPANESE GOVERNMENT page 10 C 500 * Kokai-No. 62-289 581 (DEMITSU KOSAN CO LTD) * --	1-5, 7	A 61 K 31/55 C 07 D 233/32// (C 07 D 235:00 C 07 D 29:00) (C 07 D 487/04 C 07 D 235:00 C 07 D 223:00) (C 07 D 471/04 C 07 D 235:00 C 07 D 221:00)
A	PATENT ABSTRACTS OF JAPAN, unexamined applications, C field, vol. 12, No. 186, May 31, 1988 THE PATENT OFFICE JAPANESE GOVERNMENT page 114 C 500 * Kokai-No. 62-292 783 (IDEMITSU KOSAN CO LTD) * ----	1-3	TECHNICAL FIELDS SEARCHED (Int. Cl. 4) C 07 D 487/00 C 07 D 471/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 18-10-1991	Examiner MAZZUCCO
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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D3 41

12 **EUROPEAN PATENT APPLICATION**

21 Application number: 85305958.0

22 Date of filing: 22.08.85

51 Int. Cl.⁴: **C 07 D 487/04**
A 61 K 31/41
/(C07D487/04, 235:00, 209:00)

30 Priority: 24.08.84 US 643989

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64 Derivatives of dihydro-1H-pyrrolo[1,2-c]imidazol-3,5-dione as cognition activators.

57 Certain derivatives of dihydro-1H-pyrrolo-[1,2-c]imidazol-3,5 [2H,6H] are cognition-activating compounds, possessing pharmacological activity for treating senility or for reversing the effects of electroconvulsive shock-induced amnesia. Pharmaceutical compositions including these compounds, a method of preparing the compounds, and of treating senility or of reversing the effects of induced amnesia are also disclosed.

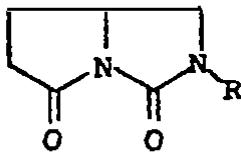
EP 0 174 136 A1

Continuation Divisional Proceedings: 1st

This invention relates to compounds and pharmaceutical compositions useful in the treatment of senility or for reversing the effects of electroconvulsive shock-induced amnesia, a method of preparing the compounds, and of treating senility or of reversing amnesia. More particularly, this invention is concerned with certain derivatives of dihydro-1H-pyrrolo[1,2-c]-imidazo-3,5[2H,6H]-dione having pharmacological activity for treating senility or for reversing the effects of electroconvulsive shock-induced amnesia, pharmaceutical compositions including these compounds, a method of preparing the compounds, and of treating senility or of reversing the effects of induced amnesia.

The compound, 5-oxo-2-pyrrolidineacetic acid, also known in the optically active form as ecgoninic acid, is disclosed in the literature (G. L. Evans, et. al., J Am Chem Soc, 72: 2727-2728 (1950), and E. Hardegger, et. al., Helv Chim Acta, 19: 312-319 (1955)). This compound is employed as a starting material for the preparation of compounds in accordance with the present invention.

In its broadest aspect, the present invention provides cognition activating compounds of formula I:



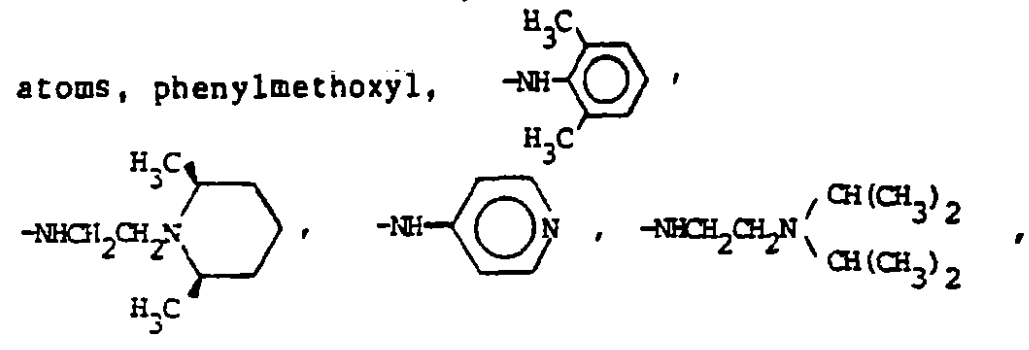
I

wherein R is selected from hydrogen; alkyl of from one to four carbon atoms; alkenyl of from one to four

DJU-2

-3-

carbon atoms; phenylmethyl; or $-\text{CH}_2\text{COR}_1$ where R_1 is selected from OH, alkoxy of from one to four carbon



5 or NR_2R_3 where R_2 and R_3 are independently hydrogen, or alkyl of from one to four carbon atoms; and the pharmaceutically acceptable salts thereof, when basic.

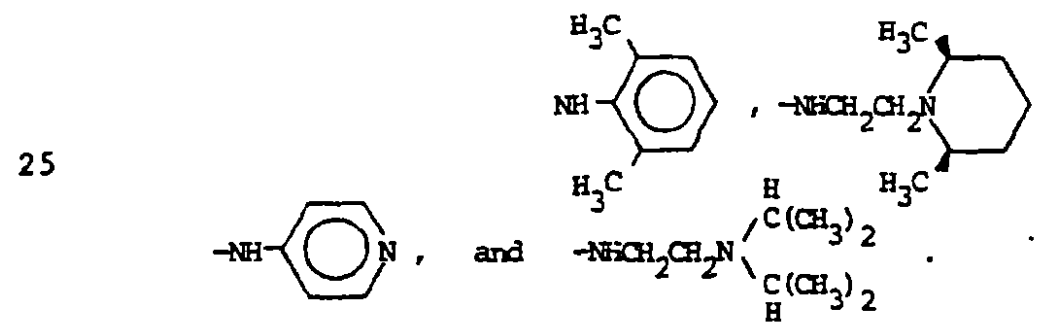
In one subgeneric aspect, compounds of the present invention possess structural formula I where R is alkyl of from one to four carbon atoms, alkenyl of from one to four carbon atoms, or phenylmethyl.

10 In another subgeneric aspect, compounds of the present invention possess structural formula I where R is $-\text{CH}_2\text{COR}_1$ where R_1 is alkoxy of from one to four carbon atoms, phenylmethoxyl, or $-\text{OH}$ and the pharmaceutically acceptable salts thereof.

In a further subgeneric aspect, compounds of the present invention possess structural formula I where R is $-\text{CH}_2\text{COR}_1$ where R_1 is $-\text{NR}_2\text{R}_3$ where R_2 and R_3 are 20 independently hydrogen or alkyl of from one to four carbon atoms.

In another subgeneric aspect, compounds of the present invention possess structural formula I where R

is $-\text{CH}_2\text{COR}_1$ where R_1 is selected from



In another aspect of the present invention, there are provided pharmaceutical compositions for the treatment of senility or for reversing the effects of electroconvulsive shock-induced amnesia comprising a
5 pharmaceutically effective amount of a compound having structural formula I as defined above, in combination with a pharmaceutically acceptable carrier.

In yet another aspect of the present invention, there is provided a method of treating senility or of
10 reversing the effects of electroconvulsive shock-induced amnesia in a mammal comprising administering to a mammal in need of such treatment a pharmaceutical composition including an amnesia-reversing effective amount of a compound having structural formula I as
15 defined above, in combination with a pharmaceutically acceptable carrier.

As used throughout this specification and the appended claims, the term "alkyl" is meant to encompass
20 groups derived by removal of one hydrogen atom from branched or unbranched saturated hydrocarbons of from one to four carbon atoms.

The term "alkoxy" is meant to encompass groups of the structure -OR where R is alkyl as previously
25 defined.

The term "alkenyl" is meant to encompass groups derived by removal of one hydrogen atom from branched or unbranched hydrocarbons of one to four carbon atoms containing at least one carbon-carbon double bond.

30 The compounds of the present invention are capable of existing both in solvated and unsolvated forms including hydrates. In general, the forms solvated with such pharmaceutically acceptable solvents as water, ethanol, and the like are equivalent to the
35 unsolvated forms for the purposes of the present invention.

Further, the compounds of the present invention are capable of existence in both the d- and l-isomeric forms. The biological activity may reside in either or both isomers. The present invention contemplates
5 both isomeric forms.

Examples of compounds falling within the scope of the present invention include, but are not necessarily limited to the following:

Dihydro-1H-pyrrolo[1,2-c]imidazo-3,5[2H,6H]-dione.
10 Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid and the pharmaceutically acceptable salts thereof.

Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid methyl ester.

15 Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid ethyl ester.

Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid phenymethyl ester.

Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-20 2(3H)-acetamide.

Tetrahydro-N-methyl-3,5-dioxo-1H-pyrrolo[1,2-c]-imidazole-2(3H)-acetamide.

Tetrahydro-N,N-dimethyl-3,5-dioxo-1H-pyrrolo-[1,2-c]imidazole-2(3H)-acetamide.

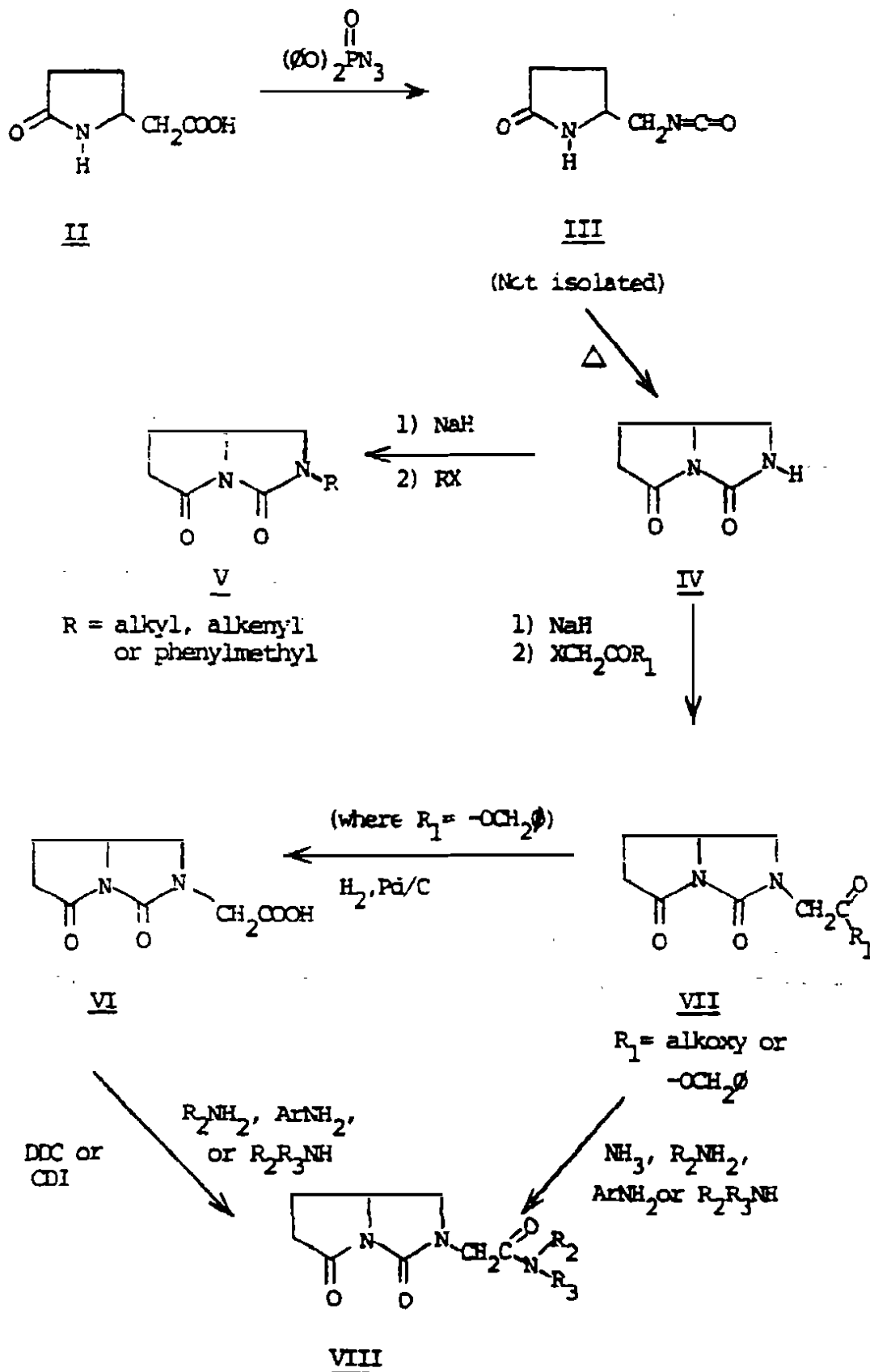
25 Tetrahydro-N-(2,6-dimethylphenyl)-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetamide.

N-[2-[bis(1-Methylethyl)amino]ethyl]tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetamide and the pharmaceutically acceptable salts thereof.

30 cis-N-[2-(2,6-Dimethyl-1-piperidinyl)ethyl]-tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]-imidazole-2(3H)-acetamide.

Tetrahydro-3,5-dioxo-N-4-pyridinyl-1H-pyrrolo[1,2-c]imidazole-2(3H)acetamide and the
35 pharmaceutically acceptable salts thereof.

Compounds of the present invention are prepared in accordance with the general reaction scheme illustrated below.



The known starting material, II, is reacted with diphenylphosphoryl azide in an inert solvent such as dichloromethane, followed by treatment with triethylamine to produce 5-isocyanatomethyl-2-pyrrolidinone, III.

- 5 The solvent is removed under vacuum, and the crude isocyanate is reacted further without purification.

The crude 5-isocyanatomethyl-2-pyrrolidinone, III, is dissolved in a hydrocarbon solvent such as toluene, and the mixture is heated under reflux to effect the
10 cyclization of the compound III to dihydro-1H-pyrrolo[1,2-c]imidazo-3,5[2H,6H]-dione, IV.

Compound IV is employed as an intermediate for the preparation of other compounds in accordance with the current invention by conventional chemical means. For
15 example, reaction of IV with a strong base such as sodium hydride, followed by treatment with an alkyl, or alkenyl halide, converts IV into the N-alkyl, or N-alkenyl derivative of V.

Reaction of compound IV with a strong base such as
20 sodium hydride, followed by treatment with a haloacetic ester produces esters of formula VII. The phenylmethyl ester, VII ($R_1 = -OCH_2\text{phenyl}$), is readily converted to the free acid, VI ($R_1 = -OH$) by conventional hydro-
genolysis. Reaction of the ester compounds, VII, with
25 ammonia or the appropriate amine in a conventional ammonolysis reaction converts VII to the corresponding acetamides, VIII.

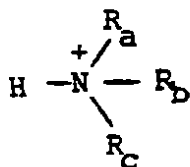
Alternatively, the free acid, VI, is readily coupled with the desired amine to produce the acetamide
30 in the presence of well-known activating agents such as dicyclohexylcarbodiimide (DCC), carbonyldiimidazole (CDI), or chloroformates.

The compounds of the present invention in which the R group contains a basic nitrogen atom, such as when R is N-[2-bis(1-methylethyl)amino]ethyl]-acetamido-, cis-N-[2-(2,6-dimethyl-1-piperidinyl)-ethyl]acetamido-, or N-4-pyridinyl-acetamido- are capable of forming acid addition salts with pharmaceutically acceptable organic or inorganic acids. Suitable acids include hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic, and the like.

The salts are prepared by contacting the free base form of compounds of the present invention with a sufficient amount of the desired acid in the conventional manner. The salt is isolated by filtration, evaporation, or other conventional means. The free base may be regenerated, if desired, by contacting the salt with an aqueous solution of a base such as dilute sodium hydroxide, potassium carbonate, ammonia, sodium bicarbonate, and the like.

Likewise, the compound dihydro-1H-pyrrolo[1,2-c]-imidazole-2(3H)-acetic acid, by virtue of its carboxylic acid functionality, is capable of forming salts with pharmaceutically acceptable metal, ammonium, or organic amine cations. Examples of pharmaceutically acceptable metal and amine cations for purposes of forming salts include positively charged metal ions such as those derived from sodium, potassium, calcium, magnesium, aluminum, iron, zinc, and the positively-charged ions derived from ammonia and organic nitrogenous bases strong enough to form such cations. Bases useful for the formation of pharmaceutically acceptable nontoxic acid addition salts of compounds containing a carboxyl acid function form a class whose limits are readily understood by those skilled in the art.

Merely for illustration, this class of amines can be said to comprise, in cationic form, those of the formula:



- 5 wherein R_a , R_b , and R_c independently are hydrogen, alkyl of from one to six carbon atoms, cycloalkyl of from about three to six carbon atoms, aryl, aralkyl of from about seven to about ten carbon atoms, hydroxyalkyl of from two to four carbon atoms, or monoarylhydroxy-
- 10 alkyl of from about eight to about fifteen carbon atoms. Further, when taken together with the nitrogen atom to which they are attached, any two of R_a , R_b , and R_c may form part of a five- or six-membered nitrogen-containing heterocyclic aromatic or nonaromatic ring
- 15 containing carbon or oxygen, said nitrogen-containing heterocyclic rings being unsubstituted, monosubstituted, or disubstituted with alkyl groups or from one to six carbon atoms.

- Specific examples of organic amine cations contemplated as falling within the scope of the present
- 20 invention include mono-, di-, and trimethylammonium, mono-, di-, and triethylammonium, mono-, di-, and tripropylammonium (n-propyl and isopropyl), ethyldimethylammonium, benzylammonium, dibenzylammonium,
- 25 benzyldimethylammonium, cyclohexylammonium, piperidinium, morpholinium, pyrrolidinium, 4-ethylmorpholinium, 1-n-butylpiperidinium, 2-methylpiperidinium, 1-ethyl-2-methylpiperidinium, mono-, di-, and triethanolammonium, ethyldiethanolammonium, n-butylmonoethanolammonium,
- 30 tris(hydroxymethyl)methylammonium, phenylmonoethanolammonium, and the like.

The ammonium, amine, or metal salts are prepared by reaction of the appropriate acetic or propanoic acid compound of this invention with an equivalent amount of an organic amine base or an inorganic base such as ammonium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, calcium carbonate, sodium bicarbonate, and the like in an appropriate solvent such as water or an aqueous alcohol, followed by removal of the solvent under reduced pressure.

10 The free acid form of the compound may be regenerated from the salts, if desired, by contacting the salt with a dilute aqueous solution of an acid such as hydrochloric.

The compounds of the present invention may differ somewhat from the salt forms in such physical properties as melting point and solubility in polar solvents such as water, but the salts are otherwise equivalent to the free base forms for the purposes of this invention.

20 For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersable granules, capsules, cachets, and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be encapsulating material. In powders, the carrier is
30 a finely-divided solid which is in admixture with the finely divided active compound. In the tablet, the active compound is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The

powders and tablets preferable contain from five to ten to about 70 percent of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, 5 gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule 10 in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

15 For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into 20 convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions. As an example, it may be mentioned water or water propylene glycol solutions 25 for parenteral injection. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, 30 stabilizing, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium 35 carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions, and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternately, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid from preparation as with a syringe, teaspoon, or other volumetric container. When multiple liquid doses are so prepared, it is preferred to maintain the unused portion of said liquid doses at low temperature (i.e., under refrigeration) in order to retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like. The liquid utilized for preparing the liquid from preparation may be water, isotonic water, ethanol, glycerine, propylene glycol, and the like as well as mixtures thereof. Naturally, the liquid utilized will be chosen with regard to the route of administration, for example, liquid preparations containing large amounts of ethanol are not suitable for parenteral use.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be

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a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 500 mg, preferably to 5 to 100 mg according to the particular application and the potency of the active ingredient. The compositions can, if desired, also contain other compatible therapeutic agents such as 3-phenoxy pyridine, N-[2-[bis(1-methylethyl)amino]-ethyl]-2-oxo-1-pyrrolidineacetamide or dihydro-1H-pyrrolizine-3,5(2H,6H)-dione.

In therapeutic use as cognition activators, the mammalian dosage range for a 70 kg subject is from 1 to 1500 mg/kg of body weight per day or preferably 25 to 750 mg/kg of body weight per day. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

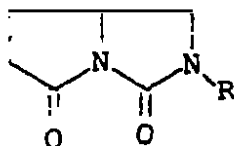
The effectiveness of the aforementioned compounds was determined by the test designed to show the compound's ability to reverse amnesia produced by electroconvulsive shock. The test is fully described in US Patent Number 4,145,347, issued March 20, 1979, and is herein incorporated by reference. The test compounds in the present instance were administered orally and the length of electroconvulsive shock was 1.0 second.

The following criteria are used in interpreting the percent of amnesia reversal scores: 40 percent or

more (active = A), 25 to 39 percent (borderline = C), and 0 to 24 percent (inactive = N).

The table below indicates the percent amnesia reversal determined for representative examples of compounds in accordance with the present invention when administered orally to standard laboratory animals in the test referenced above.

TABLE



10

15

Compound	R	Dose (mg/kg) of Body Weight		
		100	10	1
1	H	26 (C)	40 (A)	56 (A)
2	-CH ₂ COOC ₂ H ₅	36 (C)	27 (C)	60 (A)

20

The following preparative examples are provided to enable one skilled in the art to practice the present invention. The examples are merely illustrative of the present invention and should not be viewed as limiting its scope as defined by the appended claims.

EXAMPLE 1

Dihydro-1H-pyrrolo[1,2-c]imidazo-3,5[2H,6H]-dione

A solution of 5-oxo-2-pyrrolidinescetic acid, 13.3 g, 0.09 mol) in methylene chloride, 250 ml, is stirred and is treated with diphenylphosphoryl azide (33 g, 0.12 mol) followed by triethylamine (11 g, 0.11 mol). The solution is stirred 16 hours and is concentrated in vacuo. The resulting yellow oil (5-oxo-pyrrolidine-2-methylisocyanate) is dissolved in toluene, 100 ml, and the solution is heated at 80°C for six hours. The product forms as a white precipitate and is isolated by filtration. After sublimation at 170°C and 0.5 mm pressure, dihydro-1H-pyrrolo[1,2-c]imidazo-3,5(2H,6H)-dione has a mp of 223-225°C.

EXAMPLE 2

Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid ethyl ester

A slurry of dihydro-1H-pyrrolo[1,2-c]imidazo-3,5-[2H,6H]-dione (4.3 g, 0.03 mol) in tetrahydrofuran, 250 ml, is treated with a 50% sodium hydride in mineral oil suspension (1.73 g, 0.036 mol). After H₂ evolution is complete, ethyl bromoacetate (6.0 g, 0.036 mol) is added and the mixture is refluxed for one hour. The mixture is filtered and concentrated in vacuo. The residue is treated with anhydrous diethyl ether and filtered. After purification using flash chromatography over silica gel, elution with 10% methanol: methylene chloride, tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid ethyl ester has a mp of 99-101°C.

EXAMPLE 3

Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-
2(3H)-acetic acid methyl ester

- A slurry of dihydro-1H-pyrrolo[1,2-c]imidazo-
- 5 3,5[2H,6H]-dione (4.4 g, 0.03 mol) in tetrahydrofuran, 250 ml, is treated with a 50% sodium hydride in mineral oil suspension (1.73 g, 0.036 mol). After H₂ evolution is complete, methyl bromoacetate (5.5 g, 0.036 mol) is added and the mixture is refluxed for one hour.
- 10 The mixture is filtered, concentrated in vacuo. The residue is treated with anhydrous diethyl ether and filtered. Purification using flash chromatography over silica gel, elution with 10% methanol:methylene chloride yields tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]-
- 15 imidazole-2(3H)-acetic acid methyl ester.

EXAMPLE 4

Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-
2(3H)-acetic acid benzyl ester

- A slurry of dihydro-1H-pyrrolo[1,2-c]imidazo-
- 20 3,5[2H,6H]-dione (4.4 g, 0.03 mol) in tetrahydrofuran, 250 ml, is treated with a 50% sodium hydride in mineral oil suspension (1.73 g, 0.036 mol). After H₂ evolution is complete, benzyl bromoacetate (8.3 g, 0.036 mol) is added and the mixture is refluxed for one hour.
- 25 The mixture is filtered, concentrated in vacuo. The residue is treated with anhydrous diethyl ether and filtered. Purification using flash chromatography over silica gel, elution with 10% methanol:methylene chloride yields tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]-
- 30 imidazole-2(3H)-acetic acid benzyl ester.

EXAMPLE 5

Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid

5 A solution of tetrahydro-3,5-dioxo-1H-pyrrolo-
[1,2-c]imidazole-2(3H)-acetic acid benzyl ester
(2.9 g, 0.01 mol) in tetrahydrofuran, 250 ml, is
treated with H₂ gas in the presence of a Pd/C
catalyst. After H₂ uptake is complete, the solution
is filtered through filter aid and concentrated in
10 vacuo to yield tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]-
imidazole-2(3H)-acetic acid.

EXAMPLE 6

2(3H)-methyl-tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]-imidazole

15 A slurry of dihydro-1H-pyrrolo[1,2-c]imidazo-
3,5(2H,6H)-dione (8.8 g, 0.06 mol) in tetrahydrofuran,
250 ml, is treated with a 50% sodium hydride in mineral
oil suspension (3.5 g, 0.072 mol). After H₂ evolution
is complete, iodomethane (10.2 g, 0.072 mol) is added
20 and the mixture is refluxed for one hour. The mixture
is filtered, concentrated in vacuo. The residue is
treated with anhydrous diethyl ether and filtered.
Purification using flash chromatography over silica
gel, elution with 10% methanol: methylene chloride
25 yields 2(3H)-methyl-tetrahydro-3,5-dioxo-1H-
pyrrolo[1,2-c]imidazole.

EXAMPLE 7

2(3H)-ethyl-tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]-imidazole

A slurry of dihydro-1H-pyrrolo[1,2-c]imidazo-
5 3,5(2H,6H)-dione (8.8 g, 0.06 mol) in tetrahydrofuran,
250 ml, is treated with a 50% sodium hydride in mineral
oil suspension (35 g, 0.072 mol). After H₂ evolution
is complete, iodoethane (11.3 g, 0.072 mol) is added
and the mixture is refluxed for one hour. The mixture
10 is filtered, concentrated in vacuo. The residue is
treated with anhydrous diethyl ether and filtered.
Purification using flash chromatography over silica
gel, elution 10% methanol: methylene chloride yields
2(3H)-ethyl-tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]-
15 imidazole.

EXAMPLE 8

2(3H)-allyl-tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]-imidazole

A slurry of dihydro-1H-pyrrolo[1,2-c]imidazo-
20 3,5(2H,6H)-dione (13.2 g, 0.09 mol) in tetrahydrofuran,
250 ml, is treated with a 50% sodium hydride in mineral
oil suspension (5.2 g, 0.09 mol). After H₂ evolution
is complete, allylchloride (6.9 g, 0.09 mol) is added
and the mixture is refluxed for one hour. The mixture
25 is filtered, concentrated in vacuo. The residue is
treated with anhydrous diethyl ether and filtered.
Purification using flash chromatography over silica
gel, elution with 10% methanol:methylene chloride
yields 2(3H)-allyl-tetrahydro-3,5-dioxo-
30 1H-pyrrolo[1,2-c]-imidazole.

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EXAMPLE 9

2(3H)-phenylmethyl-tetrahydro-3,5-dioxo-1Hpyrrolo-
[1,2-c]-imidazole

- A slurry of dihydro-1H-pyrrolo[1,2-c]imidazo-
- 5 3,5[2H,6H]-dione (4.4 g, 0.03 mol) in tetrahydrofuran, 250 ml, is treated with a 50% sodium hydride in mineral oil suspension (1.73 g, 0.036 mol). After H₂ evolution is complete, phenylmethylchloride (4.6 g, 0.036 mol) is added and the mixture is refluxed for one hour.
- 10 The mixture is filtered, concentrated in vacuo. The residue is treated with anhydrous diethyl ether and filtered. Purification using flash chromatography over silica gel, elution with 10% methanol:methylene chloride yields 2(3H)-phenylmethyl-tetrahydro-3,5-
- 15 dioxo-1H-pyrrolo[1,2-c]imidazole.

EXAMPLE 10

Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-
acetic acid amide

- A solution of tetrahydro-3,5-dioxo-1H-pyrrolo-
- 20 [1,2-c]imidazole-2(3H)-acetic acid methyl ester (1.0 g, 0.004 mol) in methanol, 150 ml, is saturated with anhydrous ammonia. The mixture is allowed to stand 24 hours at room temperature. The solution is concentrated at reduced pressure to yield tetrahydro-3,5-
- 25 dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid amide.

EXAMPLE 11

Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid amide N-(N,N-diisopropylaminoethyl)

5 Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid ethyl ester (1.0 g, 0.004 mol) in methanol, 150 ml, is treated with N-(N,N-diisopropylaminoethylamine (0.55 g, 0.004 mol) and the mixture is stirred at room temperature for 48 hours. The mixture is concentrated in vacuo to yield tetrahydro-10 3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid amide N-(N,N-diisopropylaminoethyl).

EXAMPLE 12

Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid amide N-(cis-2,6-dimethylpiperidinoethyl)

15 A mixture of tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]-imidazole-2(3H)-acetic acid ethyl ester (1.0 g, 0.004 mol) and cis-2,6-dimethylpiperidinoethylamine (0.63 g, 0.004 mol) in methanol, 150 ml, is stirred at room temperature for 72 hours. The mixture is concentrated in vacuo to yield after purification by chromatography on SiO₂ (elution with 10% methanol saturated with gaseous ammonia in methylene chloride) tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid amide N-(cis-2,6-dimethylpiperidinoethyl).

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EXAMPLE 13

Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid amide N-(4-pyridinyl)

A solution of tetrahydro-3,5-dioxo-1H-pyrrolo
5 [1,2-c]imidazole-2(3H)-acetic acid (1.0 g, 0.005 mol)
and triethylamine (0.505 g, 0.005 mol) in methylene
chloride, 150 ml, is treated with isobutyl chloro-
formate (0.683 g, 0.005 mol) with stirring at 0°C until
the free acid is converted into the activated mixed
10 anhydride. The solution is filtered to remove the
triethylamine hydrochloride and the filtrate is treated
with 4-aminopyridine (0.47 g, 0.005 mol). The mixture
is stirred at 24 hours at room temperature and
concentrated in vacuo to yield after purification by
15 chromatography over silica gel (elution with 10%
methanol saturated with anhydrous gaseous ammonia in
methylene chloride) tetrahydro-3,5-dioxo-1H-pyrrolo
[1,2-c]imidazole-2(3H)-acetic acid amide N-(4-
pyridinyl).

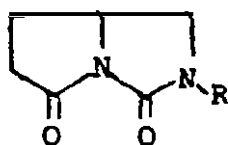
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EXAMPLE 14

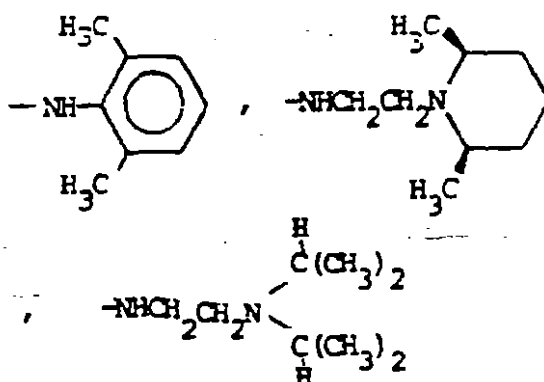
Tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid amide N-(2,6-dimethylphenyl)

A solution of tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]-
2(3H)-acetic acid (1.0 g, 0.005 mol) and dicyclohexyl
25 carbodimide (1.04 g, 0.005 mol) in methylene chloride,
150 ml, is stirred and treated with 2,6-dimethylaniline
(0.6 g, 0.005 mol) at 0°C. The mixture is allowed to
warm to 25°C and filtered to remove dicyclohexylurea.
The filtrate is concentrated in vacuo to yield after
30 purification by chromatography over silica gel (elution
with 10% methane in methylene chloride) tetrahydro-3,5-
dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid
amide N-(2,6-dimethylphenyl).

1. A compound having the formula



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3. A compound in accordance with Claim 1,

wherein R is $-\text{CH}_2\text{COR}_1$ where R_1 is alkoxy of from one to four carbon atoms; phenylmethoxy; or $-\text{OH}$; or a pharmaceutically acceptable salt thereof.

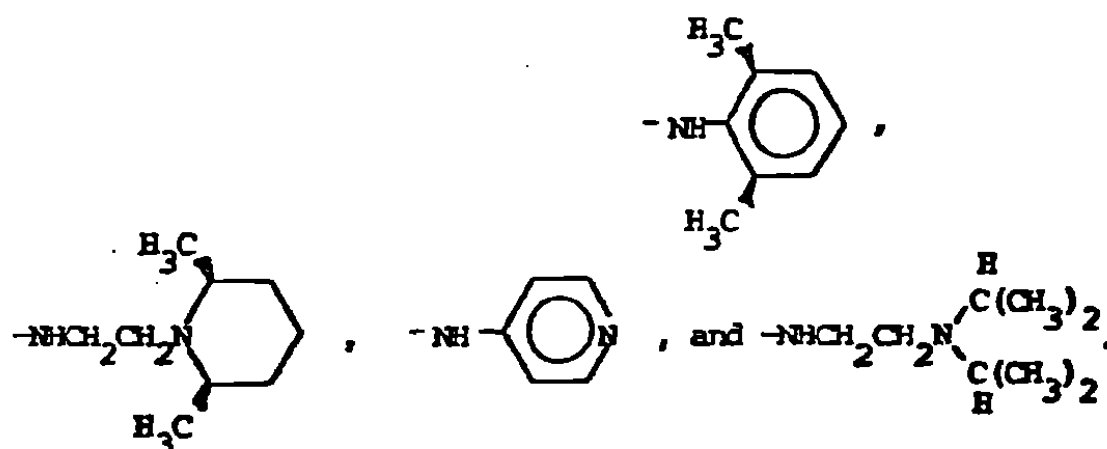
4. A compound in accordance with Claim 1, wherein R is $-\text{CH}_2\text{COR}_1$ where R_1 is $-\text{NR}_2\text{R}_3$ where R_2 and R_3 are independently hydrogen or alkyl of from one to four carbon atoms.

5. A compound in accordance with Claim 1, wherein R is $-\text{CH}_2\text{COR}_1$ where R_1 is selected from

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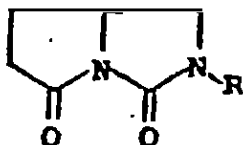
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6. A compound in accordance with Claim 1, selected from dihydro-1H-pyrrolo[1,2-c]imidazo-3,5[2H,6H]-dione; tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid, or a pharmaceutically acceptable salt thereof; tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid methyl ester; tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid ethyl ester; tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid phenylmethyl ester; tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetamide;

- tetrahydro-N-methyl-3,5-dioxo-1H-pyrrolo[1,2-c]-
imidazole-2(3H)-acetamide;
tetrahydro-N,N-dimethyl-3,5-dioxo-1H-pyrrolo-
[1,2-c]imidazole-2(3H)-acetamide;
5 N-2[bis(1-methylethyl)amino]tetrahydro-3,5-dioxo-
1H-pyrrolo[1,2-c]imidazole-2(3H)-acetamide;
tetrahydro-N-(2,6-dimethylphenyl)-3,5-dioxo-1H-
pyrrolo[1,2-c]imidazole-2(3H)-acetamide;
cis-N-[2-(2,6-dimethyl-1-piperidinyl)ethyl]tetra-
10 hydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-
acetamide; and
tetrahydro-3,5-dioxo-N-4-pyridinyl-1H-pyrrolo-
[1,2-c]imidazole-2(3H)-acetamide.
- 15 7. A method of preparing a compound having the
structural formula



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- wherein R is selected from hydrogen; alkyl of from
one to four carbon atoms; alkenyl of from one to
25 four carbon atoms; phenylmethyl; or -CH₂COR₁
where R₁ is selected from OH, alkoxy of from one
to four carbon atoms, or phenylmethoxy; comprising
the steps of:
a) heating 5-isocyanatomethyl-2-pyrrolidione to
30 form dihydro-1H-pyrrolo[1,2-c]imidazo-3,5[2H,6H]-
dione, and thereafter, if desired,

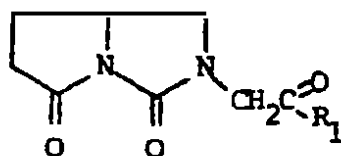
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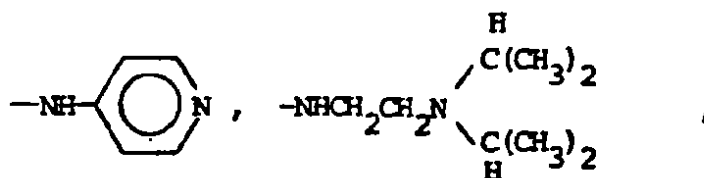
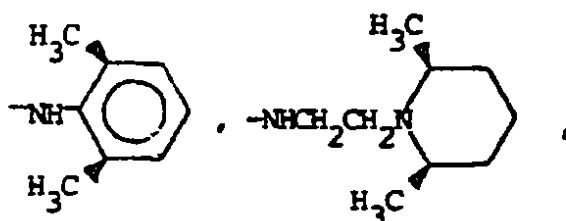
b) reacting said dihydro-1H-pyrrol [1,2-c]imidazo-3,5[2H,6H]-dione with an alkali metal hydride, followed by reaction with a reagent having the formula R'X where X is chlorine, bromine, or iodine and R' is alkyl of from one to four carbon atoms, alkenyl of from one to four carbon atoms, phenylmethyl, or -CH₂COR₁ where R₁ is alkoxy of from one to four carbon atoms, or phenylmethoxy; and thereafter, if desired,

c) converting the product of step b wherein R₁ is phenylmethoxy to tetrahydro-3,5-dioxo-1H-pyrrolo-[1,2-c]imidazole-2(3H)-acetic acid by hydrogenolysis and converting, if desired, said acid to a pharmaceutically acceptable salt.

8. A method of preparing a compound having the structural formula

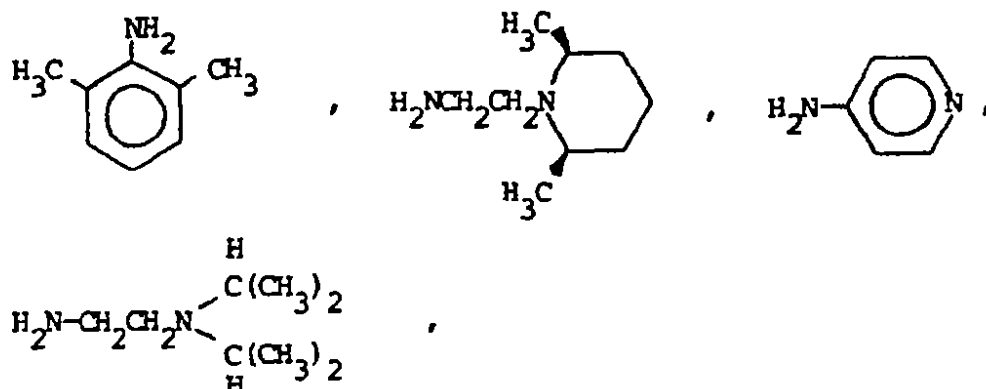


wherein R₁ is



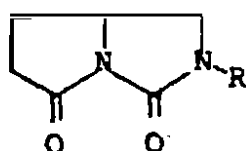
or NR₂R₃ where R₂ and R₃ are independently hydrogen, or alkyl of from one to four carbon atoms; and, when basic, a pharmaceutically acceptable acid addition salt thereof, comprising the steps of:

a) reacting tetrahydro-3,5-dioxo-1H-pyrrolo-
[1,2-c]imidazole-2-(3H)-acetic acid with an amine
selected from the group consisting of



15 and R_2R_3NH wherein R_2 and R_3 are independently
hydrogen or alkyl of from one to four carbon atoms
to form an acetamide; and thereafter, if desired,
b) converting said acetamide product of step
a), when basic, to a pharmaceutically acceptable
acid addition salt.

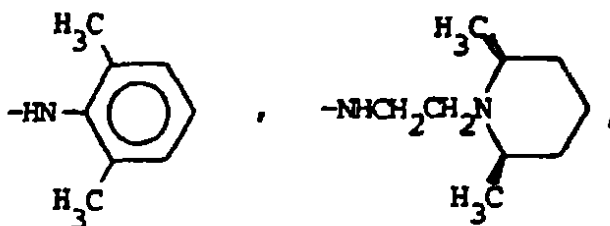
20 9. A pharmaceutical composition for treating senility
or for reversing the effects of electroconvulsive
shock-induced amnesia, comprising a pharmaceutically
effective amount of a compound having the
25 structural formula



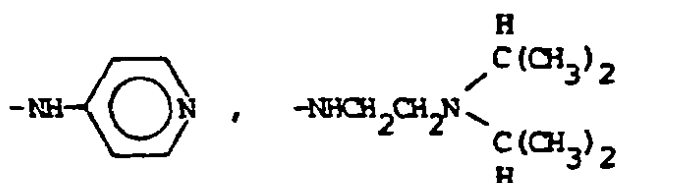
35 wherein R is selected from hydrogen; alkyl of from
one to four carbon atoms; alkenyl of from one to
four carbon atoms; phenylmethyl; and $-CH_2COR_1$

where R_1 is selected from OH, alkoxy f fr m one
to for carbon atoms, phenylmethoxyl,

5



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and NR_2R_3 where R_2 and R_3 are independently
hydrogen, or alkyl of from one to four carbon
atoms; and, when basic, a pharmaceutically
acceptable acid addition salt thereof, together
with a pharmaceutically acceptable carrier.

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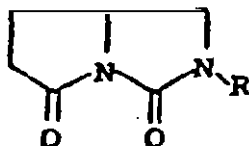
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CLAIMS: (for AT):

1. A process for preparing a compound having the structural formula



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wherein R is selected from hydrogen; alkyl of from one to four carbon atoms; alkenyl of from one to four carbon atoms; phenylmethyl; or $-\text{CH}_2\text{COR}_1$ where R_1 is selected from OH, alkoxy of from one to four carbon atoms, and phenylmethoxy; comprising the steps of:

- 15 a) heating 5-isocyanatomethyl-2-pyrrolidione to form dihydro-1H-pyrrolo[1,2-c]imidazo-3,5[2H,6H]-dione; and thereafter, if desired,
- 20 b) reacting said dihydro-1H-pyrrolo[1,2-c]imidazo-3,5[2H,6H]-dione with an alkali metal hydride, followed by reaction with a reagent having the formula $\text{R}'\text{X}$ where X is chlorine, bromine, or iodine and R' is alkyl of from one to four carbon
- 25 atoms, alkenyl of from one to four carbon atoms, phenylmethyl, or $-\text{CH}_2\text{COR}_1$ where R_1 is alkoxy of from one to four carbon atoms, or phenylmethoxy; and thereafter, if desired,
- 30 c) converting the product of step b wherein R_1 is phenylmethoxy to tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetic acid by hydrogenolysis and converting, if desired, said acid to a pharmaceutically acceptable salt.

35

2. A process in accordance with Claim 1, wherein R is hydrogen or alkyl of from one to four carbon atoms, alkenyl of from one to four carbon atoms, or phenylmethyl.

5 3. A process in accordance with Claim 1, wherein R is $-\text{CH}_2\text{COR}_1$ where R_1 is selected from alkoxy of from one to four carbon atoms; phenylmethoxy; and $-\text{OH}$.

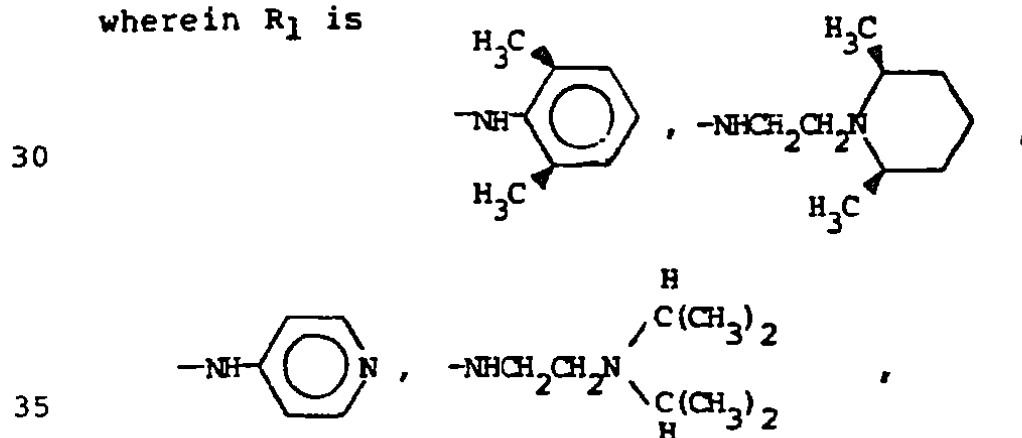
4. A process in accordance with Claim 1, for producing dihydro-1H-

10 pyrrolo[1,2-c]imidazo-3,5[2H,6H]-dione;
tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-
2(3H)-acetic acid, and the pharmaceutically
acceptable salts thereof;
tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-
15 2(3H)-acetic acid methyl ester;
tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-
2(3H)-acetic acid ethyl ester; or
tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-
2(3H)-acetic acid phenylmethyl ester.

20 5. A process for preparing a compound
having the structural formula

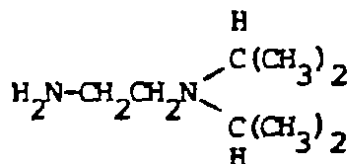
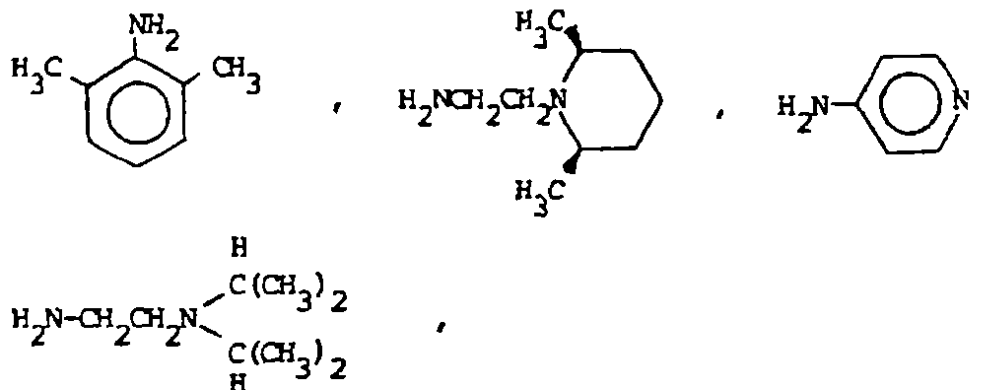


wherein R_1 is



or NR_2R_3 where R_2 and R_3 are independently hydrogen or alkyl of from one to four carbon atoms; or, when basic, a pharmaceutically acceptable acid addition salt thereof; comprising the steps of:

a) reacting tetrahydro-3,5-dioxo-1H-pyrrolo-[1,2-c]imidazole-2-(3H)-acetic acid with an amine selected from

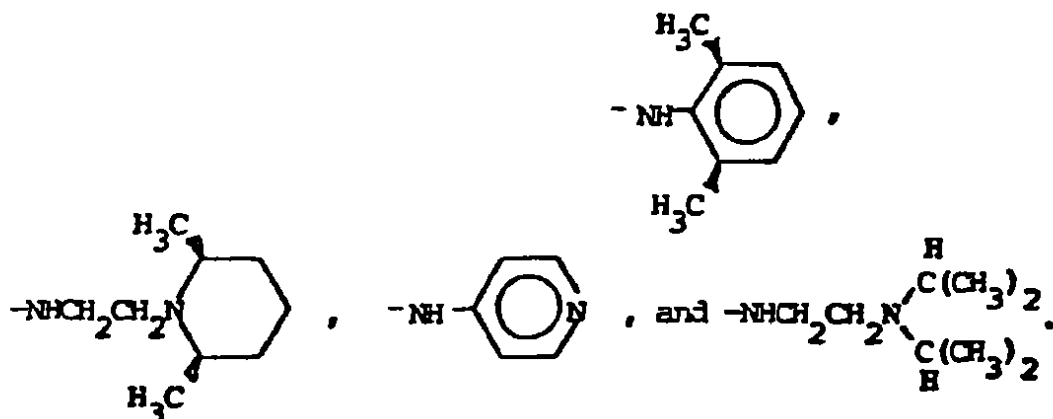


and $\text{R}_2\text{R}_3\text{NH}$ wherein R_2 and R_3 are independently hydrogen or alkyl of from one to four carbon atoms to form an acetamide; and thereafter, if desired, b) converting said acetamide product of step a), when basic, to a pharmaceutically acceptable acid addition salt.

6. A process in accordance with Claim 5, wherein R is $-\text{CH}_2\text{COR}_1$ where R_1 is $-\text{NR}_2\text{R}_3$ where R_2 and R_3 are independently hydrogen or alkyl of from one to four carbon atoms.

7. A process in accordance with Claim 5, wherein R is $-\text{CH}_2\text{COR}_1$ where R_1 is selected from

5



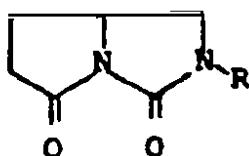
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8. A process according to Claim 5, for producing
- tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetamide;
- 15 tetrahydro-N-methyl-3,5-dioxo-1H-pyrrolo[1,2-c]-imidazole-2(3H)-acetamide;
- tetrahydro-N,N-dimethyl-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetamide;
- 20 N-2[bis(1-methylethyl)amino]tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetamide;
- tetrahydro-N-(2,6-dimethylphenyl)-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetamide;
- cis-N-[2-(2,6-dimethyl-1-piperidinyl)ethyl]tetrahydro-3,5-dioxo-1H-pyrrolo[1,2-c]imidazole-2(3H)-
- 25 acetamide; or
- tetrahydro-3,5-dioxo-N-4-pyridinyl-1H-pyrrolo[1,2-c]imidazole-2(3H)-acetamide.

9. A process for producing a pharmaceutical composition for treating senility or for reversing
- 30 the effects of electroconvulsive shock-induced amnesia, which process comprises combining a pharmaceutically effective amount of a compound having the structural formula

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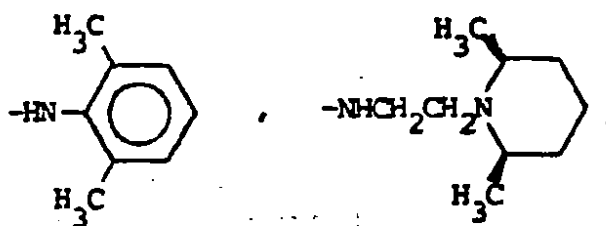
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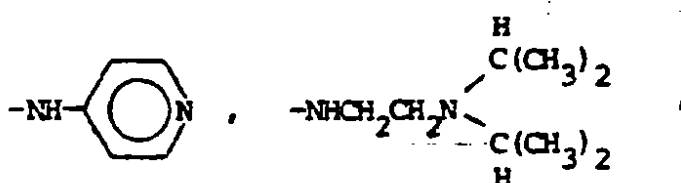
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wherein R is selected from hydrogen; alkyl of from one to four carbon atoms; alkenyl of from one to four carbon atoms; phenylmethyl; and $-\text{CH}_2\text{COR}_1$ where R_1 is selected from OH, alkoxy of from one to four carbon atoms, phenylmethoxyl,

15



20



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and NR_2R_3 where R_2 and R_3 are independently hydrogen or alkyl of from one to four carbon atoms; and, when basic, a pharmaceutically acceptable acid addition salt thereof;

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with a pharmaceutically acceptable carrier.

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European Patent
Office

EUROPEAN SEARCH REPORT

0174136

Application number

EP 85 30 5959

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	DE-A-2 354 086 (GRUPPO LEPETIT S.P.A.) * claims 1,4 *	1,7	C 07 D 487/04 A 61 K 31/41 (C 07 D 487/04 C 07 D 235:00 C 07 D 209:00)
A	DE-A-2 354 102 (GRUPPO LEPETIT S.P.A.) * claims 1,5 *	1,7	
D,A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 72, June 1950, pages 2727, 2728, Easton, Pa., US; G.L. EVANS et al. "Synthesis of Ecgoninic Acid and Related Pyrrolidones"		
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 D 487/00
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 19-11-1985	Examiner HASS C V F
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document	

EPO Form 1503, 03/82

Synthesis and Pharmacological Activity of a Series of Dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones, a Novel Class of Potent Cognition Enhancers

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SmithKline Beecham Farmaceutici, Research Laboratories, 20021 Baranzate, Milan, Italy

Received May 28, 1992^{*}

A series of dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones were synthesized. These bicyclic derivatives contain both the 2-pyrrolidinone and 4-imidazolidinone nuclei, already recognized as important for cognition enhancing activity. In addition, these structures maintain the backbone of piracetam and oxiracetam with the acetamide side chain restricted in a folded conformation. Their ability to reverse scopolamine-induced amnesia was assessed in a one trial, step-through, passive avoidance paradigm. The main features observed are a potent anti-amnesic activity after ip administration (minimal effective dose being between 0.3 and 1 mg/kg ip for most compounds), the presence of a bell-shaped dose-response curve and, generally, a reduction of biological activity after po administration. However, the unsubstituted compound (15, dimiracetam) shows no evidence of a bell-shaped dose-response curve and completely retains activity when given orally, being 10-30 times more potent than the reference drug oxiracetam.

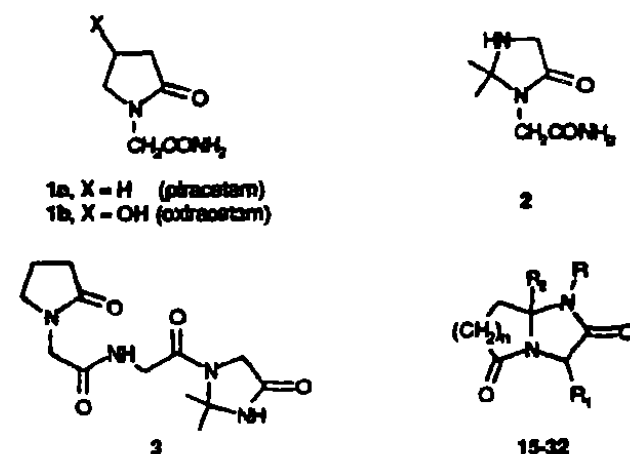
A large number of compounds belonging to many different chemical classes have been proposed as cognition enhancers.¹⁻⁴ Indeed, most of these compounds were found to be effective in mild forms of cognition impairment, while their efficacy in more severe forms of dementia still remains questionable.

Among them, pyrrolidinone cognition enhancers like piracetam (1a, Chart I) and oxiracetam (1b) form a group apart due to their unique selectivity for brain areas involved in learning and memory processes and their exceptionally safe profile.⁵⁻⁷ These features make them suitable for chronic treatment in elderly patients. Though the exact mechanism of action of pyrrolidinone cognition enhancers has not yet been elucidated, it has recently been demonstrated that they exert a variety of biochemical and electrophysiological effects related to learning and memory processes. These include the enhancement of cholinergic and glutamatergic hippocampal and cortical systems and the induction of hippocampal long-term potentiation in rodent brain slices.⁸⁻¹¹

Thus, taking oxiracetam^{12,13} as the model drug, we continued research in the field with the aim of finding compounds endowed with increased potency and efficacy and with a similar profile in terms of safety. Within this framework we had already shown that the 2-pyrrolidinone nucleus, which can be considered a mimic of a dipeptide with a restricted conformation,¹⁴ can be isosterically replaced by the 4-imidazolidinone ring, to give, for example, compound 2, which retains anti-amnesic activity.¹⁵ Combination of the two features, namely 2-pyrrolidinone and 4-imidazolidinone, in a single molecule, such as in compound 3, further enhanced the activity.¹⁶

The finding of an anti-amnesic activity confirmed that the 4-imidazolidinone nucleus possessed the required properties of stability and brain penetration and retained a similar and complementary pharmacological activity to that of 2-pyrrolidinone.

Chart I



On the basis of these results, we decided to combine, in the most compact way and with possible advantages for stability, the two γ -lactamic heterocycles into a novel fused bicyclic structure. In addition, the designed structure maintains the backbone of piracetam and oxiracetam with the acetamide side chain restricted in a folded conformation.

Thus, a series of variously substituted dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones 15-32 and the homologous compounds 33 and 34, where the 2-pyrrolidinone was enlarged to six- and seven-membered rings, were prepared, and their ability to reverse the scopolamine-induced amnesia in rats was assessed.

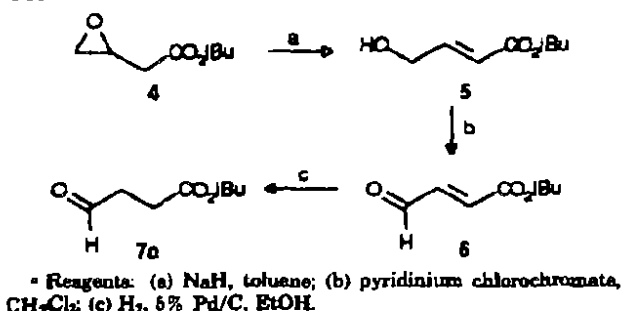
Chemistry. Compounds 15-27, 33, and 34 were prepared by condensation of the suitable α -amino amides with oxoesters 7. All starting materials have been previously described in the literature, apart from isobutyl 4-oxobutanoate (7a), which was obtained (Scheme I) from isobutyl 3,4-epoxybutanoate (4)¹⁷ by base-catalyzed rearrangement to isobutyl γ -hydroxycrotonate (5), oxidation with pyridinium chlorochromate to 6, and, finally, selective hydrogenation of the double bond.

Reaction in refluxing water (method A) of 7a with glycine (8a), DL-alanine (DL-8b), and L-serine-

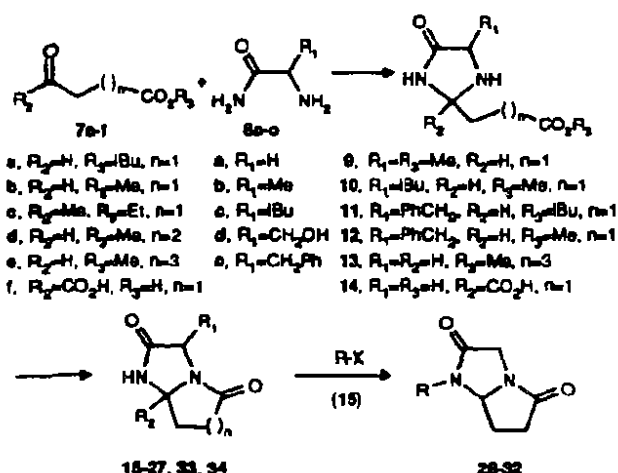
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^{*} Abstract published in *Advance ACS Abstracts*, December 1, 1993.

Scheme I^a

Scheme II

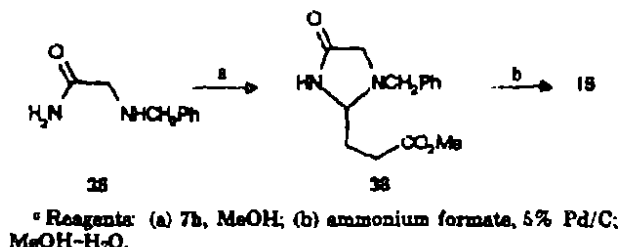


mide (L-8d) and of ethyl levulinate (7c) with 8a,b (Scheme II) gave directly the bicyclic compounds 15, 17–19, 21, and 24 (Table I) without isolation of the intermediate 4-imidazolidinones. The homologous piperidone derivative 33 was prepared from glycineamide (8a) and methyl 5-oxovalerate (7d). This method was very quick and straightforward, but yields were generally low (19–30%) and the reaction mixtures contained several side products from which the desired compounds were obtained by tedious chromatographic purifications. Moreover, when L-phenylalanineamide (L-8e) was used or ethyl 6-oxohexanoate (7e) was employed as the oxoester, only the 4-imidazolidinonic intermediates 11 and 13 could be obtained in low yields.

When the methyl ester 7b¹⁸ was used in place of the isobutyl ester 7a, the reaction did not occur, probably due to a faster degradation of 7b under the reaction conditions.

Thus, to overcome the above difficulties, a two-step synthesis was set up, involving condensation in refluxing methanol to the 4-imidazolidinone and subsequent cyclization. In this manner, L-alanineamide (L-8b), L-leucineamide (L-8c), and D-phenylalanineamide (D-8e) with 7b in methanol afforded exclusively the 4-imidazolidinones 9, 10, and 12, respectively. Generally, further cyclization of 4-imidazolidinones to the final compounds required drastic conditions and occurred with low yields: compounds 9 and 10 were cyclized to 16 and 20 by heating without solvent and under vacuum at 120 °C (method B) while compounds 11–13 were refluxed in xylene (method C) to give 22, 23, and 34, respectively.

Compounds 25, 26, and 27 (Table I) were obtained through the corresponding 4-oxoimidazolidinedicarboxylic acid 14, prepared, in turn, by reacting glycineamide (8a)

Scheme III^a

with 2-oxoglutaric acid (7f). In this case, cyclization was accomplished by treatment with hexamethyldisilazane and trimethylchlorosilane.¹⁹ The obtained 7a-carboxy derivative 25 was converted into the ester 26 and finally into the corresponding amide 27. Compound 15 was alkylated under phase-transfer-catalysis conditions either with ethyl bromide or ethyl bromoacetate to give 28 and 29. The ethyl ester 29, treated with methanolic ammonia, yielded the corresponding amide 30. Compound 15 was also acylated either with acetic anhydride or benzyl chloroformate to afford the imides 31 and 32.

Since, during the continuation of our study, substantial amounts of compound 15 were required for biological and toxicological studies, and yields of the above described methods were not satisfactory for that purpose, an alternative synthesis was developed. We reasoned that the main causes of the low yields obtained with method A were the instability of the reagents under reaction conditions and the rather high basicity of glycineamide (pK_B = 8.05), leading to polymerization of the aldehyde group and/or hydrolysis of the ester group as well as the possibility of an equilibrium between the cyclic (imidazolidinone) and open (Schiff base) form. Therefore, we studied the reaction of the less basic and more stable 2-(benzylamino)acetamide²⁰ (35, pK_B = 7.2), with methyl 4-oxobutanoate (7b) and we found that it proceeds very smoothly in refluxing methanol, affording methyl 1-benzyl-4-oxo-2-imidazolidinepropanoate (36) in very good yields (Scheme III).

Surprisingly, when hydrogenolytic debenzylation was performed with ammonium formate as the hydrogen source, the desired bicyclic compound 15 was obtained directly in greater than 80% yield. Such an easy cyclization was most probably due to the catalytic action of ammonia produced (as ammonium carbonate) during the reaction; in fact, we confirmed that added ammonium hydroxide as well as other bases, such as triethylamine or 4-(dimethylamino)pyridine, were capable of accelerating the cyclization of the intermediate methyl 4-oxo-2-imidazolidinepropanoate (37, obtained from 36 by replacing ammonium formate with cyclohexene or hydrogen). The catalytic efficacy of ammonia in the intramolecular aminolysis was so strong that, even in the presence of a very large excess of ammonium hydroxide, no evidence of amide formation by ester ammonolysis was observed.

Pharmacology. Since the mechanism of action of 2-pyrrolidinone cognition enhancers is still under investigation, the search for new drugs in this area generally relies on behavioral tests,^{21,22} although their predictive validity has been debated.²³ Among them, the reversal of the experimentally-induced amnesia evaluated in a passive avoidance test has been widely used for screening purposes,^{24–26} and in particular, scopolamine-induced amnesia has been considered to mimic, in animals²⁷ and humans,^{28,29} the cholinergic impairment associated with

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Table I. Substituted Dihydro-1*H*-pyrrolo[1,2-*c*]imidazole-2,6-(3*H*,5*H*)-diones 15-32 and Homologues 33 and 34

no.	R	R ₁	R ₂	n	config at C-3	method (% yield)	mp (°C)	formula ^a	reversal (%) of scopolamine-induced amnesia ^b							
									mg/kg ip				mg/kg po			
15	H	H	H	1	-	A (22.6) (or 81 ^c)	155-157	C ₉ H ₉ N ₃ O ₃		18	68	70	28	75	80	40
16	H	Me	H	1	S ^d	B (61.2)	129-132	C ₉ H ₁₀ N ₃ O ₃		0	63	3				
17	H	Me	H	1	RS	A (24)	84-88	C ₉ H ₁₀ N ₃ O ₃			38	38		9	33	
18	H	Me	Me	1	S ^e	A (19.1)	228-230	C ₁₀ H ₁₁ N ₃ O ₃		10	65	64		21	26	87
19	H	Me	Me	1	RS	A (23.6)	184-192	C ₁₀ H ₁₁ N ₃ O ₃		30	34	0		17	43	
20	H	tBu	H	1	S ^f	B (28)	156-157	C ₁₂ H ₁₅ N ₃ O ₃			3	0				
21	H	CH ₂ OH	H	1	S ^g	A (19)	150-162	C ₉ H ₁₁ N ₃ O ₄	3	30	28			0	42	0
22	H	CH ₂ Ph	H	1	S ^h	C (50)	141-145	C ₁₀ H ₁₁ N ₃ O ₃	0	53	53	0	0	43	0	7
23	H	CH ₂ Ph	H	1	R ⁱ	C (42.9)	134-138	C ₁₀ H ₁₁ N ₃ O ₃	15	43	19	0				
24	H	H	Me	1		A (21)	187-189	C ₉ H ₁₀ N ₃ O ₃		0	40	46			0	28
25	H	H	CO ₂ H	1		(50) ^j	207 dec	C ₉ H ₉ N ₃ O ₄			14	88		1	39	
26	H	H	CO ₂ Et	1		(49) ^k	118-117	C ₁₀ H ₁₁ N ₃ O ₄			26	82		0	0	
27	H	H	CONH ₂	1		(77) ^l	295 dec	C ₇ H ₉ N ₃ O		88	62	88				
28	Et	H	H	1		(51.3) ^m	53-56	C ₁₀ H ₁₃ N ₃ O ₃			0	0				
29	CH ₂ CO ₂ Et	H	H	1		(92) ⁿ	75-80	C ₁₀ H ₁₁ N ₃ O ₄			3	0				
30	CH ₂ CONH ₂	H	H	1		(75) ^o	182-185	C ₈ H ₁₁ N ₃ O ₃			49	82		0	9	
31	COMe	H	H	1		(78.4) ^p	68-72	C ₉ H ₁₀ N ₃ O ₃			0	0				
32	CO ₂ CH ₂ Ph	H	H	1		(29) ^q	120-121	C ₁₀ H ₁₁ N ₃ O ₄			31	12				
33	H	H	H	2		A (30)	170-174	C ₉ H ₁₀ N ₃ O ₃			27	27		0	0	
34	H	H	H	3		C (23)	176-176	C ₉ H ₁₀ N ₃ O ₃			22	12				
1b	oxiracetam									12	53			27	69	

^a For all compounds, elemental analyses were within ±0.4% of the theoretical values. ^b Values reported in boldface are significantly different from those of the scopolamine group (*p* < 0.05) in the Fisher's exact probability test. For statistical calculations, see Experimental Section. ^c See Experimental Section for methodology. ^d [α]_D = +85.8 (*c* = 2, MeOH). ^e [α]_D = +50.7 (*c* = 3, water). ^f [α]_D = +35.5 (*c* = 1, MeOH). ^g [α]_D = +10.3 (*c* = 1, MeOH).

the aging of the brain and senile dementia.³⁰ Moreover, tacrine, which antagonizes the antiamnesic effect of scopolamine in the passive avoidance test,³¹ was shown, by means of extensive clinical trials, to be effective in patients with Alzheimer's disease.³²

Therefore, we evaluated the ability of new compounds to protect rats from scopolamine-induced amnesia in a one-trial passive avoidance test. All compounds were administered intraperitoneally and those showing a good profile in terms of potency were also tested orally. Most of them were also evaluated up to very high doses in the Irwin test on the mouse³³ to rule out in a preliminary way other important pharmacological or toxic effects.

Results and Discussion. The antiamnesic activity of all the new compounds is reported in Table I, in comparison to that of oxiracetam, assumed as the standard drug.

As far as the intraperitoneal administration is considered, most of the new compounds are able to reverse scopolamine-induced amnesia at a level of between 20 and 68% at 1 mg/kg whereas oxiracetam shows only a 12% reversal of this deficit at the same dose. The unsubstituted derivative 15 is active from the dose of 1 mg/kg; substitution at position 3, i.e. replacement of the glycine moiety with other natural amino acids such as alanine, serine and phenylalanine, in general slightly increases the potency. However, compounds 19, 21, 22, and 23 show a narrow, inverted U-shaped dose-response curve. An exception is the complete lack of activity, at the tested doses, of the derivative of L-leucine, 20. All the compounds bearing a substituent at position 3 are diastereoisomeric mixtures since the chiral center at 7a is formed during the reaction. Referring to the chirality at position 3, it does not seem to be of great importance for activity even if the comparison between compounds 22 and 23 (derivatives of L- and

D-phenylalanine, respectively) indicates that compounds derived from natural amino acids might have some advantages.

Substitution at position 1, i.e. alkylation or acylation of the imidazolidinone NH, generally removes activity with the exception of compound 30, which features the acetamide side chain typical of piracetam-like cognition enhancers. The effect of substitution at 7a was checked with the derivatives of levulinic acid 18, 19, and 24 and with those of 2-oxoglutaric acid, 25, 26, and 27; all the considered compounds exhibited some antiamnesic activity, but again, only the amide 27 showed an increased potency, being active from 0.3 to 10 mg/kg. The marked antiamnesic activity of 27 and 30 suggests that an increase in hydrophilic character, within certain limits, positively influences cognition-enhancing activity, as already observed for oxiracetam in comparison with the nonhydroxylated piracetam. This fact appears rather surprising for centrally active compounds. Also the importance of the 2-pyrrolidinone moiety has been confirmed: homologues 33 and 34, with enlarged six and seven-membered lactamic rings, completely lose antiamnesic activity.

When oral administration is considered it is readily apparent that while compound 15 maintains the activity over a wide dose range, any kind of substitution produces negative effects since either antiamnesic activity disappears or a very narrow, inverted U-shaped dose-response curve becomes evident. Such a reduction of activity after oral administration was frequently encountered during our work on cognition enhancers and this could not have been predicted purely on the basis of the chemical structure.

When compounds 15, 18, 19, 21, 22, 24-27, and 30 were submitted to the Irwin test,³³ no mortality or evident modification of gross behavior was noted. These results

Table II. Effect of Scopolamine and Compound 15 Plus Scopolamine in the Radial Maze in the Rat^a

treatment	no. of rats	day before treatment		day of treatment		day after treatment	
		efficiency in responding (%)	running time (s)	efficiency in responding (%)	running time (s)	efficiency in responding (%)	running time (s)
scopolamine ^b	21	87.3 ± 3.0	14.3 ± 0.8	83.9 ± 4.1 ^c	34.6 ± 6.4 ^c	83.9 ± 2.8	19.6 ± 3.9
15 (1 mg/kg sc) + scopolamine ^b	17	86.3 ± 1.7	16.8 ± 2.7	75.6 ± 4.1 ^{c,d}	34.6 ± 6.4 ^c	88.6 ± 4.3	19.6 ± 3.9

^a Values (reported as mean ± SEM) for the days preceding and following a pharmacological treatment were used as controls. ^b Scopolamine was given at the dose of 50 µg/kg sc. ^c *p* < 0.05 against control days. ^d *p* < 0.05 against scopolamine.

suggest good selectivity and a safe profile for this novel class of dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-diones.

On the whole, the unsubstituted derivative 15 exhibits a good bioavailability after oral administration and the highest potency/efficacy combination within the narrow, inverted U-shaped dose response-curve noticed with other cognition enhancers.^{2,26} Moreover, it is practically devoid of any significant acute toxic effect.

To corroborate and better characterize the antiamnesic properties, compound 15, the most potent of the series, was evaluated with the same model of scopolamine-induced memory impairment in an eight-armed-radial-maze test.²⁴ This task provides measures of working memory which are known to be impaired in dementia. Compound 15 at 1 mg/kg partially antagonized the reduction of efficiency produced by scopolamine in solving the maze (Table II), while it was completely unable to counteract the increase of running time produced by scopolamine. This finding suggests that cholinergic mechanisms involved in learning and memory can be selectively enhanced without affecting motor behavior.

On these bases, 15 (dimiracetam) was selected for further studies and its evaluation will be extended to other multitrial behavioral tests on several animal models and to neurochemical investigations in order to confirm its suitability as a candidate cognition enhancing drug and to identify its exact mechanism of action.

Experimental Section

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 197 spectrophotometer. Proton nuclear magnetic resonance spectra (NMR) were recorded on a Varian FT-80A spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained with a Varian MAT 112 instrument via direct inlet (EI, 70 eV, 1.5 mA). Elemental analyses were within 0.4% of the theoretical values for the indicated elements. Column chromatographies were performed with Merck 0.063–0.200 mm silica gel. Thin-layer chromatographies were performed on Merck 60 F 254 silica gel plates and revealed by UV or iodine vapors or by chlorine vapors followed by spraying with a KI-starch solution.

Starting α-amino amides 8a–c were either commercially available or were prepared from the corresponding α-amino acids as described in the literature.²⁵ Oxacetam 7c,f were commercially available while 7b,d,e were prepared according to the literature procedures from methyl 4-chloro-4-oxobutanoate,¹⁴ valerolactone,²² and caprolactone,²⁷ respectively.

Chemistry. Isobutyl (E)-4-Hydroxy-2-butenate (5). To an ice-cold solution of isobutyl 3,4-epoxybutanoate²⁷ (4; 300 g, 1.9 mol) in toluene (2.5 L) was added 55% sodium hydride in oil (3 g, 0.07 mol) portionwise. The solution was stirred at 0–5 °C for 1 h, then 55% sodium hydride (3 g, 0.07 mol) was added again. After stirring at room temperature for 1 h the solution was washed with brine (0.4 L) containing 10% hydrochloric acid (80 mL) and then twice with brine (300 mL each). The organic solution was dried over anhydrous sodium sulfate and evaporated to dryness. Distillation of the residue afforded 175 g (58.3%) of 5 as a colorless oil: bp 89–90 °C (0.5 mmHg); NMR (CDCl₃) δ

7.05 (dt, *J* = 15, 4 Hz, 1H, CH=CHCO), 6.15 (dt, *J* = 15, 2 Hz, 1H, CH=CHCO), 4.35 (m, 2H, CH₂OH), 3.95 (d, *J* = 6 Hz, 2H, CO₂CH₃), 2.20–1.75 (m, 1H, CH(CH₃)₂), 1.85 (br s, 1H, OH), 0.95 (d, *J* = 6 Hz, 6H, CH(CH₃)₂); MS *m/z* 127 (M – CH₂OH), 85 (M – C₂H₅O₂). Anal. (C₈H₁₄O₃) C, H.

Isobutyl (E)-4-Oxo-2-butenate (6). To a suspension of pyridinium chlorochromate (100 g, 0.463 mol) in dichloromethane (350 mL) was added a solution of isobutyl (E)-4-hydroxybutanoate (5; 50 g, 0.316 mol) in dichloromethane (150 mL). The internal temperature gradually rose to 40 °C and stirring was continued for 2 h without cooling. Diethyl ether (0.9 L) was added and the supernatant was decanted from the black gum. The insoluble residue was washed twice with 300-mL portions of diethyl ether. The combined organic solutions were filtered through a short pad of Florisil and the solvent was removed by distillation, to yield 45.3 g (91.6%) of 6 as a pale yellow oil: *R*_f = 0.5 (cyclohexane-ethyl acetate 6:4); NMR (CDCl₃) δ 9.80 (ABX, *J* = 8, 2 Hz, 1H, CHO), 6.98 and 6.75 (ABX, *J*_{AB} = 16 Hz, 2H, CH=CHCHO), 4.00 (d, *J* = 6 Hz, 2H, CO₂CH₃), 2.20–1.80 (m, 1H, CH(CH₃)₂), 0.95 (d, *J* = 6 Hz, 6H, CH(CH₃)₂); MS *m/z* 155 (M – H), 85 (M – C₂H₅O₂). Anal. (C₈H₁₂O₃) C, H.

Isobutyl 4-Oxobutanoate (7a). To a solution of isobutyl (E)-4-oxo-2-butenate (6; 97 g, 0.62 mol) in 96% ethanol (700 mL) was added 5% palladium on charcoal (9.7 g) and hydrogen was bubbled through the solution at 5–10 °C for 20 h. Removal of the catalyst and evaporation of the solvent gave an oil which was distilled through a short Vigreux column (80–85 °C, 3 mbar) to afford 68 g (67.3%) of 7a; *R*_f = 0.41 (cyclohexane-ethyl acetate 6:4); iodine vapors; NMR (CDCl₃) δ 9.85 (t, *J* = 1 Hz, 1H, CHO), 3.80 (d, *J* = 6 Hz, 2H, CO₂CH₃), 2.80–2.60 (m, 4H, CH₂CH₂), 2.25–1.75 (m, 1H, CH(CH₃)₂), 0.80 (d, *J* = 6 Hz, 6H, CH(CH₃)₂); MS *m/z* 101 (M – C₂H₅), 85 (M – C₂H₅O₂), 57 (M – C₂H₅O). Anal. (C₈H₁₄O₂) C, H.

General Procedure for the Synthesis of Alkyl 4-Oxo-2-imidazolidinone-3-carboxylates 9–13. To a mixture of α-amino amide hydrochloride 6 (0.1 mol) in methanol (100 mL) adjusted to pH 8.3 with 2 N NaOH in methanol was added oxoceter 7 (0.1 mol) and the solution was refluxed for 2.5 h. After cooling, the solvent was evaporated under vacuum and the residue was chromatographed over silica gel (dichloromethane-methanol 8:1).

Methyl (2*RS*,5*S*)-5-methyl-4-oxo-2-imidazolidinone-3-carboxylate (9) was prepared, according to the general procedure, from L-alaninamide hydrochloride (12.5 g, 0.1 mol) and 7b (11.6 g, 0.1 mol) to afford 6.54 g (36%) of 9 as an oil, which was characterized as the hydrochloride: mp 136–142 °C dec (acetone-diisopropyl ether); [α]_D²⁰ = +14.5 (*c* = 1, MeOH); NMR (DMSO-*d*₆) δ 10.75 (br s, 2H, NH₂⁺), 9.25 (br s, 1H, CONH), 4.97 and 4.87 (t, *J* = 5 Hz, 1H, HNCHNH), 4.3–3.9 (m, 1H, COCHNH), 3.82 (s, 3H, CO₂CH₃), 2.75–2.50 (m, 2H, CH₂CO₂), 2.40–1.85 (m, 2H, CHCH₃), 1.39 (d, *J* = 6 Hz, CHCH₃); MS *m/z* 186 (M), 171 (M – CH₃), 127 (M – CO₂CH₃).

Methyl (2*RS*,5*S*)-5-isobutyl-4-oxo-2-imidazolidinone-3-carboxylate (10) was prepared, according to the general procedure, from L-leucinamide hydrochloride (16.7 g, 0.1 mol) and 7b (11.6 g, 0.1 mol) to afford 3.88 g (17%) of 10 as an oil. The hydrochloride salt had mp 184–189 °C dec; [α]_D²⁰ = –24.7 (*c* = 1.15, H₂O); NMR (DMSO-*d*₆) δ 10.8 (br s, 2H, NH₂⁺), 9.20 (br s, 1H, CONH), 4.96 and 4.85 (t, *J* = 6 Hz, 1H, HNCHNH), 4.20–3.80 (m, 1H, COCHNH), 3.64 (s, 3H, CO₂CH₃), 2.80–2.45 (m, 2H, CH₂CO₂), 2.40–2.00 (m, 2H, CHCH₃), 2.00–1.50 (m, 3H, CH₂CH(CH₃)₂), 0.94 (d, *J* = 5 Hz, 6H, CH(CH₃)₂). MS *m/z* 228 (M), 197 (M – OCH₃), 141 (M – C₂H₅O₂).

Isobutyl (2*RS*,5*S*)-5-benzyl-4-oxo-2-imidazolidinopropionate (11) was prepared, according to the general procedure, from L-phenylalaninamide hydrochloride (20 g, 0.1 mol) and 7a (16 g, 0.1 mol) in isobutyl alcohol to afford 6 g (20%) of 11, as an oil, which was characterized as the hydrochloride: mp 152–155 °C dec (ethanol-diethyl ether); $[\alpha]_D^{25} = -40$ ($c = 0.125$, MeOH); NMR (DMSO- d_6 + CDCl $_3$) δ 11.0 (br s, 2H, NH $_2^+$), 9.25 (br s, 1H, CONH), 7.6–7.1 (m, 5H, PhH), 4.80 (t, $J = 6$ Hz, 1H, NHCHNH), 4.17 (t, $J = 6$ Hz, 1H, COCHNH), 3.84 (d, $J = 7$ Hz, 2H, CO $_2$ CH $_2$), 3.35 (m, 2H, CH $_2$ Ph), 2.50–1.60 (m, 5H, CH $_2$ CH $_2$ and CH(CH $_3$) $_2$), 0.90 (d, $J = 6$ Hz, 6H, CH(CH $_3$) $_2$); MS m/z 304 (M), 213 (M – C $_7$ H $_7$), 84 (C $_4$ H $_8$ N $_2$ O).

Methyl (2*RS*,5*SR*)-5-benzyl-4-oxo-2-imidazolidinopropionate (12) was prepared, according to the general procedure, from D-phenylalaninamide hydrochloride (5 g, 25 mmol) and 7b (2.9 g, 25 mmol) to afford 4.26 g (65%) of 12, as an oil: $[\alpha]_D^{25} = +21.5$ ($c = 2$, MeOH); NMR (CDCl $_3$) δ 7.25 (s, 5H, PhH), 7.20 (br s, 1H, CONH), 4.85 and 4.42 (t, $J = 5$ Hz, 1H, NHCHNH), 4.00–3.50 (m, 1H, COCHNH), 2.65 and 2.62 (s, 3H, CO $_2$ CH $_3$), 3.25–2.75 (m, 2H, PhCH $_2$), 2.5–2.20 (m, 2H, CH $_2$ CO $_2$), 2.13 (br s, 1H, NH), 2.0–1.7 (m, 2H, CHCH $_2$); MS m/z 175 (M – C $_7$ H $_7$ O), 171 (M – C $_7$ H $_7$).

Methyl 4-oxo-2-imidazolidinopropionate (13) was prepared, according to the general procedure, from glycineamide hydrochloride (8.73 g, 61 mmol) and methyl 6-oxohexanoate²² (7e; 8.8 g, 61 mmol) to afford 3.95 g (32.5%) of 13: mp 58–60 °C; NMR (DMSO- d_6) δ 8.15 (br s, 1H, CONH), 4.40 (m, 1H, NHCHNH), 3.60 (s, 3H, CO $_2$ CH $_3$), 3.10 (s, 2H, COCH $_2$ NH), 2.45–2.15 (m, 2H, CH $_2$ CO $_2$), 1.75–1.10 (m, 6H, CH $_2$ CH $_2$ CH $_2$); MS m/z 201 (M + H), 169 (M – OCH $_3$), 141 (M – C $_4$ H $_7$ O $_2$).

Method A. Dihydro-1*SR*-pyrrolo[1,2-*a*]imidazole-2,5-(3*SR*,6*SR*)-dione (15). To a solution of glycineamide hydrochloride (8a; 18.4 g, 0.166 mol) in water (200 mL), adjusted to pH 9.5 with 10% sodium hydroxide (about 60 mL) was added 7a (22.2 g, 0.14 mol). The solution was refluxed for 20 h. Water was evaporated under vacuum and the residue was chromatographed over silica gel (dichloromethane-methanol 9:1) to afford 4.44 g (22.6%) of 15: mp 156–157 °C; NMR (DMSO- d_6) δ 8.65 (br s, 1H, CONH), 5.20 (t, $J = 6$ Hz, 1H, NCHNH), 3.80 and 3.40 (AB q, $J = 15$ Hz, 2H, COCH $_2$ NH), 2.85–1.55 (m, 4H, CH $_2$ CH $_2$); MS m/z 140 (M), 97 (M – CONH).

Method B. (3*SR*,7*SR*)-Dihydro-3-ethyl-1*SR*-pyrrolo[1,2-*a*]imidazole-2,5-(3*SR*,6*SR*)-dione (16). Compound 9 (4.85 g, 0.026 mol) was heated at 120 °C under vacuum (20–30 mmHg) for 5 h. The crude residue was chromatographed over silica gel (dichloromethane-methanol 9:1), the appropriate fractions were evaporated and the residue was crystallized from acetone-diisopropyl ether to afford 2.05 g (51.2%) of 16 as a white powder: mp 129–132 °C; $[\alpha]_D^{25} = +85.8$ ($c = 2$, MeOH); NMR (CDCl $_3$) δ 9.02 (br s, 1H, CONH), 5.35 (t, $J = 5$ Hz, 1H, NCHNH), 4.80 (q, $J = 8$ Hz, 1H, NCHCO), 2.9–1.8 (m, 4H, CH $_2$ CH $_2$), 1.38 (d, $J = 8$ Hz, 3H, CHCH $_3$); MS m/z 184 (M), 139 (M – CH $_3$), 111 (M – CHNH), 98 (M – C $_4$ H $_7$ O).

Method C. (3*SR*,7*SR*)-3-Benzyl-1*SR*-pyrrolo[1,2-*a*]imidazole-2,5-(3*SR*,6*SR*)-dione (23). A solution of 13 (3.2 g, 12.2 mmol) in xylene (120 mL) was refluxed for 3 days. After evaporation, the crude residue was flash chromatographed over silica gel (dichloromethane-methanol 95:5). The collected fractions were evaporated, and the residue was triturated with diisopropyl ether to afford 1.2 g (42.9%) of 23: mp 134–138 °C, $[\alpha]_D^{25} = -97.3$ ($c = 2$, MeOH); NMR (CDCl $_3$) δ 7.75 (br s, 1H, CONH), 7.25 (br s, 5H, PhH), 4.65 (t, $J = 4.5$ Hz, 1H, NCHCO), 4.45 (t, $J = 5$ Hz, 1H, NCHNH), 3.15 (d, $J = 4.5$ Hz, 2H, PhCH $_2$), 2.8–1.6 (m, 4H, CH $_2$ CH $_2$); MS m/z 230 (M), 139 (M – C $_7$ H $_7$).

2-Carboxy-4-oxo-2-imidazolidinopropionic Acid (14). A solution of 2-oxoglutaric acid (10 g, 68.4 mmol), glycineamide hydrochloride (8.8 g, 75.2 mmol), and sodium hydroxide (8.2 g, 205.2 mmol) in water (120 mL) was refluxed for 4 h. After cooling, the solution was adjusted to pH 2.5 and the resulting precipitate was collected and dried under vacuum at 60 °C to afford 5.9 g (43%) of 14: mp 202–205 °C dec; NMR (DMSO- d_6) δ 8.5 (s, 1H, CONH), 7.00–4.00 (br s, 3H, NH, CO $_2$ H), 3.22 and 3.18 (AB q, $J = 16$ Hz, 2H, COCH $_2$ NH), 2.40–1.75 (m, 4H, CH $_2$ CH $_2$); MS m/z 140 (M – H $_2$ O – CO $_2$), 84 (C $_4$ H $_8$ N $_2$ O).

2,5-Dioxahexahydro-1*SR*-pyrrolo[1,2-*a*]imidazole-7*a*-carboxylic Acid (25). A mixture of 14 (2 g, 9.89 mmol), hexa-

methylaldiazane (20 mL), and trimethylchlorosilane (10 mL) in dry acetonitrile (50 mL) was refluxed under nitrogen for 4 h. After cooling, the precipitate was filtered off and the filtrate was evaporated under vacuum. The residue was dissolved in methanol (20 mL) containing a few drops of concentrated hydrochloric acid and stirred for 10 min. The insoluble material was filtered off and the filtrate was evaporated to dryness. The residue was triturated with acetonitrile and crystallized with tetrahydrofuran (250 mL) to yield 0.9 g (50%) of 25: mp 207 °C dec; NMR (DMSO- d_6) δ 13.0 (br s, 1H, CO $_2$ H), 9.15 (br s, 1H, CONH), 3.82 and 3.48 (AB q, $J = 16$ Hz, 2H, NCH $_2$ CO); 2.9–1.8 (m, 4H, CH $_2$ CH $_2$); MS m/z 184 (M), 139 (M – CO $_2$ H), 83 (C $_4$ H $_8$ N $_2$ O).

Ethyl 2,5-dioxahexahydro-1*SR*-pyrrolo[1,2-*a*]imidazole-7*a*-carboxylate (26). A suspension of 25 (0.8 g, 4.34 mmol) in dry tetrahydrofuran (100 mL) was cooled to 0 °C and treated with oxalyl chloride (0.55 g, 4.34 mmol) and a drop of dimethylformamide. After stirring for 2 h at 0 °C, the resulting solution was allowed to reach room temperature and vacuum was applied for 10 min. After cooling to 0 °C, 4-(dimethylamino)pyridine (0.53 g, 4.34 mmol) and dry ethanol (2 mL) were added. The suspension was stirred at 0 °C for 30 min and at room temperature for 30 min. The precipitate was filtered off and the filtrate was evaporated under vacuum. The residue was chromatographed over silica gel (ethyl acetate-methanol 95:5) to afford 0.45 g (49%) of 26, mp 116–117 °C; NMR (DMSO- d_6) δ 9.22 (br s, 1H, CONH), 4.16 (q, $J = 7.5$ Hz, 2H, CH $_2$ CH $_3$), 3.85 and 3.48 (AB q, $J = 15$ Hz, 2H, NCH $_2$ CO), 2.85–2.05 (m, 4H, CH $_2$ CH $_2$), 1.2 (t, $J = 7.5$ Hz, 3H, CH $_2$ CH $_3$); MS m/z 183 (M – Et), 139 (M – CO $_2$ Et), 83 (C $_4$ H $_8$ N $_2$ O).

2,5-Dioxahexahydro-1*SR*-pyrrolo[1,2-*a*]imidazole-7*a*-carbamamide (27). An ice-cold solution of 26 (2.55 g, 12 mmol) in dry methanol (20 mL) was treated with a saturated solution of ammonia in methanol (40 mL) and stirred for 1 h at 0 °C. The precipitate was collected, washed with acetone, and dried to afford 1.7 g (77%) of 27: mp 295 °C dec; NMR (DMSO- d_6) δ 9.05 (br s, 1H, CONH), 7.50 (br s, 2H, CONH $_2$), 3.80 and 3.60 (AB q, $J = 15$ Hz, 2H, NCH $_2$ CO), 2.85–1.95 (m, 4H, CH $_2$ CH $_2$); MS m/z 139 (M – CONH $_2$), 83 (C $_4$ H $_8$ N $_2$ O).

Dihydro-1-ethyl-1*SR*-pyrrolo[1,2-*a*]imidazole-2,5-(3*SR*,6*SR*)-dione (28). A mixture of 15 (4 g, 28.5 mmol), tetrabutylammonium bromide (4.56 g, 14.1 mmol), and potassium carbonate (20 g, 144.7 mmol) in dry acetonitrile (60 mL) was stirred at room temperature for 1 h. Ethyl bromide (2.3 mL, 30.8 mmol) was added and the suspension was heated at 60 °C for 2.5 h. The precipitate was filtered off, the filtrate was evaporated under vacuum and the residue was chromatographed over silica gel (dichloromethane-methanol 9:1). The appropriate fractions were evaporated under vacuum, and the residue was triturated with light petroleum to afford 2.75 g (57.3%) of 28: mp 63–66 °C; NMR (CDCl $_3$) δ 5.25 (t, $J = 5$ Hz, 1H, NCHN), 4.20 and 3.66 (AB q, $J = 16$ Hz, 2H, NCH $_2$ CO), 3.40 (m, 2H, CH $_2$ CH $_3$), 2.80–1.75 (m, 4H, CH $_2$ CH $_2$), 1.15 (t, $J = 7.5$ Hz, 3H, CH $_2$ CH $_3$); MS m/z 168 (M), 139 (M – C $_4$ H $_8$), 112 (M – C $_4$ H $_7$ O).

Ethyl 2,5-dioxahexahydro-1*SR*-pyrrolo[1,2-*a*]imidazole-1-acetate (29). A mixture of 15 (0.5 g, 3.57 mmol), tetrabutylammonium bromide (0.57 g, 1.77 mmol), and potassium carbonate (2.5 g, 18.1 mmol) in dry acetonitrile (6 mL) was stirred at room temperature for 1 h. Ethyl bromoacetate (0.5 mL, 4.5 mmol) was added and the suspension was heated at 60 °C for 2.5 h. The precipitate was filtered off, the filtrate was evaporated under vacuum, and the residue was chromatographed over silica gel (ethyl acetate-acetone-methanol 8:3:1) to afford 0.7 g (92%) of 29: mp 75–80 °C; NMR (CDCl $_3$) δ 6.4 (m, 1H, NCHN), 4.21 (q, $J = 7$ Hz, 2H, CH $_2$ CH $_3$), 4.32 and 3.68 (AB q, $J = 16$ Hz, 2H, NCH $_2$ CO), 4.30 and 3.80 (AB q, $J = 16$ Hz, 2H, NCH $_2$ CO $_2$), 2.8–1.7 (m, 4H, CH $_2$ CH $_2$), 1.28 (t, $J = 7$ Hz, 3H, CH $_2$ CH $_3$); MS m/z 226 (M), 163 (M – CO $_2$ Et), 139 (M – CH $_2$ CO $_2$ Et).

2,5-Dioxahexahydro-1*SR*-pyrrolo[1,2-*a*]imidazole-1-acetamide (30). A solution of 29 (1.4 g, 6.18 mmol) in methanol (25 mL) was saturated with ammonia at 0 °C. After stirring at room temperature for 16 h the precipitate was collected, washed with methanol, and dried to yield 0.9 g (75%) of 30: mp 182–185 °C; NMR (DMSO- d_6) δ 7.50 and 7.10 (br s, 2H, CONH $_2$), 5.25 (m, 1H, NCHN), 3.94 and 3.65 (AB q, $J = 16$ Hz, 2H, NCH $_2$ CO); 3.85 and 3.70 (AB q, $J = 16.5$ Hz, 2H, NCH $_2$ CONH $_2$); 2.80–1.80 (m, 4H, CH $_2$ CH $_2$); MS m/z 139 (M – CH $_2$ CONH $_2$).

1-Acetyldihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione (31). A solution of 15 (4 g, 28.5 mmol) in acetic anhydride (20 mL) was refluxed for 2 h. After cooling, the mixture was evaporated and the residue chromatographed over silica gel (ethyl acetate-acetone-methanol 6:3:1), and the appropriate fractions were evaporated under vacuum. The residue was triturated with diethyl ether to afford 4 g (78.4%) of 31: mp 68–72 °C; NMR (CDCl₃) δ 5.87 (t, *J* = 5 Hz, 1H, NCHN), 4.45 and 3.76 (AB q, *J* = 17.5 Hz, 2H, NCH₂CO), 3.20–1.75 (m, 4H, CH₂CH₂), 2.50 (s, 3H, CH₃); MS *m/z* 182 (M), 154 (M – CO), 139 (M – COCH₃).

1-[(Benzyloxy)carbonyl]dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione (32). To a suspension of 15 (7 g, 50 mmol) in dry acetonitrile (140 mL) cooled to 0–5 °C and maintained under a nitrogen atmosphere was added 55% sodium hydride in oil (2.4 g, 55 mmol) portionwise during 15 min. After 2.5 h at 0–5 °C, a solution of benzyl chloroformate (7.8 mL, 55 mmol) in dry acetonitrile (24 mL) was added dropwise and the mixture was stirred at room temperature for 2 h and at 40 °C for 30 min. After cooling, the mixture was evaporated and the residue, diluted with ethyl acetate (200 mL), was washed twice with water (100 mL). The organic layer was dried and evaporated under vacuum and the residue was triturated with diethyl ether and crystallized from ethanol to yield 4 g (28%) of 32: mp 120–121 °C; NMR (CDCl₃) δ 7.37 (s, 5H, PhH), 5.57 (t, *J* = 5 Hz, 1H, NCHN), 6.30 (s, 2H, CH₂Ph), 4.35 and 3.68 (AB q, *J* = 17 Hz, 2H, NCH₂CO), 3.0–1.9 (m, 4H, CH₂CH₂); MS *m/z* 274 (M), 166 (M – C₇H₅O).

Methyl 1-Benzyl-4-oxo-2-imidazolidinopropionate (34). To a solution of 2-(benzylamino)acetamide²⁰ (35, 67.9 g, 0.41 mol) in methanol (500 mL) was added 7b (60.3 g, 0.52 mol). The mixture was refluxed for 3 h and most of the solvent was evaporated under vacuum. On addition of water (435 mL) and stirring at 0–5 °C for 1 h, the precipitate was collected by filtration and dried at 40 °C under vacuum to afford 91.7 g (85.3%) of 34 as a yellow solid: mp 84–85 °C; NMR (CDCl₃) δ 7.80 (br s, 1H, CONH), 7.30 (s, 5H, PhH), 4.38 (ABX, *J*_{AX+BX} = 3 Hz, 1H, NHCHN), 4.01 and 3.53 (AB q, *J* = 13 Hz, 2H, CH₂Ph), 3.65 (s, 3H, CH₃), 3.37 and 3.01 (ABX, *J*_{AB} = 16 Hz, 1H, NCH₂CO), 2.60–2.26 (m, 2H, CH₂CO₂), 2.15–1.75 (m, 2H, CHCH₂); MS *m/z* 175 (M – C₇H₅O₂), 91 (C₇H₅).

Dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione (15). A mixture of 34 (100 g, 0.38 mol), ammonium formate (40.9 g, 0.65 mol), and 5% palladium on charcoal (10 g) in water (112 mL) and methanol (400 mL) was heated at reflux for 3 h. After cooling, the catalyst was filtered off through a Celite pad and the solution was evaporated under vacuum. The residue was dissolved in water (200 mL) and treated batchwise with the ion exchangers Amberlite IR 120 (15 mL) and Amberlite IRA 68 (9 mL) and charcoal (3 g). After filtration the aqueous solution was diluted with 1-butanol (600 mL) and water was azeotropically removed under vacuum. The residue was crystallized from 2-propanol to afford 43.2 g (81%) of 15 as a white crystalline solid, mp 156–157 °C.

Methyl 4-Oxo-2-imidazolidinopropionate Hydrochloride (37). A mixture of 34 (25 g, 95.3 mmol), water (3.7 mL), and 10% palladium on charcoal (3.75 g) in cyclohexane (250 mL) and 2-propanol (125 mL) was refluxed for 2 h. After cooling, the catalyst was filtered off and the solvent was evaporated under vacuum. The residue was dissolved in methanol and treated with 4 N HCl/MeOH. The precipitate was collected and crystallized from MeOH to afford 11.3 g (58.8%) of 37: mp 161–162 °C; NMR (DMSO-*d*₆) δ 10.75 (br s, 2H, NH₂⁺), 9.25 (br s, 1H, CONH), 5.00 (t, *J* = 5.5 Hz, 1H, NHCHNH), 3.65 and 3.58 (AB q, *J* = 15 Hz, 2H, NCH₂CO), 3.60 (s, 3H, CO₂CH₃), 2.75–2.35 (m, 2H, CH₂CO₂), 2.30–1.80 (m, 2H, CHCH₂); MS *m/z* 172 (M), 157 (M – CH₃), 141 (M – OCH₃).

Pharmacology. **Passive Avoidance Test.** Male Wistar rats (Charles River) weighing 200–220 g were housed three per cage and maintained in the animal house for at least 1 week before the experiment. The experimental procedure and the apparatus were similar to those previously described.²⁴ The passive avoidance apparatus consisted of a two-compartment plexiglass box with an electrifiable grid floor. The transparent side (25 × 25 × 25 cm, lit by a 60-W lamp) was connected with the dark side (painted black and covered by a removable lid) by a guillotine-type door. During the learning trial, the rat was gently placed

in the illuminated compartment. As soon as the rat entered the dark side of the apparatus, the door was closed and an inescapable foot shock (1 mA for 1 s) was delivered through the grid floor. Immediately afterward the rat was put back into its home cage. Twenty-four hours later the rat was again placed in the lighted side of the box with the door open and if the animal did not step into the dark compartment within 120 s (cutoff time) it was considered to have learned the task. The group's percentage of animals that did not enter the dark compartment was taken as an index of learning (percent of retention).

Animals received scopalamine hydrobromide (0.66 mg/kg sc) or saline 60 min before the learning session and the compounds tested or the vehicle 30 min before scopalamine.

In each experiment 45 rats were randomly assigned to three groups of treatment: (1) a saline control group injected with saline 80 and 30 min before the learning session; (2) a scopalamine group treated with saline and scopalamine to evaluate the degree of amnesia produced by scopalamine in that particular experiment, and (3) a treated group injected with the tested compound and scopalamine.

Typically, 80–90% of saline-treated animals remained in the lighted compartment more than 120 s while only 20–30% of scopalamine-treated animals remembered the task. When the difference between saline and scopalamine control groups was less than 40%, the entire experiment was discarded. Since there were some day-to-day and animal variability in the percent of retention of saline and scopalamine groups, in order to make comparisons between the effect of treatments, the results were expressed as percent of amnesia reversal employing the following formula:²⁵

$$\% \text{ amnesia reversal} =$$

$$\frac{\% \text{ retention of treated group} - \% \text{ retention of scopalamine group}}{\% \text{ retention of saline group} - \% \text{ retention of scopalamine group}}$$

× 100

Data were analyzed as percent of retention by means of Fisher's exact probability test²⁶ by comparing each treated group with the scopalamine control group in the same experiment. The results obtained are reported in Table I.

Irwin Test. The action of new compounds on gross behavior was tested in mice according to the method of Irwin.²⁷ Briefly, the compounds were administered at the doses of 100, 300, and 1000 mg/kg ip (three animals per dose were used). The mice were observed continuously for 3 h after treatment and once a day for the following 3 days during which 30 behavioral, neurological, and autonomic signs were assessed and scored as described in the literature. Neither lethality nor pharmacological effects were observed for any of the compounds up to the highest dose tested.

Right-Armed Radial Maze. Twenty-one male Wistar rats, 2-month-old and weighing 250 g at the beginning of experiments, were used. The rats were gradually reduced to 80–85% of their body weight and trained once a day for 5 days a week in a right-armed radial maze until they solved the task in no more than nine choices for at least 3 consecutive days (criterion). Training was carried out in a testing room lit by two 70-W halogen lamps. Several visually distinct cues (e.g., door, shelf, posters) were present in the room and remained in the same position with respect to the maze. A television camera was located 200 cm above the maze and transmitted the image to both a closed-circuit television and to an interfaced IBM AT computer located in an adjacent room. A rat's position in the maze was then determined by means of a computerized motion analyzer program (Biomedica Mangoni, Pisa, Italy) and was automatically elaborated and stored on a floppy disk. The following measures of the rat's performance in the maze were taken into account for each trial: (i) efficiency of responding, defined as 8/total number of choices × 100 and (ii) mean running time (in s) obtained by dividing the total running time (the total time spent by the rat to complete the task) by the total number of choices.²⁴

Drug treatments (80 µg/kg sc scopalamine and 1 mg/kg sc compound 15 plus 50 µg/kg sc scopalamine) were begun after the performance had been established. Drugs were dissolved in isotonic saline so that test compound was administered in a volume of 2 mL/kg. Scopalamine was injected 60 min before

testing; 15 was administered 90 min before the test. The tests on the drugs were separated by at least 3 days, during which the rats were trained again to criterion. Seventeen rats received each of the two treatments in a random sequence: the four remaining animals received only scopolamine treatment.

Performance in the days immediately preceding and following a pharmacological treatment was used for comparison. The values for efficiency for each given treatment were compared with each other and with values obtained in the days preceding and following the treatment by means of the one-way ANOVA test. Paired comparisons were subsequently made using Duncan's test for multiple comparison. Values for running time were analyzed in a similar manner.

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(54) Title: COMPOUNDS WITH NOOTROPIC ACTION, THEIR PREPARATION, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM, AND USE THEREOF

(57) Abstract: Described herein are new bicyclic arylimidazolones having nootropic action (i.e., protecting and stimulating cerebral functions), analgesic action and anti hyperalgesic action, also described is the process for their preparation and pharmaceutical compositions comprising them, useful for the treatment of cognitive deficits, and of various types of pain.

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COMPOUNDS WITH NOOTROPIC ACTION, THEIR PREPARATION,
PHARMACEUTICAL COMPOSITIONS CONTAINING THEM, AND USE
THEREOF

Field of the invention

- 5 The present invention relates to new compounds of formula (I) appearing hereinafter, their process of preparation, the pharmaceutical compositions containing them, and their use as nootropic, neuroprotective, analgesic and anti-hyperalgesic agents.

State of the art

- 10 Compounds that possess nootropic activity are already known in the literature. In particular, the derivatives substituted in position 4 of 2-oxo-1-pyrrolidineacetamide are valid psychotropic agents that re-establish damaged cognitive functions. These compounds are described, for example, in *Pharm. Res. Commun.* 16, 67, 1984 by Banfi et al. and in *Drug Development Res.* 2, 447, 1982 by Ilil et al.

- 15 Amongst the most widely known molecules belonging to the class mentioned above there may be cited: 2-oxo-1-pyrrolidineacetamide (piracetam), 4-hydroxy-2-oxo-1-pyrrolidineacetamide (oxiracetam), 2-(2-oxopyrrolidin-1-yl) butyramide (levetiracetam) and *N*-(2,5-dimethylphenyl)-2-oxo-1-pyrrolidineacetamide (nefiracetam).

- 20 Another chemical class that possesses nootropic activity is represented by imidazolic condensed derivatives, in particular 2,5-dioxohexahydro-1H-pyrrolo[1,2-a]imidazole (dimiracetam), described in EP 335483 and in WO-9309120, and in *J. Med. Chem.*, 36, 4214, 1993 by Pinza M. et al.

- 25 Recently, it has been demonstrated that nefiracetam could be a good therapeutic agent in the treatment of neuropathic pain. The anti-hyperalgesic action induced by nefiracetam appears to be of non-opioid nature and is probably due to the stimulation of the nicotinic cholinergic system at a spinal and supraspinal level (Rashid Harunor M.D. *J. Pharmacol. Exp. Ther.*, 303, 226, 30 2002).

Summary of the invention

The present applicant has now found new *N*-substituted bicyclic imidazolones of formula (I), appearing hereinafter, that have demonstrated improved

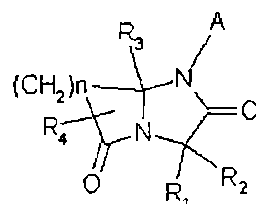
psychotropic properties and more marked analgesic and antihyperalgesic effects in numerous models of neuropathic pain, with respect to the already known nootropic agents.

The present compounds of formula (I) are consequently useful in the treatment of many disorders of the central nervous system (CNS), for example in the deterioration of learning, dysfunctions of the cognitive sphere and of the memory, Alzheimer's disease, dementias, including senile dementia of the Alzheimer type, post stroke vascular type dementia, epilepsy, cerebral ischaemia, mood disorders, including depression, chronic, inflammatory,

neuropathic and visceral pain, and emesis.

Consequently, representative of the subject of the present invention are compounds of the general formula (I)

(I)



in which:

A is chosen among carbocyclic aromatic groups, heterocyclic aromatic groups and arylC₁₋₄alkyl;

R₁ is chosen among:

- hydrogen,
- arylC₁₋₇alkyl, optionally substituted on the aryl moiety with one or more groups chosen among hydroxy, C₁₋₄alkoxy, halogen, haloC₁₋₄alkyl;
- heterocyclylC₁₋₇alkyl, optionally substituted on the heterocyclyl moiety with one or more groups chosen among C₁₋₄alkyl and hydroxy;
- C₁₋₇ alkyl, optionally interrupted by an oxygen or sulphur atom or optionally substituted at any position by one or more groups chosen among hydroxy, thio, amino, carboxyl, aminocarbonyl, guanidiny.

R₂ is chosen among hydrogen, C₁₋₄alkyl, arylC₁₋₄alkyl and phenyl;
or else R₁ and R₂, taken together, form a saturated carbocyclic ring containing
from 3 to 8 carbon atoms;

R₃ is chosen among hydrogen, C₁₋₄alkyl, arylC₁₋₄alkyl, CONH₂ and COOR₅ in
5 which R₅ is chosen between hydrogen and C₁₋₄alkyl;

R₄ is chosen among hydrogen, C₁₋₄alkyl, aryl, arylC₁₋₄alkyl and heterocyclyl;
and

n is 2, 3 or 4;

in the form of a racemic mixture or in the form of enantiomers, and
10 pharmaceutically acceptable salts or solvates thereof.

The process of preparation of the compounds of formula (I) appearing above,
the pharmaceutical compositions containing them and their use for the
preparation of medicaments with nootropic and neuroprotective action, with
analgesic and/or anti-hyperalgesic action, and anti-emetic action, constitute a
15 further subject of the invention.

Characteristics and advantages of the present compounds of formula (I) will be
illustrated in detail in the following description.

Description of the figures

Figures 1a, 1b: non limiting examples of aminoacids of formula (IV), useful in
20 the synthesis of the compounds of formula (I). The encircled portion indicates
the substituent R₁.

Detailed description of the invention

In the framework of the present invention, the term "carbocyclic aromatic group"
means single or fused aromatic rings with 6 to 12 ring members, optionally
25 substituted.

The terms "heterocyclic aromatic group" and "heterocyclyl" mean single or
fused aromatic rings, each ring having 5 to 12 members and comprising up to
four hetero atoms, chosen among oxygen, sulphur and nitrogen, optionally
substituted.

30 Whenever not otherwise specified, the term "aryl" means single or fused
unsaturated rings, each ring having from 5 to 8 members, and preferably 5 or 6
members, optionally substituted; by the term "arylC₁₋₄alkyl" is indicated a group

having an aryl group, as defined above, and a C₁₋₄ alkyl moiety connecting the aryl group to the point of substitution.

All the aforesaid C₁₋₄ alkyl groups, including those being part of the arylC₁₋₄alkyl group, may be indifferently linear or branched or cyclic (i.e. cyclopropyl, cyclopropylmethyl or methylcyclopropyl). Preferred C1-C4 alkyl groups are Me, Et, i-Pr, i-Bu, and cyclopropylmethyl.

All the aforesaid C₁₋₇ alkyl groups, including those being part of C₁₋₇ alkyl-containing groups, can either be linear, branched or cyclic, and may include double or triple bonds. The term "C₁₋₇ alkyl groups interrupted by oxygen or sulphur" means, respectively, any ether and thioether groups containing from 1 to 7 carbon atoms.

By the term "heterocyclylC₁₋₇alkyl" is indicated a group having an heterocyclyl group, as defined above, and a C₁₋₇ alkyl moiety connecting the aryl group to the point of substitution.

By the term "arylC₁₋₇alkyl" is indicated a group having an aryl group, as defined above, and a C₁₋₇ alkyl moiety connecting the aryl group to the point of substitution.

By "halogen" is meant an atom chosen among fluorine, chlorine, bromine or iodine; by "haloC₁₋₄alkyl" is meant a C₁₋₄ alkyl group substituted at any position by one or more halogen atoms, e.g. trifluoromethyl.

Unless differently specified, "optionally substituted" groups are groups optionally substituted with 1 to 3 substituents, chosen preferably among Me, Et, i-Pr, OH, COOEt, COOH, CH₂OH, SO₂NH₂, SO₂Me, OMe, Cl, F, CN and CF₃, and more preferably among Me, Et, i-Pr, OH, CN, Cl and CF₃; the substituents may be in any position of the group to be substituted.

Preferred compounds according to the invention are the compounds of formula (I), in which A is a optionally substituted phenyl, optionally substituted benzyl, or else a optionally substituted heterocyclic aromatic group with 5 or 6 members and comprising up to two hetero atoms chosen between oxygen, sulphur and nitrogen, R₁, R₂, R₃ and R₄ are chosen among hydrogen, C₁₋₄ alkyl or benzyl, and n is equal to 2 or 3.

Preferably, A is phenyl, thienyl, pyridyl, pyrimidinyl group, optionally substituted, benzyl or 4-methylbenzyl; R₁ is hydrogen, C₁₋₄ alkyl (for example methyl,

isopropyl or isobutyl), benzyl, -CH₂OH, -CH₂CH₂CONH₂, -CH₂COOH, indol(3-yl)methyl, R₂ is hydrogen, C₁₋₄ alkyl or benzyl, R₃ and R₄ are hydrogen or methyl, and n is 2.

More preferably, A is a phenyl, optionally substituted, R₁, R₂, R₃ and R₄ are hydrogen, and n is equal to 2.

When R₁ and R₂, taken together, form a saturated carbocyclic ring containing from 3 to 8 carbon atoms, the resulting compound of formula (I) is a spirocyclic compound.

10 Preferred compounds of formula (I) according to the invention are chosen in the group consisting of:

1-Phenyl-tetrahydro-1H-pyrrolo[1,2-a]imidazole-2,5-dione;

1-o-tolyl-tetrahydro-1H-pyrrolo[1,2-a]imidazole-2,5-dione;

1-(2,6-Dimethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

15 1-Thiophen-2-yl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-m-Tolyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-p-Tolyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-(5-Fluoro-2-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-(3-Fluoro-2-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

20 1-(2-Trifluoromethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-(4-Chloro-2-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-(3-Chloro-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-(3-Methoxy-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-(3-Cyano-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

25 1-(4-Chloro-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-(3-Hydroxy-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-(3-Trifluoromethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-(4-Trifluoromethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-(4-Methoxy-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

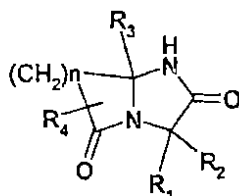
30 1-(3,5-Dimethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-(3,4-Dimethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-Naphthalen-2-yl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

1-(3-Isopropyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

- 1-(4-Chloro-3-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
3-Benzyl-1-phenyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
3-Methyl-1-phenyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
3-Isobutyl-1-phenyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
5 1-(3-Fluoro-5-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(3-Fluoro-4-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
7a-Methyl-1-phenyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
(S)-1-o-Tolyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
(R)-1-o-Tolyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
10 1-(4-Ethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(4-Isopropyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(4-Hydroxymethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
4-(2,5-Dioxo-hexahydro-pyrrolo[1,2-a]imidazol-1-yl)-benzoic acid;
4-(2,5-Dioxo-hexahydro-pyrrolo[1,2-a]imidazol-1-yl)-benzoic acid ethyl ester;
15 1-(4-Methanesulfonyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(4-Fluoro-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(4-Cyano-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-Pyridin-2-yl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-Pyridin-3-yl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
20 1-(5-Methylpyridin-2-yl)-tetrahydropyrrolo[1,2-a]imidazole-2,5-dione;
1-(2-Cyano-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(3-Fluoro-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-Benzyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(4-methylbenzyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione.
25 It will be noted that some compounds of formula (I) can contain one or more
stereogenic centres. The present invention extends to all the optical isomers of
these compounds in their forms entirely or partially resolved and in the form of
racemic mixtures.
A further subject of the invention is a process for the preparation of the
30 compounds of formula (I), or one of their salts, and/or one of their solvates,
comprising the reaction of a compound of formula (II)



(II)

with a compound of formula (III)

A-X

5

(III)

in which A, R₁, R₂, R₃, R₄ and n are defined as above for the compounds of formula (I), and X is a halogen atom, chosen preferably between bromine and iodine.

When A is a aromatic carbocyclic group or a heterocyclic aromatic group as above defined, the reaction between the compounds of formula (II) and the compound of formula (III) can be conducted according to the appropriate conditions of the Goldberg reaction (*Angew. Chem. Int. E.*, 39, 4492, 2000). In particular, the compounds of formula (II) are dissolved in a suitable solvent, such as *N*-methylpyrrolidone, together with the compounds of formula (III) in the presence of a catalytic amount of copper salt such as copper iodide, and a base such as potassium carbonate, at any temperature that will yield an adequate percentage of formation of the product required, suitably at a high temperature, such as a temperature of between 60°C and 140°C, for example at 120°C. The reaction mixture is heated using a system of conventional heating or a microwave reactor of adequate power, for example comprised between 25 and 250 W (*Tetrahedron Letters*, 43, 1101, 2002).

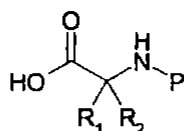
When A is arylC₁₋₄alkyl, the reaction can be carried out in a suitable solvent such as acetonitrile, methylene chloride, acetone, in the presence of a suitable base such as triethylamine, potassium carbonate, 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (also known as BEMP), *N,N*-Diisopropylethylamine (also known as Hunig base), at a suitable temperature such as reflux temperature (60-140°C, preferably 100°C).

The aforesaid compounds of formula (II) and the methods for their preparation are described in the European patent application EP-A-335463 and in the International patent application No. WO-A-93/09120 and in *J.Med.Chem.*, 36, 4214, 1993, by Pinza et al.

- 5 The compounds of formula (III) are commercially available or can be prepared from known compounds by known methods.

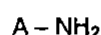
Alternatively, the compounds of formula (I) can be prepared with a process comprising the following stages:

- i) reaction of an aminoacid of formula (IV) or of one of its activated derivatives



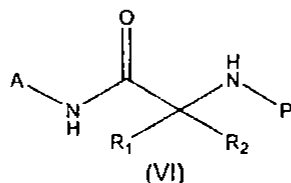
10 (IV)

with a compound of formula (V)



15 (V)

to obtain a compound of formula (VI)

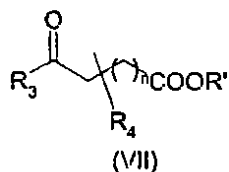


20 (VI)

in which R_1 , R_2 and A are as defined above for the compound of formula (I), and P is H or a suitable protective group. The activation of aminoacids is a well-known synthetic procedure; examples of activated derivatives of the aminoacids are mixed anhydrides, acyl chlorides and activated esters.

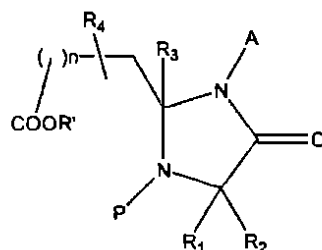
- 25 ii) reaction of the compound of formula (VI) obtained at stage i) with a compound of formula (VII)

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to obtain a compound of formula (VIII)

5



(VIII)

in which A, R₁, R₂, R₃, R₄ and n are as defined above for the compound of formula (I), P is defined as above, and R' is an alkyl group;

- 10 iii) possible removal of the protective group P by means of hydrogenolysis of the compound of formula (VIII), obtained in stage ii), to obtain the corresponding compound (VIII), in which P is H; and
- iv) cyclization of the compound of formula (VIII), in which P is H coming from stage ii) or from stage iii), to obtain the desired compound of formula (I).
- 15 According to a preferred embodiment of the invention, the alkyl residue R' is chosen between methyl and *tert*-butyl, and P is chosen between hydrogen, a benzyl or a benzyloxycarbonyl group.

The reaction in stage i) between the compound of formula (IV) and the compound of formula (V) can be performed:

- 20 (a) by preparing, in the first place, an acidic chloride of the compound of formula (IV) and uniting to said acidic chloride the compound of formula (V) in the presence of an inorganic or organic base in an adequate aprotic solvent, such

as dimethylformamide (DMF) at a temperature of between -70°C and 50°C, and preferably between -10°C and 20°C; or else:

- (b) by reacting together the compound of formula (IV) with the compound of formula (V) in the presence of a suitable condensating agent, such as *N,N'*-carbonyl diimidazole (CDI) or a carbodiimide such as dicyclohexylcarbodiimide (DCC) or *N*-dimethylaminopropyl-*N'*-ethylcarbodiimide, preferably in the presence of *N*-hydroxybenzotriazole (HOBT) to maximize the yield and prevent the processes of racemization (cf. Synthesis, 453, 1972), or *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), in an aprotic solvent, such as a mixture of acetonitrile (MeCN) and tetrahydrofuran (THF), for example, a mixture with volumetric ratio comprised between 1:9 and 7:3 (MeCN:THF), at any temperature capable of yielding an adequate percentage of formation of the product required, such as a temperature of between -70°C and 50°C, and preferably between -10°C and 25°C.

- At stage ii) of the present process, the compounds of formula (VI) and (VII) are preferably reflux-heated in a protic solvent, such as water or methanol, and possibly in the presence of a base, such as NaOH, in the case where the compound of formula (VI) is used in the form of one of its salts obtained by addition of acid, for an adequate period of time, preferably comprised between 2 and 24 hours.

Removal of the protective group P by means of hydrogenolysis at stage iii) is preferably conducted using ammonium formate as a source of hydrogen in a suitable protic solvent, such as methanol or a methanol-water mixture.

- The cyclization reaction in stage iv) is carried out directly on the compound of formula (VIII) coming from stage ii) if P is H, or else, if in said compound (VIII) P is a protective group, the first step is to remove it, as described above in stage iii).

- The cyclization reaction is conducted in drastic conditions by conventionally heating the compound of formula (VIII) without solvent at 120°C and in vacuum conditions, or else by means of reflux-heating in xylene for a suitable period of time, for example between 4 hours and 3 days, or by microwave irradiation.

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The compounds of formula (IV), (V) and (VII) are commercially available compounds or can be prepared from known compounds using known methods.

In particular, the compounds of formula (IV) can be conveniently selected from any naturally occurring aminoacids or derivatives thereof. Examples of
5 aminoacids useful in the present invention are shown in figure 1, where the part encircled corresponds to the substituent R_1 of formula (IV); accordingly, all these meanings for R_1 are also preferred in formula (I), being the object of the present invention.

The present compounds of formula (I) are useful as therapeutic agents and in
10 particular possess a nootropic and neuroprotective activity, i.e., they contribute to restoring the learning and memory functions deteriorated in the process of ageing or on account of ischaemic traumas, and are effective in various pathologies of the CNS, amongst which learning dysfunctions, dysfunctions of the cognitive sphere and of the memory, Alzheimer's disease, dementias,
15 including senile dementia of the Alzheimer type, post stroke vascular type dementia, epilepsy, cerebral ischaemia, and mood disorders, including depression.

The present compounds of formula (I) moreover possess analgesic and/or anti-hyperalgesic activity, i.e., they contribute to combat the sensations of pain, in
20 particular those caused by conditions of neuropathic pain, chronic inflammatory pain and visceral pain, and have proven their efficacy also in the treatment of emesis.

The subject of the present invention is hence also the use of the present compounds of formula (I) or of their pharmaceutically acceptable salts and/or
25 solvates for the preparation of medicaments for recovery of difficulties of learning and memory and for treatment of dementias, Alzheimer's disease, post stroke vascular type dementia, epilepsy, cerebral ischaemia, and mood disorders, including depression.

Also provided is a method to treat the aforesaid diseases and disorders
30 characterised by administering a pharmaceutically active amount of a compound of formula (I) to a patient in need thereof.

It is widely known that cognitive disorders that occur in said pathologies are correlated to the deficit of the cerebral cholinergic system, as emerges from

morphological findings (B.E. Tomlinson in "Biochemistry of Dementias"; P.J. Roberts Ed.; John Wiley & Sons, New York, N.Y. pp. 15-22, 1980) and neurochemical findings (R.T. Bartus et al. *Science*, 217, 408, 1982). It is moreover well known that the significant deteriorations of cognitive functions are the most evident and debilitating signs observed in patients suffering from Alzheimer's disease, senile dementias of the Alzheimer type, and dementia due to multiple infarcts.

The activity of the compounds of formula (I) can be determined in rats in regard to the amnesia-provoking action of scopolamine (D.A. Drachman, *Archs. Neurol., Chicago*, 30, 113, 1974; D.A. Eckerman, *Pharmacol. Biochem. Behav.* 12, 595, 1980) on the mnemonic pathway and on the reduction of the levels of acetylcholine in the hippocampus. The effect on memory and learning can be evaluated in rats using the passive-avoidance test, as described by Essman, *Pharmacol. Res. Commun.* 5, 295, 1973.

The subject of the present invention is, moreover, the use of the present compounds of formula (I) or their pharmaceutically acceptable salts or solvates in the treatment of conditions of neuropathic pain, chronic inflammatory pain and visceral pain. Also provided is a method to treat the aforesaid diseases characterised by administering a pharmaceutically active amount of a compound of formula (I) to a patient in need thereof.

It is hypothesized that the process of learning and memory is implicated in the mechanisms of chronic pain (Flor H., *Prog. Brain Res.*, 129, 313, 2000), and recent evidence supports the hypothesis that chronic inflammatory pain is an acquired maladaptive phenomenon (Arnstein P.M., *J. Neurosci. Nurs.* 29, 179, 1997; Kumazawa T., *Neurosci. Res.*, 32, 9, 1998). Cognitive dysfunction has been described in various neuropathic conditions (Kuhajda M.C., *Ann. Behav. Med.*, 20, 31, 1998), and it has recently been observed that nefiracetam, a nootropic agent, alleviates neuropathic pain thanks to its specific effects on neuropathies (Rashid Harunor M.D. *J. Pharmacol. Exp. Ther.*, 303, 226, 2002). It has been shown that the analgesic and/or anti-hyperalgesic effect of nefiracetam expresses itself through stimulation of the nicotinic cholinergic receptors at the spinal and supraspinal level, in so far as said effect is inhibited

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in a dose-dependent way by mecamylamine, a known antagonist of the nicotinic acetylcholine receptor.

The activity of the compounds of formula (I) can be determined in mice by means of the thermal-hyperalgesia test (paw-withdrawal test) and the
5 mechanical-hyperalgesia test (paw-pressure test) induced by partial ligation of the sciatic nerve or by treatment with streptozotocine, following the protocols described in *J. Pharmacol. Exp. Ther.*, 303, 226, 2002 and in the bibliography cited therein.

When used in the therapeutic treatment of humans and animals, the
10 compounds of formula (I) are normally formulated, in compliance with standard pharmaceutical practice, as a pharmaceutical composition.

Hence, a further subject of the invention is represented by a pharmaceutical composition comprising, as active principle, a compound of formula (I) or one of its pharmaceutically acceptable salts or solvates, together with vectors, diluents
15 and pharmaceutically acceptable excipients suitable for the chosen form of administration.

The compounds of formula (I) can be administered in a standard way in the treatment of the disorders indicated above, for example via oral, parenteral, rectal, transdermal route or by administration through the mucosa (for example,
20 the sublingual, buccal, or nasal mucosa).

The compounds of formula (I) which are administered orally or via sublingual route or via buccal administration, can be formulated as syrups, tablets, capsules, and lozenges. A formulation in the form of syrup consists generally of a suspension or solution of the compound or of one of its salts in a liquid vector,
25 for example ethanol, glycerine or water with a flavouring or colouring agent. When the composition is in the form of tablets, it is possible to use any pharmaceutical vector used conventionally in the preparation of solid formulations. Examples of said vectors comprise magnesium stearate, starch, lactose and sucrose. When the composition is in the form of capsules, any
30 conventional method of encapsulation is suitable, for example using the vectors mentioned above in a capsule of hard gelatine. When the composition is in the form of capsules made of soft gelatine, it is possible to use any pharmaceutical vector used conventionally in the preparation of dispersions or suspensions, for

example aqueous gums, cellulose, silicates or oils, to be incorporated into a shell made of soft gelatine.

Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) in a aqueous or non-aqueous sterile vector, possibly
5 containing an oil acceptable for the parenteral route, for example polyethylene-glycol, polyvinylpyrrolidone, lecithin, peanut oil, or sesame oil.

The typical formulation in suppositories comprises a compound of formula (I), which is active if administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatine, cocoa butter, or other low-
10 melting waxes or vegetable fats.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vector, for example cream, ointment, lotion or paste, or can be in the form of medicated plasters, patches or membranes.

Preferably, the composition is in a unit-dose form, for example tablets or
15 capsules, so that the patient can take a single dose.

Oxiracetam is a compound used in the treatment of senile dementia and of pathological conditions correlated thereto. The compounds of formula (I) can be administered with regimes similar to the ones established for oxiracetam with any appropriate adjustment of the levels of dosage or of the frequency of
20 dosage in relation to the greater activity and to the better pharmacological profile of the compounds of formula (I).

Each dosage unit for oral administration may expediently contain from 0.05 mg/kg to 50mg/kg, more expediently from 0.1 mg/kg to 25mg/kg of a compound of formula (I). The active ingredient can be administered from 1 to 6
25 times a day. The compounds of formula (I) can be co-administered with other pharmaceutically active compounds, for example in association, concurrently or sequentially, in particular together with other compounds used in the treatment of elderly patients, such as tranquilizers, diuretics, anti-hypertensive drugs, vasodilator drugs, and inotropic agents.

30 Examples of the present invention are provided in what follows, purely for illustrative and non-limiting purposes.

EXPERIMENTAL PART

Description 1. *3-Isobutyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione*.

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To a solution of DL-leucinamide hydrochloride (1.5 g, 9 mmol) in water (40 ml), adjusted to pH 9.5 with 10% sodium hydroxide, ethyl-4-oxobutanoate (1 g, 7.5 mmol) was added. The mixture was placed in a microwave oven and refluxed for 1 hour. Water was then evaporated under vacuum and the residue was chromatographed over silica gel (CH₂Cl₂ / MeOH / NH₄OH 98 / 2 / 0.1) to afford 1.1 g of the title compound.

¹H-NMR (CDCl₃) δ: 6.48 (broad s, 1H); 5.30 (t, 1H); 4.23 (dd, 1H); 2.71-2.39 (m, 3H); 2.20-1.93 (m, 1H); 1.86-1.73 (m, 1H); 1.70-1.42 (m, 2H), 1.05 (d, 3H); 0.96 (d, 3H).

MS: EI TSQ 700; source 180 C; 70 V; 200 uA: 196 (M⁺), 97.

Example 1. 1-Phenyl-tetrahydro-1H-pyrrolo[1,2-a]imidazole-2,5-dione.

To a solution of tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione (1 g, 7.14 mmol; prepared as described in *J. Med. Chem.* 36, 4214-4220, 1994,) in N-methylpyrrolidone (NMP, 12 cc), CuI (0.2 g, 1.05 mmol), K₂CO₃ (1 g, 7.14 mmol) and iodobenzene (5 g, 24.5 mmol) were added under stirring. The suspension was heated in a microwave apparatus (250 Watt) for 45 min. Ethyl acetate was added to the suspension and the solid was filtered. The organic phase was washed with water and the aqueous phase was re-extracted with CH₂Cl₂. The organic phases were gathered and dried over Na₂SO₄, filtered and concentrated to dryness. The residue was triturated with isopropyl ether. The solid was filtered, triturated with water and filtered to yield 0.18 g of the title compound, mp = 185-188°C.

¹H-NMR (CDCl₃) δ: 7.46-7.37 (m, 4H); 7.28-7.21 (m, 1H); 5.84 (m, 1H); 4.48 (d, 1H); 3.74 (d, 1H); 2.78-2.60 (m, 2H); 2.51-2.38 (m, 1H); 2.08-1.96 (m, 1H).

MS: EI TSQ 700; source 180 C; 70 V; 200 uA: 216 (M⁺), 160, 97.

Example 2. 1-o-tolyl-tetrahydro-1H-pyrrolo[1,2-a]imidazole-2,5-dione.

To a solution of tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione (1.3 g, 9.28 mmol, prepared as described in *J. Med. Chem.* 36, 4214, 1994) in N-methylpyrrolidone (NMP, 12 cc), CuI (0.5 g, 2.62 mmol), K₂CO₃ (1.3 g, 9.28 mmol) and 2-bromotoluene (6 g, 35 mmol) were added under stirring. The suspension was heated in a microwave apparatus (250 Watt) for 1 h. Ethyl acetate was added to the suspension and the solid was filtered. The organic phase was washed with water and the aqueous phase was re-extracted with CH₂Cl₂. The organic

phases were gathered and dried over Mg_2SO_4 , filtered and concentrated to dryness. The residue was triturated with Et_2O . The solid was filtered, and crystallized the first time with $i\text{PrOH}$ and then with AcOEt to yield 0.33 g of the title compound, mp = 138-139°C.

- 5 $^1\text{H-NMR}$ (CDCl_3) δ : 7.35-7.23 (m, 4H); 7.13-7.06 (m, 1H); 5.69 (m br, 1H); 4.45 (d, 1H); 3.78 (d, 1H); 2.68 (ddd, 1H); 2.48 (ddd, 1H); 2.40-2.29 (m, 1H); 2.24 (s, 3H); 1.93 (m br, 1H).

MS: EI TSQ 700; source 180 C; 70 V; 200 uA; 230(M+), 143, 118, 97.

- 10 **Example 3-44 (Table 1).** *General procedure for arylation of tetrahydro-pyrrolo[1,2-a]imidazole-2,5-diones with aryl halides.*

- To a solution of tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione (3.5 mmol; prepared as described in *J. Med. Chem.* 36, 4214-4220, 1994 or in WO-9309120), in *N*-methylpyrrolidone (NMP 1 ml), CuI (0.19 g, 1 mmol), K_2CO_3 (0.5 g, 3.5 mmol) and the appropriate aryl halide (7 mmol) were added under stirring. The suspension was heated in a microwave apparatus (25 Watt) for 20 min. Ethyl acetate (50 ml) and water (5 ml) were added to the suspension and the mixture was stirred for 30' in the presence of celite. The reaction was filtered and the ethyl acetate was washed with a saturated solution of NaCl , dried over Na_2SO_4 , filtered and concentrated to dryness. The residue was triturated with Et_2O to give the desired compound. Yields vary from 30% to 60%.

- 20 **Example 45. 1-Benzyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione.**

- A solution of tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione (0.5 g, 3.5 mmol, prepared as described in *J. Med. Chem.* 36, 4214, 1994), BEMP (2 ml, 7 mmol) and benzylbromide (0.6ml, 5 mmol) in CH_3CN (20 ml) was refluxed for 1 hour. The reaction mixture was concentrated to dryness; the residue was then re-dissolved in ethyl acetate and washed with a saturated solution of NaCl , dried over Na_2SO_4 , filtered and evaporated under vacuum. The residue was purified by flash chromatography over silica gel (CH_2Cl_2 / MeOH / NH_4OH 95 / 5 / 0.5) to afford 0.7 g of the title compound as yellow oil.

- 30 Yield: 87%

$^1\text{H-NMR}$ (CDCl_3) δ : 7.39-7.10 (m, 5H); 5.03 (dd, 1H); 4.71 (d, 1H); 4.29 (d, 1H); 4.28 (d, 1H); 3.59 (d, 1H); 2.57 (ddd, 1H); 2.39-2.125 (m, 2H); 1.92-1.77 (m, 1H).

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MS: EI TSQ 700; source 180 C; 70 V; 200 uA: 230.13 (M+), 174.09, 139.04, 91.03.

Example 46. 1-(4-methylbenzyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione.

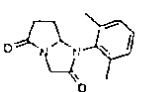
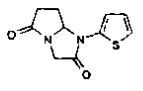
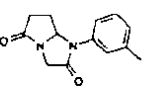
A solution of tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione (0.5 g, 3.5 mmol, prepared as described in *J. Med. Chem.* 36, 4214, 1994), BEMP (2 ml, 7 mmol) and 4-methylbenzylbromide (0.95 ml, 5 mmol) in CH₃CN (20 ml) was refluxed for 1 hour. The reaction mixture was concentrated to dryness; the residue was then re-dissolved in ethyl acetate and washed with a saturated solution of NaCl, dried over Na₂SO₄, filtered and evaporated under vacuum. The residue was purified by flash chromatography over silica gel (CH₂Cl₂ / MeOH / NH₄OH 95 / 5 / 0.5) to afford 0.8 g of the title compound as yellow oil.

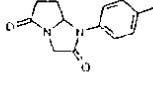
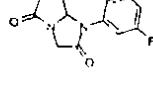
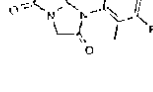
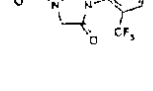
Yield: 93%

¹H-NMR (CDCl₃) δ: 7.29-7.11 (m, 4H); 5.01 (m, 1H); 4.69 (d, 1H); 4.29 (d, 1H); 4.23 (d, 1H); 3.58 (d, 1H); 2.65-2.50 (m, 1H); 2.40-2.24 (m, 2H); 2.33 (s, 3H); 1.93-1.78 (m, 1H).

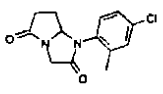
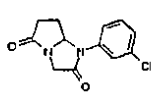
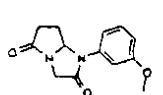
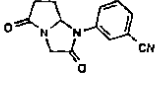
MS: EI TSQ 700; source 180 C; 70 V; 200 uA: 244.13 (M+), 161.05, 105.02

TABLE I
Structure, chemical name (generated by Beilstein's Automon), ¹H-NMR, MS and melting point data for compounds prepared according to the general procedure described above.

Ex.	Structure	Chemical name	Analytical data
3		1-(2,6-Dimethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ 7.24-7.10 (m, 3H); 5.63 (dd, 1H); 4.48 (d, 1H); 3.62 (d, 1H); 2.70 (ddd, 1H); 2.51 (ddd, 1H); 2.33-2.18 (m, 1H); 2.26 (s, 3H); 2.20 (s, 3H); 2.06-1.91 (m, 1H). MS: EI TSQ 700; source 180 °C; 70 V, 200 uA: 244 (M ⁺); 97.
4		1-Thiophen-2-yl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ 7.05 (dd, 1H); 6.93 (dd, 1H); 6.65 (dd, 1H); 5.67 (m, 1H); 4.49 (d, 1H); 3.77 (d, 1H); 2.88-2.69 (m, 2H); 2.58-2.45 (m, 1H); 2.33-2.21 (m, 1H). MS: EI TSQ 700; source 180 °C; 70 V, 200 uA: 222 (M ⁺); 194; 166; 97. mp 170-171 °C.
5		1-m-Tolyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ 7.30 (dd, 1H); 7.24 (dd, 1H); 7.13 (dd, 1H); 7.07 (dd, 1H); 5.82 (m, 1H); 4.46 (d, 1H); 3.74 (d, 1H); 2.79-2.57 (m, 2H); 2.45 (m, 1H); 2.38 (s, 3H); 1.08-1.94 (m, 1H). MS: EI TSQ 700; source 180 °C; 70 V, 200 uA: 230 (M ⁺); 174; 97. mp: 92-93 °C.

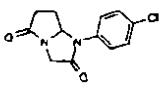
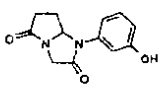
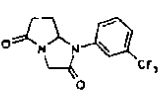
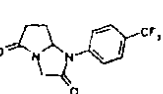
6		1-p-Tolyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ 7.27 (d, 2H); 7.24 (d, 2H); 5.79 (m, 1H); 4.45 (d, 1H); 3.73 (d, 1H); 2.72 (ddd, 1H); 2.70 (m, 1H); 2.47 (dd, 1H); 2.38 (s, 3H); 2.08-1.98 (m, 1H). MS: EI TSQ 700; source 180 °C; 70 V, 200 uA: 230 (M ⁺); 174; 118 mp 117-118 °C
7		1-(5-Fluoro-2-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ 7.28 (m, 1H); 7.00 (ddd, 1H); 6.95 (dd, 1H); 5.14 (m br, 1H); 4.43 (d, 1H); 3.77 (d, 1H); 2.70 (dt, 1H); 2.53-2.31 (m, 2H); 2.18 (s, 3H); 1.90 (broad m, 1H). MS: EI TSQ 700; source 180 °C; 70 V, 200 uA: 248 (M ⁺); 97. mp 147-148 °C
8		1-(3-Fluoro-2-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ 7.25 (ddd, 1H); 7.07 (dd br, 1H); 6.92 (d, 1H); 5.83-5.41 (broad m, 1H); 4.46 (d, 1H); 3.78 (d, 1H); 2.69 (ddd, 1H); 2.48 (ddd, 1H); 2.45-2.29 (m, 1H); 2.14 (d, 3H); 1.89 (broad m, 1H). MS: EI TSQ 700; source 180 °C; 70 V, 200 uA: 248 (M ⁺); 136; 109 mp: 135-137 °C
9		1-(2-Trifluoromethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ 7.43 (d, 1H); 7.66 (dd, 1H); 7.54 (broad dd, 1H); 7.27 (d, 1H); 5.64 (m, 1H); 4.42 (broad d, 1H); 3.72 (d, 1H); 2.53 (m, 1H); 2.48 (m, 1H); 2.38 (m, 1H); 2.03 (m, 1H). MS: EI TSQ 700; source 180 °C; 70 V, 200 uA: 284 (M ⁺); 226; 198;

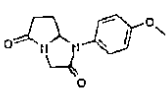
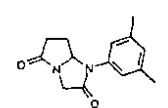
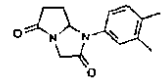
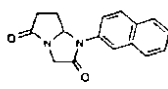
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10		1-(4-Chloro-2-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.32 (d, 1H); 7.24 (dd, 1H); 7.03 (d, 1H); 5.63 (broad m, 1H); 4.44 (d, 1H); 3.77 (d, 1H); 2.69 (ddd, 1H); 2.48 (ddd, 1H); 2.35 (m, 1H); 2.22 (s, 3H); 1.92 (m, 1H). MS: EI TSO 700; source 180 °C; 70 V; 200 uA: 264 (M ⁺); 97. mp: 122-124 °C.
11		1-(3-Chloro-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.46 (m, 1H); 7.39-7.28 (m, 2H); 7.22 (ddd, 1H); 5.81 (m, 1H); 7.48 (d, 1H); 3.73 (d, 1H); 2.85-2.64 (m, 2H); 2.46(m, 1H); 2.03 (m, 1H). MS: EI TSO 700; source 180 °C; 70 V; 200 uA: 250 (M ⁺); 194, 138, 111. mp: 123-125 °C.
12		1-(3-Methoxy-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.31 (dd, 1H); 7.06 (dd, 1H); 6.91 (dd, 1H); 6.79 (dd, 1H); 5.80 (m, 1H); 4.46 (d, 1H); 3.82 (s, 3H); 3.73 (d, 1H); 2.79-2.61 (m, 2H); 2.45 (m, 1H); 2.12-1.96 (m, 1H). MS: EI TSO 700; source 180 °C; 70 V; 200 uA: 246 (M ⁺); 190. mp: 94-95 °C.
13		1-(3-Cyano-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.73 (m, 2H); 7.52 (m, 2H); 5.81 (m, 1H); 4.51 (d, 1H); 3.73 (d, 1H); 2.84-2.65 (m, 2H); 2.47 (dd, 1H); 2.11-1.95 (m, 1H). MS: EI TSO 700; source 180 °C; 70 V; 200 uA: 241 (M ⁺); 185, 129. mp: 128-130 °C.

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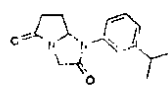
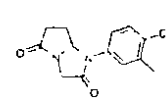
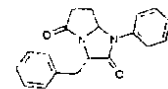
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14		1-(4-Chloro-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.42-7.32 (m, 4H); 5.80 (m, 1H); 4.46 (d, 1H); 3.73 (d, 1H); 2.79-2.60 (m, 2H); 2.45 (m, 1H); 2.09-1.93 (m, 1H). MS: EI TSO 700; source 180 °C; 70 V; 200 uA: 250 (M ⁺); 194. mp: 159-160 °C.
15		1-(3-Hydroxy-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.16 (dd, 1H); 6.96 (dd, 1H); 6.76 (dd, 1H); 6.69 (dd, 1H); 5.74 (m, 1H); 4.38 (d, 1H); 3.67 (d, 1H); 2.74-2.55 (m, 2H); 2.38 (m, 1H); 2.07-1.90 (m, 1H). MS: EI TSO 700; source 180 °C; 70 V; 200 uA: 232(M ⁺); 176. mp: 210-211 °C.
16		1-(3-Trifluoromethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.68 (d, 1H); 7.66 (broad s, 1H); 7.56 (dd, 1H); 7.50 (d, 1H); 5.98 (m, 1H); 4.50 (d, 1H); 3.76 (d, 1H); 2.73 (m, 2H); 2.48 (m, 1H); 2.04 (m, 1H). MS: EI TSO 700; source 180 °C; 70 V; 200 uA: 284 (M ⁺); 228; 172; 145. mp: 124-125 °C.
17		1-(4-Trifluoromethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.66 (d, 2H); 7.57 (d, 2H); 5.88 (m, 1H); 4.50 (d, 1H); 3.75 (d, 1H); 2.82-2.67 (m, 2H); 2.48 (m, 1H); 2.12-1.96 (m, 1H). MS: EI TSO 700; source 180 °C; 70 V; 200 uA: 284 (M ⁺); 228; 172; 145.

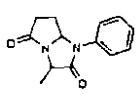
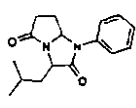
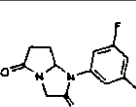
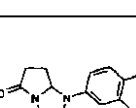
18		1-(4-Methoxy-phenyl)- tetrahydro-pyrrolo[1,2- a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ 7.20 (d, 2H), 6.95 (d, 2H), 5.74 (m, 1H), 4.44 (d, 1H); 3.81 (s, 3H), 3.73 (d, 1H), 2.79-2.39 (m, 3H); 2.08-1.94 (m, 1H). MS: EI TSO 700, source 180 °C; 70 V; 200 uA. 246 (M ⁺), 190; 134. mp: 210-211 °C.
19		1-(3,5-Dimethyl-phenyl)- tetrahydro-pyrrolo[1,2- a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ 6.98 (s, 2H); 6.89 (s, 1H); 5.79 (m, 1H), 4.45 (d, 1H); 3.72 (d, 1H); 2.77-2.53 (m, 2H), 2.44 (m, 1H), 2.33 (s, 6H), 2.00 (m, 1H). MS: EI TSO 700, source 180 °C; 70 V; 200 uA. 244 (M ⁺); 188; 97. mp: 103-104 °C.
20		1-(3,4-Dimethyl-phenyl)- tetrahydro-pyrrolo[1,2- a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ 7.18 (d, 1H), 7.16 (d, 1H), 7.04 (dd, 1H); 5.77 (dd, 1H); 4.44 (d, 1H); 3.72 (d, 1H); 2.78-2.52 (m, 2H), 2.44 (m, 1H); 2.28 (s, 3H); 2.25 (s, 3H), 2.08-1.93 (m, 1H). MS: ZQ, ESI POS, spray 3,25 KV; source 30 V, probe 250°C. 245 (MH ⁺). mp: 142-143 °C.
21		1-Naphthalen-2-yl- tetrahydro-pyrrolo[1,2- a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ 7.90 (d, 1H), 7.83 (m, 2H), 7.76 (d, 1H); 7.61 (dd, 1H); 7.55-7.45 (m, 2H); 5.97 (m, 1H); 4.53 (d, 1H); 2.80 (d, 1H), 2.86-2.86 (m, 2H), 2.47 (m, 1H); 2.15-1.99 (m, 1H). MS: ZQ, ESI POS, spray 3,25 KV; source 30 V, probe 250°C. 267 (MH ⁺)

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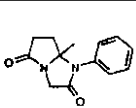
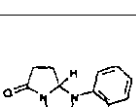
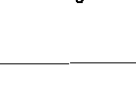
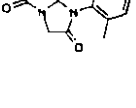
			mp: 175-176 °C.
22		1-(3-Isopropyl-phenyl)- tetrahydro-pyrrolo[1,2- a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ 7.33 (dd, 1H), 7.27 (m, 1H), 7.17 (d br, 1H), 7.12 (broad d, 1H); 5.83 (m, 1H), 4.46 (d, 1H); 3.74 (d, 1H), 2.92 (m, 1H); 2.80-2.57 (m, 2H), 2.46 (m, 1H), 2.04 (m, 1H), 1.26 (d, 6H). MS: ZQ, ESI POS, spray 3,25 KV; source 30 V, probe 250°C. 259 (MH ⁺). mp: 81-82 °C.
23		1-(4-Chloro-3-methyl- phenyl)-tetrahydro- pyrrolo[1,2-a]imidazole- 2,5-dione	¹ H-NMR (CDCl ₃) δ 7.37 (d, 1H); 7.33 (d, 1H), 7.12 (dd, 1H), 5.73 (m, 1H), 4.46 (d, 1H), 3.72 (d, 1H), 2.79-2.56 (m, 2H), 2.52-2.37 (m, 1H), 2.40 (s, 3H), 2.09-1.93 (m, 1H). MS: ZQ, ESI POS, spray 3,25 KV; source 30 V, probe 250°C. 265 (MH ⁺). mp: 138-139 °C.
24		3-Benzyl-1-phenyl- tetrahydro-pyrrolo[1,2- a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ 7.36 (dd, 2H), 7.28-7.17 (m, 6H); 7.03 (d, 2H), 4.77 (m, 1H), 4.59 (dd, 1H), 3.32 (dd, 1H), 3.16 (dd, 1H), 2.64 (ddd, 1H), 2.46-2.27 (m, 2H), 1.81 (m, 1H). MS: AQA, ESI Pos, 3.5kV; source 30V, probe 250°C. 307 (MH ⁺) mp: 134-136 °C.

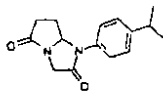
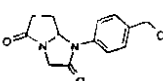
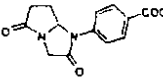
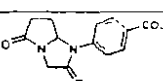
3
B

25		3-Methyl-1-phenyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.42 (m, 4H); 7.23 (m, 1H); 5.83 (m, 1H); 4.54 (q, 1H); 2.76-2.59 (m, 2H); 2.45 (m, 1H); 2.10-1.93 (m, 1H); 1.47 (d, 3H). MS: AQA, ESI Pos, 3.5KV, source 30V, probe 250°C. 231 (MH ⁺). mp: 137-138 °C.
26		3-Isobutyl-1-phenyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.41 (m, 4H); 7.22 (m, 1H); 5.81 (m, 1H); 4.50 (dd, 1H); 2.78-2.58 (m, 2H); 2.45 (m, 1H); 2.07-1.65 (m, 3H); 1.54 (m, 1H); 1.08 (d, 3H); 0.98 (d, 3H). MS: AQA, ESI Pos, 3.5KV; source 30V; probe 250°C: 273 (MH ⁺). mp: 101-102 °C.
27		1-(3-Fluoro-5-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 6.95 (m, 2H); 6.77 (d br, 1H); 5.78 (m, 1H); 4.46 (d, 1H); 3.73 (d, 1H); 2.84-2.63 (m, 2H); 2.45 (m, 1H); 2.37 (s, 3H); 2.11-1.94 (m, 1H). MS: AQA, ESI Pos, 3.5KV, source 30V; probe 250°C. 249(MH ⁺). mp: 111-113 °C.
28		1-(3-Fluoro-4-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.32-7.18 (m, 2H); 7.05 (dd br, 1H); 5.78 (m, 1H); 4.46 (d, 1H); 3.73 (d, 1H); 2.78-2.63 (m, 2H); 2.50-2.41 (m, 1H); 2.56 (s, 3H); 2.11-1.94 (m, 1H). MS: ZQ, ESI POS, spray 3.25 KV; source 30 V; probe 250°C. 248 (MH ⁺). 192, 97. mp: 136-137°C.

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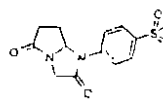
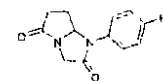
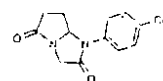
25

29		7a-Methyl-1-phenyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.52-7.20 (m, 5H); 4.44 (d, 1H); 3.78 (d, 1H); 2.83-2.68 (m, 1H); 2.56-2.42 (m, 2H); 2.18-2.30 (m, 1H); 1.63 (s, 3H). MS: ZQ, ESI POS, spray 3.25 KV; source 30 V; probe 250°C: 230 (MH ⁺). mp: 154-155°C.
30		(S)-1-o-Tolyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.35-7.23 (m, 4H); 7.13-7.06 (m, 1H); 5.69 (m br, 1H); 4.45 (d, 1H); 3.78 (d, 1H); 2.68 (ddd, 1H); 2.48 (ddd, 1H); 2.40-2.29 (m, 1H); 2.24 (s, 3H); 1.93 (m br, 1H). MS: AQA, ESI Pos, 3.5KV; source 30V; probe 250°C 230(M ⁺), 143, 118, 97. [α] _D = -51.39 (c= 0.4, MeOH)
31		(R)-1-o-Tolyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.35-7.23 (m, 4H); 7.13-7.06 (m, 1H); 5.69 (m br, 1H); 4.45 (d, 1H); 3.78 (d, 1H); 2.68 (ddd, 1H); 2.48 (ddd, 1H); 2.40-2.29 (m, 1H); 2.24 (s, 3H); 1.93 (m br, 1H). MS: AQA, ESI Pos, 3.5KV; source 30V; probe 250°C 230(M ⁺), 143, 118, 97. [α] _D = +52.24 (c= 0.4, MeOH).
32		1-(4-Ethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.29 (d, 2H); 7.25 (d, 2H); 5.80 (m, 1H); 4.45 (d, 1H); 3.74 (d, 1H); 2.78-2.56 (m, 2H); 2.65 (q, 2H); 2.51-2.38 (m, 1H);

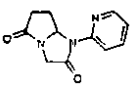
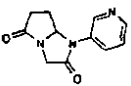
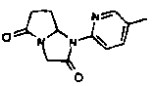
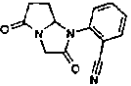
			MS: AQA, ESI Pos, 3.5KV, source 30V, probe 250°C. 245.1 (MH+). mp: 96-99°C.
33		1-(4-Isopropyl-phenyl)- tetrahydro-pyrrolo[1,2- a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.22-7.25 (m, 4H); 5.58 (m, 1H); 4.46 (d, 1H), 3.74 (d, 1H); 2.91 (m, 1H); 2.78-2.57 (m, 2H); 2.51-2.40 (m, 1H), 2.15-1.96 (m, 1H), 1.24 (d, 6H). MS: AQA, ESI Pos, 3.5KV, source 30V, probe 250°C. 259.1 (MH+). mp: 124-125°C.
34		1-(4-Hydroxymethyl- phenyl)-tetrahydro- pyrrolo[1,2-a]imidazole- 2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.41 (m, 4H), 5.83 (m, 1H), 4.70 (s, 2H), 4.47 (d, 1H), 3.74 (d, 1H), 2.79-2.59 (m, 2H), 2.52-2.37 (m, 1H), 2.10-1.93 (m, 1H); 1.72 (s br, 1H). MS: AQA, ESI Pos, 3.5KV, source 30V, probe 250°C. 247.1 (MH+). mp: 159-161°C.
35		4-(2,5-Dioxo-hexahydro- pyrrolo[1,2-a]imidazol-1- yl)-benzoic acid	¹ H-NMR (CDCl ₃) δ: 8.06 (d, 2H), 7.47 (d, 2H); 5.85 (m, 1H), 4.43 (d, 1H); 3.71 (d, 1H), 2.77-2.61 (m, 2H); 2.5-2.36 (m, 1H), 2.05-1.91 (m, 1H). MS: AQA, ESI Pos, 3.5KV, source 30V, probe 250°C. 261.0 (MH+) mp: 252-253°C.
36		4-(2,5-Dioxo-hexahydro- pyrrolo[1,2-a]imidazol-1- yl)-benzoic acid ethyl ester	¹ H-NMR (CDCl ₃) δ: 8.10 (d, 2H), 7.52 (d, 2H), 5.88 (m, 1H), 4.50 (d, 1H); 4.38 (q, 2H); 3.75 (d, 1H); 2.82-2.66 (m, 2H); 2.56-2.38 (m, 1H); 2.12-1.94 (m, 1H); 1.39 (t, 3H).

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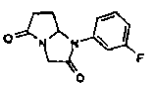
			MS: AQA, ESI Pos, 3.5KV, source 30V, probe 250°C. 289.4 (MH+), 218.4. mp: 158-159°C.
37		1-(4-Methanesulfonyl- phenyl)-tetrahydro- pyrrolo[1,2-a]imidazole- 2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.98 (d, 2H), 7.65 (d, 2H), 5.80 (m, 1H), 4.52 (d, 1H), 3.77 (d, 1H), 3.05 (s, 3H), 2.84-2.68 (m, 2H), 2.57-2.42 (m, 1H), 2.11-1.93 (m, 1H). MS: AQA, ESI Pos, 3.5KV, source 30V, probe 250°C. 295.1 (MH+), 312.1 (MH+NH ₃ +). mp: 143-145°C.
38		1-(4-Fluoro-phenyl)- tetrahydro-pyrrolo[1,2- a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.57 (m, 2H), 7.12 (dd, 2H), 5.78 (m, 1H), 4.47 (d, 1H), 3.74 (d, 1H), 2.80-2.56 (m, 2H), 2.46 (m, 1H); 2.08-1.93 (m, 1H). MS: AQA, ESI Pos, 3.5KV, source 30V, probe 250°C. 235.1 (MH+) mp: 158-159°C.
39		1-(4-Cyano-phenyl)- tetrahydro-pyrrolo[1,2- a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.72 (d, 2H), 7.60 (d, 2H), 5.87 (m, 1H), 4.52 (d, 1H), 3.76 (d, 1H), 2.64-2.68 (m, 2H), 2.57-2.43 (m, 1H), 2.14-1.94 (m, 1H). MS: AQA, ESI Pos, 3.5KV, source 30V, probe 250°C. 242.1 (MH+) mp: 175-176°C.

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40		1-Pyridin-2-yl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 8.34 (ddd, 1H); 8.20 (ddd, 1H); 7.75 (ddd, 1H); 7.11 (ddd, 1H); 6.04 (dd, 1H); 4.52 (d, 1H); 3.79 (d, 1H); 3.09-2.97 (m, 1H); 2.78-2.64 (m, 1H); 2.41 (ddd, 1H); 2.15-2.00 (m, 1H). MS: AQA, ESI Pos, 3.5KV; source 30V; probe 250°C: 218.4 (MH ⁺). mp: 139-140°C.
41		1-Pyridin-3-yl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 8.55 (m, 2H); 8.04 (d, 1H); 7.39 (m, 1H); 5.88 (m, 1H); 4.50 (d, 1H); 3.75 (d, 1H); 2.84-2.67 (m, 2H); 2.58-2.40 (m, 1H); 2.14-1.95 (m, 1H). MS: AQA, ESI Pos, 3.5KV; source 30V; probe 250°C: 218.4 (MH ⁺) mp: 180-182°C.
42		1-(5-Methylpyridin-2-yl)-tetrahydropyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 8.15 (d, 1H); 8.07 (d, 1H); 7.55 (dd, 1H); 6.02 (dd, 1H); 4.49 (d, 1H); 3.77 (d, 1H); 3.05-2.94 (m, 1H); 2.77-2.62 (m, 1H); 2.40 (ddd, 1H); 2.31 (s, 3H); 2.12-1.97 (m, 1H). MS: AQA, ESI Pos, 3.5KV; source 30V; probe 250°C: 232.1 (MH ⁺). mp: 158-159°C.
43		1-(2-Cyano-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.78 (d, 1H); 7.70 (dd, 1H); 7.48 (dd, 1H); 7.38 (d, 1H); 5.95 (m, 1H); 4.50 (d, 1H); 3.81 (d, 1H); 2.85-2.64 (m, 1H); 2.58-2.41 (m, 2H); 2.08-1.93 (m, 1H). MS: AQA, ESI Pos, 3.5KV; source 30V; probe 250°C: 242.1 (MH ⁺). mp: 94-95°C.

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44		1-(3-Fluoro-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione	¹ H-NMR (CDCl ₃) δ: 7.38 (ddd, 1H); 7.29 (ddd, 1H); 7.15 (ddd, 1H); 6.95 (dddd, 1H); 5.81 (m, 1H); 4.49 (d, 1H); 3.75 (d, 1H); 2.85-2.65 (m, 2H); 2.53-2.40 (m, 1H); 2.13-1.97 (m, 1H). MS: AQA, ESI Pos, 3.5KV; source 30V; probe 250°C: 235.1 (MH ⁺). mp: 148-149°C.
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Pharmacological Methods

Chronic constriction injury model

A peripheral mononeuropathy was produced in adult rats by placing loosely constrictive ligatures around the common sciatic nerve according to the method described by Bennett & Xie (*Pain* 1988, 33, 87-107).

Rats were anesthetized with chloral hydrate. The common sciatic nerve was exposed at the level of the middle of the thigh by blunt dissection through biceps femoris. Proximal to sciatica's trifurcation, about 1 cm of the nerve was freed of adhering tissue and four ligatures (3/0 silk thread) were tied loosely around it with about 1 mm spacing. The length of the nerve thus affected was 1 cm long. Great care was taken to tie the ligatures such that the diameter of the nerve was seen to be just barely constricted when viewed with 40 x magnification. The left paw was untouched.

Paw pressure test

The nociceptive threshold in the rat was determined with an analgesimeter (Ugo Dasile, Varese, Italy), according to the method described by Leighton *et al.* (*Br. J. Pharmacol.* 1988, 93, 553-560). Rats scoring below 40 g or over 75 g during the test before drug administration (25%) were rejected. An arbitrary cut-off value of 250 g was adopted.

All experiments were performed on rats submitted to paw-pressure test 14 days after the operation since at this time a significant reduction of the pain threshold of the injured paw (dx) was observed.

Gabapentin (30 µg i.c.v.), levoracemate (300 µg i.c.v.), dimiracetam (100 µg i.c.v.), Example 1 (10 µg i.c.v.), Example 2 (10 µg i.c.v.), Example 5 (3 µg i.c.v.), Example 6 (3 µg i.c.v.), Example 13 (30 µg i.c.v.) and Example 22 (30 µg i.c.v.) of the present invention showed an antihyperalgesic effect when compared with saline or vehicle treated group. All compounds did not modify pain threshold in controlateral, non operated, paw. It should be noted that all compounds elicited their antihyperalgesic effect without changing animals' gross behavior and spontaneous

motility in comparison with saline/vehicle treated rats. Furthermore no modification of motor coordination was revealed by the rat rota-rod test (Vaught J. *et al. Neuropharmacology* 1985, 24, 211-216).

EFFECT OF COMPOUNDS OF THE INVENTION AND
REFERENCE COMPOUNDS (i.c.v.) IN A RAT MODEL OF
MONONEUROPATHY dx EVALUATED IN THE PAW-
PRESSURE TEST

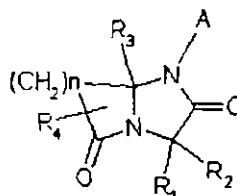
			<i>Paw pressure in rats (g)</i>	
TREATMENT	(i.c.v.)	PAW	Before Treatment	After Treatment
SALINE		dx	24.3 ± 2.9	23.7 ± 2.5
VEHICLE		dx	26.5 ± 3.5	22.9 ± 3.6
GABAPENTIN	30 µg	dx	24.5 ± 4.7	46.3 ± 4.2*
LEVETIRACETAM	300 µg	dx	24.0 ± 3.9	37.3 ± 4.6^
DIMIRACETAM	100 µg	dx	25.1 ± 2.4	42.8 ± 2.5*
EXAMPLE 1	10 µg	dx	26.0 ± 2.2	36.3 ± 5.1^
EXAMPLE 2	10 µg	dx	23.5 ± 4.0	42.2 ± 3.9*
EXAMPLE 5	3 µg	dx	27.7 ± 2.8	39.3 ± 4.5^
EXAMPLE 6	3 µg	dx	26.7 ± 3.6	46.1 ± 5.0^
EXAMPLE 13	30 µg	dx	28.5 ± 2.9	55.4 ± 4.7*
EXAMPLE 22	30 µg	dx	25.4 ± 2.7	48.5 ± 4.6*

Each value represents the mean of at least 8 rats (two separate experiments).
All compounds were administered 30-45 min before test. ^ P< 0.05, * P<0.01

CLAIMS

1. Compounds of the general formula (I)

(1)



In which:

5 **A** is chosen among carbocyclic aromatic groups, heterocyclic aromatic groups, and arylC₁₋₄alkyl;

R_1 is chosen among:

- hydrogen,
- arylC₁₋₇alkyl, optionally substituted on the aryl moiety with one or more groups chosen among hydroxy, C₁₋₄alkoxy, halogen, haloC₁₋₄alkyl;
- heterocyclylC₁₋₇alkyl, optionally substituted on the heterocyclyl moiety with one or more groups chosen among C₁₋₄alkyl and hydroxy;
- C₁₋₇ alkyl, optionally interrupted by an oxygen or sulphur atom or optionally substituted at any position by one or more groups chosen among hydroxy, thio, amino, carboxyl, aminocarbonyl, guanidinyI.

R₂ is chosen among hydrogen, C₁₋₄alkyl, arylC₁₋₄alkyl and phenyl;

or else R₁ and R₂, taken together, form a saturated carbocyclic ring containing from 3 to 8 carbon atoms;

R_3 is chosen among hydrogen, C_{1-4} alkyl, aryl C_{1-4} alkyl, $CONH_2$ and $COOR_5$ in which R_5 is chosen between hydrogen and C_{1-4} alkyl;

R₄ is chosen among hydrogen, C₁₋₄alkyl, aryl, arylC₁₋₄alkyl and heterocyclyl;

n is 2, 3 or 4;

in the form of a racemic mixture or in the form of enantiomers, and pharmaceutically acceptable salts or solvates thereof.

25 2. The compounds according to Claim 1, in which: A is phenyl, thienyl, pyridyl, pyrimidinyl group, optionally substituted, benzyl or 4-methylbenzyl; R₁ is

hydrogen, C₁₋₄ alkyl, benzyl, -CH₂OH, -CH₂CH₂CONH₂, -CH₂COOH, indol(3-yl)methyl; R₂ is hydrogen, C₁₋₄ alkyl or benzyl; R₃ and R₄ are hydrogen or methyl, and n is 2.

3. The compounds according to Claim 2, in which: A is phenyl optionally substituted; R₁, R₂, R₃ and R₄ are hydrogen; and n is 2.

4. The compounds according to Claims 1-3, in which A is substituted with 1 to 3 substituents chosen among Me, Et, i-Pr, OH, COOEt, COOH, CH₂OH, SO₂NH₂, SO₂Me, OMe, Cl, F, CN and CF₃.

5. The compounds according to Claim 4, in which A is substituted with 1 to 3 substituents chosen among Me, Et, i-Pr, OH, CN, Cl and CF₃.

6. The compounds according to Claim 1 or 2, in which said C₁₋₄alkyl group is chosen among Me, Et, i-Pr, i-Bu and cyclopropylmethyl.

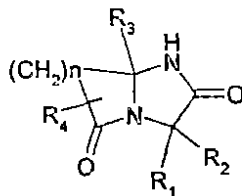
7. The compounds according to Claim 1, chosen in the group consisting of:

- 1-Phenyl-tetrahydro-1H-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-*o*-tolyl-tetrahydro-1H-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(2,6-Dimethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-Thiophen-2-yl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-*m*-Tolyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-*p*-Tolyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(5-Fluoro-2-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(3-Fluoro-2-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(2-Trifluoromethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(4-Chloro-2-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(3-Chloro-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(3-Methoxy-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(3-Cyano-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(4-Chloro-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(3-Hydroxy-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(3-Trifluoromethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(4-Trifluoromethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(4-Methoxy-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(2,5-Dimethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
- 1-(3,4-Dimethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;

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- 1-Naphthalen-2-yl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(3-Isopropyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(4-Chloro-3-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
3-Benzyl-1-phenyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
5 3-Methyl-1-phenyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
3-Isobutyl-1-phenyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(3-Fluoro-5-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(3-Fluoro-4-methyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
7a-Methyl-1-phenyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
10 (S)-1-o-Tolyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
(R)-1-o-Tolyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(4-Ethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(4-Isopropyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(4-Hydroxymethyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
15 4-(2,5-Dioxo-hexahydro-pyrrolo[1,2-a]imidazol-1-yl)-benzoic acid;
4-(2,5-Dioxo-hexahydro-pyrrolo[1,2-a]imidazol-1-yl)-benzoic acid ethyl ester;
1-(4-Methanesulfonyl-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(4-Fluoro-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(4-Cyano-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
20 1-Pyridin-2-yl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-Pyridin-3-yl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(5-Methylpyridin-2-yl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(2-Cyano-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
1-(3-Fluoro-phenyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione;
25 1-Benzyl-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione.
1-(4-methylbenzyl)-tetrahydro-pyrrolo[1,2-a]imidazole-2,5-dione.

8. A process for the preparation of the compounds of formula (I) as described in Claim 1, comprising the reaction of a compound of formula (II)



(II)

with a compound of formula (III)

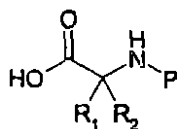
A-X

(III)

- 5 in which A, R₁, R₂, R₃, R₄ and n are defined as in Claim 1, and X is a halogen atom, to obtain the desired compounds of formula (I).
9. The process according to Claim 8, in which in the compound of formula (III) X is chosen between bromine and iodine.
10. The process according to Claims 8-9, for the preparation of the compounds of formula (I) wherein A is a carbocyclic aromatic group or a heterocyclic aromatic group, optionally substituted, in which the compound of formula (II) is dissolved in an appropriate solvent together with the compound of formula (III) in the presence of a base and of a catalytic amount of a copper salt, at a temperature of between 60°C and 140°C.
11. The process according to Claim 10, in which said solvent is *N*-methylpyrrolidone, said base is potassium carbonate, said copper salt is copper iodide, and the reaction is conducted at a temperature of 120°C.
12. The process according to Claims 8-9, for the preparation of the compounds of formula (I) wherein A is arylC₁₋₄alkyl, in which the compound of formula (II) is dissolved in an appropriate solvent together with the compound of formula (III), in the presence of a suitable base at a temperature between 60°C and 140°C.
13. The process according to claim 12, in which said solvent is chosen among acetonitrile, methylene chloride, acetone, said base is chosen among triethylamine, potassium carbonate, 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, *N,N*-Diiso-propylethylamine, at a temperature of 100°C.
14. The process for the preparation of compounds of formula (I) as described in Claim 1, comprising the following stages:

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i) reaction of an aminoacid of formula (IV) or of one of its activated derivatives



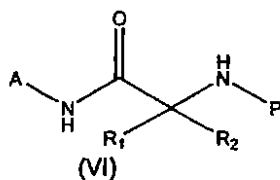
(IV)

with a compound of formula (V)

5 A-NH₂

(V)

to obtain a compound of formula (VI):



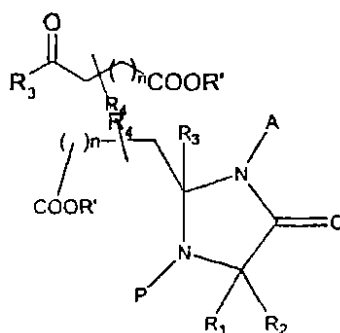
10

in which R₁, R₂ and A are as defined above in Claim 1, and P is H or a suitable protective group;

ii) reaction of the compound of formula (VI) obtained in stage i) with a compound of formula (VII)

15

(VII)



to obtain a compound of formula (VIII)

(VIII)

in which A, R₁, R₂, R₃, R₄ and n are as defined in Claim 1, P is defined as above, and R' is an alkyl group;

5 iii) possible removal of the protective group P by means of hydrogenolysis of the compound of formula (VIII) obtained from stage ii), to obtain the corresponding compound (VIII), in which P is H; and

iv) cyclization of the compound of formula (VIII), in which P is H coming from stage ii) or from stage iii), to obtain the desired compound of formula (I).

10 15. The process according to Claim 14, in which R' is chosen between methyl and *tert*-butyl, and P is chosen between H, benzyl and benzyloxycarbonyl.

16. The process according to Claim 14, in which, in said stage iv), the cyclization reaction is carried out by heating the compound (VIII) in the absence of solvent at 120°C and in vacuum conditions, or else by reflux-heating the compound (VIII) in xylene for a time comprised between 4 hours and 3 days.

15 17. The process according to Claim 14, in which said stage ii) is conducted by reflux-heating the compounds of formula (VI) and (VII) in a protic solvent for a time comprised between 2 and 24 hours, possibly in the presence of a base.

18. The process according to Claim 14, in which the reaction described in stage i) is conducted between the acidic chloride of the compound (IV) and the compound (V) in the presence of an inorganic or organic base in a suitable aprotic solvent at a temperature of between -70°C and 50°C.

19. The process according to Claim 14, in which the reaction of stage i) is conducted by reacting together the compound (IV) and the compound (V) in the presence of a suitable condensing agent, in an aprotic solvent at a temperature of between -70°C and 50°C.

20. The process according to Claims 18 or 19, in which said temperature is comprised between -10°C and 20°C.

21. A pharmaceutical composition comprising as active principle one or more compounds of formula (I) as described in Claim 1, or pharmaceutically acceptable salts or solvates thereof.

22. The pharmaceutical composition according to Claim 21, further comprising vectors, diluents and/or pharmaceutically acceptable excipients suitable for

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forms of administration chosen between oral, parenteral, rectal, transdermal, and transmucosal.

23. The pharmaceutical composition according to Claims 21 and 22, in the form of solutions, suspensions, soluble powders, granules, microcapsules, capsules, 5 lozenges, tablets, coated tablets, suppositories, creams, ointments, lotions, pastes, medicated plasters, membranes or gels.

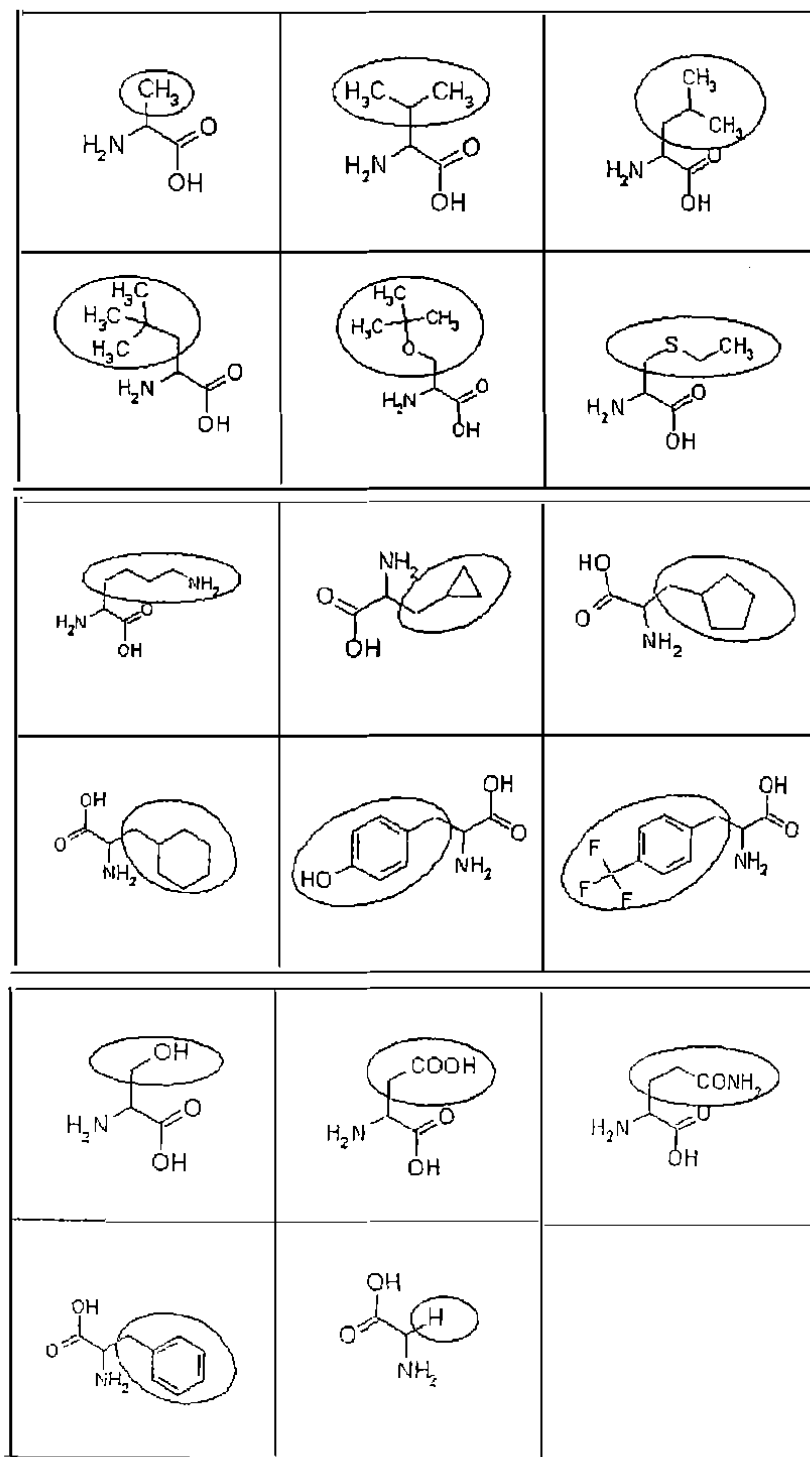
24. The use of a compound of formula (I) as described in Claim 1 or of one of its pharmaceutically acceptable salt or solvate for the preparation of a medicament having nootropic and/or neuroprotective, analgesic and/or anti-hyperalgesic, 10 and anti-emetic action.

25. The use according to Claim 24, for the treatment of learning and memory deficits, Alzheimer's disease, dementia, senile dementia, post stroke vascular type dementia, epilepsy, cerebral ischaemia, mood disorders, depression, for the treatment of conditions of chronic pain, inflammatory pain, neuropathic pain, 15 visceral pain, and for the treatment of emesis.

26. The use according to Claim 24, in which said compound of formula (I) is administered in association, concurrently or sequentially, with one or more other active principles.

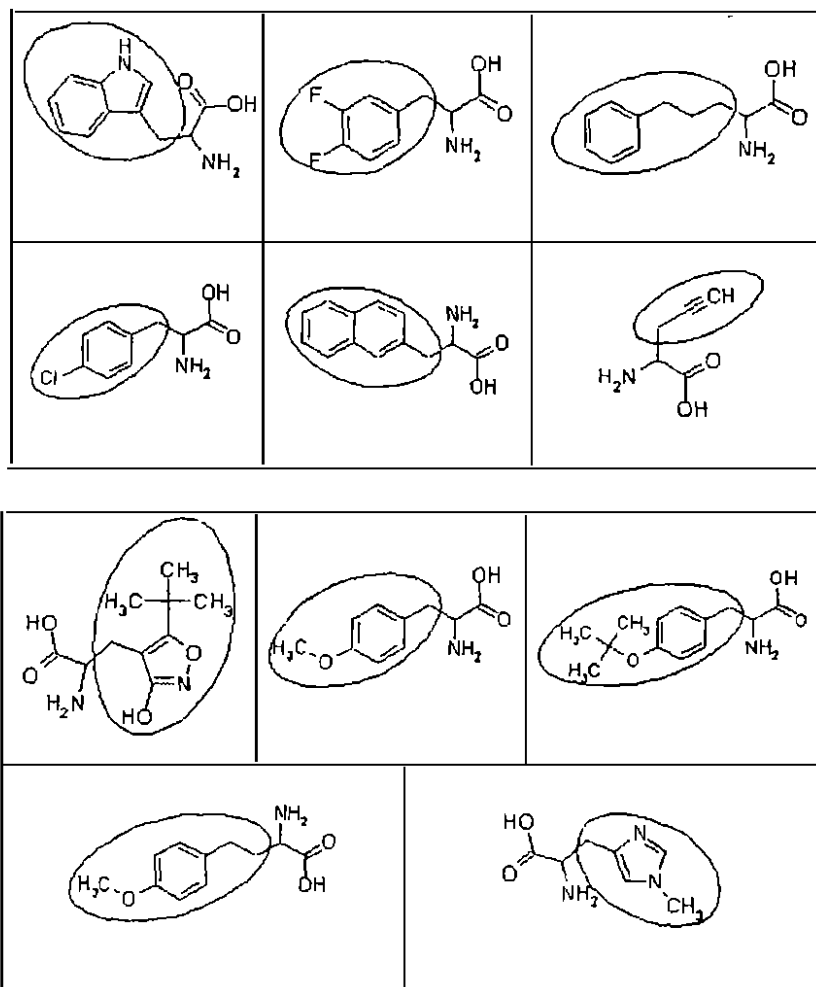
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FIGURE 1a



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FIGURE 1b



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0	For receiving Office use only	
0-1	International Application No.	PCT/EP200 4 / 0 5 0 3 3 9
0-2	International Filing Date	(22.03.04) 22 MAR 2004
0-3	Name of receiving Office and *PCT International Application*	EUROPEAN PATENT OFFICE PCT INTERNATIONAL APPLICATION
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT Online Filing Version 3.50 (Build 0001.159)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	4050PTWO/er
I	Title of Invention	COMPOUNDS WITH NOOTROPIC ACTION, THEIR PREPARATION, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM, AND USE THEREOF
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name:	NIKEM RESEARCH S.R.L.
II-5	Address:	Via Zambeletti 25 20021 BARANZATE DI BOLLATE Italy
II-6	State of nationality	IT
II-7	State of residence	IT
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
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III-1-4	Name (LAST, First)	FARINA, Carlo
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III-1-6	State of nationality	IT
III-1-7	State of residence	IT

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III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
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III-2-4	Name (LAST, First)	GAGLIARDI, Stefania
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III-2-6	State of nationality	IT
III-2-7	State of residence	IT
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	PARINI, Carlo
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III-3-7	State of residence	IT
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	MARTINELLI, Marisa
III-4-5	Address:	c/o NIKEM RESEARCH S.R.L. Via Zambeletti 25 20021 BARANZATE DI BOLLATE Italy
III-4-6	State of nationality	IT
III-4-7	State of residence	IT

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III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	GHELARDINI, Carla
III-5-5	Address:	c/o Dipartimento di Farmacologia Preclinica e Clinica "M. Aiazzi Mancini" Università di Firenze Viale G. Pieraccini 6 50139 FIRENZE Italy
III-5-6	State of nationality	IT
III-5-7	State of residence	IT
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	GERVASI, Gemma
IV-1-2	Address:	NOTARBARTOLO & GERVASI S.p.A. Corso di Porta Vittoria 9 20122 MILAN Italy
IV-1-3	Telephone No.	+39 025417991
IV-1-4	Facsimile No.	+39 0254179920
IV-1-5	e-mail	e.rossetti@ngpatent.it
IV-1-6	Agent's registration No.	40510.0
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	24 March 2003 (24.03.2003)
VI-1-2	Number	MI2003A000573
VI-1-3	Country	IT
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

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VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	1	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

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VIII-4-1	Declaration: Inventorship (only for the purposes of the designation of the United States of America) Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to the international application of which it forms a part (if filing declaration with application). I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications", by application number, country or Member of the World Trade Organization, day, month, and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.
VIII-4-1-1	Prior applications:	

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		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1-1-1	Name (LAST, First)	FARINA, Carlo
VIII-4-1-1-2	Residence: (city and either US State, if applicable, or country)	Milano, Italy
VIII-4-1-1-3	Mailing address.	c/o NIKEM RESEARCH S.R.L. Via Zambeletti 25 I-20021 BARANZATE DI BOLLATE Italy
VIII-4-1-1-4	Citizenship:	IT
VIII-4-1-1-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	/C. FARINA/
VIII-4-1-1-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	30 December 1899 (30.12.1899)

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VIII-4-1-2-1	Name (LAST, First)	GAGLIARDI, Stefania
VIII-4-1-2-2	Residence: (city and either US State, if applicable, or country)	Vimercate, Italy
VIII-4-1-2-3	Mailing address:	c/o NIKEM RESEARCH S.R.L. Via Zambeletti 25 I-20021 BARANZATE DI BOLLATE Italy
VIII-4-1-2-4	Citizenship:	IT
VIII-4-1-2-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	/S. GAGLIARDI/
VIII-4-1-2-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	30 December 1899 (30.12.1899)
VIII-4-1-3-1	Name (LAST, First)	PARINI, Carlo
VIII-4-1-3-2	Residence: (city and either US State, if applicable, or country)	Magenta, Italy
VIII-4-1-3-3	Mailing address:	c/o NIKEM RESEARCH S.R.L. Via Zambeletti 25 I-20021 BARANZATE DI BOLLATE Italy
VIII-4-1-3-4	Citizenship:	IT
VIII-4-1-3-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	/C. PARINI/
VIII-4-1-3-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	30 December 1899 (30.12.1899)

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VIII-4-1-4-1	Name (LAST, First)	MARTINELLI, Marisa
VIII-4-1-4-2	Residence: (city and either US State, if applicable, or country)	Villa Guardia, Italy
VIII-4-1-4-3	Mailing address:	c/o NIKEM RESEARCH S.R.L. Via Zambeletti 25 I-20021 BARANZATE DI BOLLATE Italy
VIII-4-1-4-4	Citizenship:	IT
VIII-4-1-4-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	/M. MARTINELLI/
VIII-4-1-4-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	30 December 1899 (30.12.1899)
VIII-4-1-5-1	Name (LAST, First)	GHELARDINI, Carla
VIII-4-1-5-2	Residence: (city and either US State, if applicable, or country)	Firenze, Italy
VIII-4-1-5-3	Mailing address:	c/o Dipartimento di Farmacologia Preclinica e Clinica "M. Aiazzi Mancini" Università di Firenze Viale G. Pieraccini 6 I-50139 FIRENZE Italy
VIII-4-1-5-4	Citizenship:	IT
VIII-4-1-5-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	/C. GHELARDINI/
VIII-4-1-5-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	30 December 1899 (30.12.1899)

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IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	9	✓
IX-2	Description	32	✓
IX-3	Claims	7	✓
IX-4	Abstract	1	✓
IX-5	Drawings	2	✓
IX-7	TOTAL	51	
Accompanying Items		paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	-	✓
IX-17	PCT-SAFE physical media	-	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	(PKCS7 Digital Signature)	
X-1-1	Name (LAST, First)	GERVASI Gemma	
X-1-2	Name of signatory		
X-1-3	Capacity		

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10-1	Date of actual receipt of the purported international application	(22.03 2004) 22 mar 2004
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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FIGURA 1a

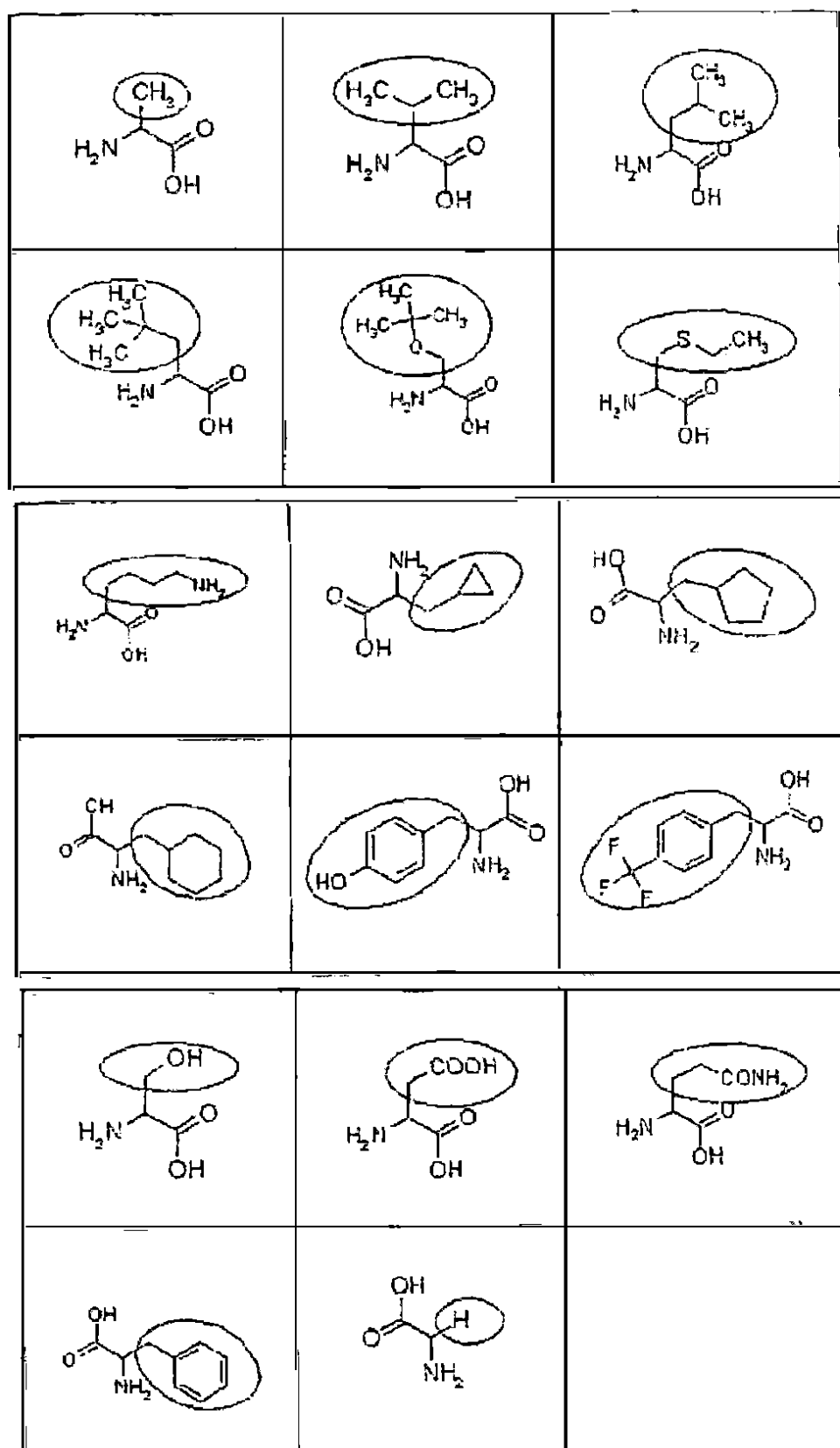
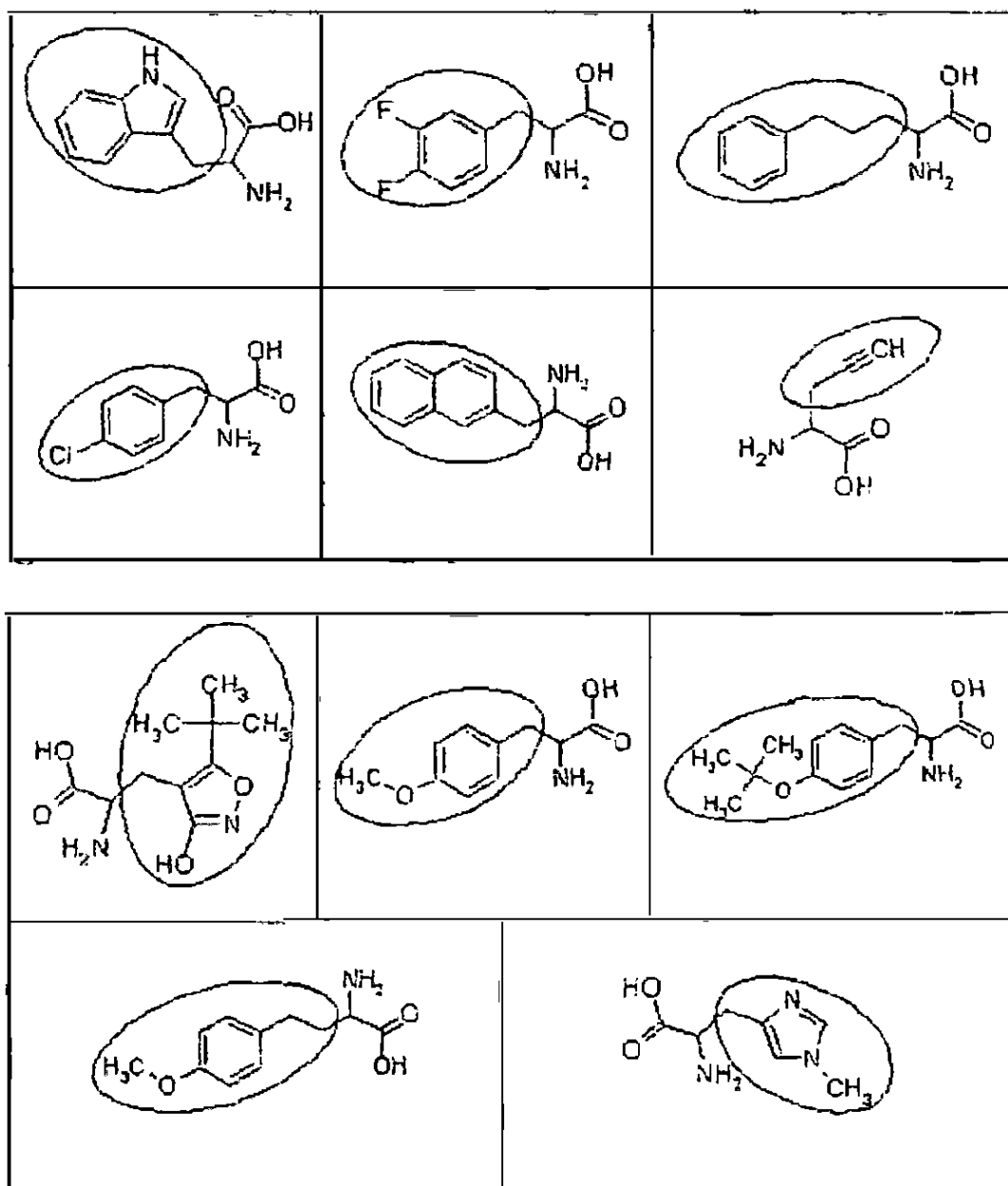


FIGURA 1b



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**DERIVADOS DE PIRROLOIMIDAZOLE, SU PREPARACIÓN,
COMPOSICIÓN FARMACÉUTICA QUE LOS CONTIENE Y SU
UTILIZACIÓN COMO AGENTES NOOTRÓPICOS**

5 Campo de la Invención

La presente invención está relacionada con nuevos compuestos de la fórmula (I) que aparece de aquí en adelante, el proceso para su preparación, las composiciones farmacéuticas que lo contienen, y su utilización como agentes
10 nootrópicos, neuroprotectores, analgésicos y anti-hiperalgésicos.

Estado de la Técnica

Compuestos del estado del arte que poseen actividad nootrópica ya se
15 conocen en la literatura. En particular, los derivados sustituidos en posición 4 de 2-oxo-1-pirrolidineacetamida son agentes psicotrópicos válidos que re-establecen funciones cognitivos dañados. Estos compuestos se describen, por ejemplo, en *Pharm. Res. Commun.* 16, 67, 1984 por Banfi, et al. y en *Drug Development Res.* 2, 447, 1982 por Útil et al.

20

Entre las moléculas más ampliamente conocidas que pertenecen a la arriba mencionada clase se pueden citar: 2-oxo-1-pirrolidineacetamida (piracetam), 4-hidroxi-2-oxo-1-pirrolidineacetamida (oxiracetam), 2-(2-oxopirrolidin-1-il)butiramida (levetiracetam) y N-(2, 5-dimetilfenilo)-2-oxo-1-
25 pirrolidineacetamida (nafiracetam).

Otra clase química que posee actividad nootrópica esta representada por derivados imidazolic condensados, en particular 2,5-dioxohexahidro-1H-pirrol[1,2-a]imidazole(dimiracetam), descrito en EP 335483 y en WO-9309120, y en *J. Med. Chem.*, 36, 4214, 1993 por Pinza M. et al.

5

Recientemente, se ha demostrado que nefiracetam podría ser un buen agente terapéutico en el tratamiento de dolor neuropático. La acción anti-hiperalgésica inducida por nefiracetam parece ser de naturaleza no-opioide y probablemente es debida a la estimulación del sistema nicotínico colinérgico a nivel espinal y súper espinal (Rashid Harunor M. D. *J. Pharmacol. Exp. Ther.*, 303,226, 2002).

10

Breve Descripción de la Invención

15

El solicitante actual ahora ha encontrado nuevos imidazolones bicíclicos *N*-sustituídos de la fórmula (I), que aparecerán en seguida, que han demostrado propiedades psicotrópicos mejorados y efectos anti-hiperalgésicos y analgésicos mas marcados en varios modelos de dolor neuropático, comparado con los agentes nootrópicos ya conocidos.

20

Consecuentemente los compuestos actuales de la fórmula (I) son útiles en el tratamiento de muchos desordenes del sistema central nervioso (SCN), por ejemplo en el deterioro del aprendizaje, disfunción de la esfera cognitiva y de la memoria, enfermedad de Alzheimer, demencias, incluyendo demencia senil del tipo de Alzheimer, demencia vascular post-apoplejía, epilepsia, isquemia

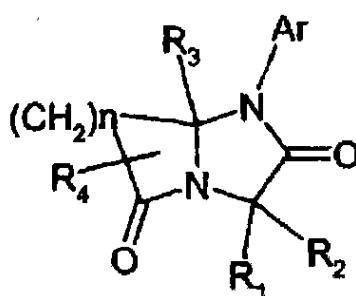
25

cerebral, desórdenes del humor, incluyendo depresión, dolor crónico, inflamatorio, neuropático y visceral, y emesis.

En consecuencia, compuestos de la fórmula general (I) son
5 representativos del tema de la invención actual

(I)

10



en la cual:

15

A se escoge entre los grupos aromáticos carbocíclicos, grupos aromáticos heterocíclicos y arilC₁₋₄alquilo;

R₁ se escoge de entre:

20

- hidrógeno;
- aril C₁₋₇alquilo, opcionalmente sustituido en la fracción alquilo con uno o mas grupos escogidos de entre hidroxí, C₁₋₄alkoxi, halógeno, haloC₁₋₄alquilo;

25

- heterociclilC₁₋₇alquilo, opcionalmente sustituido en la fracción heterociclil con uno o más grupos escogidos de entre C₁₋₄alquilo e hidroxil;
- C₁₋₇alquilo, opcionalmente interrumpido por un átomo de oxígeno o azufre o opcionalmente sustituido en cualquier posición por uno o mas grupos escogidos de entre hidroxil, tio, amino, carboxil, amino-carboxil, guanidinil.

R₂ se escoge de entre: hidrógeno, C₁₋₄alquilo, arilC₁₋₄alquilo y fenil;
 10 o bien se toman juntos R₁ y R₂, de un anillo carbocíclico saturado que contiene entre 3 y 8 átomos de carbón;

R₃ se escoge de entre hidrógeno, C₁₋₄alquilo, arilC₁₋₄alquilo, CONH₂ y COOR₅ en donde R₅ se escoge de entre hidrógeno y C₁₋₄alquilo;

15 **R₄** se escoge de entre hidrógeno, C₁₋₄alquilo, aril, arilC₁₋₄alquilo y heterociclil;

y

20 **n** es 2, 3 ó 4;

en la forma de una mezcla racémica o en la forma de enantiómeros, y sales farmacéuticamente aceptables o solvatos de éstas.

25

El proceso de preparación de los compuestos de la fórmula (I) que aparece arriba, los compuestos farmacéuticos que la contiene y su uso en la preparación de medicamentos con acción nootrópica y neuroprotectora, con acción analgésico y/o anti-hiperalgésica, y acción anti-emética, constituyen otra
5 materia de la invención.

Se ilustrarán las características y ventajas de los compuestos actuales de la fórmula (I) en detalle en la siguiente descripción.

10 Descripción de las Figuras

Las Figuras 1a, 1b son ejemplos no-limitantes de aminoácidos de la fórmula (IV), útiles en la síntesis de los compuestos de la fórmula (I). La porción dentro del círculo indica el sustituyente R_1 .

15

Descripción Detallada de la Invención

Dentro del marco de la invención actual, el término “grupo aromático carbocíclico” significa anillos aromáticos sencillos o fusionados con 6 a 12
20 elementos del anillo, opcionalmente sustituidos.

Los términos “grupo aromático heterocíclico” y “heterociclil” significan anillos sencillos o fusionados no-saturados, cada anillo con entre 5 y 12 elementos que consisten en hasta cuatro hetero átomos, escogidos de entre
25 oxígeno, azufre y nitrógeno, opcionalmente sustituidos.

Cuando no está especificado, el término “aril” significa anillos insaturados sencillos o fusionados, cada anillo tiene entre 5 y 8 elementos, y de preferencia de 5 o 6 elementos, opcionalmente sustituidos; por el término “arilC₁₋₄alquilo” se indica un grupo que tiene un grupo aril, como se definió
5 arriba, y una fracción alquiloC₁₋₄ que conecta el grupo aril al punto de sustitución.

Todos los arriba mencionados grupos C₁₋₄alquilo, incluyendo aquéllos que forman parte del grupo arilC₁₋₄alquilo, pueden ser indistintamente lineales o
10 ramales o cíclicos (por ejemplo, ciclo-propil, ciclo-propil-metil o metilciclopropil). Los grupos alquilo C1-C4 preferidos son Me, Et, i-Pr, i-Bu, y ciclopropilmetil

Todos los arriba mencionados grupos C₁₋₇alquilo, incluyendo aquéllos
15 que forman parte de los grupos que contienen C₁₋₇alquilo, pueden ser indistintamente lineales, ramales o cíclicos, y pueden incluir enlaces dobles o triples. El término “grupos C₁₋₇alquilos interrumpidos por oxígeno o azufre” significa, respectivamente, cualquier grupo éter y tio-éter que contiene entre 1 y
7 átomos de carbón.

20

El término “heterociclilC₁₋₇alquilo” indica un grupo que tiene un grupo heterociclil, como se definió arriba, y una fracción alquiloC₁₋₇ que conecta el grupo aril con el punto de sustitución.

25

El término "arilC₁₋₇alquilo" indica un grupo que tiene un grupo aril, como se definió arriba, y una fracción alquiloC₁₋₇ que conecta el grupo aril con el punto de sustitución.

- 5 "Halógeno" significa un átomo escogido entre flúor, cloro, bromo y yodo; "haloC₁₋₄alquilo" significa un grupo alquiloC₁₋₄ sustituido en cualquier posición por uno o más átomos de halógeno, por ejemplo trifluorometil.

- Si no se indica lo contrario, grupos "sustituidos opcionalmente" son
10 grupos sustituidos opcionalmente con 1 a 3 sustituyentes escogidos, de preferencia, de entre Me, Et, i-Pr, OH, COOEt, COOH, CH₂OH, SO₂NH₂, SO₂Me, OMe, Cl, F, CN y CF₃, y más preferentemente Me, Et, i-Pr, OH, CN, Cl y CF₃; los sustituyentes pueden estar en cualquier posición en el grupo que se vaya a sustituir.

15

- Los compuestos preferidos según la invención son compuestos de la fórmula (I), en los cuales A es un fenil sustituido opcionalmente, un bencilo sustituido opcionalmente o un grupo aromático heterocíclico sustituido opcionalmente con 5 ó 6 elementos, y que consiste en hasta dos átomos hetero
20 escogidos de entre oxígeno, azufre o nitrógeno, R₁, R₂, R₃ y R₄ se escogen entre hidrógeno, C₁₋₄alquilo o bencilo, y n es igual a 2 ó 3.

- De preferencia, A es fenil, tienil, piridil, grupo pirimidinil, opcionalmente sustituidos, bencil o 4-metilbencil; R₁ es hidrógeno, C₁₋₄alquilo
25 (por ejemplo metil, isopropil o isobutil), bencil, -CH₂OH, -CH₂CH₂CONH₂,

100

-CH₂COOH, indol(3-il)metil, R₂ es hidrógeno, C₁₋₄alquilo o bencil, R₃ y R₄ son hidrógeno o metil, y n es 2.

Más preferentemente, A es un fenil opcionalmente sustituido, R₁, R₂, R₃
5 y R₄ son hidrógeno, y n es igual a 2.

Cuando R₁ y R₂, tomados juntos, forman un anillo carbocíclico saturado que contiene entre 3 y 8 átomos de carbón, el compuesto que resulta de la fórmula (I) es un compuesto espirocíclico.

10

Compuestos preferidos de la fórmula (I) de acuerdo con la invención se eligen de un grupo compuesto por:

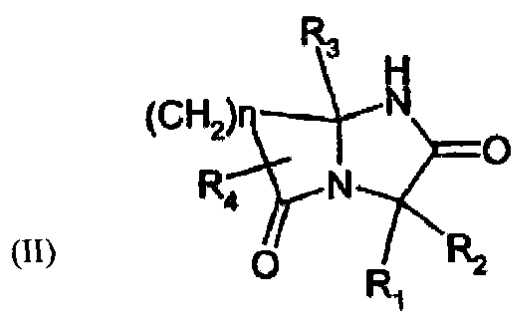
- 1-Fenilo-tetrahidro-1H-pirrol[1,2-a]imidazole-2,5-diona;
- 1-o-tolil-tetrahidro-1H-pirrol[1,2-a]imidazole-2,5-diona;
- 15 1-(2,6-Dimetil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-Tiofeno-2-il-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-m-Tolil-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-p-Tolil-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(5-Fluoro-2-metil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 20 1-(3-Fluoro-2-metil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(2-Trifluorometil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(4-Cloro-2-metil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3-Cloro-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3-Metoxi-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 25 1-(3-Ciano-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;

- 1-(4-Cloro-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3-Hidroxi-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3-Trifluorometil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(4-Trifluorometil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 5 1-(4-Metoxi-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3,5-Dimetil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3,4-Dimetil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-Naftalen-2-il-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3-Isopropil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 10 1-(4-Cloro-3-metil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 3-Bencil-1-fenilo-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 3-Metil-1-fenilo-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 3-isobutil-1-fenilo-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3-Fluoro-5-metil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 15 1-(3-Fluoro-4-metil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 7a-Metil-1-fenilo-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- (S)-1-*o*-Tolil-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- (R)-1-*o*-Tolil-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(4-Etil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 20 1-(4-Isopropil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(4-Hidroximetil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 4-(2,5-Dioxo-hexahidro-pirrol[1,2-a]imidazole-1-il)-ácido benzoico;
- 4-(2,5-Dioxo-hexahidro-pirrol[1,2-a]imidazole-1-il)-ácido benzoico etil éster;
- 1-(4-Metanosulfonil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 25 1-(4-Fluoro-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;

- 1-(4-Ciano-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-Piridina-2-il-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-Piridina-3-il-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(5-Metilpiridin-2-il)-tetrahidropirrol[1,2-a]imidazole-2,5-diona;
- 5 1-(2-Ciano-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3-Fluoro-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-Bencil-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(4-metilbencil)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona.

10 Se debe notar que algunos de los compuestos de la fórmula (I) pueden contener uno o más centros estereogénicos. La invención actual se extiende a todos los isómeros ópticos de los compuestos en sus formas enteramente o parcialmente resueltas y en la forma de mezclas racémicas.

15 Otra materia de la invención es el proceso para la preparación de los compuestos de la fórmula (I), o de una de sus sales, y/o uno de sus solvatos, que consiste en la reacción de un compuesto de la fórmula (II)



con un compuesto de la fórmula (III)



(III)

5

en que A, R₁, R₂, R₃ y R₄ y n se definen como arriba para los compuestos de la fórmula (I), y X es un átomo de halógeno, escogido de preferencia entre bromo y yodo.

10

Cuando A es un grupo aromático carbocíclico o un grupo aromático heterocíclico como se definió arriba, la reacción entre los compuestos de la fórmula (II) y el compuesto de la fórmula (III) puede llevarse a cabo según las condiciones apropiadas de la reacción Goldberg (*Angew. Chem. Int. E.*, 39, 4492, 2000). En particular, los compuestos de la fórmula (II) se disuelven en un

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solvente adecuado, tal como N-metilpirrolidona, junto con los compuestos de la fórmula (III) en la presencia de una cantidad catalítica de sal de cobre tal como yoduro de cobre, y una base tal como carbonato potásico, a cualquier temperatura que producirá un porcentaje adecuado de formación del producto que se requiere, adecuadamente a una temperatura alta, por ejemplo a una

20

temperatura de entre 60°C y 140°C, por ejemplo a 120°C. La mezcla de la reacción se calienta utilizando un sistema convencional de calentamiento o un reactor de microondas de potencia adecuada, por ejemplo, que consiste en entre 25 y 250W (*Tetrahedron Letters*, 43,1101, 2002).

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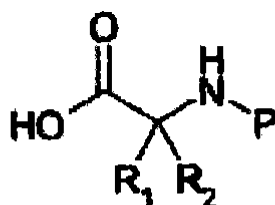
Cuando A es arilC₁₋₄alkil, la reacción se puede llevar a cabo en un solvente adecuado tal como acetonitrilo, diclorometano, acetona, en la presencia de una base adecuada tal como trietilamina, carbonato potásico, 2-*tert*-Butilimino-2-dietilamino-1,3-dimetilperhidro-1,3,2-diasafosforina (también conocido como BEMP), N,N-Diisopropiletilamina (también conocido como base Hunig), a una temperatura adecuada tal como la temperatura de reflujo (60-140°C, de preferencia 100°C).

Los antemencionados compuestos de la fórmula (II) y los métodos para su preparación se describen en la solicitud de patente Europea EP-A-335483 y en la solicitud para patente Internacional No. WO-A-93/09120 y en *J. Med. Chem.*, 36, 4214, 1993, por Pinza et al.

Los compuestos para la fórmula (III) están disponibles comercialmente o se pueden preparar desde compuestos conocidos con métodos conocidos.

De manera alterna, los compuestos de la fórmula (I) se pueden preparar con el proceso que consiste en los siguientes pasos:

- i) reacción de un aminoácido de la fórmula (IV) o uno de sus derivados activados



(IV)

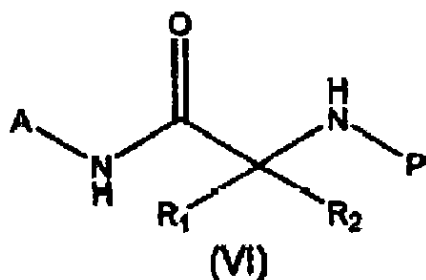
con un compuesto de la fórmula (V)



(V)

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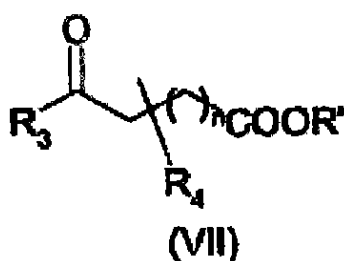
para obtener un compuesto de la fórmula (VI)



10

en que R_1 , R_2 y A son como se definió arriba para el compuesto de la fórmula (I), y P es H o un grupo protector adecuado. La activación de los aminoácidos es un procedimiento sintético bien conocido; ejemplos de derivados activados de aminoácidos se mezclan con anhídridos, cloruros acílicos y ésteres activados;

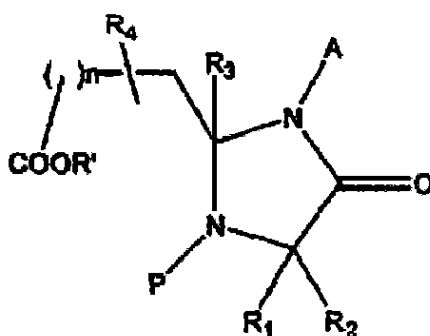
ii) reacción del compuesto de la fórmula (VI) obtenido en el paso i) con el compuesto de la fórmula (VII)



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para obtener un compuesto de la fórmula (VIII)

5



(VIII)

10 en que A, R₁, R₂, R₃ y R₄ y n son como se definió arriba para el compuesto de la fórmula (I), P se define como arriba, y R' es un grupo alquilo;

iii) remoción posible del grupo P protector por medio de hidrogenólisis de los compuestos de la fórmula (VIII), obtenido en el paso ii), para obtener el
15 compuesto correspondiente (VIII), en que P es H; y

iv) ciclización del compuesto de la fórmula (VIII), en que P es H que viene del paso ii) o del paso iii), para obtener el compuesto deseado de la fórmula (I).

20 Según una incorporación preferida de la invención, el residuo alquilo R' se escoge entre metil y *tert*-butil, y P se escoge entre hidrógeno, un grupo bencilo o bencilo-oxicarbonílico.

La reacción en el paso i) entre el compuesto de la fórmula (IV) y el
25 compuesto de la fórmula (V) se puede llevar a cabo:

(a) preparando, en primer lugar, un cloruro ácido en el compuesto de la fórmula (IV) y uniendo a dicho cloruro ácido el compuesto de la fórmula (V) en presencia de una base inorgánica u orgánica en un solvente aprótico
5 adecuado, como dimetilformamida (DMF) a una temperatura de entre -70°C y 50°C, y de preferencia entre -10°C y 20°C; o:

(b) haciendo reacción juntos el compuesto de la fórmula (IV) con el compuesto de la fórmula (V) en la presencia de un agente condensador
10 adecuado, por ejemplo *N,N'*-carbonil diimidazole (CDI) o una carbodiimida como diciclohexilcarbodiimida (DCC) o *N*-dimetilaminopropil-*N'*-etilcarbodiimida, de preferencia de *N*-hidroxibenzotriazol (HOBt) para maximizar el rendimiento y prevenir los procesos de racemización (cf. Síntesis, 453,1972) u *O*-benzotriazol-1-il-*N,N,N',N'*-tetrametiluronio hexafluorofosfato
15 (HBTU), en un solvente aprótico, por ejemplo una mezcla de acetonitrilo (MeCN) y tetrahidrofurano (THF), por ejemplo, una mezcla con la relación volumétrica entre 1:9 y 7:3 (MeCN:THF), a cualquier temperatura capaz de rendir un porcentaje adecuado de formación del producto requerido, por ejemplo una temperatura de entre -70°C y 50°C, y de preferencia de entre -
20 10°C y 25°C.

En el paso ii) del proceso actual, se calientan, de preferencia con calor de reflujo, los compuestos de las fórmulas (VI) y (VII) en un solvente prótico, tal como agua o metanol, y posiblemente en presencia de una base, tal como
25 NaOH, en el caso en donde se utiliza el compuesto de la fórmula (VI) para

formar una de sus sales que se obtiene a través de la incorporación de un ácido, durante un período de tiempo adecuado, de preferencia entre 2 y 24 horas.

Se lleva a cabo la remoción del grupo P protector a través de
5 hidrogenólisis en el paso iii) utilizando formiato de amonio como la fuente de hidrógeno en un solvente prótico adecuado, por ejemplo metanol o una mezcla de agua y metanol.

Se lleva a cabo la reacción de ciclización en el paso iv) directamente en
10 el compuesto de la fórmula (VIII) que viene del paso ii) si P es H, o si dicho compuesto (VIII) P es un grupo protector, el primer paso es removerlo, como se describió arriba en el paso iii).

Se lleva a cabo la reacción de ciclización bajo condiciones drásticas a
15 través del calentamiento convencional del compuesto de la fórmula (VIII) sin solvente a 120°C y en condiciones de vacío, o bien por medio de calentamiento de reflujo en xileno durante un período adecuado de tiempo, por ejemplo durante entre 4 horas y 3 días, o a través de la irradiación con microondas.

20 Los compuestos de las fórmulas (IV), (V) y (VII) están comercialmente disponibles, o se pueden preparar desde compuestos conocidos a través de métodos conocidos.

En particular, se pueden escoger los compuestos de la fórmula (IV) de
25 cualquier aminoácido que existe naturalmente o derivados de éstos. En la

Figura 1 se muestran ejemplos de aminoácidos que son útiles en la invención actual, en donde la parte dentro del círculo corresponde al sustituyente R_1 de la fórmula (IV); y por lo tanto se prefieren todos estos significados de R_1 en la fórmula (I), siendo el objeto de la invención actual.

5

Son útiles como agentes terapéuticos los compuestos actuales de la fórmula (I) y en particular poseen actividad nootrópica y neuroprotectora, por ejemplo, contribuyen a la restauración del aprendizaje y de funciones de la memoria que se hayan deteriorado con la edad o debido a traumas de isquemia, y son efectivos en varias patologías del SNC, entre ellas son disfunciones de aprendizaje, disfunciones de la esfera cognitiva y de la memoria, enfermedad de Alzheimer, demencias, incluyendo demencia senil del tipo Alzheimer, demencia tipo post-apoplejía, epilepsia, isquemia cerebral y afecciones del estado de ánimo, incluyendo la depresión.

15

Además, los compuestos actuales de la fórmula (I) poseen actividad analgésica y/o anti-hiperalgésica, por ejemplo, contribuyen a combatir las sensaciones de dolor, en particular aquellas causadas por condiciones de dolor neuropático, dolor inflamatorio crónico y dolor visceral, y han probado ser eficaces también en el tratamiento de emesis.

20

La materia de la invención actual también es, por tanto, el uso de los compuestos actuales de la fórmula (I) o de sus sales y/o solvatos farmacéuticamente aceptables en la preparación de medicamentos para la recuperación de padecimientos de aprendizaje y memoria y para el tratamiento

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de demencias, enfermedad de Alzheimer, demencia tipo vascular post-apoplejía, epilepsia, isquemia cerebral y afecciones del estado de ánimo, incluyendo la depresión.

5 También proporciona un método para el tratamiento de los arriba mencionados padecimientos y enfermedades, caracterizado por la administración de una cantidad farmacéuticamente activa de un compuesto de la fórmula (I) a un paciente que la necesita.

10 Es bien conocido que los desórdenes cognitivos que ocurren en dichas patologías son correlacionadas con el déficit del sistema colinérgico cerebral, como se descubre a través de resultados morfológicos (B.E.Tomlinson en "Biochemistry of Dementias"; P.J.Roberts Ed.; John Wiley & Sons, New York, N.Y. pp. 15-22, 1980) y descubrimientos neuroquímicos (R. T. Bartus et al.
15 *Science*, 217, 408, 1982). Además es bien conocido que los deterioros significativos de las funciones cognitivas son los signos más evidentes y debilitantes que se observan en pacientes que sufren de la enfermedad de Alzheimer, demencia senil del tipo Alzheimer, y demencia debida a infartos múltiples.

20 Se puede determinar la actividad de los compuestos de la fórmula (I) en ratas con relación a la acción que provoca amnesia de escopolamina (D. A. Drachman, *Archs. Neurol.*, Chicago, 30,113, 1974; D. A. Eckerman, *Pharmacol. Biochem. Behav.* 12,595, 1980) en la ruta mnémica y en la
25 reducción de los niveles de acetilcolina en el hipocampo. Se puede evaluar en

ratas el efecto en la memoria y el aprendizaje utilizando la prueba de evitar pasiva, como se describe en Essman, *Pharmacol Res. Commun.* 5, 295, 1973.

La materia de la invención actual es, además el uso de los compuestos
5 actuales de la fórmula (I) o sus sales o solvatos farmacéuticamente aceptables en el tratamiento de condiciones de dolor neuropático, dolor inflamatorio crónico y dolor visceral. También se proporciona un método para el tratamiento de dichas enfermedades caracterizado por la administración de una cantidad farmacéuticamente activa de un compuesto de la fórmula (I) a un paciente que
10 lo necesita.

Se plantea como hipótesis que el proceso de aprendizaje y memoria esta implicado en los mecanismos del dolor crónico (Flor H., *Prog. Brain Res.* , 129, 313, 2000), y evidencia reciente apoya la hipótesis de que el dolor inflamatorio
15 crónico es un fenómeno maladaptivo adquirido (Arnstein P. M. , *J. Neurosci. Nurs.* 29, 179, 1997; Kumazava T., *Neurosci. Res* , 32, 9, 1998). Se ha descrito la disfunción cognitiva en varias condiciones neuropáticas. (Kuhajda M. C., *Ann. Behav. Med*, 20, 31, 1998), y recientemente se ha observado que el nefiracetam, un agente nootrópico, alivia el dolor neuropático gracias a sus
20 efectos en neuropatías (Rashid Harunor M. D. J. *Pharmacol. Exp. Ther.*, 303,226, 2002). Se ha mostrado que el efecto analgésico y/o anti-hiperalgésico del nefiracetam se expresa a través de la estimulación de los receptores nicotínicos colinérgicos a nivel espinal y supraespinal, en cuanto dicho efecto esta inhibido de manera dosis-dependiente por mecamilamina, un antagonista
25 conocido del receptor colinérgico nicotínico.

La actividad de los compuestos de la fórmula (I) se puede determinar en ratones a través del ensayo hiperalgesia-termal (ensayo de retirar la pata) y el ensayo hiperalgesia-mecánica (ensayo de presión en la pata) inducido por la ligación parcial del nervio ciática o por tratamiento con estreptozotocina, siguiendo los protocolos descritos en *J. Pharmacol. Exp. Ther.*, 303, 226, 2002 y en la bibliografía citada en el mismo.

Cuando se utilizan en tratamiento terapéutico en humanos y animales, se formulan los compuestos de la fórmula (I) normalmente según la práctica farmacéutica estándar, como compuesto farmacéutico.

Por lo tanto, otra materia de la invención esta representada por un compuesto farmacéutico que consiste en, como principio activo, un compuesto de la fórmula (I) o una de sus sales o solvatos farmacéuticamente aceptables, junto con vectores, diluyentes y excipientes adecuados para la forma de administración que se escoge farmacéuticamente aceptables.

Se pueden administrar los compuestos de la fórmula (I) de forma estándar en el tratamiento de las enfermedades que arriba se indicaron, por ejemplo vía oral, parenteral, rectal, vía transdérmica o por la administración a través de la mucosa (por ejemplo, la mucosa sublingual, bucal o nasal).

Los compuestos de la fórmula (I) que se administran vía oral o vía sublingual o vía bucal, se pueden formular como jarabes, tabletas, cápsulas y pastillas. Una formulación en forma de jarabe consiste generalmente en una

suspensión o solución del compuesto o una de sus sales en un vector líquido, por ejemplo etanol, glicerina o agua con un agente saborizante o colorante.

Cuando el compuesto está en la forma de tableta, es posible usar cualquier vector farmacéutico que se usa convencionalmente en la preparación de formulaciones sólidas. Ejemplos de dichos vectores consisten en estereato de magnesio, almidón, lactosa y sucrosa. Cuando el compuesto está en la forma de cápsulas, es adecuado cualquier método convencional de encapsulación, por ejemplo, el uso de los vectores mencionados arriba en una cápsula de gelatina endurecida. Cuando el compuesto está en la forma de cápsulas hechas de gelatina suave, es posible usar cualquier vector farmacéutico que se usa convencionalmente en la preparación de dispersiones o suspensiones, por ejemplo gomas acuosas, celulosa, silicatos o aceites, que se incorporarán en la cáscara hecha de gelatina suave.

15

Compuestos parenterales típicos consisten en una solución o suspensión del compuesto de la fórmula (I) en un vector estéril acuoso o no-acuoso, que posiblemente contiene un aceite aceptable para la vía parenteral, por ejemplo, polietileno-glicol, polivinil-pirrolidona, lecitina, aceite de cacahuate o aceite de ajonjolí.

20

La formulación típica en supositorios consiste en un compuesto de la fórmula (I), que se activa si se administra de esta manera, con un agente aglutinante y/o lubricante, por ejemplo glicoles poliméricos, gelatina, manteca de cacao, u otras ceras de bajo punto de fusión o aceites vegetales.

25

Formulaciones transdérmicas típicas consisten en un vector acuoso o no-acuoso convencional, por ejemplo crema, ungüento, loción o pasta, o puede ser en la forma de plastas medicadas, parches o membranas.

- 5 De preferencia, el compuesto está en la forma de unidad de dosis, por ejemplo tabletas o cápsulas, de manera que el paciente puede tomar una dosis sencilla.

Oxiracetam es un compuesto que se usa en el tratamiento de demencia
10 senil y las condiciones patológicas relacionados con ésta. Se pueden administrar los compuestos de la fórmula (I) con regímenes similares a aquellos establecidos para oxiracetam, con cualquier ajuste apropiado de los niveles en la dosis o de la frecuencia de la dosis en relación a la mayor actividad y al perfil farmacéutico mejorado de los compuestos de la fórmula (I).

15

Cada unidad de dosis para la administración oral puede contener convenientemente desde 0.05 mg/kg hasta 50 mg/kg, más convenientemente desde 0.1 mg/kg hasta 25 mg/kg de un compuesto de la fórmula (I). Se puede administrar el ingrediente activo de 1 a 6 veces por día. Se pueden
20 coadministrar los compuestos de la fórmula (I) con otros compuestos farmacéuticamente activos, por ejemplo en asociación, concurrencia o secuencia con, en particular junto con, otros compuestos usados en el tratamiento de pacientes mayores, tales como tranquilizantes, diuréticos, drogas anti-hipersensibles, drogas vasodilatadoras, y agentes inotrópicos.

25

Se proporcionan ejemplos de la invención actual en lo siguiente, con fines estrictamente ilustrativos y no limitativos.

PARTE EXPERIMENTAL

5

Descripción 1. *3-Isobutil-tetrahidro-pirrolol[1,2-a]imidazole-2,5-diona.*

A una solución de DL-hidrocloruro de leucinamida (1.5 g, 9 mmol) en agua (40 ml), ajustado a un pH de 9.5 con 10% de hidróxido sódico, se agregó
10 etil-4-oxobutanoato (1 g, 7.5 mmol). Se introdujo la mezcla en un horno de microondas y se mantuvo en condición de reflujo durante 1 hora. Entonces se evaporó el agua al vacío y se cromatografé el residuo sobre gel de sílice. (CH₂Cl₂ / MeOH / NH₄OH 98 / 2 / 0.1) para rendir 1.1 g del compuesto titular.

15 ¹H-NMR (CDCl₃) δ: 6.48 (amplio s, 1H); 5.30 (t, 1H); 4.23 (dd, 1H); 2.71-2.39 (m, 3H); 2.20-1.93 (m, 1H); 1.86-1.73 (m, 1H); 1.70-1.42 (m, 2H), 1.05 (d, 3H); 0.96 (d, 3H).

MS: EI TSQ 700; fuente 180 C; 70 V; 200 uA: 196 (M⁺), 97.

20

Ejemplo 1. *1-Fenilo-tetrahidro-1H-pirrolol[1,2-a]imidazole-2,5-diona*

A una solución de tetrahidro-pirrolol[1,2-a]imidazole-2,5-diona (1 g, 7.14 mmol; preparado como se describe en *J. Med. Chem.* 36, 4214-4220, 1994,) en N-metilpirrolidona (NMP, 12 cc), CuI (0.2 g, 1.05 mmol), K₂CO₃ (1
25

g, 7.14 mmol) y iodobenceno (5 g, 24.5 mmol) se agregaron moviendo constantemente. Se calentó la suspensión en un aparato de microondas (250 Watts) durante 45 min. Se agregó acetato de etilo a la suspensión y se filtró el sólido. Se lavó la fase orgánica con agua y se re-extrajo la fase acuosa con
 5 CH₂Cl₂. Se recolectaron y se secaron las fases orgánicas sobre Na₂SO₄, se filtraron y se concentraron a sequedad. Se trituró el residuo con éter isopropílico. Se filtró el sólido, se trituró con agua y se filtró para rendir 0.18 g del compuesto titular, mp = 185-188°C.

10 ¹H-NMR (CDCl₃) δ: 7.46-7.37 (m, 4H); 7.28-7.21 (m, 1H); 5.84 (m, 1H); 4.48 (d, 1H); 3.74 (d, 1H); 2.78-2.60 (m, 2H); 2.51-2.38 (m, 1H); 2.08-1.96 (m, 1H).

MS: EI TSQ 700; fuente 180 C; 70 V; 200 uA: 216 (M⁺), 160,97.

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Ejemplo 2. *1-o-tolil-tetrahidro-1H-pirrolol[1,2-a]imidazole-2,5-diona.*

A una solución de tetrahidro-pirrolol[1,2-a]imidazole-2,5-diona (1.3 g, 9.28 mmol, preparado como se describe en *J. Med. Chem.* 36, 4214, 1994) en
 20 N-metilpirrolidona (NMP, 12 cc), CuI (0.5 g, 2.62 mmol), K₂CO₃ (1.3 g, 9.28 mmol) y 2-bromotolueno (6 g, 35 mmol) se agregó mientras se movía. Se calentó la suspensión en un aparato de microondas (250 Watts) durante 1 h. Se agregó acetato de etilo a la suspensión y se filtró el sólido. Se lavó la fase orgánica en agua y se re-extrajo la fase acuosa con CH₂Cl₂. Se recolectaron y se
 25 secaron las fases orgánicas sobre Na₂SO₄, se filtraron y se concentraron a

sequedad. Se trituró el residuo con Et₂O. Se filtró el sólido y se cristalizó la primera vez con iPrOH y después con AcOEt para rendir 0.33 g del compuesto titular, mp = 138-139°C.

¹H-NMR (CDCl₃) δ: 7.35-7.23 (m, 4H); 7.13-7.06 (m, 1H); 5.69 (m br, 1H); 4.45 (d, 1H); 3.78 (d, 1H); 2.68 (ddd, 1H); 2.48 (ddd, 1H); 2.40-2.29 (m, 1H); 2.24 (s, 3H); 1.93 (m br, 1H).

MS: EI TSQ 700; fuente 180 C; 70 V; 200 uA; 230 (M⁺), 143, 118, 97.

10 **Ejemplo 3-44 (Tabla 1).** *Procedimiento general para la arilación de tetrahydro-pirroló[1,2-a]imidazole-2,5-dionas con haluros de aril.*

A una solución de tetrahydro-pirroló[1,2-a]imidazole-2,5-diona (3.5 mmol; preparado como se describe en *J. Med. Chem.* 36, 4214-4220, 1994 o en
15 WO-9309120), en N-metilpirrolidona (NMP 1 ml), se agregaron moviendo constantemente CuI (0.19 g, 1 mmol), K₂CO₃ (0.5 g, 3.5 mmol) y el haluro de aril apropiado (7 mmol). Se calentó la suspensión en un aparato de microondas (25 Watt) durante 20 min. Se agregaron acetato de etilo (50 ml) y agua (5 ml) a la suspensión y se mezcló la mezcla durante 30' en la presencia de celite. Se
20 filtró la reacción y se lavó el acetato de etilo con una solución saturada de NaCl, se secó sobre Na₂SO₄, se filtró y se concentró a la sequedad. Se trituró el residuo con Et₂O para rendir el compuesto deseado. El rendimiento varía entre 30% y 60%.

Ejemplo 45. 1-Bencil-tetrahidro-pirrolol[1,2-a]imidazole-2,5-diona.

Se preparó una solución de tetrahidro-pirrolol[1,2-a]imidazole-2,5-diona (0.5 g, 3.5 mmol, como se describe en *J. Med. Chem.* 36, 4214, 1994), BEMP (2 ml, 7 mmol) y bencilbromuro (0.6 ml, 5 mmol) en CH₃CN (20 ml) se mantuvo en condiciones de reflujo durante 1 hora.

Se concentró la reacción a sequedad; luego se re-disolvió el residuo en acetato de etilo y se lavó con una solución saturada de NaCl, se secó sobre Na₂SO₄, se filtró y se evaporó al vacío. Se purificó el residuo a través de cromatografía por desorción súbita sobre gel de sílice. (CH₂Cl₂ / MeOH / NH₄OH 95 / 5 / 0.5) para rendir 0.7 g del compuesto titular como aceite amarillo.

Rendimiento: 87%

¹H-NMR (CDCl₃) δ: 7.39-7.10 (m, 5H); 5.03 (dd, 1H); 4.71 (d, 1H); 4.29 (d, 1H); 4.28 (d, 1H); 3.59 (d, 1H); 2.57 (ddd, 1H); 2.39-2.125 (m, 2H); 1.92-1.77 (m, 1H).

MS: EI TSQ 700; fuente 180 C; 70 V; 200 uA: 230.13 (M⁺), 174.09, 139.04, 91.03.

Ejemplo 46. 1-(4-metilbencil)-tetrahydro-pirrol[1,2-a]imidazole-2,5-diona.

Se preparó una solución de tetrahydro-pirrol[1,2-a]imidazole-2,5-diona (0.5 g, 3.5 mmol, como se describe en *J. Med. Chem.* 36, 4212, 1994), BEMP (2 ml, 7 mmol) y 4-metilbencilbromuro (0.95 ml, 5 mmol) en CH₃CN (20 ml) y se mantuvo bajo condiciones de reflujo durante 1 hora. Se concentró la reacción a la sequedad; entonces se re-disolvió la mezcla del residuo en acetato de etilo y se lavó con una solución saturada de NaCl, se secó sobre Na₂SO₄, se filtró y se evaporó al vacío. Se purificó el residuo a través de cromatografía súbita sobre gel de sílice. (CH₂Cl₂ / MeOH / NH₄OH 95 / S / 0.5) para rendir 0.8 g del compuesto titular como aceite amarillo.

Rendimiento: 93%

¹H-NMR (CDCl₃) δ: 7.29-7.11 (m, 4H); 5.01 (m, 1H); 4.69 (d, 1H); 4.29 (d, 1H); 4.23 (d, 1H); 3.58 (d, 1H); 2.65-2.50 (m, 1H); 2.40-2.24 (m, 2H); 2.33 (s, 3H); 1.93-1.78 (m, 1H).

MS: EI TSQ 700; fuente 180 C; 70 V; 200 uA: 244.13 (M⁺), 161.05, 105.02

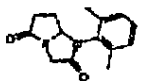
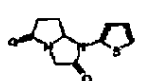
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TABLA 1

Estructura, nombre químico (generado por Beilstein's Autonom), datos de ¹H NMR, MS y punto de fusión para compuestos preparados según el procedimiento general arriba descrito.

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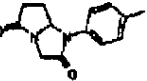
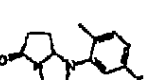
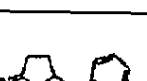
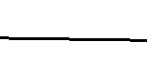
Ex.	Estructura	Nombre Químico	Datos Analíticos
3		1-(2,6-Dimetil-fenil)-tetrahidro-pirrola[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.24-7.10 (m, 3H); 6.83 (dd, 1H); 4.48 (d, 1H); 3.82 (d, 1H); 2.70 (ddd, 1H); 2.61 (ddd, 1H); 2.33-2.18 (m, 1H); 2.26 (s, 3H); 2.20 (s, 3H); 2.06-1.81 (m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA: 244 (M ⁺); 97.
4		1-clofen-2-il-tetrahidro-pirrola[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.05 (dd, 1H); 6.83 (dd, 1H); 6.89 (dd, 1H); 5.87 (m, 1H); 4.48 (d, 1H); 3.77 (d, 1H); 2.86-2.68 (m, 2H); 2.58-2.45 (m, 1H); 2.33-2.21 (m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA: 222 (M ⁺); 164; 166; 97. mp: 170-171 °C.
5		1-m-Tolil-tetrahidro-pirrola[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.50 (dd, 1H); 7.24 (dd, 1H); 7.19 (dd, 1H); 7.07 (dd, 1H); 5.82 (m, 1H); 4.48 (d, 1H); 3.74 (d, 1H); 2.78-2.67 (m, 2H); 2.45 (m, 1H); 2.38 (s, 3H); 1.08-1.94 (m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA: 230 (M ⁺); 174; 97. mp: 82-83 °C.

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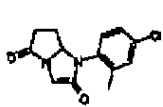
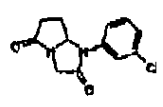
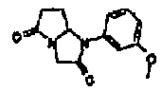
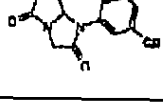
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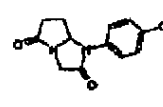
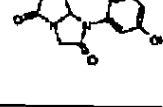
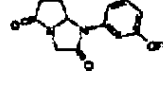
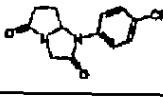
6		1-p-Tolil-tetrahidro-pirrola[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.27 (d, 2H); 7.24 (d, 2H); 5.78 (m, 1H); 4.48 (d, 1H); 3.73 (d, 1H); 2.72 (ddd, 1H); 2.70 (m, 1H); 2.47 (dd, 1H); 2.38 (s, 3H); 2.08-1.88 (m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA: 230 (M ⁺); 174; 118. mp: 117-118 °C
7		1-(5-Fluoro-2-metil-fenil)-tetrahidro-pirrola[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.28 (m, 1H); 7.02 (ddd, 1H); 6.86 (dd, 1H); 6.84 (m br, 1H); 4.43 (d, 1H); 3.77 (d, 1H); 2.70 (d, 1H); 2.53-2.31 (m, 2H); 2.18 (s, 3H); 1.80 (broad m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA: 248 (M ⁺); 97. mp: 147-148 °C
8		1-(3-Fluoro-2-metil-fenil)-tetrahidro-pirrola[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.23 (ddd, 1H); 7.07 (dd br, 1H); 6.82 (d, 1H); 6.83-6.41 (broad m, 1H); 4.48 (d, 1H); 3.78 (d, 1H); 2.69 (ddd, 1H); 2.48 (ddd, 1H); 2.45-2.20 (m, 1H); 2.14 (d, 3H); 1.89 (broad m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA: 248 (M ⁺); 138; 168. mp: 135-137 °C.
9		1-(2-trifluorometil-fenil)-tetrahidro-pirrola[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.81 (d, 1H); 7.68 (dd, 1H); 7.34 (broad dd, 1H); 7.27 (d, 1H); 5.84 (m, 1H); 4.42 (broad d, 1H); 3.72 (d, 1H); 2.83 (m, 1H); 2.48 (m, 1H); 2.38 (m, 1H); 2.03 (m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA: 284 (M ⁺); 228; 188;

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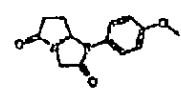
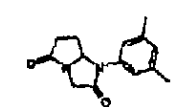
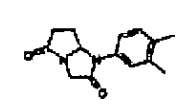
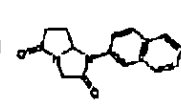
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10		1-(4-Cloro-2-metil-fenil)-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.32 (d, 1H); 7.24 (dd, 1H); 7.04 (d, 1H); 6.63 (broad m, 1H); 4.44 (d, 1H); 3.77 (d, 1H); 2.69 (ddd, 1H); 2.48 (ddd, 1H); 2.35 (m, 1H); 2.22 (s, 3H); 1.82 (m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA; 264 (M ⁺); 97. mp: 122-124 °C.
11		1-(3-Cloro-fenil)-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.48 (m, 1H); 7.39-7.28 (m, 2H); 7.22 (ddd, 1H); 6.81 (m, 1H); 7.48 (d, 1H); 3.73 (d, 1H); 2.65-2.64 (m, 2H); 2.46 (m, 1H); 2.03 (m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA; 260 (M ⁺); 184, 138, 111. mp: 123-125 °C.
12		1-(3-Metoxi-fenil)-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.31 (dd, 1H); 7.08 (dd, 1H); 6.91 (dd, 1H); 6.78 (dd, 1H); 6.80 (m, 1H); 4.46 (d, 1H); 3.82 (s, 3H); 3.73 (d, 1H); 2.79-2.61 (m, 2H); 2.45 (m, 1H); 2.12-1.98 (m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA; 246 (M ⁺); 190. mp: 84-88 °C.
13		1-(3(ciano-fenil)-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.73 (m, 2H); 7.62 (m, 2H); 6.81 (m, 1H); 4.51 (d, 1H); 3.73 (d, 1H); 2.84-2.65 (m, 2H); 2.47 (dd, 1H); 2.11-1.85 (m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA; 241 (M ⁺); 188, 129. mp: 128-130 °C.

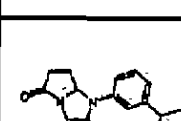
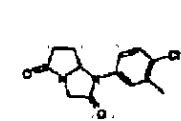
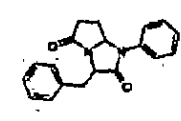
14		1-(4-Cloro-fenil)-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.42-7.32 (m, 4H); 5.60 (m, 1H); 4.48 (d, 1H); 3.73 (d, 1H); 2.78-2.80 (m, 2H); 2.45 (m, 1H); 2.09-1.83 (m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA; 250 (M ⁺); 194. mp: 150-160 °C.
15		1-(3-Hidroxi-fenil)-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.16 (dd, 1H); 6.86 (dd, 1H); 6.78 (dd, 1H); 6.69 (dd, 1H); 6.74 (m, 1H); 4.38 (d, 1H); 3.67 (d, 1H); 2.74-2.65 (m, 2H); 2.38 (m, 1H); 2.07-1.90 (m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA; 232 (M ⁺); 178. mp: 210-211 °C.
16		1-(3-Trifluorometil-fenil)-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.68 (d, 1H); 7.66 (broad s, 1H); 7.68 (dd, 1H); 7.50 (d, 1H); 5.88 (m, 1H); 4.50 (d, 1H); 3.78 (d, 1H); 2.73 (m, 2H); 2.48 (m, 1H); 2.04 (m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA; 284 (M ⁺); 228; 172; 145. mp: 124-125 °C.
17		1-(4-Trifluorometil-fenil)-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.68 (d, 2H); 7.57 (d, 2H); 5.88 (m, 1H); 4.50 (d, 1H); 3.76 (d, 1H); 2.82-2.07 (m, 2H); 2.48 (m, 1H); 2.12-1.88 (m, 1H). MS: EI TSO 700; fuente 180 °C; 70 V; 200 uA; 284 (M ⁺); 228; 172; 145.

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18		1-(4-Metoxi-fenil)- tetrahidro-pirrol[1,2-a] imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.20 (d, 2H); 6.86 (d, 2H); 5.74 (m, 1H); 4.44 (s, 1H); 3.81 (s, 3H); 3.73 (d, 1H); 2.79-2.39 (m, 3H); 2.00-1.94 (m, 1H). MS: EI TSD 700; fuente 180 °C; 70 V; 200 uA; 248 (M ⁺); 190; 134. mp: 210-211 °C.
19		1-(3,5-Dimetil-fenil)- tetrahidro-pirrol[1,2-a] imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 6.98 (s, 2H); 6.89 (s, 1H); 6.79 (m, 1H); 4.45 (d, 1H); 3.72 (d, 1H); 2.77-2.53 (m, 2H); 2.44 (m, 1H); 2.33 (s, 6H); 2.00 (m, 1H). MS: EI TSD 700; fuente 180 °C; 70 V; 200 uA; 244 (M ⁺); 188; 97. mp: 103-104 °C.
20		1-(3,4-Dimetil-fenil)- tetrahidro-pirrol[1,2-a] imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.18 (d, 1H); 7.16 (d, 1H); 7.04 (dd, 1H); 5.77 (dd, 1H); 4.44 (d, 1H); 3.72 (d, 1H); 2.78-2.62 (m, 2H); 2.44 (m, 1H); 2.28 (s, 3H); 2.26 (s, 3H); 2.08-1.83 (m, 1H). MS: ZQ, ESI POS, spray 3.25 KV; fuente 30 V; prueba 250 °C; 246 (M ⁺). mp: 142-143 °C.
21		1-Naftalen-2-il- tetrahidro-pirrol[1,2-a] imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.90 (d, 1H); 7.83 (m, 2H); 7.78 (d, 1H); 7.81 (dd, 1H); 7.55-7.45 (m, 2H); 5.97 (m, 1H); 4.53 (d, 1H); 2.80 (d, 1H); 2.88-2.69 (m, 2H); 2.47 (m, 1H); 2.15-1.99 (m, 1H). MS: ZQ, ESI POS, spray 3.25 KV; source 30 V; prueba 250 °C; 287 (M ⁺).

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22		1-(3-Isopropil-fenil)- tetrahidro-pirrol[1,2-a] imidazol-2,5-diona	mp: 175-176 °C. ¹ H-NMR (CDCl ₃) δ: 7.33 (dd, 1H); 7.27 (m, 1H); 7.47 (d br, 1H); 7.12 (broad d, 1H); 6.83 (m, 1H); 4.48 (d, 1H); 3.74 (d, 1H); 2.92 (m, 1H); 2.50-2.67 (m, 2H); 2.48 (m, 1H); 2.04 (m, 1H); 1.28 (d, 6H). MS: ZQ, ESI POS, spray 3.25 KV; fuente 30 V; prueba 50 °C; 269 (M ⁺). mp: 81-82 °C.
23		1-(4-cloro-3-metil-fenil)- tetrahidro-pirrol[1,2-a]imidazol- 2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.57 (d, 1H); 7.33 (d, 1H); 7.12 (dd, 1H); 5.78 (m, 1H); 4.48 (d, 1H); 3.72 (d, 1H); 2.78-2.68 (m, 2H); 2.52-2.37 (m, 1H); 2.40 (s, 3H); 2.08-1.83 (m, 1H). MS: ZQ, ESI POS, spray 3.25 KV; fuente 30 V; prueba 50 °C; 266 (M ⁺). mp: 139-139 °C.
24		1-benzil-1-fenil- tetrahidro-pirrol[1,2-a] imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.84 (dd, 2H); 7.28-7.17 (m, 6H); 7.03 (d, 2H); 4.77 (m, 1H); 4.68 (dd, 1H); 3.32 (dd, 1H); 3.16 (dd, 1H); 2.84 (ddd, 1H); 2.48-2.27 (m, 2H); 1.81 (m, 1H). MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 250 °C; 307 (M ⁺). mp: 134-138 °C.

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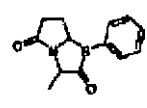
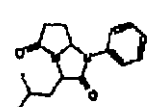
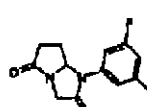
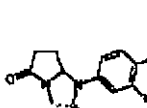
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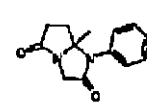
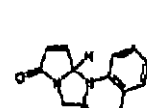
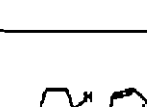
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25		3-Metil-1-fenil-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.42 (m, 4H); 7.25 (m, 1H); 5.83 (m, 1H); 4.54 (q, 1H); 2.78-2.69 (m, 2H); 2.48 (m, 1H); 2.10-1.93 (m, 1H); 1.47 (d, 3H). MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 250°C: 231 (M ⁺). mp: 137-138 °C.
28		3-isobutil-1-fenil-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.41 (m, 4H); 7.22 (m, 1H); 5.81 (m, 1H); 4.50 (dd, 1H); 2.78-2.58 (m, 2H); 2.48 (m, 1H); 2.07-1.63 (m, 3H); 1.54 (m, 1H); 1.08 (d, 3H); 0.88 (d, 3H). MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 260°C: 273 (M ⁺). mp: 101-102 °C.
27		1-(3-fluoro-5-metil-fenil)-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 6.99 (m, 2H); 6.77 (d br, 1H); 5.78 (m, 1H); 4.48 (d, 1H); 3.73 (d, 1H); 2.84-2.63 (m, 2H); 2.48 (m, 1H); 2.37 (s, 3H); 2.11-1.94 (m, 1H). MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 250°C: 249 (M ⁺). mp: 111-113 °C.
28		1-(3-fluoro-4-metil-fenil)-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.32-7.18 (m, 2H); 7.05 (dd br, 1H); 5.78 (m, 1H); 4.48 (d, 1H); 3.73 (d, 1H); 2.78-2.63 (m, 2H); 2.60-2.41 (m, 1H); 2.58 (s, 3H); 2.11-1.94 (m, 1H). MS: ZQ, ESI POS, spray 3.25 KV; fuente 30 V; prueba 250°C: 248 (M ⁺), 192, 97. mp: 136-137 °C.

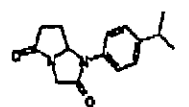
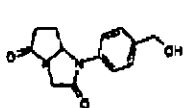
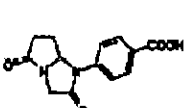
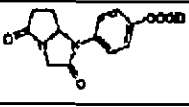
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29		7a-Metil-1-fenil-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.52-7.20 (m, 6H); 4.44 (d, 1H); 3.78 (d, 1H); 2.83-2.68 (m, 1H); 2.58-2.42 (m, 2H); 2.18-2.30 (m, 1H); 1.83 (s, 3H). MS: ZQ, ESI POS, spray 3.25 KV; fuente 30 V; prueba 250°C: 230 (M ⁺). mp: 154-155 °C.
30		(S)-1-o-Tolil-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.35-7.23 (m, 4H); 7.13-7.08 (m, 1H); 5.89 (m br, 1H); 4.45 (d, 1H); 3.78 (d, 1H); 2.68 (ddd, 1H); 2.48 (ddd, 1H); 2.40-2.28 (m, 1H); 2.24 (s, 3H); 1.83 (m br, 1H). MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 250°C: 230 (M ⁺), 143, 118, 97. [α] _D ²⁰ = -51.35 (c= 0.4, MeOH).
31		(R)-1-o-Tolil-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.35-7.23 (m, 4H); 7.13-7.08 (m, 1H); 5.89 (m br, 1H); 4.45 (d, 1H); 3.78 (d, 1H); 2.68 (ddd, 1H); 2.48 (ddd, 1H); 2.40-2.28 (m, 1H); 2.24 (s, 3H); 1.83 (m br, 1H). MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 250°C: 230 (M ⁺), 143, 118, 97. [α] _D ²⁰ = +52.24 (c= 0.4, MeOH).
32		1-(4-Etil-fenil)-tetrahidro-pirrol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.29 (d, 2H); 7.25 (d, 2H); 5.80 (m, 1H); 4.45 (d, 1H); 3.74 (d, 1H); 2.78-2.68 (m, 2H); 2.65 (q, 2H); 2.91-2.38 (m, 1H);

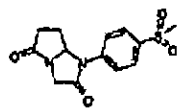
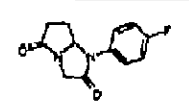
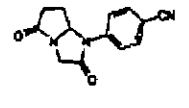
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			MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 250°C: 248.1 (MH+). mp: 90-99°C.
33		1-(4-isopropil-fenil)- tetrahidro-pirrol[1,2- a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.32-7.25 (m, 4H); 5.68 (m, 1H); 4.46 (d, 1H); 3.74 (d, 1H); 2.91 (m, 1H); 2.78-2.67 (m, 2H); 2.51-2.40 (m, 1H); 2.15-1.98 (m, 1H); 1.24 (d, 6H). MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 250°C: 259.1 (MH+). mp: 124-125°C.
34		1-(4-Hidroximetil-fenil)-tetrahidro- pirrol[1,2-a]imidazol- 2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.41 (m, 4H); 5.83 (m, 1H); 4.70 (s, 2H); 4.47 (d, 1H); 3.74 (d, 1H); 2.78-2.68 (m, 2H); 2.62-2.37 (m, 1H); 2.10-1.93 (m, 1H); 1.73 (s br, 1H). MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 250°C: 247.1 (MH+). mp: 158-161°C.
35		4-(2,5-Dioxo- hexahidro-pirrol[1,2- a]imidazol-1-il)acido benzico	¹ H-NMR (CDCl ₃) δ: 8.06 (d, 2H); 7.47 (d, 2H); 5.85 (m, 1H); 4.43 (d, 1H); 3.71 (d, 1H); 2.77-2.61 (m, 2H); 2.5-2.36 (m, 1H); 2.05-1.81 (m, 1H). MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 250°C: 261.0 (MH+). mp: 262-253°C.
36		4-(2,5-Dioxo-hexahidro- pirrol[1,2-a]imidazol-1- il)acido benzoico etil ester	¹ H-NMR (CDCl ₃) δ: 8.10 (d, 2H); 7.52 (d, 2H); 5.88 (m, 1H); 4.50 (d, 1H); 4.38 (q, 2H); 3.76 (d, 1H); 2.82-2.68 (m, 2H); 2.58-2.36 (m, 1H); 2.12-1.94 (m, 1H); 1.39 (t, 3H).

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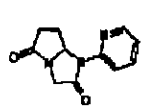
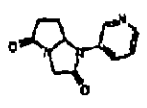
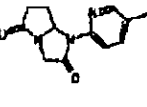
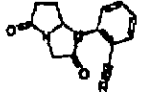
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			MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 250°C: 288.4 (MH+). 218.4. mp: 158-159°C.
37		1-(4-Metanesulfonyl-fenil)-tetrahidro- pirrol[1,2-a]imidazol- 2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.88 (d, 2H); 7.65 (d, 2H); 6.90 (m, 1H); 4.52 (d, 1H); 3.77 (d, 1H); 3.06 (s, 3H); 2.84-2.68 (m, 2H); 2.57-2.42 (m, 1H); 2.11-1.83 (m, 1H). MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 250°C: 295.1 (MH+) 312.; (MH+NH ₃ +). mp: 143-145°C.
38		1-(4-Fluoro-fenil)- tetrahidro-pirrol[1,2- a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.37 (m, 2H); 7.12 (dd, 2H); 5.78 (m, 1H); 4.47 (d, 1H); 3.74 (d, 1H); 2.80-2.60 (m, 2H); 2.48 (m, 1H); 2.09-1.93 (m, 1H). MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 250°C: 235.1 (MH+). mp: 158-159°C.
39		1-(4-Ciano-fenil)- tetrahidro-pirrol[1,2- a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.72 (d, 2H); 7.60 (d, 2H); 5.87 (m, 1H); 4.52 (d, 1H); 3.76 (d, 1H); 2.84-2.68 (m, 2H); 2.57-2.43 (m, 1H); 2.14-1.94 (m, 1H). MS: AQA, ESI Pos, 3.5KV; fuente 30V; prueba 250°C: 242.1 (MH+). mp: 175-176°C.

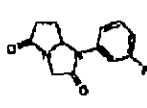
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40		1-Piridin-2-il-tetrahidro-pirrolol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 8.34 (odd, 1H); 8.20 (odd, 1H); 7.75 (ddd, 1H); 7.11 (ddd, 1H); 6.04 (dd, 1H); 4.62 (d, 1H); 3.79 (d, 1H); 3.09-2.87 (m, 1H); 2.78-2.64 (m, 1H); 2.41 (odd, 1H); 2.15-2.00 (m, 1H). MS: AQA, ESI Pos, 3.5KV;fuente : 30V;prueba250°C: 218.4 (MH+). mp: 139-140°C.
41		1-Piridin-3-il-tetrahidro-pirrolol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 8.55 (m, 2H); 8.04 (d, 1H); 7.39 (m, 1H); 6.88 (m, 1H); 4.60 (d, 1H); 3.76 (d, 1H); 2.84-2.67 (m, 2H); 2.68-2.40 (m, 1H); 2.14-1.85 (m, 1H). MS: AQA, ESI Pos, 3.5KV;fuente : 30V;prueba250°C: 218.4 (MH+). mp: 160-162°C.
42		1-(5-Metilpiridin-2-il)-tetrahidropirrolol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 8.16 (d, 1H); 8.07 (d, 1H); 7.65 (dd, 1H); 6.02 (dd, 1H); 4.46 (d, 1H); 3.77 (d, 1H); 3.05-2.94 (m, 1H); 2.77-2.62 (m, 1H); 2.40 (odd, 1H); 2.31 (s, 3H); 2.12-1.97 (m, 1H). MS: AQA, ESI Pos, 3.5KV;fuente : 30V;prueba250°C: 232.1 (MH+). mp: 159-159°C.
43		1-(2-Clano-fenil)-tetrahidro-pirrolol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.76 (d, 1H); 7.70 (dd, 1H); 7.48 (dd, 1H); 7.38 (d, 1H); 6.85 (m, 1H); 4.50 (d, 1H); 3.81 (d, 1H); 2.85-2.64 (m, 1H); 2.66-2.41 (m, 2H); 2.08-1.93 (m, 1H). MS: AQA, ESI Pos, 3.5KV;fuente : 30V;prueba250°C: 242.1 (MH+). mp: 94-95°C.

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44		1-(3-Fluoro-fenil)-tetrahidro-pirrolol[1,2-a]imidazol-2,5-diona	¹ H-NMR (CDCl ₃) δ: 7.38 (ddd, 1H); 7.29 (ddd, 1H); 7.16 (ddd, 1H); 6.85 (dddd, 1H); 5.81 (m, 1H); 4.49 (d, 1H); 3.75 (d, 1H); 2.85-2.65 (m, 2H); 2.53-2.40 (m, 1H); 2.13-1.97 (m, 1H). MS: AQA, ESI Pos, 3.5KV;fuente : 30V;prueba260°C: 236.1 (MH+). mp: 148-149°C.
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Métodos farmacológicos

Modelo de herida crónica de constricción

5 Se produjo una mono-neuropatía periférica en ratas adultas a través de rodear el nervio ciática común con ligaduras constrictivas sin apretar según el método descrito por Bennett & Xie (*Pain* 1988, 33, 87-107).

10 Se anestesiaron las ratas con hidrato de cloral. Se expuso el nervio ciática común a nivel del muslo medio a través de disección contundente por el bíceps femoris. Se liberó de tejido aproximadamente 1 cm del nervio próximo a la trifurcación del ciática y se amarraron cuatro ligaduras (3/0 hilo de seda) sin apretar alrededor con aproximadamente 1mm de espaciado. La longitud del nervio que así se afectó fue de 1 cm. Se tomaron medidas de cuidado en
15 amarrar las ligaduras para asegurar que el diámetro del nervio estuviera apenas restringido cuando se vio con una amplificación de 40 x. Se dejó sin afectar la pata izquierda.

Prueba de presión en la pata

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 Se determinó el umbral nociceptivo de la rata con un analgesímetro (Ugo Basile, Varese, Italia), según el método que describe Leighton et al. (*Br. J. Pharmacol.* 1988, 93, 553-560). Se rechazaron a las ratas con calificaciones debajo de 40 g o arriba de 75 g (25%) durante la prueba, antes de la
25 administración de la droga. Se adoptó un valor arbitrario de límite de 250 g.

Se llevaron a cabo todos los experimentos en ratas sometidas a la prueba de presión en la pata 14 días después de la operación porque en ese momento se observó una reducción significativa en el umbral de dolor de la pata lastimada (dx).

5

Gabapentin (30µg i.c.v.), levetiracetam (300µg i.c.v.), dimiracetam (100µg i.c.v.), Ejemplo 1 (10µg i.c.v.), Ejemplo 2 (10µg i.c.v.), Ejemplo 5 (3µg i.c.v.), Ejemplo 6 (3µg i.c.v.), Ejemplo 13 (30µg i.c.v.) y Ejemplo 22 (30µg i.c.v.) de la invención actual mostraron un efecto anti-hiperálgico cuando se compararon con el grupo tratado con salina o un vehículo. Ninguno de los compuestos modificó el umbral de dolor en la pata contro-lateral no operada. Se debe de notar que todos los compuestos provocaron su efecto anti-hiperálgico sin cambiar la conducta general de los animales ni su motilidad individual en comparación con ratas tratadas con vehículo/salino. Además no se reveló ninguna modificación en la coordinación motriz como medida por la prueba rota-rod para ratas (Vaught J. et al. *Neuropharmacology* 1285, 24, 211-216).

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EFFECTO DE LOS COMPUESTOS DE LA INVENCION Y COMPUESTOS DE REFERENCIA (i.c.v.) EN UN MODELO DE RATAS DE MONO-NEUROPATIA dx EVALUADO EN LA PRUEBA DE PRESION DE PATA

5

				Presión de pata en ratas (g)	
				ANTES DEL TRATAMIENTO	DESPUES DEL TRATAMIENTO
10	TRATAMIENTO	(i.c.v.)	PATA		
	SALINA		dx	24.3 ± 2.9	23.7 ± 2.5
	VEHICULO		dx	26.5 ± 3.5	22.9 ± 3.6
	GABAPENTIN	30 µg	dx	24.5 ± 4.7	46.3 ± 4.2*
	LEVETIRACETAM	300 µg	dx	24.0 ± 3.9	37.3 ± 4.6^
	DIMIRACETAM	100 µg	dx	25.1 ± 2.4	42.8 ± 2.5*
	EJEMPLO 1	10 µg	dx	26.0 ± 2.2	36.3 ± 5.1^
	EJEMPLO 2	10 µg	dx	23.5 ± 4.0	42.2 ± 3.9*
	EJEMPLO 5	3 µg	dx	27.7 ± 2.8	39.3 ± 4.5^
	EJEMPLO 6	3 µg	dx	26.7 ± 3.6	46.1 ± 5.0^
15	EJEMPLO 13	30 µg	dx	28.5 ± 2.9	55.4 ± 4.7*
	EJEMPLO 22	30 µg	dx	25.4 ± 2.7	48.5 ± 4.6*
Cada valor representa el medio de por lo menos 8 ratas (en dos experimentos por separado). Se administraron todos los compuestos 30-45 min. antes de la prueba. ^ P<0.05; * P<0.01					

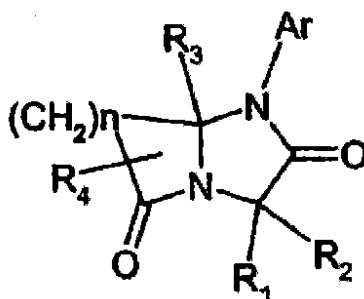
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REIVINDICACIONES

1. Compuestos de la fórmula (I) general

5



(I)

en la que:

10

A se escoge entre los grupos aromáticos carbocíclicos, grupos aromáticos heterocíclicos, y arilC₁₋₄alquilo;

R₁ se escoge de entre:

15

- hidrógeno,
- aril C₁₋₇alquilo, opcionalmente sustituido en una fracción aril con uno o más de los grupos que se escoge entre hidroxil, C₁₋₄alkoxil, halógeno, haloC₁₋₄alquilo;
- heterociclilC₁₋₇alquilo, opcionalmente sustituido en la fracción de heterocíclico con uno o mas grupos escogidos de entre C₁₋₄alquilo e hidroxil;
- C₁₋₇alquilo, opcionalmente interrumpido por un átomo de oxigeno o azufre o opcionalmente sustituido en cualquier posición por uno o mas grupos que se escoge entre hidroxil, tio, amino, carboxilo, aminocarbonil, guanidinil.

25

R_2 se escoge de entre hidrógeno, C_{1-4} alquilo, aril C_{1-4} alquilo y fenilo; o bien R_1 y R_2 que en conjunto forman un anillo carbocíclico que contiene entre 3 y 8 átomos de carbón;

- 5 R_3 se escoge de entre hidrógeno, C_{1-4} alquilo, aril C_{1-4} alquilo, $CONH_2$ y $COOR_5$ en donde R_5 se escoge de entre hidrógeno y C_{1-4} alquilo;

R_4 se escoge de entre hidrógeno, C_{1-4} alquilo, aril, aril C_{1-4} alquilo y heterociclil;

- 10 n es 2, 3 o 4;

en la forma de una mezcla racémica o en la forma de enantiómeros, y sales o solvatos de éstas farmacéuticamente aceptables.

- 15 2. Los compuestos según la Reivindicación 1, en que: A es fenilo, tienil, piridil, grupo pirimidinil, opcionalmente sustituido, bencil o 4-metilbencil; R_1 es hidrógeno, C_{1-4} alquilo, bencil, $-CH_2OH$, $-CH_2CH_2CONH_2$, $-CH_2COOH$, indol(3-il)metil; R_2 es hidrógeno, C_{1-4} alquilo o bencil; R_3 y R_4 son hidrógeno o metil, y n es 2.

20

3. Los compuestos según la Reivindicación 2, en que: A es fenilo opcionalmente sustituido; R_1 , R_2 , R_3 y R_4 son hidrógeno; y n es 2.

25

4. Los compuestos según las Reivindicaciones 1-3, en que: A es sustituido con 1 a 3 sustituyentes escogidos de entre ME, Et, i-Pr, OH, COOEt, COOH, CH₂OH, SO₂NH₂, SO₂Me, OMe, Cl, F, CN y CF₃.
5. Los compuestos según la Reivindicación 4, en que: A es sustituido con 1 a 3 sustituyentes escogidos de entre Me, Et, i-Pr, OH, CN, Cl y CF₃.
6. Los compuestos según la Reivindicación 1 ó 2, en que: dicho grupo C₁₋₄alquilo se escoge de entre Me, Et, i-Pr, i-Bu y ciclopropilmetil.
- 10 7. Los compuestos según la Reivindicación 1, escogido en el grupo que consiste en:
 - 1-Fenilo-tetrahidro-1H-pirrol[1,2-a]imidazole-2,5-diona;
 - 15 1-*o*-tolil-tetrahidro-1H-pirrol[1,2-a]imidazole-2,5-diona;
 - 1-(2,6-Dimetil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
 - 1-Tiofeno-2-il-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
 - 1-*m*-Tolil-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
 - 1-*p*-Tolil-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
 - 20 1-(5-Fluoro-2-metil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
 - 1-(3-Fluoro-2-metil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
 - 1-(2-Trifluorometil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
 - 1-(4-Cloro-2-metil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
 - 1-(3-Cloro-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
 - 25 1-(3-Metoxi-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;

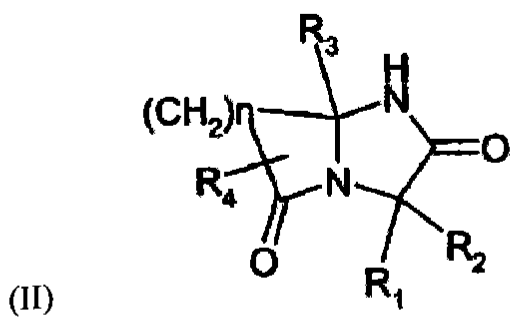
- 1-(3-Ciano-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(4-Cloro-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3-Hidroxi-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3-Trifluorometil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 5 1-(4-Trifluorometil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(4-Metoxi-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3,5-Dimetil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3,4-Dimetil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-Naftalen-2-il-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 10 1-(3-Isopropil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(4-Cloro-3-metil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 3-Bencil-1-fenilo-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 3-Metil-1-fenilo-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 3-Isobutil-1-fenilo-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 15 1-(3-Fluoro-5-metil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3-Fluoro-4-metil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 7a-Metil-1-fenilo-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- (S)-1-*o*-Tolil-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- (R)-1-*o*-Tolil-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 20 1-(4-Etil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(4-Isopropil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(4-Hidroximetil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;
- 4-(2,5-Dioxo-hexahidro-pirrol[1,2-a]imidazole-1-il)-ácido benzoico;
- 4-(2,5-Dioxo-hexahidro-pirrol[1,2-a]imidazole-1-il)-ácido benzoico etil éster;
- 25 1-(4-Metanosulfonil-fenilo)-tetrahidro-pirrol[1,2-a]imidazole-2,5-diona;

- 1-(4-Fluoro-fenilo)-tetrahydro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(4-Ciano-fenilo)-tetrahydro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-Piridina-2-il-tetrahydro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-Piridina-3-il-tetrahydro-pirrol[1,2-a]imidazole-2,5-diona;
- 5 1-(5-Metilpiridin-2-il)-tetrahidropirrol[1,2-a]imidazole-2,5-diona;
- 1-(2-Ciano-fenilo)-tetrahydro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(3-Fluoro-fenilo)-tetrahydro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-Bencil-tetrahydro-pirrol[1,2-a]imidazole-2,5-diona;
- 1-(4-metilbencil)-tetrahydro-pirrol[1,2-a]imidazole-2,5-diona.

10

8. Un proceso para la preparación de los compuestos de la fórmula (I) como se describe en la Reivindicación 1, que consiste en la reacción de un compuesto de la fórmula (II)

15



20 Con un compuesto de la fórmula (III)

A-X
(III)

25

En que A_1 , R_1 , R_2 , R_3 , R_4 y n se definen como en la Reivindicación 1, y X es un átomo de halógeno, para obtener los compuestos deseados de la fórmula (I).

9. El proceso según la Reivindicación 8, en que en el compuesto de la
5 fórmula (III) se escoge X de entre bromo y yodo.

10. El proceso según las Reivindicaciones 8-9, para la preparación de los compuestos de la fórmula (I) en que: A es un grupo aromático carbocíclico o un grupo aromático heterocíclico, opcionalmente sustituido, en que el compuesto
10 de la fórmula (II) se disuelve en un solvente apropiado junto con los compuestos de la fórmula (III) en la presencia de una base y de una cantidad catalítica de una sal de cobre, a una temperatura de entre 60°C y 140°C .

11. El proceso según la Reivindicación 10, en que dicho solvente es
15 *N*-metilpirrolidona, dicha base es carbonato potásico, dicha sal de cobre es yoduro de cobre, y la reacción se lleva a cabo a una temperatura de 120°C .

12. El proceso según las Reivindicaciones 8-9, para la preparación de los compuestos de la fórmula (I) en que: A es aril C_{1-4} alquilo, en que: el compuesto
20 de la fórmula (II) se disuelve en un solvente apropiado junto con el compuesto de la fórmula (III), en la presencia de una base adecuada a una temperatura de entre 60°C y 140°C .

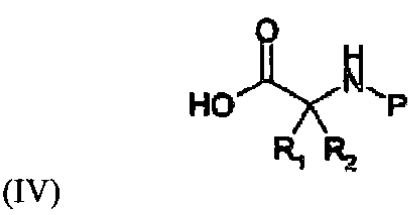
13. El proceso según la Reivindicación 12, en que: dicho solvente se escoge
25 de entre acetonitrilo, diclorometano, acetona, y se escoge dicha base de entre

trietilamina, carbonato potásico, 2-*tert*-Butilimino-2-dietilamino-1,3-dimetilperhidro-1,3,2-diazafosforina, N,N-Diiso-propiletilamina, a una temperatura de 100°C.

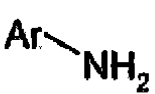
14. El proceso para la preparación de compuestos de la fórmula (I) como se describe en la Reivindicación 1, que consiste en los siguientes pasos:

i) la reacción de un aminoácido de la fórmula (IV) o de uno de sus derivados activados

10

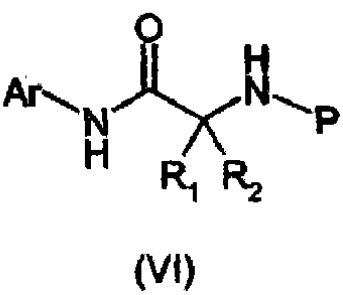


15 con un compuesto de la fórmula (V)



(V)

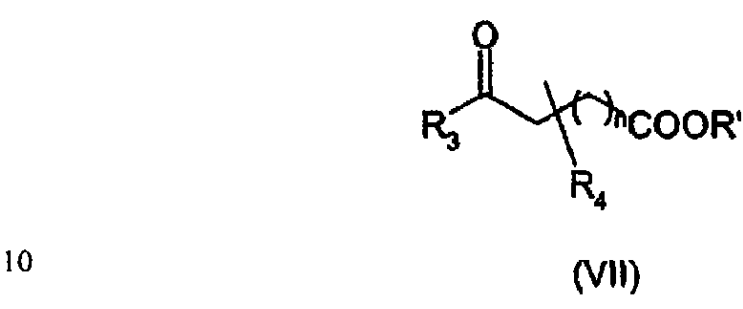
20 Para obtener un compuesto de la fórmula (VI):



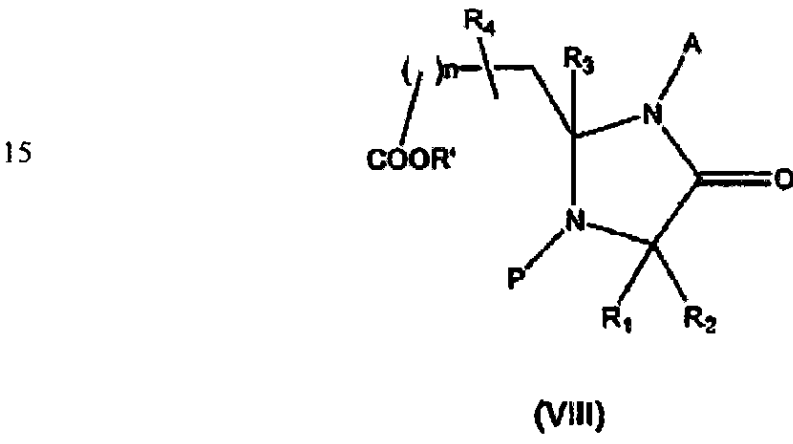
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En que R₁, R₂ y A son como se define arriba en la Reivindicación 1, y P es H o un grupo protector adecuado;

ii) la reacción del compuesto de la fórmula (VI) obtenido en el paso i) con
5 un compuesto de la fórmula (VII)



para obtener un compuesto la fórmula (VIII)



20 en que: A, R₁, R₂, R₃, R₄ y n son como se define en la Reivindicación 1, P se define como arriba, y R' es un grupo alquilo;

iii) la posible remoción del grupo protector P a través de hidrogenólisis del
compuesto de la fórmula (VIII) que se obtiene del paso ii), para obtener el
25 compuesto correspondiente (VIII), en que: P es H; y

iv) la ciclización del compuesto de la fórmula (VIII), en que: P es H que viene del paso iii), para obtener el compuesto deseado de la fórmula (I).

5 15. El proceso según la Reivindicación 14, en que: R' se escoge de entre metil y *tert*-butil, y P se escoge entre H, bencil y benciloxicarbonil.

16. El proceso según la Reivindicación 14, en que en dicho paso iv), se lleva a cabo la reacción de ciclización calentando el compuesto (VIII) en la ausencia
10 de un solvente a 120°C y en condiciones de vacío, o bien a través de calentamiento de reflujo del compuesto (VIII) en xileno durante un tiempo que consiste en entre 4 horas y 3 días.

17. El proceso según la Reivindicación 14, en que dicho paso ii) se lleva a
15 cabo a través de calentamiento de reflujo de los compuestos de la fórmula (VI) y (VII) en un solvente prótico durante un tiempo que consiste en entre 2 y 24 horas, posiblemente en la presencia de una base.

18. El proceso según la Reivindicación 14, en que la reacción que se
20 describe en el paso i) se lleva a cabo entre el cloruro ácido del compuesto (IV) y el compuesto (V) en la presencia de una base inorgánica u orgánica en un solvente prótico adecuado a una temperatura de entre -70°C y 50°C.

19. El proceso según la Reivindicación 14, en que se lleva a cabo la
25 reacción del paso i) a través de la reacción del compuesto (IV) junto con el

compuesto (V) en la presencia de un agente condensante adecuado, en un solvente aprótico a una temperatura de entre -70°C y 50°C.

20. El proceso según las Reivindicaciones 18 o 19, en que dicha
5 temperatura consiste en entre -10°C y 20°C.

21. La composición farmacéutica que consiste en un principio activo, uno o
más compuestos de la fórmula (I) como se describe en la Reivindicación 1, o
sales o solvatos de éstas farmacéuticamente aceptables.

10

22. La composición farmacéutica según la Reivindicación 21, que además
consiste en vectores, diluyentes y/o excipientes adecuados farmacéuticamente
aceptables para formas de administración escogidas de entre oral, parenteral,
rectal, transdérmica, y a través de la mucosa.

15

23. La composición farmacéutica según las Reivindicaciones 21 y 22, en la
forma de soluciones, suspensiones, polvos solubles, gránulos, microcápsulas,
cápsulas, pastillas, tabletas, tabletas cubiertas, supositorios, cremas, ungüentos,
lociones, pastas, plastas medicadas, membranas o geles.

20

24. La utilización de un compuesto de la fórmula (I) como se describe en la
Reivindicación 1 o de una de las sales o solvatos farmacéuticamente aceptables
para la preparación de un medicamento que tenga acción nootrópica y/o
neuroprotectora, analgésica y/o anti-hiperalgésica, y anti-emética.

25

25. La utilización según la Reivindicación 24, para el tratamiento de déficit de aprendizaje y memoria, la enfermedad de Alzheimer, demencia, demencia senil, demencia vascular del tipo post-apoplejía, epilepsia, isquemia cerebral, alteraciones en el estado de ánimo, depresión, para el tratamiento de
5 condiciones de dolor crónico, dolor inflamatorio, dolor neuropático, dolor visceral, y para el tratamiento de emesis.

26. La utilización según la Reivindicación 24, en que dicho compuesto de la fórmula (I) se administra en asociación, concurrentemente o secuencialmente,
10 con uno o más otros principios activos.

15

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RESUMEN

Se describen nuevos arilimidazolones bicíclicos con acción nootrópica (por ejemplo, protección y estimulación de funciones cerebrales), acción analgésica y acción anti-hiperalgésica; también se describe el proceso para su preparación y composiciones farmacéuticas que los contienen, útiles en el tratamiento de déficit cognitivo, y de varios tipos de dolor.

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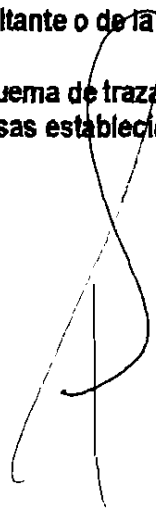
SUPERINDUSTRIA Y COMERCIO
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Fecha (AMD): 2005-09-23 16:37:33
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL
TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION <i>PCT</i> MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.	()	(X)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	(X)
- Descripción de la invención.	()	(X)
- Dibujos de ser estos pertinentes.	()	(X)
- Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA <i>(X)</i> INCOMPLETA	()	()
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA () INCOMPLETA	()	()
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solcitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA () INCOMPLETA	()	()

Firma Responsable:

Fecha:



PETITORIO



SUPERINDUSTRIA Y COMERCIO

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 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT

ENTRADA EN FASE NACIONAL 24-10-05

1

SOLICITUD DE :

☒

Patenté de Invención

☐ Patente de Modelo de Utilidad

☒

Capítulo I.

☐ Capítulo II.

2

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 COMPOSICIÓN FARMACEUTICA QUE LOS CONTIENE Y SU
 UTILIZACIÓN COMO AGENTES NOOTROPICOS

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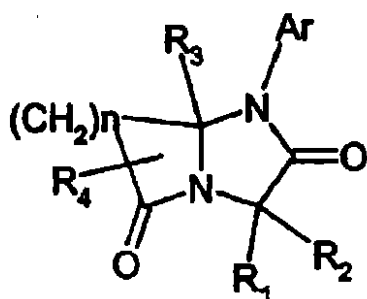
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REIVINDICACIONES

1. Compuestos de la fórmula (I) general

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(I)

en la que:

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A se escoge entre los grupos aromáticos carbocíclicos, grupos aromáticos heterocíclicos, y arilC₁₋₄alquilo;

R₁ se escoge de entre:

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- hidrógeno,
- aril C₁₋₇alquilo, opcionalmente sustituido en una fracción aril con uno o más de los grupos que se escoge entre hidroxil, C₁₋₄alkoxil, halógeno, haloC₁₋₄alquilo;
- heterociclilC₁₋₇alquilo, opcionalmente sustituido en la fracción de heterocíclico con uno o mas grupos escogidos de entre C₁₋₄alquilo e hidroxil;
- C₁₋₇alquilo, opcionalmente interrumpido por un átomo de oxigeno o azufre o opcionalmente sustituido en cualquier posición por uno o mas grupos que se escoge entre hidroxil, tio, amino, carboxilo, aminocarbonil, guanidinil.

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R_2 se escoge de entre hidrógeno, C_{1-4} alquilo, aril C_{1-4} alquilo y fenilo; o bien R_1 y R_2 que en conjunto forman un anillo carbocíclico que contiene entre 3 y 8 átomos de carbón;

- 5 R_3 se escoge de entre hidrógeno, C_{1-4} alquilo, aril C_{1-4} alquilo, $CONH_2$ y $COOR_5$ en donde R_5 se escoge de entre hidrógeno y C_{1-4} alquilo;

R_4 se escoge de entre hidrógeno, C_{1-4} alquilo, aril, aril C_{1-4} alquilo y heterociclil;

- 10 n es 2, 3 o 4;

en la forma de una mezcla racémica o en la forma de enantiómeros, y sales o solvatos de éstas farmacéuticamente aceptables.

- 15 2. Los compuestos según la Reivindicación 1, en que: A es fenilo, tienil, piridil, grupo pirimidinil, opcionalmente sustituido, bencil o 4-metilbencil; R_1 es hidrógeno, C_{1-4} alquilo, bencil, $-CH_2OH$, $-CH_2CH_2CONH_2$, $-CH_2COOH$, indol(3-il)metil; R_2 es hidrógeno, C_{1-4} alquilo o bencil; R_3 y R_4 son hidrógeno o metil, y n es 2.

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3. Los compuestos según la Reivindicación 2, en que: A es fenilo opcionalmente sustituido; R_1 , R_2 , R_3 y R_4 son hidrógeno; y n es 2.

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