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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 01-019802- -00009-0000

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Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 444 RESPUESTAREQUE Folios: 11

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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 002 Evento : 001 Actuación : 444

Referencia : Expediente No. 01019802
Asunto : Solicitud de patente para: **NUEVO USO DE (R)-(-)-2-[5-(4-FLOROFENIL)-3-PIRIDILMETIL-AMINOMETIL]-CROMANO Y DE SUS SALES ACEPTABLES PARA USO FISIOLÓGICO**
Solicitante : MERCK PATENT GMBH
Fecha de Solicitud : 12 de marzo de 2001

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al Oficio No. **10098** notificado por fijación en lista del 23 de agosto de 2007.

2. Mediante el Oficio No. **10098** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente.

Atiendo a las observaciones de la manera siguiente:

2.1. CLARIDAD DE LA SOLICITUD Y UNIDAD DE INVENCION

Para subsanar la objeción que sobre claridad y unidad de invención hizo su Despacho, presento nuevo pliego reivindicatorio con 2 reivindicaciones en el cual se han hecho los cambios respectivos sugeridos por su despacho, que permiten apreciar claramente el objeto reivindicado en la presente solicitud de patente. Las modificaciones al capítulo reivindicatorio fueron las siguientes:

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- El fármaco anti-Parkinsoniano convencional ha sido limitado a L-Dopa de acuerdo con el alcance de la descripción de la presente solicitud de patente, y por lo tanto la composición y el kit reivindicados especifican los elementos presentes en los mismos y corresponden a un concepto inventivo particular.

Adicionalmente, respetuosamente ponemos de presente que la mezcla de compuestos activos objeto de la invención exhibe un efecto inesperado y sorprendente, tal como lo evidencia el artículo *"Multicenter, Open-label, Trial of Sarizotan in Parkinson Disease Patient With Levodopa-Induced Dyskinesias"* (Anexo 5.4).

Dicho estudio analiza la combinación de la terapia L-Dopa / Sarizotan ((R)-(-)-2-[-(4-fluorofenilo)-3-pirimidilmetilaminometilo]-cromano y muestra que en la mayoría de los pacientes se ha inducido una reducción significativa sobre la disquinesia (Sección de Discusión que empieza en la página No. 60).

A este respecto, es importante señalar que el técnico medio versado en la materia al combinar un fármaco anti-Parkinsoniano agonista I (por ejemplo L-Dopa) y un antagonista II (Sarizotan) esperaría que los efectos de dichos fármacos se neutralizaran mutuamente, de tal modo que el efecto anti-parkinsoniano del fármaco I podría reducirse o podría en conjunto abolirse.

Sin embargo, en vista de que de manera sorpresiva la combinación de Sarizotan con el fármaco anti-Parkinsoniano I no sólo tiene el efecto anti-Parkinsoniano del fármaco anti-Parkinsoniano I, sino que también reduce efectivamente los efectos colaterales del mismo (como por ejemplo los desórdenes de movilidad), se puede concluir que el concepto común inventivo derivado de la mezcla de los compuestos activos objeto de la presente solicitud de patente, evidencia un resultado inesperado.

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De esta manera es claro que con las anteriores modificaciones del capítulo reivindicatorio quedan subsanadas las objeciones que por claridad y por unidad de invención hizo su Despacho, ya que ahora, dicho pliego involucra un único concepto inventivo, reivindica productos en los términos sugeridos por su Despacho y permite determinar el alcance de la protección reivindicada y compararla frente al estado del arte, de acuerdo con las disposiciones del artículo 30 de la Decisión 486.

3. Por lo tanto, le solicito se sirva continuar con el trámite de la presente solicitud pues las reivindicaciones se presentan de una forma clara y en consecuencia, con fundamento en las mismas una persona versada en la materia podría realizar el examen de patentabilidad del producto objeto de esta invención. A pesar que las objeciones que sobre claridad y unidad de invención planteó ese Despacho en el Oficio No. **10098** se deben tener por superadas, en el evento que el Despacho considere que sea necesario, respetuosamente le solicito hacer uso de la facultad que le otorga el artículo 45 inciso 2. de la Decisión 486 de la Comisión de la Comunidad Andina a efecto de requerir nuevamente de nuestra parte cualquier complementación o aclaración que considere necesaria.

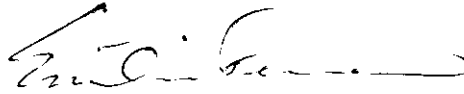
4. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

5. Anexos:

- 5.1. Nuevo pliego descriptivo y reivindicatorio con 2 reivindicaciones;
- 5.2. Formulario para modificaciones;
- 5.3. Recibo por valor de \$99.000 por concepto de modificaciones en solicitud pendiente;
- 5.4. Olowan C. W. et al. "Multicenter, Open-label, Trial of Sarizotan in Parkinson Disease Patient With Levodopa-Induced Dyskinesias". Clin Neuropharmacol. Volumen 27, Numero 2. Marzo – Abril 2004. pag. 58 a 62.

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Señora Jefe,

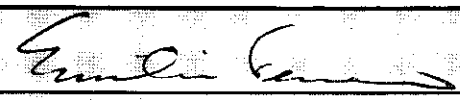


EMILIO FERRERO

T.P.A. No. 31.929

COLO-09266-801-028-0
NNJ\NNJ\ID-112546\WPCL9266
No. M-2007-112546\NNJ

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE: ☐ Corrección de Error Material ☒ Modificación a una solicitud	
2 SOLICITANTE	Nombre: MERCK PATENT GMBH. Sociedad constituida y existente bajo las leyes de Alemania. Dirección: Frankfurter Str. 250 64293 Darmstadt Alemania Domicilio: Darmstadt, Alemania Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@cavelier.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3 REPRESENTANTE O APODERADO	Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: cavelier@cavelier.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: <u>438.019 TP 31.929</u>
4	Número de expediente: <u>01.019.802</u>	
5	Descripción de la corrección o modificación solicitada: Presento con este formulario un nuevo capítulo reivindicatorio compuesto por 2 reivindicaciones con el fin de superar la falta de Claridad y Unidad de invención objetadas por su Despacho, y solicito que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones.	
6	Comprobante de pago No. <u>07-92,031</u> Fecha: <u>13 de noviembre de 2007</u>	
7	Anexos ☒ Comprobante de pago de la tasa por \$99.000.00 por concepto de modificaciones ☐ Poderes, si fuere el caso ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.	
8	NOMBRE: EMILIO FERRERO	FIRMA:  C.C. 438.019 de Usaquén T.P.A. 31.929

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REIVINDICACIONES

1) Una composición farmacéutica que comprende, como principios activos,

(i) (R) – (-) – 2 - [5-(4-fluorofenil)- 3 – piridilmetil-amonometil]- cromano o una sal fisiológicamente aceptable del mismo, y *Samol* EMD 128130

(ii) L-Dopa

en combinación con uno o mas excipientes farmacéuticamente aceptables.

2) Un kit que comprende dos composiciones separadas,

La primera que comprende (R)- (-)- 2-[5- (4-fluorofenil)-3-piridilmetil-aminometil]- cromano o uno de sus sales fisiológicamente aceptables como único activo principal.

Y la segunda que comprende L-Dopa como un compuesto activo.

Multicenter, Open-Label, Trial of Sarizotan in Parkinson Disease Patients With Levodopa-Induced Dyskinesias (the SPLENDID Study)

C. Warren Olanow, MD,* Philippe Damier,† Christopher G. Goetz,‡ Thomas Mueller,§ John Nutt,|| Olivier Rascol,¶ Alexandru Serbanescu,# Frieda Deckers,** and Hermann Russ#

Key Words: Sarizotan, Parkinson disease, SPLENDID

(*Clin Neuropharmacol* 20(4):27:58–62)

Levodopa-related dyskinesias are an important problem in the management of Parkinson disease (PD).^{1,2} They represent a major source of disability for patients and are often difficult to control with available medications. Sarizotan (2-5-[4-fluorophenyl]-3-pyridylmethyl-aminomethyl-chromane, dihydrochloride) or EMD128130 is a new chemical entity that belongs to the aminomethyl chromane chemical group. It is a full agonist for the 5-HT_{1A} receptor and an antagonist for the dopamine receptor with highest affinity for the D₄ subtype. Furthermore, the drug had no effect on psychosis in a large double-blind, placebo-controlled trial.³ Based on this receptor profile, it has been postulated that Sarizotan will provide antidyskinetic benefits without the side effects typically associated

with classic neuroleptic agents. In MPTP-lesioned monkeys, Sarizotan has been shown to suppress levodopa-induced dyskinesia effectively without worsening parkinsonian motor features.⁴

In preclinical studies, Sarizotan is also a weak inhibitor of 11 β -hydroxylase, an enzyme forming cortisol in the adrenal gland. This property has led to concern that the drug might be associated with adrenal dysfunction, particularly under conditions of stress. In clinical trials with volunteers, however, doses of Sarizotan up to 10 mg b.i.d. were well tolerated and not associated with adrenal dysfunction.⁵ Based on these data, clinical trials of Sarizotan as a treatment of PD have been performed. We now report the results of the first clinical trial assessing the safety and efficacy of Sarizotan in PD patients with dyskinesias.

METHODS

Study Design

The study was performed as an open-label, multicenter, dose escalation study to provide preliminary information on the safety, tolerability, and efficacy of Sarizotan in patients with advanced PD complicated by troublesome levodopa-induced dyskinesia.

Subject Population

Men and women of all races and younger than 80 years with a diagnosis of idiopathic PD based on the UK Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria⁶ and who experienced troublesome dyskinesia were eligible to participate in the trial. Inclusion criteria included levodopa-induced dyskinesia with a score of at least 2 points on item 33 of the Unified Parkinson's Disease Rating Scale (UPDRS), stable doses of all antiparkinsonian drug treatments for at least 1 month before entry into the study, and the capacity of the patient or caregiver to complete an accurate home diary based on office training. Exclusion criteria included a diagnosis of atypical or secondary parkinsonism, prior use of neuroleptic agents, a prior intracranial neurosurgical procedure, and de-

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Preliminary data were reported in abstract form at the 9th International Movement Disorder Society, Miami, Florida.

This study was funded by Merck Pharmaceutical KGaA, Darmstadt, Germany.

Dr. Russ and Dr. Deckers are employees of Merck Pharmaceutical KGaA. Dr. Olanow has served as a consultant to Merck Pharmaceutical KGaA.

Reprints: C. Warren Olanow, MD, FRCP, Department of Neurology, Mount Sinai School of Medicine, Annonberg 14-94, One Gustave L. Levy Place, Box 1137, New York, NY 10029, USA (E-mail: warren.olanow@mssm.edu).

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fluctuations and dyskinesia.² Although motor complications are not problematic in their early stages, and the incidence is reduced if therapy is started with a dopamine agonist, they can eventually become an important management problem for PD patients. Indeed, motor complications currently represent the most common basis for performing surgical interventions in PD. Thus, the development of a well-tolerated medical therapy such as Sarizotan that can treat troublesome dyskinesia is a welcome addition to the therapeutic armamentarium for PD. Such treatment could avoid the need for surgical intervention in some patients.

The mechanism whereby Sarizotan provides antidyskinetic effects remains to be elicited. The drug is known to be a dopamine receptor antagonist that primarily affects the D4 receptor, but like such agents probably has some D2 and D3 receptor antagonism, which could account for its antidyskinetic effect. The concomitant worsening in parkinsonism seen in many of the patients who received higher doses suggests that this receptor blockade is likely a contributing factor. Sarizotan is also a 5-HT1A agonist and there is speculation that this effect might also abate dyskinesia. Indeed, the 5-HT1A antagonist WAY100635 has been shown to eliminate the antidyskinetic effect of Sarizotan in MPTP-lesioned monkeys.⁴

Based on our data that Sarizotan treatment provided a significant reduction in troublesome dyskinesia when used as an adjunct to levodopa in PD patients, we recommend double-blind controlled trials to test further the potential value of this agent in PD.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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RECIBO OFICIAL DE CAJA : 07 - 92,031
FECHA : NOVIEMBRE 13 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	48825378	13/11/2007	23,681,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LEMAS COMERCIALES	99,000.00
		TOTAL :	\$ 99,000.00

SDN: NOVENTA Y NUEVE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

COLO: 09266-801-028-0

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Europäisches Patentamt
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(51) Int. Cl.⁶: **C07D 405/12**, C07D 311/64,
C07D 311/58, C07D 213/38,
C07D 333/20, C07C 211/27,
A61K 31/44, A61K 31/35

(84) Designated Contracting States:
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SE

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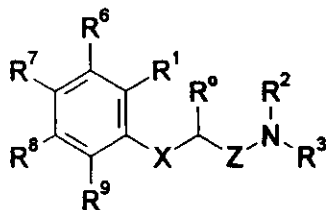
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(54) **Amino(thio)ether derivatives as CNS active agents**

(57) Amino(thio)ether derivatives of formula I



wherein R⁰, R¹, R², R³, R⁶, R⁷, R⁸, R⁹, X and Z are as defined in Claim 1, and their salts, are active on the central nervous system.

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thesized, compounds possessing two or more centres of asymmetry are generally obtained as mixtures of racemates, from which the individual racemates can be isolated in the pure form, for example by recrystallization from inert solvents. If desired, the racemates obtained can be chemically or by crystallization of conglomerates resolved into their optical antipodes by the methods known per se. Preferably, diastereoisomers are formed from the racemate by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids such as the D and L forms of protected amino acid derivatives such as tosylproline, tartaric acid, dibenzoyltartaric acid, diacetyltartaric acid, camphor-sulphonic acids, mandelic acid, malic acid or lactic acid. The different forms of the diastereoisomers can be resolved in a manner known per se, e.g. by fractional crystallization, and the optically active compounds of formula I can be liberated from the diastereoisomers in a manner known per se.

A base of formula I can be converted with an acid into the corresponding acid addition salt. Acids which produce biocompatible salts are suitable for this reaction. Thus it is possible to use inorganic acids, e.g. sulphuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid and sulphamic acid, as well as organic acids, i.e. specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono-basic or polybasic carboxylic, sulphonic or sulphuric acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methanesulphonic or ethanesulphonic acid, ethanedithiosulphonic acid, 2-hydroxyethanesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid, naphthalenemonosulphonic and naphthalenedithiosulphonic acids and laurylsulphuric acid.

If desired, the free bases of formula I can be liberated from their salts by treatment with strong bases such as sodium or potassium hydroxide or sodium or potassium carbonate provided there are no other acid groups in the molecule. In those cases where the compounds of the formula I have free acid groups, salt formation can also be achieved by treatment with bases. Suitable bases are alkali metal hydroxides, alkaline earth metal hydroxides or organic bases in the form of primary, secondary or tertiary amines.

The invention further relates to the use of the compounds of formula I and their biocompatible salts for the manufacture of pharmaceutical preparations, especially by a non-chemical route. For this purpose, they can be converted into a suitable dosage form together with at least one excipient or adjunct and, if appropriate, in combination with one or more additional active ingredients.

The invention further relates to compositions, especially pharmaceutical preparations, containing at least one compound of formula I and/or one of their biocompatible salts. These preparations can be used as drugs in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g. oral), parenteral or topical administration and which do not react with the novel compounds, examples of such excipients being water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. Tablets, coated tablets, capsules, syrups, juices, drops or suppositories are used in particular for enteral administration, solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical administration. The novel compounds can also be lyophilized and the resulting lyophilizates used e.g. to manufacture injectable preparations.

The preparations indicated can be sterilized and/or can contain adjuncts such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colourants, taste correctors and/or flavourings. If desired, they can also contain one or more additional active ingredients, e.g. one or more vitamins.

The compounds of formula I and their biocompatible salts can be used for the therapeutic treatment of the human or animal body and for controlling diseases. They can be used for treating disorders of the central nervous system, such as tension, depressions and/or psychoses, and side-effects in the treatment of hypertension (e.g. with a-methyldopa). The compounds can also be used in endocrinology and gynaecology, e.g. for the therapeutic treatment of acromegaly, hypogonadism, secondary amenorrhoea, premenstrual syndrome and undesired puerperal lactation, and also for the prophylaxis and therapy of cerebral disorders (e.g. migraine), especially in geriatrics in a manner similar to certain ergot alkaloids and for controlling the sequelae of cerebral infarction (Apoplexia cerebri), such as stroke and cerebral ischaemia.

Furthermore, they are suitable to eliminate cognitive deficiencies, to improve the power of learning and memory and to treat Alzheimer disease.

In these treatments, the substances of formula I of the invention are normally administered analogously to known, commercially available preparations (e.g. bromocriptine, dihydroergocornin), preferably in dosages of between about 0.2 and 500 mg, especially of between 0.2 and 50 mg per dosage unit. The daily dosage is preferably between about 0.001 and 10 mg/kg of body weight. The low dosages (about 0.2 to 1 mg per dosage unit; about 0.001 to 0.005 mg/kg of body weight) are particularly suitable for use as anti-migraine preparations; dosages of between 10 and 50 mg per dosage unit are preferred for the other indications. However, the particular dose for each individual patient depends on a very wide variety of factors, for example the activity of the particular compound used, age, body weight, general state

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of health, sex, diet, time and method of administration, rate of excretion, drug combination and severity of the particular disease to which the therapy is applied. Oral administration is preferred.

In the following Examples, "working-up in conventional manner" means: Water is added if necessary, extraction is carried out with methylene chloride, the organic phase is separated off, dried over sodium sulphate and filtered, the filtrate is evaporated and the residue is purified by chromatography on silica gel and/or by crystallization. Temperatures are given in °C.

Example 1

- 10 A solution of 2.8 g 2-aminomethyl-chromane [obtainable by reacting 3-(2-hydroxy-phenyl)-propanal with KCN and subsequent catalytic reduction of the 2-cyano-chromane] and 2.2 g 3-(chloromethyl)-pyridine in 250 ml of DMF are stirred together with 1 g N-methyl-morpholine for 12 hours at 20° and worked up in a conventional manner to give N-(3-pyridylmethyl)-N-(2-chromanyl-methyl)-amine. Stirring with 0.5 equivalents of maleic acid in 100 ml ethanol gives the maleate, m.p. 163-164°.
- 15 The following are obtained analogously:
- from 2-aminomethyl-chromane and 3-(chloromethyl)-5-(4-methoxyphenyl)-pyridine
N-[5-(4-methoxyphenyl)-3-pyridylmethyl]-N-(2-chromanyl-methyl)-amine, maleate, m.p. 177-178°;
 - from 2-aminomethyl-chromane and 3-(chloromethyl)-5-phenyl-pyridine
N-(5-phenyl-3-pyridylmethyl)-N-(2-chromanyl-methyl)-amine, maleate, m.p. 184°;
 - 20 from 2-aminoethyl-chromane and 3-(chloromethyl)-biphenyl N-3-biphenylethyl-N-(2-chromanyl-methyl)-amine, maleate, m.p. 162°;
 - from 2-aminomethyl-6-phenyl-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(6-phenyl-2-chromanyl-methyl)-amine, maleate, m.p. 222-224°;
 - from 2-aminomethyl-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
25 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-chromanyl-methyl)-amine, maleate, m.p. 182-183°;
 - from 2-aminomethyl-chromane and 3-(chloromethyl)-biphenyl
N-3-biphenylmethyl-N-(2-chromanyl-methyl)-amine, maleate, m.p. 174-175°;
 - from 2-aminomethyl-chromane and 3-(chloromethyl)-4'-fluorobiphenyl
N-(4'-fluoro-3-biphenylmethyl)-N-(2-chromanyl-methyl)-amine, maleate, m.p. 183-184°
 - 30 from 2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(8-methoxy-2-chromanyl)-methyl]-amine, maleate, m.p. 160-165°;
 - from 2-aminomethyl-7-methoxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(7-methoxy-2-chromanyl)-methyl]-amine, maleate, m.p. 170,5-172°;
 - from 2-aminomethyl-6-methoxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
35 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(6-methoxy-chroman-2-yl)-methyl]-amine, maleate;
 - from 2-aminomethyl-5-methoxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(5-methoxy-chroman-2-yl)-methyl]-amine, maleate, m.p. 181-183°;
 - from 2-aminomethyl-8-nitro-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(8-nitro-chroman-2-yl)-methyl]-amine, maleate;
 - 40 from 2-aminomethyl-2,3,4,5-tetrahydro-1-benzoxepine and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[2-(2,3,4,5-tetrahydro-1-benzoxepinyl)-methyl]-amine, maleate, m.p. 194-195°;
 - from 2-aminoethyl-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-chromanylethyl)-amine, maleate, m.p. 160°;
 - from 3-amino-2,3,4,5-tetrahydro-1-benzoxepine and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
45 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-3-(2,3,4,5-tetrahydro-1-benzoxepinyl)-amine, maleate, m.p. 179-180°;
 - from 2-aminomethyl-8-hydroxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(8-hydroxy-2-chromanyl)-methyl]-amine, maleate, m.p. 173°;
 - from 2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-4'-fluorobiphenyl
N-(4'-fluoro-3-biphenylmethyl)-N-[(8-methoxy-2-chromanyl)-methyl]-amine, maleate, m.p. 176°;
 - 50 from 2-aminomethyl-6-fluorochromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine
N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(6-fluoro-2-chromanyl)-methyl]-amine, maleate, m.p. 169-170°;
 - from 2-aminomethyl-chromane and 3-(2-pyridyl)-chloromethyl-benzene
N-[3-(2-pyridyl)-phenylmethyl]-N-2-chromanyl-methyl-amine, maleate, m.p. 201°;
 - from 2-aminomethyl-chromane and 3-(3-pyridyl)-chloromethyl-benzene
55 N-[3-(3-pyridyl)-phenylmethyl]-N-2-chromanyl-methyl-amine, dimaleate, m.p. 120°;
 - from 2-aminomethyl-8-methoxy-chromane and 3-(3-pyridyl)-chloromethyl-benzene
N-[3-(3-pyridyl)-phenylmethyl]-N-[(8-methoxy-2-chromanyl)-methyl]-amine, maleate, m.p. 85°;
 - from 2-aminomethyl-8-methoxy-chromane and 3-(2-pyridyl)-chloromethyl-benzene
N-[3-(2-pyridyl)-phenylmethyl]-N-[(8-methoxy-2-chromanyl)-methyl]-amine, maleate, m.p. 167°.

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Example 2

By reaction of 2-aminomethyl-2,3-dihydrobenzofuran with 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine analogously to Example 1, N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(2,3-dihydrobenzofuran-2-yl)-methyl]-amine is obtained.

5 maleate, m.p. 178-180°.

The following are obtained analogously:

- from 2-aminomethyl-2,3-dihydrobenzofuran and 3-(chloromethyl)-5-(4-methoxyphenyl)-pyridine
- N-[5-(4-methoxyphenyl)-3-pyridylmethyl]-N-[(2,3-dihydro-benzofuran-2-yl)-methyl]-amine, maleate;
- from 2-aminomethyl-2,3-dihydrobenzofuran and 3-(chloromethyl)-5-(3,4-dimethoxyphenyl)-pyridine
- 10 N-[5-(3,4-dimethoxyphenyl)-3-pyridylmethyl]-N-[(2,3-dihydro-benzofuran-2-yl)-methyl]-amine, maleate;
- from 2-aminomethyl-2,3-dihydrobenzofuran and 3-(chloromethyl)-5-(2,4-dimethoxyphenyl)-pyridine
- N-[5-(2,4-dimethoxyphenyl)-3-pyridylmethyl]-N-[(2,3-dihydro-benzofuran-2-yl)-methyl]-amine, maleate;
- from 2-aminomethyl-2,3-dihydrobenzofuran and 3-(chloromethyl)-5-(3,4,5-trifluorophenyl)-pyridine
- N-[5-(3,4,5-trifluorophenyl)-3-pyridylmethyl]-N-[(2,3-dihydro-benzofuran-2-yl)-methyl]-amine, maleate;
- 15 from 2-aminomethyl-2,3-dihydrobenzofuran and 3-(chloromethyl)-5-(2,3,4,5,6-pentafluorophenyl)-pyridine
- N-[5-(2,3,4,5,6-pentafluorophenyl)-3-pyridylmethyl]-N-[(2,3-dihydrobenzofuran-2-yl)-methyl]-amine, maleate.

Example 3

- 20 A mixture of 2.2 g 3-methyl-phenol, preferably the sodium salt thereof, and 5.6 g N-(2-chloroethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine ("A") [obtainable by reaction from phthalimid potassium salt and 5-(4-fluorophenyl)-3-chloromethyl-pyridine, cleavage of the product with hydrazine and subsequent reaction with 1,2-dichloroethane] in 50 ml acetonitrile is stirred for 5 hours at 50° and worked up in the conventional manner.

N-[2-(3-methylphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine is obtained. Stirring with 0.5 equivalents of maleic acid in 100 ml ethanol gives the maleate, m.p. 152-154°.

25 The following are obtained analogously:

- from 2,4-dichlorophenol sodium salt and "A"
- N-[2-(2,4-dichlorophenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 148-150°;
- from 3-methoxyphenol sodium salt and "A"
- 30 N-[2-(3-methoxyphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 122-124°;
- from 4-methoxyphenol sodium salt and "A"
- N-[2-(4-methoxyphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, m.p. 94-96°;
- from 3-chlorophenol sodium salt and "A"
- N-[2-(3-chlorophenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 150-152°;
- 35 from 2-chlorophenol sodium salt and "A"
- N-[2-(2-chlorophenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 153-155°;
- from 2-methoxyphenol sodium salt and "A"
- N-[2-(2-methoxyphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 134-136°;
- from 4-chlorophenol sodium salt and "A"
- 40 N-[2-(4-chlorophenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 163-164°;
- from 2-ethylphenol sodium salt and "A"
- N-[2-(2-ethylphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 128-130°;
- from 3-cyanophenol sodium salt and "A"
- N-[2-(3-cyanophenyl)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, oxalate, m.p. 245°;
- 45 from 4-cyanophenol sodium salt and "A"
- N-[2-(4-cyanophenyl)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, oxalate, m.p. 250°;
- from phenol sodium salt and N-[3-phenoxy-benzyl]-amine N-(2-phenoxyethyl)-N-(3-phenoxy-benzyl)-amine, maleate, m.p. 166-168°;
- from phenol sodium salt and "A"
- 50 N-(2-phenoxy-ethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, m.p. 84-86°.

Example 4

- 55 By reaction of 2-aminomethyl-6-methoxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine analogously to Example 1 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(6-methoxy-2-chromanyl)-methyl]-amine is obtained. Stirring with hydrochloric acid gives the dihydrochloride, m.p. 205-206°.

By reaction of 2-aminomethyl-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine analogously to Example 1, N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-chloromethyl)-N-(2-chlorophenyl)-amine is obtained. Stirring with hydrochloric acid gives the dihydrochloride-hemihydrate, m.p. 210-213°.

Example 5

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A solution of 1.8 g 3-aminomethyl-biphenyl [obtainable by reducing 3-cyano-biphenyl and 1.6 g 2-chloroethyl-phenylether (obtainable by reaction of sodium phenolate with dichloroethane) in 200 ml of acetonitrile is stirred for 8 hours at room temperature and worked up in a conventional manner to give N-(3-biphenylmethyl)-N-(2-phenoxyethyl)-amine. Stirring with 0.5 equivalents of maleic acid in 100 ml ethanol gives the maleate, m.p. 178-180°.

The following are obtained analogously:

15 N-(4-fluoro-3-biphenylmethyl)-N-(2-phenoxyethyl)-amine, maleate, m.p. 194-196°; from 3-aminomethyl-2',4'-difluoro-biphenyl and 2-chloroethyl-phenylether

N-(2',4'-difluoro-3-biphenylmethyl)-N-(2-phenoxyethyl)-amine; from 2-aminomethyl-4-methoxy-thiophen and 2-chloroethyl-phenylether

N-(4-methoxy-2-thienylmethyl)-N-(2-phenoxyethyl)-amine; from 2-aminomethyl-4-methoxy-thiophen and 2-chloroethyl-phenylether

N-(4-methyl-2-thienylmethyl)-N-(2-phenoxyethyl)-amine; from 2-aminomethyl-4-methyl-thiophen and 2-chloroethyl-phenylether

N-(4-(3-thienyl)-2-thienylmethyl)-N-(2-phenoxyethyl)-amine, m.p. 96-98°; from 2-aminomethyl-4-(3-thienyl)-thiophen and 2-chloroethyl-phenylether

N-(4-ethyl-2-thienylmethyl)-N-(2-phenoxyethyl)-amine; from 2-aminomethyl-4-ethyl-thiophen and 2-chloroethyl-phenylether

N-(4-chloro-2-thienylmethyl)-N-(2-phenoxyethyl)-amine; from 2-aminomethyl-4-chloro-thiophen and 2-chloroethyl-phenylether

30 N-(4-fluoro-3-biphenylmethyl)-N-(2-(3-cyano-phenoxy-ethyl)-amine, maleate, m.p. 158-160°; from 3-aminomethyl-4-fluoro-biphenyl and 2-chloroethyl-(3-cyano-phenyl)-ether

from 3-aminomethyl-biphenyl and 2-chloroethyl-(2-methoxy-phenyl)-ether

N-(3-biphenylmethyl)-N-(2-(2-methoxy-phenoxy)-ethyl)-amine, m.p. 72-74°; from 3-aminomethyl-biphenyl and 2-chloroethyl-2-biphenyl-ether

35 N-(3-biphenylmethyl)-N-(2-(2-biphenyloxy)-ethyl)-amine, maleate, m.p. 146-148°; from 3-aminomethyl-5-(4-fluoro-phenyl)-pyridine and 2-chloroethyl-(2-biphenyl)-ether

N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-(2-biphenyloxy)-ethyl)-amine, m.p. 134-136°; from 3-aminomethyl-biphenyl and 2-chloroethyl-(2-hydroxyphenyl)-ether

40 N-(3-biphenylmethyl)-N-(2-(2-hydroxyphenoxy)-ethyl)-amine, m.p. 88-90°; from 3-aminomethyl-biphenyl and 2-chloroethyl-(2-hydroxyphenyl)-ether

Example 7

A solution of 1.2 g 2-hydroxy-benzonitrile and 2.5 g N-(2-chloroethyl)-N-(5-phenyl-3-pyridylmethyl)-amine [obtainable by reaction of 2-hydroxyaniline with 3-chloromethyl-5-phenylpyridine and subsequent transformation of the product to the 2-chloroethyl-compound by reaction with PCl₅] in 200 ml of acetonitrile is stirred for 5 hours at room temperature and worked up in a conventional manner to give N-[2-(2-cyano-phenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine. Stirring with 0.5 equivalents of oxalic acid in 100 ml ethanol gives the oxalate, m.p. 208°.

The following are obtained analogously:

50 N-[2-(2-chlorophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine; from 2-chloro-phenol and N-(2-chloroethyl)-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(2-methylphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine; from 2-methyl-phenol and N-(2-chloroethyl)-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(4-chlorophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine; from 4-chloro-phenol and N-(2-chloroethyl)-N-(5-phenyl-3-pyridylmethyl)-amine

55 N-[2-(4-cyano-phenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine; from 4-cyano-phenol and N-(2-chloroethyl)-N-(5-phenyl-3-pyridylmethyl)-amine

from 3-ethyl-phenol and N-(2-chloroethyl)-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(3-ethylphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine; from 4-trifluoromethyl-phenol and N-(2-chloroethyl)-N-(5-phenyl-3-pyridylmethyl)-amine



US005767132A

United States Patent [19]**Böttcher et al.**[11] **Patent Number:** **5,767,132**[45] **Date of Patent:** **Jun. 16, 1998**[54] **PYRIDYL CHROMAN**

[75] **Inventors:** Henning Böttcher; Ralf DeVant, both of Darmstadt; Hartmut Greiner; Gerd Bartoszyk, both of Weiterstadt, all of Germany; Jean-Jacques Berthelon; Marc Noblet, both of Lyons, France; Jean-Jacques Zeiller, Villenbonne, France; Michel Brunet, Toussieu, France

[73] **Assignee:** Merck Patent Gesellschaft Mit Beschränkter Haftung, Germany

[21] **Appl. No.:** 543,727[22] **Filed:** Oct. 16, 1995[30] **Foreign Application Priority Data**Oct. 14, 1994 [EP] **European Pat. Off.** 94116223[51] **Int. Cl.⁶** C07D 405/12; A61K 31/44[52] **U.S. Cl.** 514/337; 514/456; 514/444; 549/60; 549/404; 549/407; 546/282.1[58] **Field of Search** 546/282.1; 549/60, 549/404, 407; 514/337, 456, 444[56] **References Cited****U.S. PATENT DOCUMENTS**

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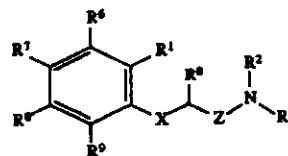
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Primary Examiner—Jane Fan*Attorney, Agent, or Firm*—Millen, White, Zelano & Branigan, P.C.[57] **ABSTRACT**

Amino(thio)ether derivatives of formula I



wherein R⁰, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, X and Z are as defined herein, and their salts, are active on the central nervous system.

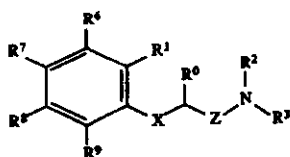
15 Claims, No Drawings

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PYRIDYL CHROMAN

The invention relates to novel amino(thio)ether derivatives of formula I



wherein

X is oxygen, sulphur, sulfinyl, sulfonyl or, in the case where R⁰ and R¹ are not together an alkylene chain with 1-3 atoms, also CH₂.

Z is —(CH₂)_{n1}—(CH₂)_{n2}—(CH₂)_{n3} with
n₁=0, 1, 2 or 3;
n₂=0 or 1;
n₃=0, 1, 2 or 3 and the proviso that
n₁+n₂+n₃<4.

R⁰ is hydrogen or A.

R¹ is hydrogen, A, OA, phenoxy, Ph, OH, F, Cl, Br, CN, CF₃, COOH, COOA, acyloxy with 1-4 C atoms, carboxamido, —CH₂NH₂, —CH₂NHA, —CH₂NA₂, —CH₂NHAc, —CH₂NHSO₂CH₃, or

R⁰ and R¹ are together an alkylene chain with 1-3 C atoms or an alkenylene chain with 2-3 C atoms.

R² is hydrogen, A, Ac or —CH₂—R⁴.

R³ is —CH₂—R⁴, or —CH₂—R⁴.

R⁴ is Ph, 2-, 3- or 4-pyridyl which is unsubstituted or monosubstituted by R⁵, or thiophene which is unsubstituted, mono- or disubstituted by A, OA, OH, F, Cl, Br, CN and/or CF₃, or by another thienyl group.

R⁵ is a phenyl group which is unsubstituted, or mono-, di-, tri-, tetra- or pentasubstituted by F, CF₃, partially or completely fluorinated A, A and/or OA.

R⁶, R⁷, R⁸ are independently of each other H, A, OA, phenoxy, OH, F, and

R⁹ Cl, Br, I, CN, CF₃, NO₂, NH₂, NHA, NA₂, Ac, Ph, cycloalkyl with 3-7 C atoms, —CH₂NH₂, —CH₂NHA, —CH₂NA₂, —CH₂NHAc or —CH₂NHSO₂CH₃ or two adjacent residues are together an alkylene chain with 3 or 4 C atoms, and/or

R¹ and R⁶ are together an alkylene chain with 3 or 4 C atoms.

A is alkyl with 1-6 C atoms.

Ac is alkanoyl having 1-10 C atoms or aroyl having 7-11 C atoms.

Ph is phenyl which is unsubstituted or substituted by R⁵, 2-, 3- or 4-pyridyl or phenoxy.

and the physiologically acceptable salts thereof.

An object of the invention is to provide novel compounds capable of being used for the preparation of drugs.

Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

It has been found that the compounds of formula I and their biocompatible acid addition salts possess valuable pharmacological properties. Thus, in particular, they are active on the central nervous system, especially as serotonin agonists and antagonists. They inhibit the binding of tritiated serotonin ligands to hippocampal receptors (Cossery et al., European J. Pharmacol. 140 (1987), 143-155). They also

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modify the accumulation of DOPA in the corpus striatum and the accumulation of 5-HTP in the nuclei raphe (Seyfried et al., European J. Pharmacol. 160 (1989), 31-41). They also have analgesic and hypotensive effects; thus, in catheterized, conscious, spontaneously hypertensive rats (strain: SHR/Okamoto/NIH-MO-CHB-Kisslegg; method: q.v. Weeks and Jones, Proc. Soc. Exptl. Biol. Med. 104 (1960), 646-648), the directly measured blood pressure is lowered after oral administration of the compounds. They are also useful for prophylaxis and control of the sequelae of cerebral infarction (Apoplexia cerebri) such as stroke and cerebral ischaemia.

These substances can be used in the treatment of diseases which are related to interferences in the serotonergic and dopaminergic systems and which involve the ligands with high affinity to the 5-hydroxytryptamin (5HTTA type) or/and dopamine (D2 type) receptors.

They are suitable for the treatment of disorders of the central nervous system such as anxiety, tension and depression states, sexual dysfunctions caused by the central nervous system, disturbances in sleep or absorption of food. Furthermore, they are suitable to eliminate cognitive deficiencies, to improve powers of learning and memory and to treat Alzheimer's disease. They are also suitable for psychosis (schizophrenia).

Compounds of formula I and their biocompatible acid addition salts can therefore be used as active ingredients for anxiolytics, antidepressants, neuroleptics, and/or antihypertensives, and also as intermediates for the preparation of other pharmaceutical active ingredients.

The invention relates to the amino(thio)ether derivatives of formula I and to their biocompatible acid addition salts.

The radical A is alkyl having 1, 2, 3, 4, 5 or 6 C atoms, especially 1 or 2 C atoms, preferably methyl and also ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl. OA is preferably methoxy and also ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy. NHA is preferably methylamino and also ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, sec-butyl amino or tert-butylamino. NA₂ is preferably dimethylamino and also N-ethyl-N-methylamino, diethylamino, di-n-propylamino, diisopropylamino or di-n-butylamino.

Ac is preferably alkanoyl having 1-6, in particular 1, 2, 3 or 4 C atoms, in detail preferably formyl or acetyl. Furthermore, preferably propionyl, butyryl, isobutyryl, pentanoyl or hexanoyl, and in addition preferably benzoyl, o-, m- or p-tolyl, 1- or 2-naphthoyl.

X is preferably oxygen or sulphur, whereas Z stands chiefly for —CH₂—, —(CH₂)₂—, —(CH₂)₃—, —CHCH₃—, furthermore also preferably for —CH₂—(CHCH₃)—, —(CH₂)₂—CHCH₃—, —CH₂—(CHCH₃)—CH₂— or —(CHCH₃)—(CH₂)₂—.

The residue R⁰ is preferably H or methyl, but R⁰ and R¹ are preferably together an alkylene chain, especially a chain having 2 C atoms. If R¹ is different from the meaning given previously it is preferably hydrogen, A, OA, CONH₂ or CN.

R² is preferably H or A and R³ is preferably 2-, 3- or 4-pyridylmethyl or phenyl which is substituted by another phenyl or furthermore, R³ is thienyl which is preferably substituted by another thienyl group.

The meaning of R³ is chiefly 2-, 3-, 4-pyridylmethyl, 5-phenyl-3-pyridylmethyl, 5-(fluorophenyl)-3-pyridylmethyl, 5-methoxyphenyl-3-pyridylmethyl, 4'-fluoro-3-biphenylmethyl, 3-biphenylmethyl or 4-(thienyl)-2-thienylmethyl. Furthermore, the meaning of R³ is preferably 2-, 4-, 5- or 6-(q-fluorophenyl)-3-pyridylmethyl, 3-, 4-, 5- or 6-(q-fluorophenyl)-2-pyridyl methyl or 2- or 3-(q-

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-fluorophenyl)-4-pyridyl methyl whereby q stands for the prefixes mono-, di-, tri-, tetra- or penta-.

R⁶, R⁷, R⁸ and R⁹ are preferably independently of each other H, A, OA, Cl, CN or CF₃. Furthermore, R¹ and R⁶ are preferably together an alkylene chain with 4 C atoms. Furthermore, another preferred meaning is that two adjacent residues selected from R⁶, R⁷, R⁸ and R⁹ are together an alkylene chain with 3 or 4 C atoms.

Accordingly, the invention relates particularly to those compounds of formula I in which at least one of said radicals has one of the meanings indicated above, especially one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following partial formulae Ia to II, which correspond to formula I and in which the radicals and parameters not described in greater detail are as defined for formula I, but in which:

in Ia, X is oxygen, R⁰ and R¹ are together —(CH₂)₂—, Z is methylene and R⁶, R⁷, R⁸ and R⁹ are hydrogen;

in Ib, X is oxygen, R⁰ and R¹ are together —(CH₂)₂—, Z is methylene and R⁴ is pyridyl or biphenyl which is unsubstituted or monosubstituted;

in Ic, X is oxygen, R⁰ and R¹ are together —(CH₂)₂—, Z is methylene and R⁴ is 5-(4-fluorophenyl)-3-pyridyl;

in Id, X is oxygen, R⁰ and R¹ are together methylene and R⁴ is 5-(4-fluorophenyl)-3-pyridyl;

in Ie, X is oxygen, R⁰ is hydrogen, Z is methylene and R⁴ is 5-(4-fluorophenyl)-3-pyridyl;

in If, X is oxygen, R⁰ and R¹ are hydrogen, Z is methylene and R⁴ is 5-(4-fluorophenyl)-3-pyridyl;

in Ig, X is oxygen, R⁰ is hydrogen, R¹ is chlorine, ethyl or methoxy, Z is methylene and R⁴ is 4-(4-fluorophenyl)-3-pyridyl;

in Ih, X is oxygen, Z is methylene and R⁴ is 5-phenyl-3-pyridyl;

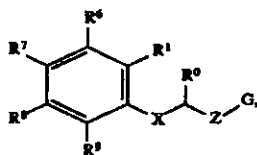
in II, X is oxygen, Z is —(CH₂)₂—, —(CH₂)₃— or —(CHCH₃)— and R⁴ is 5-(4-fluorophenyl)-3-pyridyl,

and the salts thereof.

Especially preferred compounds are those of partial formulae Ik and Iak to Iik, which correspond to partial formulae I and Ia to II, but in which additionally:

X is sulphur, sulfinyl or sulfonyl.

The invention further relates to a process for the preparation of derivatives of formula I and their salts, characterized in that a compound of formula II



wherein

G is Cl, Br, I, OH or an OH group functionally modified to form a reactive group, especially a suitable leaving group, and R⁰, R¹, R⁶, R⁷, R⁸, R⁹, X and Z are as defined,

is reacted with an amine of formula III

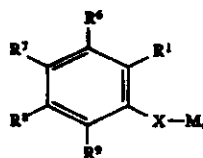


wherein

R² and R³ are as defined,

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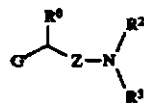
or in that a compound of the formula IV



IV

wherein,

M is H, Li⁺, Na⁺, K⁺, NH₄⁺ or another suitable metal ion, and X, R¹, R⁶, R⁷, R⁸ and R⁹ are as defined, is reacted with a compound of formula V

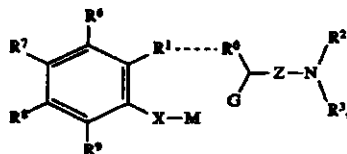


V

wherein

G' has the definitions given for G and R⁰, R², R³ and Z are as defined,

or in that a compound of formula VI



VI

wherein

R⁰ and R¹ are together an alkylene chain with 1-3 C atoms, and R², R³, R⁶, R⁷, R⁸, R⁹, X, Z, M and G are as already defined,

is cyclised to an aminoether or aminothioether derivative of formula I, or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C—C and/or C—N bonds is treated with a reducing agent, or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more solvolizable groups is treated with a solvolizing agent, and/or in that an OA group is optionally cleaved to form an OH group, and/or an Ar group is converted into another Ar group, and/or in that a resulting base or acid of formula I is converted into one of its salts by treatment with an acid or base.

The compounds of formula I are otherwise prepared by methods known per se, such as those described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York), namely under reaction conditions such as those which are known and suitable for said reactions. It is also possible to make use of variants known per se, which are not mentioned in greater detail here.

If desired, the starting materials for the claimed process can also be formed in situ in such a way that they are not isolated from the reaction mixture but are immediately reacted further to give the compounds of formula I.

In the derivatives of formula II, G is preferably Cl or Br, but it can also be I, OH or an OH group functionally modified to form a reactive group, especially alkylsulphonyloxy having 1-6 C atoms (e.g. methanesulphonyloxy) or arylsulphonyloxy having 6-10 C atoms (e.g.

benzenesulphonyloxy, p-toluenesulphonyloxy, naphthalene-1- or -2-sulphonyloxy).

Some of the compounds of formulae II and, in particular, III are known; the unknown compounds of formulae II and III can easily be prepared analogously to the known compounds.

Primary alcohols of the formula II can be obtained e.g. by reducing the appropriate carboxylic acids or their esters. Treatment with thionyl chloride, hydrogen bromide, phosphorus tribromide or similar halogen compounds yields the corresponding halides of the compounds of the formula II. The corresponding sulphonyloxy compounds can be obtained from the alcohols of formula II by reaction with the appropriate sulphonyl chlorides.

The iodine compounds of the formula II can be obtained, e.g., by reacting potassium iodide with the appropriate p-toluenesulphonic acid esters.

Most of the amine derivatives of formula III are known and can be obtained, e.g., by alkylation or acylation of known amines.

The reaction of the compounds of formulae II and III proceeds according to methods such as those known from the literature for the alkylation of amines. The components can be melted together in the absence of a solvent, in a sealed tube or an autoclave if necessary. It is also possible, however, to react the compounds in the presence of an inert solvent. Examples of suitable solvents are hydrocarbons such as benzene, toluene or xylene; ketones such as acetone or butanone; alcohols such as methanol, ethanol, isopropanol or n-butanol; ethers such as tetrahydrofuran (THF) or dioxane; amides such as dimethylformamide (DMF) or N-methyl-pyrrolidone; or nitriles such as acetonitrile, or else, if desired, mixtures of these solvents with one another or mixtures with water. It can be favourable to add an acid-binding agent, for example an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or another alkali metal or alkaline earth metal salt of a weak acid, preferably a potassium, sodium or calcium salt, or to add an organic base such as triethylamine, dimethylamine, pyridine or quinoline, or an excess of the amine component. The reaction time is between a few minutes and 14 days depending on the conditions used, and the reaction temperature is preferably about 0°–150°, normally 20°–130°.

It is also possible to obtain a compound of formula I by reacting a compound of formula IV with a compound of formula $G'(CHR^0)-Z-NR^2R^3$ (V).

Some of the compounds of formulae V and, in particular, IV are known; the unknown compounds can easily be prepared analogously to the known compounds. Thus, compounds of formula IV can easily be prepared by metalation of a phenol or thiophenol with for example hydrides such as NaH, KH, or with phenyllithium or methyllithium. It is also possible to obtain compounds of formula IV by the oxidation of thiophenols to yield sulfinyl or sulfonyl-compounds.

The amines of formula V can be prepared starting from a primary amine by means of the diverse possibilities of alkylation or acylation of amines known per se. It is also possible to convert appropriately substituted nitro compounds into the amines of formula V by reduction and subsequent alkylation.

The reaction of compounds of formulae IV and V proceeds according to methods which are known from the literature for the formation of ethers, thioethers or esters. The components can be melted with one another directly, without the presence of a solvent, if appropriate in a closed tube or in an autoclave, at normal pressure or at elevated pressure, an inert gas such as, e.g., N_2 being added to

increase the pressure. However, it is also possible to react the compounds in the presence of an inert solvent. Suitable solvents are those mentioned previously for the reaction of compounds of formula II with those of formula III. The addition of an acid-binding agent to the reaction mixture can also have a favorable effect. The same bases are suitable as those previously described for the reaction of compounds of formulae II and III.

Depending on the reaction conditions chosen, the optimum reaction time is between a few minutes and 14 days, and the reaction temperature is preferably about 0°–150°, usually 20°–130°.

Furthermore, a compound of formula I can be obtained by cyclization of a compound of formula VI wherein R^0 and R^1 are together an alkylene chain with 1 to 3 C atoms.

Compounds of the formula VI can be obtained, for example, by the reduction of ketones which are similar to compounds of formula VI but wherein the CHG-group is replaced by a carbonyl group.

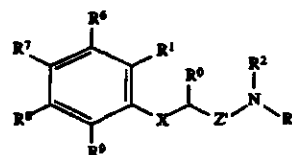
The cyclization reaction of a compound of the formula VI proceeds according to the methods described previously for the reaction of the compounds of formulae IV and V under equal reaction conditions.

A compound of formula I can also be obtained by treating a precursor, in which hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C—C and/or C—N bonds, with a reducing agent, preferably at temperatures of about –80° to +250°, in the presence of at least one inert solvent.

Reducible groups (groups replaceable by hydrogen) are, in particular, oxygen in a carbonyl group, hydroxyl, arylsulphonyl (e.g., p-toluenesulphonyloxy), N-benzenesulphonyl, N-benzyl or O-benzyl.

In principle, compounds containing only one of the above-mentioned groups or additional bonds, or compounds containing two or more of the above-mentioned groups or additional bonds adjacent to one another, can be converted into a compound of formula I by reduction, it being possible simultaneously to reduce substituents which are present in the starting compound. This is, for example, carried out using nascent hydrogen or complex metal hydrides or by means of a Wolff-Kishner reduction or the reductions with hydrogen gas under transition metal catalysis.

Preferred starting materials for the reduction have formula VII



wherein

Z is a chain which corresponds to the radical Z except that one or more $-CH_2$ groups have been replaced by $-CO-$ and/or one or more hydrogen atoms have been replaced by Cl, Br, F, SH, or OH groups.

Compounds of formula VII can be obtained by amidation of acids, acid halides, anhydrides or esters with primary or secondary amines. It is preferred to react the free carboxylic acid with the amine under the conditions of a peptide synthesis. This reaction is preferably carried out in the presence of a dehydrating agent, e.g. a carbodiimide such as dicyclohexylcarbodiimide or else N-(3-dimethylaminopropyl)-N-ethylcarbodiimide, or propanephosphonic anhydride (q.v. Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxycarbonyl-1.

2-dihydroquinoline, in an inert solvent e.g. a halogenated hydrocarbon such as methylene chloride, an ether such as THF or dioxane, an amide such as DMF or dimethylacetamide, or a nitrile such as acetonitrile, at temperatures of preferably about -10° – 40° , especially 0° – 30° .

If nascent hydrogen is used as the reducing agent, this can be produced e.g. by treating metals with weak acids or with bases. Thus it is possible e.g. to use a mixture of zinc with an alkali metal hydroxide solution or a mixture of iron with acetic acid. It is also appropriate to use sodium or another alkali metal in an alcohol such as ethanol, isopropanol, butanol, amyl or isoamyl alcohol or phenol. It is also possible to use an aluminium-nickel alloy in aqueous-alkaline solution, ethanol being added if necessary. Sodium amalgam or aluminium amalgam in aqueous-alcoholic or aqueous solution is also suitable for producing the nascent hydrogen. The reaction can also be carried out in the heterogeneous phase, in which case it is convenient to use an aqueous phase and a benzene or toluene phase.

Other reducing agents which can be used to particular advantage a complex metal hydrides such as LiAlH_4 , NaBH_4 , diisobutylaluminium hydride or $\text{NaAl}(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2\text{H}_2$, and diborane, catalysts such BF_3 , AlCl_3 or LiBr being added if desired. Solvents which are suitable for this purpose are, in particular, ethers such as diethyl ether, di-*n*-butyl ether, THF, dioxane, diglyme or 1,2-dimethoxyethane, and hydrocarbons such as benzene. Solvents which are suitable for a reduction with NaBH_4 are primarily alcohols such as methanol or ethanol, as well as water and aqueous alcohols. Reduction by these methods is preferably carried out at temperatures of preferably about -80° to $+150^{\circ}$, especially about 0° – 100° .

The reduction of $-\text{CO}$ groups in acid amides (e.g. those of formula VI in which Z' is a $-(\text{CH}_2)_n(\text{CH}_2)_m-\text{CO}$ group) to CH_2 groups can be carried out to particular advantage with LiAlH_4 in THF at temperatures of preferably about 0° – 66° .

It is also possible to reduce one or more carbonyl groups to CH_2 groups according to the Wolff-Kishner method, e.g. by treatment with anhydrous hydrazine in absolute ethanol, under pressure, at temperatures of preferably about 150° – 250° . A sodium alcoholate is advantageously used as the catalyst. The reduction can also be varied according to the Huang-Minlon method by carrying out the reaction with hydrazine hydrate in a high-boiling water-miscible solvent such as diethylene glycol or triethylene glycol, in the presence of an alkali such as sodium hydroxide. The reaction mixture is normally boiled for about 34 hours. The water is then distilled off and the hydrazone formed is decomposed at temperatures of up to about 200° . The Wolff-Kishner reduction can also be carried out with hydrazine in dimethyl sulphoxide at room temperature.

Moreover, it is possible to carry out certain reductions by using H_2 gas under the catalytic action of transition metals, such as e.g. Raney Ni or Pd. In this way, e.g. Cl, Br, I, SH or, in certain cases, even OH groups can be replaced by hydrogen. Nitro groups can also be converted into NH_2 groups by catalytic hydrogenation with Pd/H_2 in methanol.

Compounds which have formula I except that one or more H atoms have been replaced by one or more solvolyzable groups can be solvolyzed, especially hydrolyzed, to give the compounds of formula I.

The starting materials for the solvolysis can be obtained, for example, by reacting compounds of formula III with compounds which have formula II except that one or more H atoms have been replaced by one or more solvolyzable groups. Thus, in particular, 1-acylamine derivatives (which

have formula I except that, in the 1-position of the radical, they contain an acyl group, preferably an alkanoyl, alkylsulphonyl or arylsulphonyl group having up to 10 C atoms in each case, such as methanesulphonyl, benzenesulphonyl or p-toluenesulphonyl) can be hydrolyzed to give the corresponding secondary amine derivatives, e.g., in an acidic or, preferably, neutral or alkaline medium at temperatures of preferably about 0° – 200° . Sodium, potassium or calcium hydroxide, sodium or potassium carbonate, or ammonia, is conveniently used as the base. The chosen solvents are preferably water; lower alcohols such as methanol or ethanol; ethers such as THF or dioxane; sulphoses such as tetramethylene sulphose; or mixtures thereof, especially mixtures containing water. Hydrolysis can also be carried out simply by treatment with water alone, especially at the boiling point.

A compound of formula I can furthermore be converted to another compound of formula I by methods known per se.

Compounds of formula I in which for example R^2 is hydrogen can be converted to compounds with tertiary amino groups by alkylation or acylation of the secondary amino residue in an inert solvent, e.g. a halogenated hydrocarbon such as methylene chloride, an ether such as THF or dioxane, an amide such as DMF or dimethylacetamide, or a nitrile such as acetonitrile, at temperatures of about -10° to the boiling point of the solvent, preferably 0° – 70° . Furthermore, other primary amino groups can be transformed to secondary or tertiary amino groups by the known alkylation reactions.

Compounds of formula I can also be converted into other derivatives of formula I by transformations at the radical Ar.

Ethers of formula I in which the radical Ph is mono- or disubstituted by O-alkyl can be cleaved, the corresponding hydroxy derivatives being formed. It is possible, e.g. to cleave the ethers by treatment with dimethyl sulphide-boron tribromide complex, for example in toluene, ethers such as THF or dimethyl sulphoxide, or by melting with pyridine or aniline hydrohalides, preferably pyridine hydrochloride, at about 150° – 250° .

If other side reactions in the compounds of formula I are to be excluded, the radicals Ph can be chlorinated, brominated or alkylated under the conditions of the Friedel-Crafts reactions, by reacting the appropriate halogen or alkyl chloride or alkyl bromide under the catalysis of Lewis acids, such as, e.g., AlCl_3 , FeBr_3 or Fe, at temperatures of about 30° – 150° , expediently 50° – 150° in an inert solvent, such as, e.g., hydrocarbons, THF or carbon tetrachloride, with the compound of the formula I to be derivatised. Moreover, it is for example possible to reduce a nitro group to an amino group by the reactions known per se.

The compounds of formula I can possess one or more centres of asymmetry. When prepared, they can therefore be obtained as racemates or else in the optically active form if optically active starting materials are used. When synthesized, compounds possessing two or more centres of asymmetry are generally obtained as mixtures of racemates, from which the individual racemates can be isolated in the pure form, for example by recrystallization from inert solvents. If desired, the racemates obtained can be chemically or by crystallization of conglomerates resolved into their optical antipodes by the methods known per se. Preferably, diastereoisomers are formed from the racemate by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids such as the D and L forms of protected amino acid derivatives such as tosylproline, tartaric acid, dibenzoyltartaric acid, diacetyl-tartaric acid, camphor-sulphonic acids, mandelic acid, malic

acid or lactic acid. The different forms of the diastereoisomers can be resolved in a manner known per se, e.g. by fractional crystallization, and the optically active compounds of formula I can be liberated from the diastereoisomers in a manner known per se.

A base of formula I can be converted with an acid into the corresponding acid addition salt. Acids which produce biocompatible salts are suitable for this reaction. Thus it is possible to use inorganic acids, e.g. sulphuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid and sulphamic acid, as well as organic acids, i. e. specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulphonic or sulphuric acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methanesulphonic or ethanesulphonic acid, ethanedithiolphonic acid, 2-hydroxyethanesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid, naphthalenemonosulphonic and naphthalenedithiolphonic acids and laurylsulphuric acid.

If desired, the free bases of formula I can be liberated from their salts by treatment with strong bases such as sodium or potassium hydroxide or sodium or potassium carbonate provided there are no other acid group in the molecule. In those cases where the compounds of the formula I have free acid groups, salt formation can also be achieved by treatment with bases. Suitable bases are alkali metal hydroxides, alkaline earth metal hydroxides or organic bases in the form of primary, secondary or tertiary amines.

The invention further relates to the use of the compounds of formula I and their biocompatible salts for the manufacture of pharmaceutical preparations, especially by a non-chemical route. For this purpose, they can be converted into a suitable dosage form together with at least one excipient or adjunct and, if appropriate, in combination with one or more additional active ingredients.

The invention further relates to compositions, especially pharmaceutical preparations, containing at least one compound of formula I and/or one of their biocompatible salts. These preparations can be used as drugs in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g. oral), parenteral or topical administration and which do not react with the novel compounds, examples of such excipients being water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. Tablets, coated tablets, capsules, syrups, juices, drops or suppositories are used in particular for enteral administration, solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical administration. The novel compounds can also be lyophilized and the resulting lyophilizates used e.g. to manufacture injectable preparations.

The preparations indicated can be sterilized and/or can contain adjuncts such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colourants, taste correctors and/or flavourings. If desired, they can also contain one or more additional active ingredients, e.g. one or more vitamins.

The compounds of formula I and their biocompatible salts can be used for the therapeutic treatment of the human or

animal body and for controlling diseases. They can be used for treating disorders of the central nervous system, such as tension, depressions and/or psychoses, and side-effects in the treatment of hypertension (e.g. with α -methyl-dopa). The compounds can also be used in endocrinology and gynaecology, e.g. for the therapeutic treatment of acromegaly, hypogonadism, secondary amenorrhoea, premenstrual syndrome and undesired puerperal lactation, and also for the prophylaxis and therapy of cerebral disorders (e.g. migraine), especially in geriatrics in a manner similar to certain ergot alkaloids and for controlling the sequelae of cerebral infarction (Apoplexia cerebri), such as stroke and cerebral ischaemia.

Furthermore, they are suitable to eliminate cognitive deficiencies, to improve the power of learning and memory and to treat Alzheimer disease.

In these treatments, the substances of formula I of the invention are normally administered analogously to known, commercially available preparations (e.g. bromocriptine, dihydroergocomin), preferably in dosages of about 0.2–500 mg, especially about 0.2–50 mg per dosage unit. The daily dosage is preferably about 0.001–10 mg/kg of body weight. The low dosages (about 0.2–1 mg per dosage unit; about 0.001–0.005 mg/kg of body weight) are particularly suitable for use as anti-migraine preparations; dosages of about 10–50 mg per dosage unit are preferred for the other indications. However, the particular dose for each individual patient depends on a very wide variety of factors, for example, the activity of the particular compound used, age, body weight, general state of health, sex, diet, time and method of administration, rate of excretion, drug combination and severity of the particular disease to which the therapy is applied. Oral administration is preferred.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight.

The entire disclosure of all applications, patents and publications, cited above and below, and of corresponding European application 94116223.2, are hereby incorporated by reference.

EXAMPLES

In the following Examples, "working-up in conventional manner" means: Water is added if necessary, extraction is carried out with methylene chloride, the organic phase is separated off, dried over sodium sulphate and filtered, the filtrate is evaporated and the residue is purified by chromatography on silica gel and/or by crystallization. Temperatures are given in °C.

Example 1

A solution of 2.8 g 2-aminomethyl-chromane [obtainable by reacting 3-(2-hydroxy-phenyl)-propanal with KCN and subsequent catalytic reduction of the 2-cyano-chromane] and 2.2 g 3-chloromethyl-pyridine in 250 ml of DMF are stirred together with 1 g N-methyl-morpholine for 12 hours at 20° and worked up in a conventional manner to give 65 N-(3-pyridylmethyl)-N-(2-chroman-yl-methyl)-amine. Stirring with 0.5 equivalents of maleic acid in 100 ml ethanol gives the maleate, m.p. 163°–164°.

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N-[2-(2,4-dichlorophenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridyl-methyl]-amine, maleate, m.p. 148°-150°;
from 3-methoxyphenol sodium salt and "A"
N-[2-(3-methoxyphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridyl-methyl]-amine, maleate, m.p. 122°-124°;
from 4-methoxyphenol sodium salt and "A"
N-[2-(4-methoxyphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridyl-methyl]-amine, m.p. 94°-96°;
from 3-chlorophenol sodium salt and "A"
N-[2-(3-chlorophenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 150°-152°;
from 2-chlorophenol sodium salt and "A"
N-[2-(2-chlorophenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 153°-155°;
from 2-methoxyphenol sodium salt and "A"
N-[2-(2-methoxyphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 134°-136°;
from 4-chlorophenol sodium salt and "A"
N-[2-(4-chlorophenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 163°-164°;
from 2-ethylphenol sodium salt and "A"
N-[2-(2-ethylphenoxy)ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 128°-130°;
from 3-cyanophenol sodium salt and "A"
N-[2-(3-cyanophenyl)ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, oxalate, m.p. 245° (using oxalic acid in place of maleic acid);
from 4-cyanophenol sodium salt and "A"
N-[2-(4-cyanophenyl)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, oxalate, m.p. 250°;
from phenol sodium salt and N-[3-phenoxy-benzyl]-amine N-(2-phenoxy-ethyl)-N-(3-phenoxy-benzyl)-amine, maleate, m.p. 166°-168°;
from phenol sodium salt and "A"
N-(2-phenoxyethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, m.p. 84°-86°.

Example 4

By reaction of 2-aminomethyl-6-methoxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine analogously to Example 1 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[6-methoxy-2-chroman-yl]-methyl-amine is obtained. Stirring with hydrochloric acid gives the dihydrochloride, m.p. 205°-206°.

Example 5

By reaction of 2-aminomethyl-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine analogously to Example 1 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-chroman-yl)-methyl-amine is obtained. Stirring with hydrochloric acid gives the dihydrochloride-hemihydrate, m.p. 210°-213°.

Example 6

A solution of 1.8 g 3-aminomethyl-biphenyl [obtainable by reducing 3-cyano-biphenyl] and 1.6 g 2-chloroethyl-phenylether [obtainable by reaction of sodium-phenolate with dichloroethane] in 200 ml of acetonitrile is stirred for 8 hours at room temperature and worked up in a conventional manner to give N-(3-biphenylmethyl)-N-2-phenoxyethyl-amine. Stirring with 0.5 equivalents of maleic acid in 100 ml ethanol gives the maleate, m.p. 178°-180°.

The following are obtained analogously:

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from 3-aminomethyl-4'-fluoro-biphenyl and 2-chloroethyl-phenylether
N-(4'-fluoro-3-biphenylmethyl)-N-2-phenoxyethyl-amine, maleate, m.p. 194°-196°;
from 3-aminomethyl-2',4'-difluoro-biphenyl and 2-chloroethyl-phenylether
N-(2',4'-difluoro-3-biphenylmethyl)-N-2-phenoxyethyl-amine;
from 3-aminomethyl-5-phenylpyridine and 2-chloroethyl-phenylether
N-(5-phenyl-3-pyridylmethyl)-N-2-phenoxyethyl-amine, m.p. 77°-70°;
from 2-aminomethyl-4-(3-thienyl)-thiophene and 2-chloroethyl-phenylether
N-[4-(3-thienyl)-2-thienylmethyl]-N-2-phenoxyethyl-amine, m.p. 96°-98°;
from 2-aminomethyl-4-methyl-thiophene and 2-chloroethyl-phenylether
N-(4-methyl-2-thienylmethyl)-N-2-phenoxyethyl-amine;
from 2-aminomethyl-4-methoxy-thiophene and 2-chloroethyl-phenylether
N-(4-methoxy-2-thienylmethyl)-N-2-phenoxyethyl-amine;
from 2-aminomethyl-4-ethyl-thiophene and 2-chloroethyl-phenylether
N-(4-ethyl-2-thienylmethyl)-N-2-phenoxyethyl-amine;
from 2-aminomethyl-4-chloro-thiophene and 2-chloroethyl-phenylether
N-(4-chloro-2-thienylmethyl)-N-2-phenoxyethyl-amine;
from 3-aminomethyl-4'-fluoro-biphenyl and 2-chloroethyl-(3-cyano-phenyl)-ether
N-(4'-fluoro-3-biphenylmethyl)-N-2-(3-cyano-phenoxy-ethyl)-amine, maleate, m.p. 158°-160°;
from 3-aminomethyl-biphenyl and 2-chloroethyl-(2-methoxy-phenyl)-ether
N-(3-biphenylmethyl)-N-2-(2-methoxy-phenoxy)-ethyl-amine, m.p. 72°-74°;
from 3-aminomethyl-biphenyl and 2-chloroethyl-2-biphenyl-ether
N-(3-biphenylmethyl)-N-2-(2-biphenyloxy)-ethylamine, maleate, m.p. 146°-148°;
from 3-aminomethyl-5-(4-fluoro-phenyl)-pyridine and 2-chloroethyl-(2-biphenyl)-ether
N-[5-(4-fluorophenyl-3-pyridylmethyl)]-N-2-(2-biphenyloxy)-ethyl-amine, m.p. 134°-136°;
from 3-aminomethyl-biphenyl and 2-chloroethyl-(2-hydroxyphenyl)-ether
N-(3-biphenylmethyl)-N-2-(2-hydroxyphenoxy)-ethylamine, m.p. 88°-90°;

Example 7

A solution of 1.2 g 2-hydroxy-benzonitrile and 2.5 g N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine [obtainable by reaction of 2-hydroxyethylamine with 3-chloromethyl-5-phenyl-pyridine and subsequent transformation of the product to the 2-chloroethyl-compound by reaction with PCl_3] in 200 ml of acetonitrile is stirred for 5 hours at room temperature and worked up in a conventional manner to give N-[2-(2-cyanophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine. Stirring with 0.5 equivalents of oxalic acid in 100 ml ethanol gives the oxalate, m.p. 208°.

The following are obtained analogously:
from 2-chloro-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

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N-[2-(2-chlorophenoxy)-ethyl]-N-5-phenyl-3-pyridylmethyl-amine;
from 2-methyl-phenol and N-2-chloroethyl-N-5-phenyl-3-pyridylmethyl-amine

N-[2-(2-methylphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;
from 4-chloro-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(4-chlorophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;
from 4-cyano-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(4-cyanophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;
from 3-ethyl-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(3-ethylphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;
from 4-trifluoromethyl-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(4-trifluoromethylphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;
from 2-bromo-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(2-bromophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;
from 2-aminomethyl-phenyl and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(2-aminomethylphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;
from 4-methoxy-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(4-methoxyphenoxy)-ethyl]-N-5-phenyl-3-pyridylmethyl-amine;
from 3-aminomethyl-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(3-aminomethylphenoxy)-ethyl]-N-5-phenyl-3-pyridylmethyl-amine;
from 4-aminomethyl-phenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(4-aminomethylphenoxy)-ethyl]-N-5-phenyl-3-pyridylmethyl-amine.

Example 8

A mixture of 3.1 g N-[2-(2-cyanophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine, 3 g NaOH, 50 ml of water and 40 ml of diethylene glycol monoethyl ether is stirred for 3 hours at a bath temperature of 140°. It is cooled and worked up after a conventional manner, and N-[2-(2-carboxamidophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine is obtained. Stirring with 0.5 equivalents of oxalic acid in 100 ml ethanol gives the oxalate, m.p. 230°.

Example 9

Analogously to Example 8 N-[2-(4-carboxamidophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine is obtained by partial hydrolysis of N-[2-(4-cyanophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine.

Example 10

Starting from N-[2-(4-cyanophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine analogously to Example 8,

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boiling for 16 hours and then working up in a conventional manner gives N-[2-(4-carboxyphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine.

Example 11

Starting from N-[2-(2-cyanophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine analogously to Example 8, boiling for 16 hours and then working up in a conventional manner gives N-[2-(2-carboxyphenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine.

Example 12

Analogously to Example 7 a solution of 2.3 g sodium phenolate and 2.5 g N-3-chloropropyl-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine [obtainable by reaction of 3-hydroxypropylamine with 3-chloromethyl-5-(4-fluorophenyl)-pyridine and subsequent transformation of the product to the 3-chloropropyl-compound by reaction with PCl_3] in 200 ml of acetonitrile is stirred for 5 hours at room temperature and worked up in a conventional manner to give N-(3-phenoxy-propyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine. Stirring with Q5 equivalents of oxalic acid in 100 ml ethanol/water mixture gives the oxalate-hemihydrate, m.p. 217°.

The following are obtained analogously:

from sodium phenolate and N-4-chlorobutyl-N-[5-(4-fluorophenyl)-3-pyridylmethyl]amine

N-(4-phenoxy-butyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 143°;

from sodium phenolate and N-2-chloroisopropyl-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine

N-(2-phenoxy-isopropyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, maleate, m.p. 123°-125°;

from sodium thiophenolate and N-2-chloroethyl-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine

N-(2-thiophenoxyethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, oxalate, m.p. 230°;

from sodium thiophenolate and N-4-chlorobutyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-(4-thiophenoxy-butyl)-N-(5-phenyl-3-pyridylmethyl)-amine;

from sodium thiophenolate and N-3-chloropropyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-(3-thiophenoxy-propyl)-N-(5-phenyl-3-pyridylmethyl)-amine;

from sodium thiophenolate and N-2-chloroisopropyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-(2-thiophenoxy-isopropyl)-N-(5-phenyl-3-pyridylmethyl)amine.

Example 13

According to Example 7 the following are obtained analogously:

from 2-chloro-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(2-chlorothiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 2-methyl-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(2-methylchlorothiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 4-chloro-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(4-chlorothiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

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from 4-cyano-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(4-cyanothiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 3-ethyl-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(3-ethylthiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 4-trifluoromethyl-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(4-trifluoromethylthiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 2-bromo-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(2-bromothiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 2-aminomethyl-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(2-aminomethylthiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 4-methoxy-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(4-methoxythiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 3-aminomethyl-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(3-aminomethylthiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine;

from 4-aminomethyl-thiophenol and N-2-chloroethyl-N-(5-phenyl-3-pyridylmethyl)-amine

N-[2-(4-aminomethylthiophenoxy)-ethyl]-N-(5-phenyl-3-pyridylmethyl)-amine.

Example 14

A solution of 2.8 g N-[2-(2-methoxyphenoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine [obtainable according to Example 3] and one equivalent 3-chloromethyl-5-(4-fluorophenyl)-pyridine in 125 ml of acetonitrile are stirred for 6 hours at 400 and worked up in a conventional manner to give N-[2-(2-methoxyphenoxy)-ethyl]-N-bis-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, m.p. 90°-92°.

The following are obtained analogously by reaction with 3-chloromethyl-5-(4-fluorophenyl)-pyridine:

and N-(4-phenoxy-butyl)-N-(5-phenyl-3-pyridylmethyl)-amine

N-(4-phenoxy-butyl)-N-(5-phenyl-3-pyridylmethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine;

and N-(2-phenoxy-isopropyl)-N-(5-phenyl-3-pyridylmethyl)-amine

N-(2-phenoxy-isopropyl)-N-(5-phenyl-3-pyridylmethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine;

and N-(2-thiophenoxy-ethyl)-N-(5-phenyl-3-pyridylmethyl)-amine

N-(2-thiophenoxy-ethyl)-N-(5-phenyl-3-pyridylmethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine;

and N-(4-thiophenoxy-butyl)-N-(5-phenyl-3-pyridylmethyl)-amine

N-(4-thiophenoxy-butyl)-N-(5-phenyl-3-pyridylmethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine.

Example 15

Analogously to Example 7 a solution of 2.3 g sodium 1-naphtholate and 2.9 g N-2-chloroethyl-N-[5-(4-

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fluorophenyl-3-pyridylmethyl)-amine [obtainable by reaction of 2-hydroxyethylamine with 3-chloromethyl-5-(4-fluorophenyl)-pyridine and subsequent transformation of the product to the 2-chloroethyl-compound by reaction with PCl_3] in 200 ml of acetonitrile is stirred for 5 hours at room temperature and worked up in a conventional manner to give N-[2-(1-naphthoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, m.p. 92°-94°.

The following are obtained analogously by reaction of 2-naphtholate

with N-2-chloroethyl-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine:

N-[2-(2-naphthoxy)-ethyl]-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine, m.p. 128°-130°;

with N-2-chloroethyl-N-[5-(2,4-difluorophenyl)-3-pyridylmethyl]-amine:

N-[2-(2-naphthoxy)-ethyl]-N-[5-(2,4-difluorophenyl)-3-pyridylmethyl]-amine.

Example 16

A solution of 2.1 g N-(2-phenoxy-ethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine [obtainable according to Example 3] in 100 ml THF is treated with 2 ml methyl iodide under stirring over a period of 3 hours. Working up in a conventional manner gives N-(2-phenoxy-ethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-methyl-amine, oxalate, m.p. 159°-161°.

The following are obtained analogously by alkylation of the secondary amines:

N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-chromanyl-methyl)-N-methyl-amine, m.p. 71°;

N-3-biphenylmethyl-N-(2-chromanyl-methyl)-N-methyl-amine.

Example 17

By reaction of N-[5-(4-fluorophenyl)-3-pyridylmethyl]-amine with 1-chloro-3-phenylpropane analogously to Example 1 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(3-phenylpropyl)-amine is obtained, m.p. <50°.

Example 18

Analogously to Example 3 one obtains by reaction of phenol sodium salt with N-(2-chloroethyl)-N-3-(2-pyridyl)-chloromethyl-benzene

N-[3-(2-pyridyl)-phenylmethyl]-N-[2-(phenoxy)-ethyl]-amine, maleate, m.p. 170°;

phenol sodium salt with N-(2-chloroethyl)-N-3-(3-pyridyl)-chloromethyl-benzene

N-[3-(3-pyridyl)-phenylmethyl]-N-[2-(phenoxy)-ethyl]-amine, maleate, m.p. 123°-125°.

Preparation of enantiomeric compounds:

Example 19

A solution of 4.5 g 2-aminomethyl-chromane [obtainable by reacting 3-(2-hydroxy-phenyl)-propanal with KCN and subsequent catalytic reduction of the 2-cyano-chromane] and 3.9 g tosylproline in 190 ml ethanol are refluxed for 15 minutes. Afterwards the solution is cooled down to 5° while it is stirred. During the cooling procedure a few crystals of pure (R)-2-aminomethyl-chromane were added. The solution was kept under stirring at 50 for a period of 18 hours and afterwards the pure enantiomer (R)-2-aminomethyl-chromane was separated. The crystallisation process was

repeated two times with the crystals derived from the first crystallisation in order to yield an enantiomeric excess of more than 99%.

Subsequently the (R)-2-aminomethyl-chromane was reacted with 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine analogously to Example 1 to give (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane [(R)-(-)-1 N-(5-(4-fluorophenyl)-3-pyridylmethyl)-N-2-chromanyl-methyl]-amine]. Stirring with 0.1 n hydrochloric acid solution yields the dihydrochloride, m.p. 234°-235°; $[\alpha]_D^{20} = -65^\circ$ (c=1, methanol).

Analogously by reaction of (S)-2-aminomethyl-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine (S)-(+)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane [(S)-(+)-1 N-(5-(4-fluorophenyl)-3-pyridylmethyl)-N-(2-chromanyl-methyl)-amine] is obtained. Stirring with 0.1 n hydrochloric acid solution yields the dihydrochloride, m.p. 227°-228°; $[\alpha]_D^{20} = +62^\circ$ (c=1, methanol).

Analogously by reaction of (S)-2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine: (S)-(+)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-8-methoxy-chromane [(S)-(+)-1 N-(5-(4-fluorophenyl)-3-pyridylmethyl)-N-[2-(8-methoxy-chromanyl)-methyl]-amine] is obtained. Stirring with 0.1 n hydrochloric acid solution yields the dihydrochloride, m.p. 214°-215°.

Analogously by reaction of (R)-2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine: (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-8-methoxy-chromane [(R)-(-)-1 N-(5-(4-fluorophenyl)-3-pyridylmethyl)-N-[2-(8-methoxy-chromanyl)-methyl]-amine] is obtained. Stirring with 0.1 n hydrochloric acid solution yields the dihydrochloride, m.p. 214°.

Example 20

A solution of 5 g (R)-2-aminomethyl-chromane [obtainable by reaction of 2-carboxy-chromane and (+)-phenylethylamine, separation of the mainly crystallising diastereomer purification by recrystallisation from ethanol, transformation into the ethyl chromanate, additional purification via HPLC chiral phases (Chiracel OJ™), transformation into the amide, reduction with LiAlH_4 or Vitrider™ in THF to give the (R)-2-aminomethyl-chromane] was reacted with 3-(chloromethyl)-5-phenyl-pyridine analogously to Example 1 to give (R)-(-)-2-[5-phenyl-3-pyridyl-methylaminomethyl]-chromane [(R)-(-)-1 N-(5-phenyl-3-pyridylmethyl)-N-(2-chromanyl-methyl)-amine]. Stirring with 0.1 n hydrochloric acid solution yields the dihydrochloride, m.p. 243°-244°.

Analogously by reaction of (S)-2-aminomethyl-chromane and 3-(chloromethyl)-5-phenyl-pyridine (S)-(+)-2-[5-phenyl-3-pyridyl-methylaminomethyl]-chromane [(S)-(+)-1 N-(5-phenyl-3-pyridylmethyl)-N-(2-chromanyl-methyl)-amine] is obtained. Stirring with 0.1 n hydrochloric acid solution yields the dihydrochloride, m.p. 244°-245°.

Analogously by reaction of (S)-2-aminomethyl-8-methoxychromane and 3-(chloromethyl)-4'-fluoro-biphenyl: (S)-(+)-2-[4'-fluor-3-biphenyl-yl-methylaminomethyl]-8-methoxy-chromane [(S)-(+)-1 N-(4'-fluor-3-biphenyl-yl-methyl)-N-[2-(8-methoxy-chromanyl)-methyl]-amine] is obtained. Stirring with 0.1 n hydrochloric acid solution yields the dihydrochloride, m.p. 189°-190°; $[\alpha]_D^{20} = +74^\circ$ (c=1, methanol).

Analogously by reaction of (R)-2-aminomethyl-8-methoxy-chromane and 3-(chloromethyl)-4'-fluoro-biphenyl:

(R)-(-)-2-[4'-fluor-3-biphenyl-yl-methylaminomethyl]-8-methoxy-chromane [(R)-(-)-1 N-(4'-fluor-3-biphenyl-yl-methyl)-N-[2-(8-methoxy-chromanyl)-methyl]-amine] is obtained. Stirring with 0.1 n hydrochloric acid solution yields the dihydrochloride, m.p. 189°-190°; $[\alpha]_D^{20} = -74.3^\circ$ (c=1, methanol).

The examples below relate to pharmaceutical preparations.

Example A: Injection vials

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate in 3 l of doubly distilled water is adjusted to pH 6.5 with 2 N hydrochloric acid, sterile filtered, filled into injection vials and lyophilized under sterile conditions, and the vials are closed in a sterile manner. Each injection vial contains 5 mg of active compound.

Example B: Suppositories

A mixture of 20 g of active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, and the mixture is poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: Solution

A solution of 1 g of active compound of the formula I, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride is prepared in 940 ml of doubly distilled water. The solution is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of active compound of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: Tablets

A mixture of 100 g of an active compound of the formula I, 1 kg of lactose, 600 g of microcrystalline cellulose, 600 g of maize starch, 100 g of polyvinyl-pyrrolidone, 80 g of talc and 10 g of magnesium stearate is pressed to give tablets in a customary manner, such that each tablet contains 10 mg of active compound.

Example F: Coated tablets

Tablets are pressed as stated in Example E and then coated in a customary manner with a coating of sucrose, maize starch, talc, tragacanth and colorant.

Example G: Capsules

Hard gelatin capsules are filled with an active compound of the formula I in the customary manner, so that each capsule contains 5 mg of active compound.

Example H: Inhalation spray

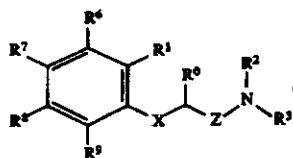
14 g of active compound of the formula I are dissolved in 10 l of isotonic NaCl solution and the solution is filled into commercially available spray containers having a pump mechanism. The solution can be sprayed into the mouth or nose. One spray burst (about 0.1 ml) corresponds to a dose of about 0.14 mg.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A compound of formula I



wherein

X is oxygen;

Z is $-(CH_2)_{n1}-(CH_2)_{n2}-(CH_2)_{n3}-$;

n1 is 0, 1, 2 or 3;

n2 is 0 or 1;

n3 is 0, 1, 2 or 3;

n1+n2+n3 is less than 4;

R⁰ and R¹ together are an alkylene chain having 2 C atoms or an alkenylene chain having 2 C atoms;

R² is H, A, Ac or $-CH_2-R^4$;

R³ is $-CH_2-R^4$ or $-CH_2A-R^4$;

R⁴ is phenyl, 2-, 3- or 4-pyridyl which is, in each case, monosubstituted by R⁵;

R⁵ is a phenyl group which is unsubstituted, or mono-, di-, tri-, tetra- or pentasubstituted by F, CF₃, A, OA, partial or completely fluorinated A, or combinations thereof;

R⁶, R⁷, R⁸ and R⁹ are independently of each other H, A, OA, phenoxy, OH, F, Cl, Br, I, CN, CF₃, NO₂, NH₂, NHA, NA₂, Ac, Ph, cycloalkyl having 3-7 C atoms, $-CH_2NH_2$, $-CH_2NHA$, $-CH_2NA_2$, $-CH_2NHAc$ or $-CH_2NHSO_2CH_3$;

A is alkyl having 1-6 C atoms;

Ac is alkanoyl having 1-10 C atoms or aroyl having 7-11 C atoms;

Ph is unsubstituted phenyl or phenyl substituted by R⁵, 2-, 3- or 4-pyridyl or phenoxy; or

a physiologically acceptable salt thereof.

2. A compound according to claim 1, wherein said compound is:

(a) N-(5-phenyl-3-pyridylmethyl)-N-2-chromanyl-methylamine or a physiologically acceptable salt thereof;

(b) N-[5-(4-methoxyphenyl)-3-pyridylmethyl]-N-2-chromanyl-methylamine or a physiologically acceptable salt thereof;

(c) N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-2-chromanyl-methylamine or a physiologically acceptable salt thereof;

(d) N-(4'-fluoro-3-biphenylmethyl)-N-2-chromanyl-methylamine or a physiologically acceptable salt thereof;

(e) N-(3-biphenylmethyl)-N-2-chromanyl-methylamine or a physiologically acceptable salt thereof.

3. A compound according to claim 1, wherein said compound is:

N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-[(8-methoxy-2-chromanyl)-methyl]-amine or a physiologically acceptable salt thereof.

4. A compound according to claim 1, wherein said is an enantiomer.

5. A compound according to claim 1, wherein Z is methylene and R⁶, R⁷, R⁸ and R⁹ are each hydrogen.

6. A compound according to claim 1, Z is methylene.

7. A compound according to claim 1, wherein Z is methylene, and R⁴ is 5-(4-fluorophenyl)-3-pyridyl.

8. A compound according to claim 1, wherein Z is methylene and R⁴ is 5-phenyl-3-pyridyl.

9. A compound according to claim 1, wherein Z is $-(CH_2)_2-$, $-(CH_2)_3-$ or $-(CHCH_3)-$ and R⁴ is 5-(4-fluorophenyl)-3-pyridyl.

10. A compound according to claim 1, wherein,

X is oxygen;

Z is $-CH_2-$, $-(CH)_2-$, $-(CH_2)_3-$, $-(CHCH_3)-$, $-CH_2-(CHCH_3)-$, $-(CH_2)_2-(CHCH_3)-$, $-CH_2-(CHCH_3)-CH_2-$ or $-(CHCH_3)-(CH_2)_2-$;

R⁰ and R¹ together are an alkylene or alkenylene chain with 2 C atoms;

R² is H or A;

R³ is 5-phenyl-3-pyridylmethyl, 5-(fluorophenyl)-3-pyridylmethyl, 5-(methoxyphenyl)-3-pyridylmethyl, 4'-fluoro-3-biphenylmethyl, 3-biphenylmethyl, 2-(q-fluorophenyl)-3-pyridylmethyl, 4-(q-fluorophenyl)-3-pyridylmethyl, 5-(q-fluorophenyl)-3-pyridylmethyl, 6-(q-fluorophenyl)-3-pyridylmethyl, 3-(q-fluorophenyl)-2-pyridylmethyl, 4-(q-fluorophenyl)-2-pyridylmethyl, 5-(q-fluorophenyl)-2-pyridylmethyl, 6-(q-fluorophenyl)-2-pyridylmethyl, 2-(q-fluorophenyl)-4-pyridylmethyl or 3-(q-fluorophenyl)-4-pyridylmethyl, wherein q stands for the prefixes mono-, di-, tri- tetra- or penta-; and

R⁶, R⁷, R⁸ and R⁹ are, in each case independently, H, A, OA, Cl, CN or CF₃.

11. A compound according to claim 1, wherein said compound is (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane.

12. A pharmaceutical composition comprising compound according to claim 1 and a pharmaceutically acceptable carrier.

13. A composition according to claim 12, wherein said composition contains 0.2-500 mg of said compound.

14. A method of treating psychosis or anxiety comprising administering an effective amount of a compound to claim 1.

15. A method according to claim 14, wherein said compound is administered in an amount of 0.001-10 mg/kg of body weight.

* * * * *

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C., 30/11/2007

Abogado
Emilio Ferrero
(Apoderado)

ASUNTO	Radicación	01 19802
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	15745
	Folios	006

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☒		
Vía PCT (fase nacional)	☐	Cap. I	☐
		Cap. II	☐

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 2 a 40
- 1.2. Reivindicaciones: Folios: 41 a 44
Folios: 108 a 110 Memorial de 11/01/2007
- 1.3. Prioridad: EP00104531 de 10/03/2000
- 1.6 Respuesta del solicitante: Folios: 118 a 128 Memorial de 16/11/2007

2. Objeto de la Invención:

Título de la solicitud

- ***“Nuevo uso de (R)-(-)-2-[5-(4-florofenil)-3-piridilmetil-aminometil]-cromano y sus sales aceptables para uso fisiológico”***
- El objeto de la presente solicitud de patente de invención consiste en el uso del compuesto (R)-(-)-2-[5-(4-florofenil)-3-piridilmetil-aminometil]-cromano o de una sal del mismo aceptable para uso fisiológico para la fabricación de un medicamento para el tratamiento de afecciones extrapiramidales relacionadas

con el movimiento y/o para la fabricación de un medicamento para el tratamiento de los efectos adversos de los fármacos contra el Parkinson mediante la estimulación de los receptores 5-HT_{1A} de las vías del rafe nigral y del rafe estriado.

Reivindicación 1: Se reivindica una composición farmacéutica que comprende como principios activos:

- i) (R)-(-)-2-[5-(4-florofenil)-3-piridilmetil-aminometil]-cromano o una sal fisiológicamente aceptable del mismo.
- ii) L-Dopa

En combinación con uno o más excipientes farmacéuticamente aceptables.

Reivindicación 2: Se reivindica un kit de dos composiciones separadas, la primera comprende como único activo principal (R)-(-)-2-[5-(4-florofenil)-3-piridilmetil-aminometil]-cromano o una de sus sales farmacéuticamente aceptables.

Y la segunda comprende L-Dopa

Sustento Descriptivo

Se afirma que en contraste con el arte previo – es decir el compuesto bupiriona – el compuesto (R)-(-)-2-[5-(4-florofenil)-3-piridilmetil-aminometil]-cromano es mucho más potente (30 veces) sobre el receptor 5-HT_{1A} con una IC₅₀ de 1nmol/L, con respecto a la bupiriona de 30nmol/L. Además las sales del compuesto en mención muestran un antagonismo frente a los receptores de D₂, bajo dosis incrementadas, hecho éste que representan una ventaja adicional en comparación con los antagonistas convencionales de 5-HT_{1A} como la bupiriona. Y es por el antagonismo D₂ que presenta el compuesto en mención que se disminuye el riesgo de las reacciones psicóticas y discinesia causadas por la estimulación de los receptores de serotonina, situación que causaba el problema técnico que pretende resolver la solicitud en estudio mediante la estimulación más selectiva de los receptores a través del antagonismo 5-HT_{1A} y la interacción el receptor D₃, el cual genera efectos ventajosos en el sistema extrapiramidal motor.

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 P²⁵/16** de la **Clasificación Internacional de Patentes**.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D. 486)

- El solicitante reclama protección para una combinación farmacológica que comprende los principios activos: Sarizotán y L-Dopa, no obstante, en la cláusula 2 del pliego reclamado incorpora un kit de partes que comprende dos composiciones separadas. Al respecto esta Dependencia se permite señalar que dado que el sinergismo de potenciación de dos sustancias activas se predica de la administración asociada de los principios activos y en dosificaciones específicas, no es claro por qué el solicitante pretende

protección para composiciones separadas cuando de las composiciones independientes de cada una de las dos sustancias se tiene noticia desde mucho antes de la presentación de la solicitud.

Al reivindicar de esa manera el producto se está haciendo alusión tanto al uso como al método de tratamiento terapéutico basado en la administración independiente de las sustancias y no como se ha planteado en el aparte reivindicatorio y descriptivo de la solicitud, en términos de una mezcla de sustancias terapéuticamente activas que disminuye la incidencia de psicosis, discinesia y fluctuaciones motoras causadas cuando se trata la enfermedad de Parkinson exclusivamente con L-dopa.

Es decir que, en tratándose de un sinergismo de Potenciación en el que uno de los fármacos presenta actividad intrínseca, es decir, es capaz de producir el efecto (para el presente caso Sarizotán) y el otro fármaco es capaz de "ayudar" a que ese efecto se realice más fácilmente, sin que por su uso en dosis elevadas se produzcan efectos colaterales indeseables (caso de L-dopa), resulta incuestionable que la mezcla de sustancias debe presentarse en forma de una composición farmacológica que contiene los dos activos y no como erróneamente se define en términos que hacen alusión al uso y método de tratamiento basado en la actividad independiente de composiciones separadas. Si ese fuere el caso, se desvirtuaría la ventaja técnica atribuida a la administración de la mezcla de sustancias y se reduciría a materia conocida en el estado del arte.

Queda claro entonces que la mera especificación de funciones o medios técnicos, en este caso atribuidas a un kit de partes y extrapoladas a partir del comportamiento de la mezcla de sustancias, no implica automáticamente que el objeto de la solicitud de patente en la cláusula 2, siendo en este caso de producto, cumpla con el requisito básico de ser de carácter técnico. Por la separación de las composiciones se pierde la ventaja técnica atribuida a la asociación física que se administra en un mismo portador y no como se muestra en el capítulo reivindicatorio solamente en un mismo embalaje, dado que entonces se trataría de un diseño para la presentación de dos productos con características técnicas distintas y diferenciadas.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 10/03/2000, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

Nº	Documento	Título	Fecha de Publicación*
D1	US5767132	"Pyridyl chroman"	16/06/1998
D2	EP0707007	"Amino(tío)ether derivatives as CNS active agentes"	17/04/1996

Anterioridades D1 y D2 en los folios 129 a 147

12. Análisis de patentabilidad (artículo 14 D. 486)

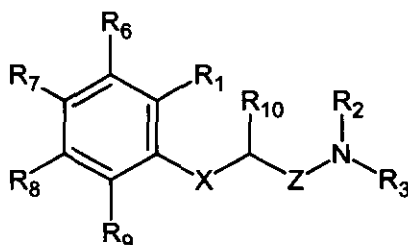
12.2 Nivel inventivo (artículo 18 D. 486)

La reivindicación 2 hace referencia a un kit que comprende dos composiciones separadas:

- La primera de (R)-(-)-2-[5-(4-florofenil)-3-piridilmetil-aminometil]-cromano o una de sus sales fisiológicamente aceptables como único activo principal
- La segunda de L-dopa como un compuesto activo

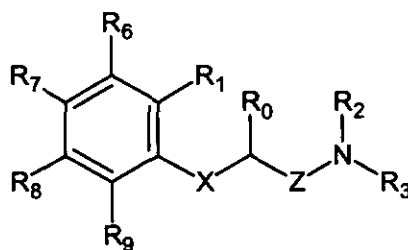
Las anterioridades relacionadas de acuerdo con el estudio del arte más próximo a la invención son:

Documento D1: En el cual se señala que compuestos derivados del núcleo de la fórmula (I), a continuación relacionado, como es el caso de (R)-(-)-2-[5-(4-florofenil)-3-piridilmetil-aminometil]-cromano (Sarizotán) pueden formularse en composiciones farmacéuticas en dosis aproximadas entre 0,2 y 500mg – ver columna 21 líneas 6 a 8 del folio 146 -.



En dicho documento también se señalan composiciones farmacéuticas constituidas por estructuras que responden a la fórmula (I) las cuales pueden formularse con Metil-dopa para el tratamiento de desordenes del sistema nervioso central como depresión y/o psicosis e incluso hipertensión – ver columna 10 líneas 1 a 4 del folio 140-.

Documento D2: Hace referencia a compuestos amino-tio-éter derivados que presentan la siguiente estructura:



Dentro de los que se encuentran la estructura 1N-[5-(4-fluorofenil)-3-piridilmetil]-N-(2-cromanil-metil)-amina del ejemplo 5, el cual junto con Metil-dopa pueden constituir composiciones farmacéuticas destinadas para el tratamiento de la tensión, depresión y/o psicosis

Como se observa, existen composiciones independientes que contienen el compuesto Sarizotán y además que lo combinan con principios activos como Metil-dopa, compuesto análogo estructural de la L-dopa. Y siendo que ésta constituye la

única diferencia técnica existente entre las características que definen las composiciones reclamadas por el interesado bajo el preámbulo de kit y la materia que revela el estado del arte, es posible concluir que dicha diferencia resulta irrelevante para efecto de la valoración de la altura inventiva dado que un conocedor de la materia hubiera podido anticipar las composiciones reclamadas.

Si bien no se trata de L- Dopa, las composiciones independientes del kit incorporan metil-dopa cuyo efecto farmacológico es similar a la l-dopa, en este sentido resulta incuestionable que la cláusula 2 se deriva evidentemente de las enseñanzas reveladas en las anterioridades en comento y por consiguiente no cumple con el requisito de altura inventiva.

De otro lado, si se tiene en cuenta que el problema técnico esbozado por el señor solicitante tienen que ver con los efectos colaterales indeseables causados por las dosificaciones elevadas de L-dopa en el tratamiento de la enfermedad de Parkinson y que la solución se deriva del efecto sinérgico de potenciación que ocurre cuando se administran concomitantemente las sustancias: Sarizotán y L-dopa en una misma composición farmacéutica resulta indiscutible que dicho efecto técnico desaparece cuando se separan los principios activos. Y en el caso de la cláusula 2, su contenido desvirtúa la ventaja técnica atribuida a la administración de la mezcla de sustancias y reduce la materia a objetos conocidos en el estado del arte.

No sobra resaltar que la mera especificación de funciones o medios técnicos, en este caso atribuidas a un kit de partes y extrapoladas a partir del comportamiento de la mezcla de sustancias, no implica automáticamente que el objeto de la solicitud de patente en la cláusula 2, siendo en este caso de producto, cumpla con el requisito básico de ser de carácter técnico y por consiguiente solucionar el problema técnico planteado. Y por la separación de las composiciones se pierde la ventaja técnica atribuida a la asociación y no puede afirmarse que las características técnicas se conservan por el mero hecho de incorporar dos composiciones independientes en un mismo embalaje ya que entonces la invención trataría de un diseño para la presentación de dos productos con características técnicas distintas y diferenciadas y no de una composición farmacológicamente activa que contiene dos ingredientes en un mismo portador.

13. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	US5767132	2	Nivel Inventivo
D2	EP0707007	2	Nivel Inventivo

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TÉCNICO No. 2438	EXAMINADOR TÉCNICO Código No. 202044
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