

Clarke, Modet

COLOMBIA

131 171
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Tra. 11 PATENTEIYII Eje: 378 FASENACIONALI
Act. 467 SOLICIPRORROGA Folios: 2

p-1939

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

E. S. D.

Re: Expediente No. 06.037.930
Solicitud de Patente a nombre de
Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Yo, DILIA RODRIGUEZ D' ALEMAN, , identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53, piso 6, obrando como apoderada, atentamente solicito a usted se sirva conceder una prórroga de 30 días para dar respuesta al oficio No. 7673 notificado por fijación en lista 10 de julio de 2009, relacionado con la solicitud de patente que se está tramitando bajo el expediente de la referencia.

Acompaño el recibo Nr. 09-65,760 de 3 de septiembre de 2009, correspondiente a la tasa de la prórroga del término.

Señor Superintendente,

DILIA RODRIGUEZ D' ALEMAN
C.C. 41.654.882 de Bogotá
T.P. 20824 del C.S.J.

MIT : 000176089-2

RECIBO OFICIAL DE CAJA : 9 - 65,760
FECHA : SEPTIEMBRE 3 DE 2009

132 172
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 06-037930-00006-0000
Fecha: 2009-10-05 15:19:46 Dep. 2020 NUECREACION
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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CLARKE MODET Y CO. COLOMBIA	CONSIGNACION	BANCO DE BOGOTA	062754387	129129744	03/09/2009	80,800,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	81,000.00
		TOTAL :	\$ 81,000.00

SON: OCHENTA Y UNO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL ASUNTO No.

P-1939



PATENT SPECIFICATION

NO DRAWINGS

956,269

Inventor: PIERRE MARIE VANHOOF

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No. 11659/60.

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Index at acceptance:—C2 C(1H2A3, 1H2A7, 1H2C3, 2A3, 2A5, 2A9, 2A14, 2B20, 2B52A4, 2B52G1, 2S16, 2T16, 2T22)

International Classification:—C 07 d

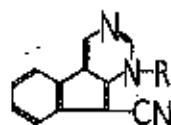
COMPLETE SPECIFICATION

Substituted Indeno-pyrimidines

We MANUFACTURE DE PRODUITS PHARMACEUTIQUES A. CHRISTIAENS S.A. a Belgian Body Corporate of 60, rue de l'Europe, Brussels, Belgium, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

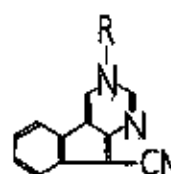
The present invention relates to new substituted indeno-pyrimidines and processes for their preparation.

The invention provides new substituted 1-H- and 3-H- 9-cyano-indeno[2,1-d]-pyrimidines of the general formulae:—



I.

and

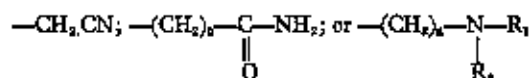


I'

in which R represents an alkyl radical, an amino (substituted or unsubstituted as herein-after defined), carboxy-, alkoxycarbonyl-, carbamoyl-, hydroxy-, aroyl-, alkanoyl-, pyridyl- or cyano-substituted alkyl radical, or an allyl, alkoxycarbonyl-substituted alkenyl or aralkyl radical. It will be appreciated that the term amino-(substituted or unsubstituted)-substituted alkyl radical includes within its scope an alkyl radical substituted by an amino group, an alkyl substituted amino group or a saturated nitrogen-containing heterocyclic group linked to the alkyl radical via the nitrogen atom.

Preferred compounds of the formulae I and I' are those in which R represents a lower alkyl radical containing 1 to 4 carbon atoms, or such a group a hydrogen atom of which has been replaced by a substituent as specified above.

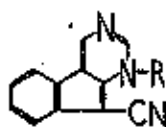
Examples of groups which may be represented by R are as follows:—



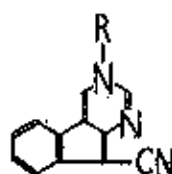
where R₁ and R₂, which are the same or different, represent alkyl radicals (preferably [Price 4s. 6d.]

WHAT WE CLAIM IS:—

1. Substituted 1-H- and 3-H-9-cyano-indeno-[2,1-d]-pyrimidines of the general formulae



and



in which R represents an alkyl radical, an amino-(substituted or unsubstituted as hereinbefore defined), carboxy-, alkoxycarbonyl-, carbamoyl-, hydroxy-, aroyl-, alkanoyl-, pyridyl- or cyano-substituted alkyl radical, or an allyl, alkoxycarbonyl-substituted alkenyl or aralkyl radical.

2. Compounds as claimed in claim 1 in which R represents a group of the formula $-(CH_2)_n-CH_2OH$, where n is a whole number.

3. Compounds as claimed in claim 1 in which R represents a group of the formula $-(CH_2)_n-COOH$, where n is a whole number.

4. Compounds as claimed in claim 1 in which R represents a group of the formula $-(CH_2)_n-COOR_1$, in which R_1 represents an alkyl radical and n is a whole number.

5. Compounds as claimed in claim 1 in which R represents a group of the formula $-(CH_2)_n-C(=O)-NH_2$, in which n is a whole number.

6. Compounds as claimed in claim 1 in which R represents a group of the formula $-(CH_2)_n-N-R_1$, in which R_1 and R_2 , which are the same or different, each



represents an alkyl radical, or together with the nitrogen atom, represents a saturated heterocyclic ring which may contain a further hetero atom.

7. Compounds according to any of claims 2 to 6 in which n represents 1, 2, 3 or 4.

8. Compounds according to claim 1 in which R represents an alkyl group containing from 1 to 4 carbon atoms, or such a group a hydrogen atom of which is replaced by a substituent as specified in claim 1.

9. 1-H-9-cyano-1-methyl-indeno-[2,1-d]-pyrimidine.

10. 3-H-9-cyano-3-methyl-indeno-[2,1-d]-pyrimidine.

11. 1-H-9-cyano-1-carboxymethyl-indeno-[2,1-d]-pyrimidine.

12. 3-H-9-cyano-3-carboxymethyl-indeno-[2,1-d]-pyrimidine.

13. 1-H-9-cyano-1-(2-carboxyethyl)-indeno-[2,1-d]-pyrimidine.

14. 3-H-9-cyano-3-(2-carboxyethyl)-indeno-[2,1-d]-pyrimidine.

15. 1-H-9-cyano-1-ethoxycarbonylmethyl-indeno-[2,1-d]-pyrimidine.

16. 3-H-9-cyano-3-ethoxycarbonylmethyl-indeno-[2,1-d]-pyrimidine.

17. 1-H-9-cyano-1-allyl-indeno-[2,1-d]-pyrimidine.

18. 3-H-9-cyano-3-allyl-indeno-[2,1-d]-pyrimidine.

19. 1-H-9-cyano-1-(2-ethoxycarbonylethyl)-indeno-[2,1-d]-pyrimidine.

20. 3-H-9-cyano-3-(2-ethoxycarbonylethyl)-indeno-[2,1-d]-pyrimidine.

21. 1-H-9-cyano-1-(γ-hydroxypropyl)-indeno-[2,1-d]-pyrimidine.

22. 3-H-9-cyano-3-(γ-hydroxypropyl)-indeno-[2,1-d]-pyrimidine.

23. 1-H-9-cyano-1-(δ-hydroxybutyl)-indeno-[2,1-d]-pyrimidine.

24. 3-H-9-cyano-3-(δ-hydroxybutyl)-indeno-[2,1-d]-pyrimidine.

25. 1-H-9-cyano-1-(β-hydroxyethyl)-indeno-[2,1-d]-pyrimidine.

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26. 3-H-9-cyano-3-(β -hydroxyethyl)-indeno-[2,1-d]-pyrimidine.
27. 1-H-9-cyano-1-cyanomethyl-indeno-[2,1-d]-pyrimidine.
28. 3-H-9-cyano-3-cyanomethyl-indeno-[2,1-d]-pyrimidine.
29. 1-H-9-cyano-1-benzoylmethyl-indeno-[2,1-d]-pyrimidine.
- 5 30. 3-H-9-cyano-3-benzoylmethyl-indeno-[2,1-d]-pyrimidine.
31. 1-H-9-cyano-1-benzyl-indeno-[2,1-d]-pyrimidine.
32. 3-H-9-cyano-3-benzyl-indeno-[2,1-d]-pyrimidine.
33. 1-H-9-cyano-1-(4-pyridylmethyl)-indeno-[2,1-d]-pyrimidine.
34. 3-H-9-cyano-3-(4-pyridylmethyl)-indeno-[2,1-d]-pyrimidine.
- 10 35. 1-H-9-cyano-1-(3-ethoxycarbonylallyl)-indeno-[2,1-d]-pyrimidine.
36. 3-H-9-cyano-3-(3-ethoxycarbonylallyl)-indeno-[2,1-d]-pyrimidine.
37. 1-H-9-cyano-1-carbamoylmethyl-indeno-[2,1-d]-pyrimidine.
38. 3-H-9-cyano-3-carbamoylmethyl-indeno-[2,1-d]-pyrimidine.
39. 1-H-9-cyano-1-(2-dimethylaminoethyl)-indeno-[2,1-d]-pyrimidine.
- 15 40. 3-H-9-cyano-3-(2-dimethylaminoethyl)-indeno-[2,1-d]-pyrimidine.
41. 1-H-9-cyano-1-(3-dimethylaminopropyl)-indeno-[2,1-d]-pyrimidine.
42. 3-H-9-cyano-3-(3-dimethylaminopropyl)-indeno-[2,1-d]-pyrimidine.
43. 1-H-9-cyano-1-(2-N-pyrrolidinoethyl)-indeno-[2,1-d]-pyrimidine.
44. 3-H-9-cyano-3-(2-N-pyrrolidinoethyl)-indeno-[2,1-d]-pyrimidine.
- 20 45. 1-H-9-cyano-1-(2-diethylaminoethyl)-indeno-[2,1-d]-pyrimidine.
46. 3-H-9-cyano-3-(2-diethylaminoethyl)-indeno-[2,1-d]-pyrimidine.
47. 1-H-9-cyano-1-(3-dibutylaminopropyl)-indeno-[2,1-d]-pyrimidine.
48. 3-H-9-cyano-3-(3-dibutylaminopropyl)-indeno-[2,1-d]-pyrimidine.
49. 1-H-9-cyano-1-(3-dipropylaminopropyl)-indeno-[2,1-d]-pyrimidine.
- 25 50. 3-H-9-cyano-3-(3-dipropylaminopropyl)-indeno-[2,1-d]-pyrimidine.
51. 1-H-9-cyano-1-(γ -N-morpholinopropyl)-indeno-[2,1-d]-pyrimidine.
52. 3-H-9-cyano-3-(γ -N-morpholinopropyl)-indeno-[2,1-d]-pyrimidine.
53. 1-H-9-cyano-1-(γ -N-piperidinopropyl)-indeno-[2,1-d]-pyrimidine.
54. 3-H-9-cyano-3-(γ -N-piperidinopropyl)-indeno-[2,1-d]-pyrimidine.
- 30 55. 1-H-9-cyano-1-(2-N-piperidinoethyl)-indeno-[2,1-d]-pyrimidine.
56. 3-H-9-cyano-3-(2-N-piperidinoethyl)-indeno-[2,1-d]-pyrimidine.
57. Compounds according to any of claims 6 and 39 to 56 in the form of their acid addition salts.
58. Compounds according to claim 57 in which the acid addition salt is a hydrochloride.
- 35 59. A process for preparing compounds as claimed in claim 1 in which an alkali metal salt of 1-H-9-cyano-indeno-[2,1-d]-pyrimidine or 3-H-9-cyano-indeno-[2,1-d]-pyrimidine is reacted with an alkylating or aralkylating agent of the formula $R-X$, in which R is as defined in any of claims 1 to 8 and X represents a group selected to react with the salt of the pyrimidine to form compounds of the formulae I and I', and if desired separating the compounds of formulae I and I' from one another.
- 40 60. A process according to claim 59 in which the compound RX is a compound in which X represents a halogen atom.
61. A process according to claim 60 in which the compound RX is a compound in which X represents a chlorine atom.
- 45 62. A process according to either of claims 60 and 61 in which the reaction is effected in the presence of an inert solvent.
63. A process according to claim 62 in which the inert solvent is an anhydrous alcohol.
- 50 64. A process according to claim 63 in which the anhydrous alcohol is anhydrous isopropanol.
65. A process according to any of claims 60 to 64 in which the reaction is effected at an elevated temperature.
66. A process according to claim 65 in which the reaction is effected under reflux conditions.
- 55 67. A process according to claim 59 in which the compound RX is a dialkyl sulphate.
68. A process according to claim 66 in which the reaction is effected in a strong aqueous alkaline solution.
- 60 69. A process for the preparation of compounds as claimed in claim 6 comprising reacting a compound of the formula

Inhibition of Monoamine Oxidase-B by 5*H*-Indeno[1,2-*c*]pyridazines: Biological Activities, Quantitative Structure-Activity Relationships (QSARs) and 3D-QSARs

Silvia Kneubühler,¹ Ulrike Thull,¹ Cosimo Altomare,² Vincenza Carta,² Patrick Gaillard,¹ Pierre-Alain Carrupt,¹ Angelo Carotti,^{2,3} and Bernard Testa^{1*}

¹Institut de Chimie Thérapeutique, Section de Pharmacie, Université de Lausanne, CH-1015 Lausanne-Dorigny, Switzerland, and ²Dipartimento Farmacochimico, Università di Bari, Via Orabona 4, I-70126 Bari, Italy

Received March 7, 1995⁴

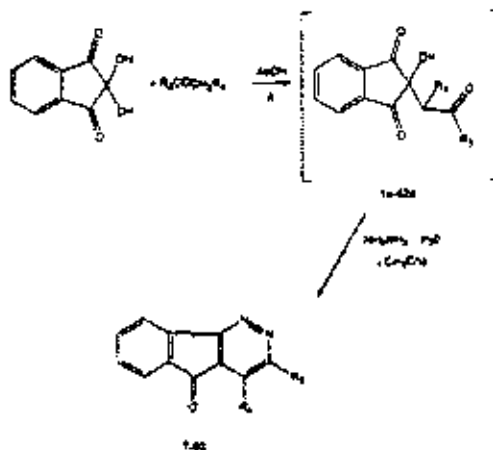
A large series (66 compounds) of indeno[1,2-*c*]pyridazin-5-ones (IPs) were synthesized and tested on their monoamine oxidase-A (MAO-A) and MAO-B inhibitory activity. All of the tested compounds acted preferentially on MAO-B displaying weak (nonmeasurable IC₅₀ values) to high (submicromolar IC₅₀ values) activities. The most active compound was *p*-CF₃-3-phenyl-IP (IC₅₀ = 90 nM). Multiple linear regression analysis of the substituted 3-phenyl-IPs yielded good statistical results ($q^2 \approx 0.74$; $r^2 = 0.86$) and showed the importance of lipophilic, electronic, and steric properties of the substituents in determining inhibitory potency. Various comparative molecular field analysis studies were performed with different alignments and including the molecular lipophilicity potential. This led to a model including the steric, electrostatic and lipophilicity fields and having a good predictive value ($q^2 = 0.75$; $r^2 = 0.93$).

Introduction

Monoamine oxidase (MAO, EC 1.4.3.4) is a flavin adenine dinucleotide (FAD)-containing flavoenzyme existing as two isozymes (MAO-A and MAO-B) and playing a key role in the regulation of various physiological amines. This enzyme is also a target for therapeutic agents, MAO-A inhibitors being used as antidepressants, while MAO-B inhibitors like selegiline coadministered with L-DOPA are of interest in the treatment of Parkinson's disease. Irreversible, mechanism-based inactivators of MAO are considered obsolete due to severe side effects such as hepatotoxicity and the well-known "cheese effect". Based on a better understanding of the biochemical and catalytic properties of MAO, recent research efforts have focused on selective and reversible inhibitors of MAO-A or MAO-B.¹⁻³

Pyridazine derivatives are currently an object of sustained interest due to the vast range of their potential activities as chemotherapeutics, antithrombotics, cardiovascular agents, antisecretory and antiulcer agents, analgetic and antiinflammatory agents, and central nervous system (CNS) stimulants or depressants.^{9,10} In a previous paper, we reported the synthesis and activity of a series of novel 5*H*-indeno[1,2-*c*]pyridazin-5-ones (IPs) acting as competitive inhibitors of MAO and mainly MAO-B.¹¹⁻¹³ Such IPs have a structural analogy (the endocyclic N-N functionality) with 2-aryl-1,3,4-oxadiazines and 5-aryl-1,3,4-oxadiazoles which have been described as selective and competitive MAO-B inhibitors.^{10,14,15} In order to improve the MAO inhibitory activity of IPs and gain an understanding of their structure-activity relationships, we designed, prepared, and tested a large congeneric series of 3- and 4-substituted indeno[1,2-*c*]pyridazine derivatives. Their synthesis, MAO inhibitory activities, and structure-activity relationships are described in this paper. The

Scheme 1. General Synthetic Method Used in This Work



very good quantitative structure-activity relationship (QSAR) and 3D-QSAR models obtained afford interesting insights into the topography of the MAO-B enzymatic site.

Results and Discussion

Chemistry. Compounds 1-62 were prepared from ninhydrin and the adequate ketone according to the reaction pathway reported in Scheme 1. In most cases the synthesis was carried out by a one-pot procedure. In the case of very low yields or when the intermediate aldol adducts 1a-62a precipitated from the reaction mixture, a classical two-step synthesis was adopted. The preparation of the condensed pyridazines 4, 6, 8-10, 12, 15, 17-25, 28-30, 33, 34, 39, 41, 43-45, 47, 53, and 55-58 has already been described by some of us.^{11,12} Reaction yields, physicochemical properties, and spectral data of the newly synthesized condensed pyridazines are given in the Experimental Section, and those of the isolated aldol adducts are reported in Table 1.

* Université de Lausanne.

³ Università di Bari.

⁴ Abstract published in *Advance ACS Abstracts*, August 1, 1995.