

BOGOTÁ - COLOMBIA  
OFICINA FUNDADA EN 1941  
APARTADO AEREO 12304  
TEL: 57-1-3264270 57-1-6069700  
FAX: 57-1-3264271 57-1-6069701  
CABLES: LLOREDA  
CALLE 72 No. 5-83 5º. PISO  
www.lloredacamacho.com  
lloco@lloredacamacho.com

Señor

SUPERINTENDENTE DE INDUSTRIA Y  
DIVISION DE NUEVAS CREACIONES

E. \_\_\_\_\_ S. \_\_\_\_\_

SECRETARÍA DE INDUSTRIA Y COMERCIO



Nº. 08-120702- -00001-0000

EXAMEN DE PATENTE DE INVENCION EN FASE NACIONAL  
EXAMEN DE PATENTE DE INVENCION EN FASE NACIONAL II  
EXAMEN DE PATENTE DE INVENCION EN FASE NACIONAL III

Re: P1.-F. HOFFMANN-LA ROCHE AG.-Solicitud de Patente de  
Invención en Fase Nacional PCT para "PIRIDIN-4-IL-ETINIL-  
IMIDAZOLES Y PIRAZOLES COMO ANTAGONISTAS DEL  
RECEPTOR MGLU5".-Clase CO7D 401/06.-Expediente número  
06-120.702.-

1. Me refiero a mi solicitud de patente de 29 de Noviembre de 2006.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **578** de 31 de Julio de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo **II**.
4. Anexo me permito acompañar recibo número 08-4.849, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

154

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No 06-120702-00001-0000

SECRETARIA DE INDUSTRIA Y COMERCIO  
DIRECCION GENERAL DE PATENTES Y MARCAS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

HIT : 30014689-2

RECIBO OFICIAL DE PAGO : 06 - 4,049  
FECHA : ABRIL 21 DE 2008

\*\*\*\*\* D E D E C L A R A C I O N \*\*\*\*\*

| DEPOSITANTE       | TIPO PAGO    | BANCO           | CUENTA   | No. PAGO | FECHA PGO  | MONT         |
|-------------------|--------------|-----------------|----------|----------|------------|--------------|
| LLORCA Y CIA S. A | CONSTRUCCION | BANCO DE BOGOTA | 60284307 | 3492410  | 28/04/2008 | 2,750,000.00 |

\*\*\*\*\* C O N C E P T O \*\*\*\*\*

| CANT. IDENTIFICACION      | CONCEPTO                               | TOTAL CONCEPTO |
|---------------------------|----------------------------------------|----------------|
| 1 2008-01-01 CALIFICACION | 114 PTO CAP Y EXAMEN DE PATENTABILIDAD | 210,000.00     |
|                           | 70 AL 1                                | 210,000.00     |

SOL: DOSCIENTOS DIEZ MIL PESOS

RESPONSABLE :

RECIBO DE PAGO APLICADO AL EXPEDIENTE No. \_\_\_\_\_

**DIVISIÓN DE NUEVAS CREACIONES**

RADICACIÓN EXPEDIENTE No. 06-120702

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **578** DE

FECHA **31 DE JULIO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **26 DE OCTUBRE DE 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI \_\_\_\_\_

NO     X

156  
156

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

202012

Bogotá, D.C., 16 de febrero de 2010

Apoderado: Alicia Lloreda Ricaurte

|        |            |           |
|--------|------------|-----------|
| ASUNTO | Radicación | 06-120702 |
|        | Trámite    | 002       |
|        | Evento     | 001       |
|        | Actuación  | 430       |
|        | Oficio     | ...       |
|        | Folios     | ...       |

Patente de Invención



Vía PCT (fase nacional)



Cap. I



Cap. II



No. Sol. Internacional

PCT/EP2005/005559

Fecha de Presentación Internal.

20/may/2005

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. | <u>Descripción:</u>      | Folios: 65 a 129                                                   | Como se radicó inicialmente.                                                                |
| 1.2. | <u>Reivindicaciones:</u> | Folios 43 a 49<br>Folios 130 a 142                                 | Como se debió presentar.<br>Modificación presentada al momento de entrada en fase nacional. |
| 1.3. | <u>Prioridad:</u>        | Folio 1: PCT/EP2004/005881, 01/06/2004<br>EP04021216.9, 07/09/2004 |                                                                                             |

**2. Modificaciones no aceptadas (artículo 34 D.486 y art. 22 Tratado PCT)**

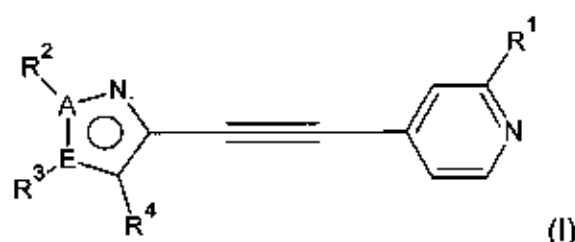
En el oficio (folio 65) mediante el cual el solicitante presentó el capítulo reivindicatorio tal como había sido presentado en la solicitud internacional, el solicitante manifiesta que en ejercicio del derecho conferido por el artículo 28 numeral 1 del tratado PCT, el capítulo reivindicatorio fue modificado al momento de su presentación en fase nacional. Esta oficina considera que el solicitante hizo una lectura errónea del artículo citado porque dicha modificación no está prevista en el momento de entrada

a fase nacional, como lo confirman el artículo 22 y 34 del mismo Tratado, sino tan sólo **después** de haberse admitido a dicha fase nacional y solo previo diligenciamiento y presentación de un formulario único de correcciones y modificaciones y pago de una tasa (numeral 1.2.1.6 del capítulo quinto, título X de la circular única de la Superintendencia de Industria y Comercio). Puesto que dicho formulario no se presentó y el pago tampoco se efectuó, dicha modificación no podía tomarse en cuenta, mucho menos a la entrada de la fase nacional de PCT.

### 3. Objeto de la invención

Título de la solicitud: PIRIDIN-4-IL-ETINIL-IMIDAZOLES Y PIRAZOLES COMO ANTAGONISTAS DEL RECEPTOR MGLU5

El objeto de la presente son los compuestos que caen bajo el alcance de la fórmula Markush:



Reivindicaciones 1-10, 17: Un compuesto de la fórmula (I).

Reivindicaciones 11,12 y 13: Procesos para obtener los derivados imidazol.

Reivindicación 14: proceso para obtener los derivados pirazol.

Reivindicación 15 y 16: Medicamento que contiene los compuestos.

Reivindicación 18: Uso.

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.):  
C07D401/06, A61K31/4439, 31/444, A61P25/22

### 4. De la solicitud de Patente

#### 4.1. Reivindicaciones (artículo 30 D 486 de la C.A.N.)

La reivindicación 1 y sus dependientes, no es clara respecto a las estructuras inequívocas que se quiere significar con la denominación genérica de "cicloalquilo".

-Las reivindicaciones 15 y 16, en primer lugar son exactamente la misma materia, en segundo lugar los usos y tratamiento terapéuticos no son características técnicas de un medicamento (Composición).

-La reivindicación 17, reclama los compuestos ya reclamados en las reivindicaciones 1-10, sin ninguna característica técnica particular, sólo se rellena el texto de una mezcla de uso con método de tratamiento.

Las reivindicaciones no cumplen con lo exigido en el art. 30 de la Decisión 486.y/o art.22 Tratado PCT.

## 5. Unidad de invención (artículo 25 D 486 de la C.A.N.)

La presente solicitud no conserva la unidad de invención, después de realizado el examen de patentabilidad se encuentran los siguientes grupos inventivos y cada uno de ellos requiere de búsquedas independientes, lo vamos a referenciar respecto al grupo heterocíclico variable, o sea, anillos imidazol y pirazol.

- (i) piridin-4-il-etinil-imidazoles
- (ii) piridin-4-il-etinil-pirazoles.

Para cada uno de estos grupos se requiere un examen de patentabilidad independiente.

## 6. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486 de la C.A.N.)

La reivindicación 18 reclama el uso de compuestos y de acuerdo con la legislación colombiana el uso no se considera para protección por patente, como se lee en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina "... Los Países Miembros otorgarán patentes para las invenciones sean de productos o procedimientos en todos los campos de la tecnología..."; aquí NO se hace alusión a que el uso sea patentable.

Los usos o segundos usos no son patentables, de conformidad con la sentencia del TJAC 89-AI-2000, en general los usos no son patentables

## 7. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el estado de la técnica fecha de presentación de la solicitud de la cual se reclama prioridad, **01/06/2004**.

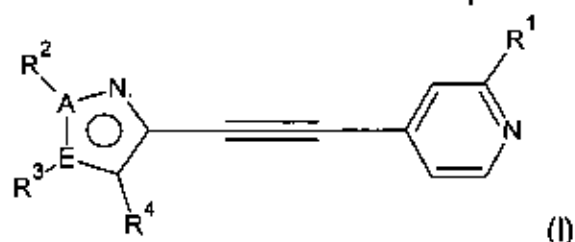
Teniendo en cuenta la fecha indicada se realizó la búsqueda del estado de la técnica, en bases de datos en las que esta oficina tiene acceso libre, en búsqueda de documentos relacionados con la materia que se reclama como nueva e inventiva en presente solicitud, encontrándose los siguientes documentos más relevantes:

| Nº | Documento    | Título                                                  | Fecha de presentación |
|----|--------------|---------------------------------------------------------|-----------------------|
| D1 | WO2004108701 | Imidazole derivatives as glutamate receptor antagonists | 05/jun/2003           |
| D2 | WO2004080998 | Imisazol-4-yl-ethynyl-pyridine derivatives              | 10/mar/2003           |

## 8. Análisis de patentabilidad (según requisito) (artículo 14 D486)

### 8.1 Novedad (artículo 16 D486 de la C.A.N.)

La solicitud en estudio reclama los compuestos de la fórmula Markush(I):



-Las anterioridades D1 y D2 escriben derivados piridin-4-il-etinil-imidazol tetra sustituidos:



que es la primera invención reivindicada y para la cual se hace este análisis de patentabilidad. Tal como puede verse en todo el contenido de las anterioridades D1 y D2 se refieren a los derivados piridin-4-il-etinil-imidazol tetra sustituidos, las composiciones que los comprenden y su método de obtención, entonces así las cosas la solicitud en estudio es una generalización de las anterioridades; por lo cual los compuestos reivindicados, su método de obtención y las composiciones que los comprenden no pueden considerarse nuevos.

Por lo tanto la solicitud en estudio no cumple con el requisito exigido en el artículo 16 D486 de la C.A.N.

## 9. Conclusión:

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

| Nº | Documento Nº | Reivindicaciones afectadas | Requisito que afecta |
|----|--------------|----------------------------|----------------------|
| D1 | WO2004108701 | 1-18                       | Novedad              |
| D2 | WO2004080998 | 1-18                       | Novedad              |

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 60 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 CESPEDES DE VERGEL**

Directora de Nuevas Creaciones (c)

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

\_\_\_\_\_ 29 FEB. 2010

CONCEPTO TÉCNICO No. 804

EXAMINADOR TÉCNICO Cód. N°202012

**(19) World Intellectual Property  
Organization  
International Bureau**



(43) International Publication Date  
23 September 2004 (23.09.2004)

**PCT**

(16) International Publication Number  
WO 2004/080998 A1

| (51) International Patent Classification <sup>7</sup>           | C07D 401/00 |
|-----------------------------------------------------------------|-------------|
| 401/14, 413/14, 417/14, A61K 31/6178, 31/6439, A61P 2/00, 25/02 |             |

(74) Agent: HPLBOTH, Utilize; Constraints: 1,24,  
C11-407D Base (CH).

(21) Internal Document Application Number:

(23) **Interview Date:** 3 March 2004 (03.03.2004)

**(25) Pāṇini Language:**

(25) Publication Language:  
Englisch

(30) Priority Date: 03/06/2003 (U.S. 2003) 12/17/2003 (U.S. 2003)

(71) Applicant for all designated States except US: E. HON-  
MAR-LLA ROCHE AG [CH421]; Orenzeherstrasse  
124, CH 4070 Basel (CH)

(72) Immunology and  
(73) Immunology/Epitopes (for 15 only): BUEHNER,MANFRED  
David [DBD]: Auswiesing 10, 79630 Schopfheim  
(0763, CECCAROLI, Smoos, Maria [HCH]), Oeffken  
buergerstrasse 29, CH-4057 Basel (CH), JASCHKE,  
Georg [DBCH], Bismarckstr. 72, CH-4051 Biele (CH),  
KOLZCZEWY, Sabina [DBD]: Schillerstrasse 35,  
79618 Rheinfelden (CH), PORTER, Richard, Bp  
Palm [DBCH]: Hermannstr. 34, CH-41453 Reinach (CH),  
VETTER, Erik [HCH]: Burgriedenstrasse 63, CH-4122  
Allschwil (CH).

(24) Disputed States (under otherwise indicated for energy head of regional protection, including: ALBA (B, R, GH, GM, KE, LS, MW, NE, SD, SL, SZ, TZ, UG, ZM, ZW), Burundi (BM, AZ, BZ, KO, KZ, MD, NI, TM), Democratic Republic of the Congo (CD, KE, CY, CG, DR, DK, EG, ES, ET, FR, GA, GN, GU, IL, IT, LU, MC, ML, NI, PT, RO, SE, SI, SK, TH, CM, BG, BF, CH, CF, CG, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TO).

**Published:**

- with international research report
- before the expiration of the time limit for submitting documents and to be republished in the event of receipt of correspondence

For two-letter codes and other abbreviations, refer to the "Crithance Notes on Conder and Alden's tables" appearing at the beginning of each regular issue of the PCT Collection.

(S4) Title: (MILPACOL-4-yl-ETHYNYL-PYREDINE DERIVATIVES)

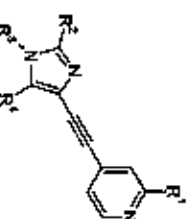
© 1997 Alkermes, 4-[1-(4-chlorophenyl)-4-pyridinyl]-2-allyl-pyridine and 1-(4-chlorophenyl)-4-pyridinyl-2-allyl-pyridine derivatives have been pharmacologically acceptable when tested for their treatment in prevention of Alzheimer's mediated full or in part by metabotropic glutamate receptor 5, e.g., stress, inflammation and chronic. Degenerative processes of the nervous system, such as Alzheimer's disease, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis, psychiatric diseases such as schizophrenia and anxiety, depression, pain and drug dependency.

## Imidazol-4-yl-ethynyl-pyridine derivatives

The present invention relates to novel imidazole derivatives, to processes for their production, their use as pharmaceuticals and to pharmaceutical compositions comprising them.

5 More particularly, the present invention provides in a first aspect novel 4-[1-aryl and 1-heteroaryl-imidazol-4-yl]ethylpyr[1,2-alkyl-pyridine derivatives as well as pharmaceutically acceptable salts thereof.

More particularly the present invention provides a compound of formula I



wherein

10  $R^3$  is  $C_1$ -Catalytic

R<sup>2</sup> is C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>3</sub>-C<sub>12</sub>cycloalkyl;

$R^3$  is aryl or heteroaryl, wherein the aryl or heteroaryl is unsubstituted or substituted by

one, two or three substituents selected from halogen,  $C_1$ -C<sub>6</sub>alkyl, 5- $C_1$ -C<sub>6</sub>alkenyl,  $C_1$ -

C-alkyl-halogen, C<sub>1</sub>-C-alkoxy, halogen-C<sub>2</sub>-C-alkoxy, C<sub>3</sub>-C<sub>1</sub>-cycloalkyl, C<sub>2</sub>-

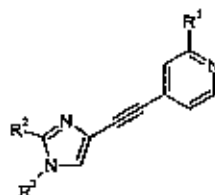
15 C<sub>11</sub> heterocycloalkyl, C<sub>1</sub>-C<sub>6</sub>alkylamino, di-C<sub>1</sub>-C<sub>6</sub>alkylamino, C<sub>1</sub>-C<sub>6</sub>alkoxylamino, (C<sub>1</sub>-

Carbonyl-C<sub>1</sub>-C<sub>2</sub>alkylamino, C<sub>3</sub>-C<sub>12</sub>cycloalkylamino, benzylamino and cyano, and

$R^1$  is hydrogen,  $C(O)H$  or  $CH_2R^5$  wherein  $R^5$  is hydrogen,  $OH$ ,  $C_1$ - $C_6$ alkyl or  $C_3$ - $C_6$ alkenyl.

C<sub>12</sub>acychoalkyl

In one embodiment the present invention provides a compound of formula 1\*



(I\*)

wherein

R<sup>1</sup> signifies lower alkyl;

R<sup>2</sup> signifies lower alkyl;

- 5 R<sup>3</sup> signifies aryl or heteroaryl, optionally substituted, preferably by one, two or three substituents, selected from the group consisting of halogen, lower alkyl, lower alkyl-halogen or cyano;

as well as to pharmaceutically acceptable salts thereof.

- 10 It has now surprisingly been found that the compounds of general formula I are metabotropic glutamate receptor 5 antagonists. Compounds of formula I are distinguished by having valuable therapeutic properties. They can be used in the treatment or prevention of mGluR5 receptor mediated disorders.

In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

- 15 Glutamate is the major excitatory neurotransmitter in the brain and plays a unique role in a variety of central nervous system (CNS) functions. The glutamate-dependent stimulus receptors are divided into two main groups. The first main group, namely the ionotropic receptors, forms ligand-controlled ion channels. The metabotropic glutamate receptors (mGluR) belong to the second main group and, furthermore, belong to the family of G-protein coupled receptors.

At present, eight different members of these mGluR are known and of these some even have sub-types. According to their sequence homology, signal transduction mechanisms and agonist selectivity, these eight receptors can be sub-divided into three sub-groups:

- 25 mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the first group can be used for the treatment or prevention of acute and/or chronic neurological disorders such as

psychosis, epilepsy, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, as well as chronic and acute pain.

- Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are ischemia, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, drug abuse/dependence such as nicotine addiction, opiate addiction, and alcohol abuse, anxiety, vomiting, dyskinesia and depressions.

- Disorders mediated full or in part by mGluR5 are for example acute, traumatic and chronic degenerative processes of the nervous system, such as Alzheimer's disease, senile dementia, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis, psychiatric diseases such as schizophrenia and anxiety, depression, pain and drug dependency [Expert Opin. Ther. Patents 12:12 (2002)].

Selective mGluR5 antagonists are especially useful for the treatment of anxiety and pain.

- Objects of the present invention are compounds of formula I and their pharmaceutically acceptable salts, the above-mentioned compounds as pharmaceutically active substances and their production. Further objects of the invention are medicaments based on a compound in accordance with the invention and their manufacture as well as the use of the compounds in the control or prevention of mGluR5 receptor mediated disorders, and, respectively, for the production of corresponding medicaments.

- The following definitions of general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination. The term "lower alkyl" used in the present description denotes straight-chain or branched saturated hydrocarbon residues with 1 to 6 carbon atoms, preferably with 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl and the like. The term "cycloalkyl" used in the present description denotes cyclic saturated hydrocarbon residues with 3 to 12 carbon atoms. Examples for cycloalkyl include cyclopropyl, cyclobutyl and cyclopentyl.

Examples for C<sub>1</sub>-C<sub>6</sub>alkoxy include methoxy, methoxyethyl and methoxyethoxy. Examples for halogenomethoxy include trifluoromethoxy.

162

162

Examples for C<sub>2</sub>-C<sub>11</sub> heterocycloalkyl include pyrrolidinyl, morpholinyl and thiomorpholinyl.

Examples for C<sub>1</sub>-C<sub>6</sub>alkylamino include methylamino and ethylamino. Examples for di-C<sub>1</sub>-C<sub>6</sub>alkylamino include dimethylamino. Examples for C<sub>1</sub>-C<sub>6</sub>alkoxyamino include methoxyethylamino. Examples for (C<sub>1</sub>-C<sub>6</sub>alkoxy)C<sub>1</sub>-C<sub>6</sub>alkylamino include (methoxyethyl)methylamino. Examples for methoxycycloalkylamino include cyclopropylamino.

The term "halogen" denotes fluorine, chlorine, bromine and iodine.

"Aryl" represents an aromatic carbocyclic group consisting of one individual ring, or one or more fused rings in which at least one ring is aromatic in nature. Examples for aryl include phenyl. Examples for substituted aryl include fluorophenyl, difluorophenyl, chlorophenyl, dichlorophenyl, chlorofluorophenyl, cyanophenyl, methylphenyl, methoxyphenyl, fluoromethylphenyl, trifluoromethylphenyl and trifluoromethoxyphenyl.

The term "heteroaryl" refers to an aromatic 5- or 6-membered ring or one or more fused rings containing one or more heteroatoms selected from nitrogen, oxygen or sulphur.

Examples of such heteroaryl groups are pyrimidinyl, pyrazinyl, pyridazinyl, pyridinyl and indolyl, e.g. pyridin-4-yl, pyridin-2-yl, pyrazin-2-yl and pyrimidin-2-yl. Examples for substituted heteroaryl include methylpyrimidinyl, dimethylpyrimidinyl, trifluoromethylpyrimidinyl, methoxypyrimidinyl, methoxyethoxypyrimidinyl, ethylpyrimidinyl, fluoropyrimidinyl, chloropyrimidinyl, bromopyrimidinyl, methylsulfonylpyrimidinyl, cyclopropylpyrimidinyl, methylpyrazinyl, cyclopropylpyrazinyl, chloropyrazinyl, methoxypyrazinyl, methoxyethoxypyrazinyl, methylaminopyrazinyl, dimethylaminopyrazinyl, cyclopropylaminopyrazinyl, morpholinylpyrazinyl, fluoropyridinyl, chloropyridinyl, bromopyridinyl, iodopyridinyl, methylpyridinyl, trifluoromethylpyridinyl, trifluoromethylmethylpyridinyl, cyclopropylpyridinyl, butylpyridinyl, methoxypyridinyl, dimethylaminopyridinyl, methylaminopyridinyl, ethylaminopyridinyl, pyrrolidinylpyridinyl, morpholinylpyridinyl, thiomorpholinylpyridinyl, (methoxyethyl)methylaminopyridinyl, methoxyethylaminopyridinyl, benzylaminopyridinyl and methyl-1H-indolyl.

The term "pharmaceutically acceptable salt" refers to any salt derived from an inorganic or organic acid.

"Pharmaceutically acceptable salts" of a compound means salts that are pharmaceutically acceptable, which are generally safe, non-toxic, and neither biologically nor otherwise undesirable, and that possess the desired pharmacological activity of the parent compound.

These salts are derived from an inorganic or organic acid. If possible, compounds of formula I may be converted into pharmaceutically acceptable salts.

It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) of the same acid addition salt.

Examples for pharmaceutically acceptable acid addition salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hydroxynaphthoic acid, 2-hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, mandelic acid, methanesulfonic acid, muconic acid, 2-naphthalenesulfonic acid, propionic acid, salicylic acid, succinic acid, dibenzoyl-L-tartaric acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid, trifluoroacetic acid, and the like.

Preferred compounds of formula I\* are those, in which R<sup>1</sup> and R<sup>2</sup> are both methyl.

Especially preferred are those compounds from this group, in which R<sup>3</sup> is substituted phenyl, wherein the substitution is fluoro, chloro, cyano or CF<sub>3</sub>.

The following are examples of compounds, wherein the substitution is fluoro or chloro:

4-[1-(4-fluoro-phenyl)-2-methyl-1H-imidazol-4-ylethynyl]-2-methyl-pyridine,  
4-[1-(3,4-dichloro-phenyl)-2-methyl-1H-imidazol-4-ylethynyl]-2-methyl-pyridine, HCl  
4-[1-(2,4-difluoro-phenyl)-2-methyl-1H-imidazol-4-ylethynyl]-2-methyl-pyridine, or  
4-[1-(3,4-difluoro-phenyl)-2-methyl-1H-imidazol-4-ylethynyl]-2-methyl-pyridine.

Examples of compounds, wherein the substitution is cyano, are as follows:

4-(2-methyl-4-(2-methyl-pyridin-4-ylethynyl)-imidazol-1-yl)-benzonitrile, or  
3-[2-methyl-4-(2-methyl-pyridin-4-ylethynyl)-imidazol-1-yl]-benzonitrile.

The following is an example of compounds, wherein the substitution is CF<sub>3</sub>:

2-methyl-4-[2-methyl-1-(3-trifluoromethyl-phenyl)-1H-imidazol-4-ylethynyl]-pyridine.

Especially preferred are further those compounds, wherein R<sup>1</sup> and R<sup>2</sup> are both methyl and R<sup>3</sup> is pyrimidinyl, for example the following compound:

2-[2-methyl-4-(2-methyl-pyridin-4-ylethynyl)-imidazol-1-yl]-pyrimidine.

163

163

In one embodiment the present invention provides a compound of formula I wherein  $R^1$  is methyl, and  $R^2$ ,  $R^3$  and  $R^4$  independently are as defined above or hereinafter.

In one embodiment the present invention provides a compound of formula I wherein  $R^2$  is  $C_1$ - $C_6$ alkyl. In another embodiment the present invention provides a compound of formula I wherein  $R^2$  is methyl or isopropyl. In another embodiment the present invention provides a compound of formula I wherein  $R^2$  is cyclopropyl. In all the above embodiments  $R^1$ ,  $R^3$  and  $R^4$  independently are as defined above or hereinafter.

In one embodiment the present invention provides a compound of formula I wherein R is unsubstituted aryl or aryl substituted by one, two or three substituents selected from halogen,  $C_1$ - $C_6$ alkyl,  $S-C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ alkyl-halogen,  $C_1$ - $C_6$ alkoxy, halogen- $C_1$ - $C_6$ alkoxy,  $C_3$ - $C_6$ alkoxy,  $C_3$ - $C_6$ heterocycloalkyl,  $C_1$ - $C_6$ alkylamino, di- $C_1$ - $C_6$ alkylamino,  $C_1$ - $C_6$ alkoxyamino,  $(C_1$ - $C_6$ alkoxy)- $C_1$ - $C_6$ alkylamino,  $C_3$ - $C_6$ cycloalkylamino, benzylamino and cyanoamino,  $(C_1$ - $C_6$ alkoxy)- $C_1$ - $C_6$ alkylamino,  $C_3$ - $C_6$ cycloalkylamino, benzylamino and cyano-

In another embodiment the present invention provides a compound of formula 1 wherein  $R^3$  is phenyl or phenyl substituted by one, two or three substituents selected from halogen,  $C_1$ -alkyl,  $C_2$ -alkyl,  $C_3$ -alkyl, halogen,  $C_1$ -alkoxy,  $C_2$ -alkoxy,  $C_3$ -alkoxy,  $C_1$ -alkylthio,  $C_2$ -alkylthio,  $C_3$ -alkylthio,  $C_1$ -alkylamino,  $C_2$ -alkylamino,  $C_3$ -alkylamino,  $\beta$ -amino,  $\beta$ -amino,  $(C_1$ -alkoxy) $C_1$ -alkylamino,  $C_2$ -alkoxyamino, benzylamino and cyano.

In another embodiment the present invention provides a compound of formula I wherein R<sup>3</sup> is phenyl or phenyl substituted by one or two substituents selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkyl halogen, C<sub>3</sub>-C<sub>4</sub>alkoxy, halogen, C<sub>1</sub>-C<sub>4</sub>alkoxy and cyano. In another embodiment the present invention provides a compound of formula I wherein R<sup>3</sup> is phenyl substituted by one or two substituents selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>3</sub>-

25 C<sub>6</sub>alkyl-halogen, C<sub>1</sub>-C<sub>6</sub>alkoxy, halogen-C<sub>1</sub>-C<sub>6</sub>alkoxy and cyano. In another embodiment the present invention provides a compound of formula I wherein R<sup>3</sup> is phenyl substituted by one or two substituents selected from fluoro, chloro, methyl, trifluoromethyl, methoxy, trifluoromethoxy and cyano. In another embodiment the present invention provides a compound of formula I wherein R<sup>3</sup> is fluorophenyl, difluorophenyl, chlorophenyl, dichlorophenyl, cyanophenyl, trifluoromethylphenyl, fluoro-methylphenyl, chloro-fluorophenyl, methoxyphenyl, methoxyphenyl or trifluoromethoxyphenyl. In all the above embodiments R<sup>1</sup>, R<sup>2</sup> and R<sup>4</sup> independently are as defined above or hactinaster.

In one embodiment the present invention provides a compound of formula I wherein R<sup>1</sup> is unsubstituted heteroaryl or heteroaryl substituted by one, two or three substituents selected from the group consisting of halogen, C<sub>1</sub>-Calkyl, S-C<sub>1</sub>-Calkyl, C<sub>2</sub>-Calkyl-halo-gen, C<sub>1</sub>-Calkoxy, halogen, C<sub>1</sub>-Calkoxy, C<sub>2</sub>-C<sub>1</sub>-xyldialkyl, C<sub>2</sub>-C<sub>n</sub>-heterocycloalkyl, C<sub>1</sub>-Calkylamino, di-C<sub>1</sub>-Calkylamino, C<sub>1</sub>-Calkoxymino, (C<sub>1</sub>-Calkoxy)C<sub>1</sub>-Calkylamino,

35

[illegible]

In one embodiment the present invention provides a compound of formula I wherein R<sup>1</sup> is hydrogen, C(O)H or CH<sub>3</sub>. In another embodiment the present invention provides a compound of formula I wherein R<sup>1</sup> is hydrogen. In all the above embodiments R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> independently are as defined above or hereinafter.

35 In one embodiment the present invention provides a compound of formula I wherein

~~791~~

R<sup>1</sup> is methyl;

R<sup>2</sup> is C<sub>1</sub>-Calkyl or C<sub>2</sub>-C<sub>2</sub>cycloalkyl;

R<sup>3</sup> is aryl or heteroaryl, wherein the aryl or heteroaryl is unsubstituted or substituted by one, two or three substituents selected from halogen, C<sub>1</sub>-Calkyl, S-C<sub>1</sub>-Calkyl, C<sub>2</sub>-C<sub>2</sub>cycloalkyl, C<sub>1</sub>-Calkoxy, halogen, C<sub>1</sub>-Calkoxy, C<sub>2</sub>-C<sub>2</sub>cycloalkyl, C<sub>2</sub>-

5

C<sub>1</sub>heterocycloalkyl, C<sub>1</sub>-Calkylamino, di-C<sub>1</sub>-Calkylamino, C<sub>1</sub>-Calkoxyamino, (C<sub>1</sub>-

Calkoxy)C<sub>1</sub>-Calkylamino, C<sub>2</sub>-C<sub>2</sub>cycloalkylamino, benzylamino and cyano; and

R<sup>4</sup> is hydrogen, C(O)H or CH<sub>2</sub>R<sup>5</sup> wherein R<sup>5</sup> is hydrogen, OH, C<sub>1</sub>-Calkyl or C<sub>2</sub>-C<sub>2</sub>cycloalkyl.

10

In another embodiment the present invention provides a compound of formula I wherein

R<sup>1</sup> is methyl;

R<sup>2</sup> is methyl, isopropyl or cyclopropyl;

R<sup>3</sup> is aryl or heteroaryl, wherein the aryl or heteroaryl is unsubstituted or substituted by one, two or three substituents selected from halogen, C<sub>1</sub>-Calkyl, S-C<sub>1</sub>-Calkyl, C<sub>2</sub>-

15

Calkyl, halogen, C<sub>1</sub>-Calkoxy, halogen, C<sub>1</sub>-Calkoxy, C<sub>2</sub>-C<sub>2</sub>cycloalkyl, C<sub>2</sub>-

C<sub>1</sub>heterocycloalkyl, C<sub>1</sub>-Calkylamino, di-C<sub>1</sub>-Calkylamino, C<sub>1</sub>-Calkoxyamino, (C<sub>1</sub>-

Calkoxy)C<sub>1</sub>-Calkylamino, C<sub>2</sub>-C<sub>2</sub>cycloalkylamino, benzylamino and cyano; and

R<sup>4</sup> is hydrogen, C(O)H or CH<sub>2</sub>R<sup>5</sup> wherein R<sup>5</sup> is hydrogen, OH, C<sub>1</sub>-Calkyl or C<sub>2</sub>-C<sub>2</sub>cycloalkyl.

20

In still another embodiment the present invention provides a compound of formula I

wherein

R<sup>1</sup> is methyl;

R<sup>2</sup> is methyl, isopropyl or cyclopropyl;

R<sup>3</sup> is aryl or heteroaryl, wherein the aryl or heteroaryl is unsubstituted or substituted by one, two or three substituents selected from halogen, C<sub>1</sub>-Calkyl, S-C<sub>1</sub>-Calkyl, C<sub>2</sub>-

25

Calkyl, halogen, C<sub>1</sub>-Calkoxy, halogen, C<sub>1</sub>-Calkoxy, C<sub>2</sub>-C<sub>2</sub>cycloalkyl, C<sub>2</sub>-

C<sub>1</sub>heterocycloalkyl, C<sub>1</sub>-Calkylamino, di-C<sub>1</sub>-Calkylamino, C<sub>1</sub>-Calkoxyamino, (C<sub>1</sub>-

Calkoxy)C<sub>1</sub>-Calkylamino, C<sub>2</sub>-C<sub>2</sub>cycloalkylamino, benzylamino and cyano; and

R<sup>4</sup> is hydrogen, C(O)H or methyl.

30

In still another embodiment the present invention provides a compound of formula I

wherein

R<sup>1</sup> is methyl;

R<sup>2</sup> is methyl, isopropyl or cyclopropyl;

R<sup>3</sup> is aryl or heteroaryl, wherein the aryl or heteroaryl is unsubstituted or substituted by one, two or three substituents selected from halogen, C<sub>1</sub>-Calkyl, S-C<sub>1</sub>-Calkyl, C<sub>2</sub>-

35

Calkyl, halogen, C<sub>1</sub>-Calkoxy, halogen, C<sub>1</sub>-Calkoxy, C<sub>2</sub>-C<sub>2</sub>cycloalkyl, C<sub>2</sub>-

C<sub>1</sub>heterocycloalkyl, C<sub>1</sub>-Calkylamino, di-C<sub>1</sub>-Calkylamino, C<sub>1</sub>-Calkoxyamino, (C<sub>1</sub>-

Calkoxy)C<sub>1</sub>-Calkylamino, C<sub>2</sub>-C<sub>2</sub>cycloalkylamino, benzylamino and cyano; and

R<sup>4</sup> is hydrogen.

5

In still another embodiment the present invention provides a compound of formula I

wherein

R<sup>1</sup> and R<sup>2</sup> are methyl;

R<sup>3</sup> is aryl or heteroaryl, wherein the aryl or heteroaryl is unsubstituted or substituted by one, two or three substituents selected from halogen, C<sub>1</sub>-Calkyl, S-C<sub>1</sub>-Calkyl, C<sub>2</sub>-

10

Calkyl, halogen, C<sub>1</sub>-Calkoxy, halogen, C<sub>1</sub>-Calkoxy, C<sub>2</sub>-C<sub>2</sub>cycloalkyl, C<sub>2</sub>-

C<sub>1</sub>heterocycloalkyl, C<sub>1</sub>-Calkylamino, di-C<sub>1</sub>-Calkylamino, C<sub>1</sub>-Calkoxyamino, (C<sub>1</sub>-

Calkoxy)C<sub>1</sub>-Calkylamino, C<sub>2</sub>-C<sub>2</sub>cycloalkylamino, benzylamino and cyano; and

R<sup>4</sup> is hydrogen.

In still another embodiment the present invention provides a compound of formula I

15

wherein

R<sup>1</sup> and R<sup>2</sup> are methyl;

R<sup>3</sup> is unsubstituted aryl or aryl substituted by one, two or three substituents selected from halogen, C<sub>1</sub>-Calkyl, S-C<sub>1</sub>-Calkyl, C<sub>2</sub>-Calkyl, halogen, C<sub>1</sub>-

Calkoxy, C<sub>2</sub>-C<sub>2</sub>cycloalkyl, C<sub>2</sub>-C<sub>2</sub>heterocycloalkyl, C<sub>1</sub>-Calkylamino, di-C<sub>1</sub>-Calkyl-

amino, C<sub>1</sub>-Calkoxyamino, (C<sub>1</sub>-Calkoxy)C<sub>1</sub>-Calkylamino, C<sub>2</sub>-C<sub>2</sub>cycloalkylamino,

20

benzylamino and cyano; and

R<sup>4</sup> is hydrogen.

In still another embodiment the present invention provides a compound of formula I

wherein

R<sup>1</sup> and R<sup>2</sup> are methyl;

R<sup>3</sup> is phenyl or phenyl substituted by one, two or three substituents selected from halogen, C<sub>1</sub>-Calkyl, S-C<sub>1</sub>-Calkyl, C<sub>2</sub>-Calkyl, halogen, C<sub>1</sub>-

Calkoxy, C<sub>2</sub>-C<sub>2</sub>cycloalkyl, C<sub>2</sub>-C<sub>2</sub>heterocycloalkyl, C<sub>1</sub>-Calkylamino, di-C<sub>1</sub>-Calkyl-

amino, C<sub>1</sub>-Calkoxyamino, (C<sub>1</sub>-Calkoxy)C<sub>1</sub>-Calkylamino, C<sub>2</sub>-C<sub>2</sub>cycloalkylamino,

30

benzylamino and cyano; and

R<sup>4</sup> is hydrogen.

In still another embodiment the present invention provides a compound of formula I

wherein

R<sup>1</sup> and R<sup>2</sup> are methyl;

165

R<sup>2</sup> is phenyl or phenyl substituted by one or two substituents selected from halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkyl-halogen, C<sub>1</sub>-C<sub>6</sub>alkoxy, halogen-C<sub>1</sub>-C<sub>6</sub>alkoxy and cyano; and  
R<sup>4</sup> is hydrogen.

In still another embodiment the present invention provides a compound of formula I

5 wherein

R<sup>1</sup> and R<sup>2</sup> are methyl;

R<sup>3</sup> is phenyl substituted by one or two substituents selected from fluoro, chloro, methyl, trifluoromethyl, methoxy, trifluoromethoxy and cyano; and

R<sup>4</sup> is hydrogen.

10 In still another embodiment the present invention provides a compound of formula I

wherein

R<sup>1</sup> and R<sup>2</sup> are methyl;

R<sup>3</sup> is fluorophenyl, difluorophenyl, chlorophenyl, dichlorophenyl, cyanophenyl, trifluoromethylphenyl, fluoro-methylphenyl, chloro-fluorophenyl, methylphenyl, methoxyphenyl or trifluoromethoxyphenyl; and  
15 R<sup>4</sup> is hydrogen.

In still another embodiment the present invention provides a compound of formula I

wherein

R<sup>1</sup> and R<sup>2</sup> are methyl;

20 R<sup>3</sup> is unsubstituted heteroaryl or heteroaryl substituted by one, two or three substituents selected from the group consisting of halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, S-C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkyl-halogen, C<sub>1</sub>-C<sub>6</sub>alkoxy, halogen-C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>3</sub>-C<sub>12</sub>cycloalkyl, C<sub>2</sub>-C<sub>11</sub>heterocycloalkyl, C<sub>1</sub>-C<sub>6</sub>alkylamino, di-C<sub>1</sub>-C<sub>6</sub>alkylamino, C<sub>1</sub>-C<sub>6</sub>alkoxyamino, (C<sub>1</sub>-C<sub>6</sub>alkoxy)C<sub>1</sub>-C<sub>6</sub>alkyl-amino, C<sub>3</sub>-C<sub>12</sub>cycloalkylamino, benzylamino and cyano; and  
25 R<sup>4</sup> is hydrogen.

In still another embodiment the present invention provides a compound of formula I

wherein

R<sup>1</sup> and R<sup>2</sup> are methyl;

R<sup>3</sup> is unsubstituted pyrimidinyl, unsubstituted pyrazinyl or unsubstituted pyridinyl; and  
30 R<sup>4</sup> is hydrogen.

In still another embodiment the present invention provides a compound of formula I

wherein

R<sup>1</sup> and R<sup>2</sup> are methyl;

R<sup>2</sup> is heteroaryl selected from pyrimidinyl, pyrazinyl, pyridinyl and indolyl wherein the heteroaryl is substituted by one or two substituents selected from halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, S-C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkyl-halogen, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>3</sub>-C<sub>12</sub>cycloalkyl, C<sub>2</sub>-C<sub>11</sub>heterocycloalkyl, C<sub>1</sub>-C<sub>6</sub>alkylamino, di-C<sub>1</sub>-C<sub>6</sub>alkylamino, C<sub>1</sub>-C<sub>6</sub>alkoxyamino, (C<sub>1</sub>-C<sub>6</sub>alkoxy)C<sub>1</sub>-C<sub>6</sub>alkylamino, C<sub>3</sub>-C<sub>12</sub>cycloalkylamino and benzylamino; and  
5 R<sup>4</sup> is hydrogen.

In still another embodiment the present invention provides a compound of formula I

wherein

R<sup>1</sup> and R<sup>2</sup> are methyl;

10 R<sup>3</sup> is pyrimidinyl substituted by one or two substituents selected from halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, S-C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkyl-halogen, C<sub>1</sub>-C<sub>6</sub>alkoxy and C<sub>3</sub>-C<sub>12</sub>cycloalkyl or pyrazinyl substituted by one substituent selected from halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>3</sub>-C<sub>12</sub>cycloalkyl, C<sub>2</sub>-C<sub>11</sub>heterocycloalkyl, C<sub>1</sub>-C<sub>6</sub>alkylamino, di-C<sub>1</sub>-C<sub>6</sub>alkylamino and C<sub>3</sub>-C<sub>12</sub>cycloalkylamino; or pyridinyl substituted by one or two substituents selected from halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkyl-halogen, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>3</sub>-C<sub>12</sub>cycloalkyl, C<sub>2</sub>-C<sub>11</sub>heterocycloalkyl, C<sub>1</sub>-C<sub>6</sub>alkylamino, di-C<sub>1</sub>-C<sub>6</sub>alkylamino, C<sub>1</sub>-C<sub>6</sub>alkoxyamino, (C<sub>1</sub>-C<sub>6</sub>alkoxy)C<sub>1</sub>-C<sub>6</sub>alkylamino and benzylamino; or methyl-1H-indolyl; and  
15 R<sup>4</sup> is hydrogen.

In still another embodiment the present invention provides a compound of formula I

20 wherein

R<sup>1</sup> and R<sup>2</sup> are methyl;

R<sup>3</sup> is methylpyrimidinyl, ethylpyrimidinyl, dimethylpyrimidinyl, trifluoromethylpyrimidinyl, methoxypyrimidinyl, methoxyethoxypyrimidinyl, fluoropyrimidinyl, chloropyrimidinyl, bromopyrimidinyl, methylsulfonylpyrimidinyl, cyclopropylpyrimidinyl, methylpyrazinyl, cyclopropylpyrazinyl, methoxypyrazinyl, chloropyrazinyl, methylaminopyrazinyl, dimethylaminopyrazinyl, cyclopropylpyrazinyl, methylpyridinyl, tri-butylpyridinyl, fluoropyridinyl, chloropyridinyl, bromopyridinyl, iodopyridinyl, trifluoromethylpyridinyl, (trifluoromethyl)methylpyridinyl, cyclopropylpyridinyl, methoxypyridinyl, methoxyethoxypyridinyl, methylaminopyridinyl, ethylaminopyridinyl, dimethylaminopyridinyl, pyrrolidinylpyridinyl, morpholinylpyridinyl, thiomorpholinylpyridinyl, (methoxyethyl)methylaminopyridinyl, methoxyethylaminopyridinyl, benzylaminopyridinyl or methyl-1H-indolyl; and  
25 R<sup>4</sup> is hydrogen.

Examples of compounds of formula I include

35 4-[1-(4-fluoro-phenyl)-2-methyl-1H-imidazol-4-ylethynyl]-2-methyl-pyridine,

(19) World Intellectual Property  
Organization  
International Bureau

PCT

(43) International Publication Date  
16 December 2004 (16.12.2004)(10) International Publication Number  
WO 2004/108701 A1(51) International Patent Classification: C07D 401/06,  
401/14, A61K 31/4439, 31/444, A61P 25/28(74) Agent: BRAUN, Axel; Grenzacherstrasse 124, CH-4070  
Basel (CH).(21) International Application Number:  
PCT/EP2004/005881

(12) International Filing Date: 1 June 2004 (01.06.2004)

(15) Filing Language: English

(16) Publication Language: English

(30) Priority Data: 03012300.6 5 June 2003 (05.06.2003) HP

(71) Applicant (for all designated States except US): F. HOFF-  
MANN-LA ROCHE AG (CH/CH); Grenzacherstrasse  
124, CH-4070 Basel (CH).

(72) Inventors; and

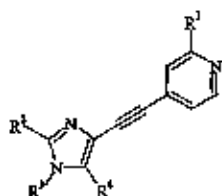
(75) Inventors/Applicants (for US only): BUETTELHANN,  
Bernd (DE/DE); Anselweg 10, 79650 Schopfheim  
(DE); CECARFELLI, Simona, Maria (IT/CH); Grenz-  
acherstrasse 29, CH-4057 Basel (CH); JÄSCHKE,  
Georg (DE/CH); Eulerstrasse 82, CH-4051 Basel (CH);  
PORTER, Richard, Hugh, Philip (GB/CH); Heckenweg  
34, CH-4153 Reinach (CH); VIRIBA, Eric (CH/CH);  
Lindenstrasse 9, CH-4402 Freudenort (CH).(81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,  
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,  
GB, GD, GF, GH, GM, GR, HU, ID, IL, IN, IS, IT, KE,  
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,  
MG, MK, MN, MW, MX, MZ, NA, NL, NO, NZ, OM, PG,  
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,  
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,  
ZW.(84) Designated States (unless otherwise indicated, for every  
kind of regional protection available): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, NA, SD, ST, SZ, TZ, UG, ZM,  
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,  
FR, GB, GR, HU, IE, IT, LU, MC, MT, NL, PT, RO, SE, SI,  
SK, TR), OAPI (BF, BI, CH, CG, CI, CM, GA, GN, GQ,  
GW, ML, MR, NE, SN, TD, TG).

Published:

with international search report

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

(54) Title: IMIDAZOLE DERIVATIVES AS GLUTAMATE RECEPTOR ANTAGONISTS

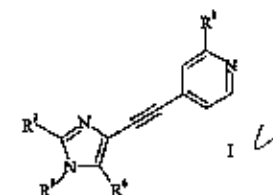


(I)

(57) Abstract: The present invention relates to imidazole derivatives which are mGluR5 receptor antagonists and which are represented by the general formula (I); wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as defined in the specification, to a process for the manufacture thereof, as well as to pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment or prevention of mGluR5 receptor mediated disorders, such as acute and/or chronic neurological disorders.

## Imidazole derivatives

The present invention relates to imidazole derivatives of the general formula



wherein

R<sup>1</sup> signifies halogen or cyano;R<sup>2</sup> signifies lower alkyl;R<sup>3</sup> signifies aryl or heteroaryl, which are optionally substituted by one, two or  
three substituents, selected from the group consisting of halogen, lower alkyl, cycloalkyl,  
lower alkyl-halogen, cyano, lower alkoxy, NR<sup>1</sup>R<sup>2</sup> or by

1-morpholinyl, or by

1-pyrrolidinyl, optionally substituted by (CH<sub>2</sub>)<sub>0,1</sub>OR, or bypiperidinyl, optionally substituted by (CH<sub>2</sub>)<sub>0,1</sub>OR, or by

1,1-dioxo-thiomorpholinyl or by

piperazinyl, optionally substituted by lower alkyl or (CH<sub>2</sub>)<sub>0,1</sub>-cycloalkyl;R is hydrogen, lower alkyl or (CH<sub>2</sub>)<sub>0,1</sub>-cycloalkyl;R<sup>1</sup>, R<sup>2</sup> are independently from each other hydrogen, lower alkyl, (CH<sub>2</sub>)<sub>0,1</sub>-cycloalkyl or  
(CH<sub>2</sub>)<sub>n</sub>OR;

n is 1 or 2;

R<sup>4</sup> is hydrogen, C(O)H, CH<sub>2</sub>R<sup>5</sup> wherein R<sup>5</sup> is hydrogen, OH, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>12</sub>-  
cycloalkyl,

as well as to pharmaceutically acceptable salts thereof.

It has now surprisingly been found that the compounds of general formula I are  
metabotropic glutamate receptor antagonists. Compounds of formula I are distinguished

167

by having valuable therapeutic properties. They can be used in the treatment or prevention of mGluR5 receptor mediated disorders.

In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

Glutamate is the major excitatory neurotransmitter in the brain and plays a unique role in a variety of central nervous system (CNS) functions. The glutamate-dependent stimulus receptors are divided into two main groups. The first main group, namely the ionotropic receptors, forms ligand-controlled ion channels. The metabotropic glutamate receptors (mGluR) belong to the second main group and, furthermore, belong to the family of G-protein coupled receptors.

At present, eight different members of these mGluR are known and of these some even have sub-types. According to their sequence homology, signal transduction mechanisms and agonist selectivity, these eight receptors can be sub-divided into three sub-groups:

mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the first group can be used for the treatment or prevention of acute and/or chronic neurological disorders such as psychosis, epilepsy, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, as well as chronic and acute pain.

Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are ischemia, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate addiction, anxiety, vomiting, dyskinesia and depressions.

Disorders mediated full or in part by mGluR5 are for example acute, traumatic and chronic degenerative processes of the nervous system, such as Alzheimer's disease, senile dementia, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis and

multiple sclerosis, psychiatric diseases such as schizophrenia and anxiety, depression, pain and drug dependency (*Expert Opin. Ther. Patents* (2002), 12, (12)).

Selective mGluR5 antagonists are especially useful for the treatment of anxiety and pain.

The invention relates to compounds of formula I and their pharmaceutically acceptable salts, to the above-mentioned compounds as pharmaceutically active substances and their production.

The invention also relates to a process for preparing a compound according to general formula I following the general procedures as outlined above for compounds of formula I.

Moreover the invention relates also to medicaments containing one or more compounds of the present invention and pharmaceutically acceptable excipients for the treatment and prevention of mGluR5 receptor mediated disorders, such as acute and/or chronic neurological disorders, in particular anxiety and chronic or acute pain.

The invention also relates to the use of a compound in accordance with the present invention as well as its pharmaceutically acceptable salt for the manufacture of medicaments for the treatment and prevention of mGluR5 receptor mediated disorders as outlined above.

The following definitions of general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination. The term "lower alkyl" used in the present description denotes straight-chain or branched saturated hydrocarbon residues with 1 to 6 carbon atoms, preferably with 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl and the like.

The term "lower alkoxy" denotes a lower alkyl residue in the sense of the foregoing definition bound via an oxygen atom. Examples of "lower alkoxy" residues include methoxy, ethoxy, isopropoxy and the like.

The term "halogen" denotes fluorine, chlorine, bromine and iodine.

"Aryl" represents an aromatic carbocyclic group consisting of one individual ring, or one or more fused rings in which at least one ring is aromatic in nature. Preferred aryl group is phenyl.

168.

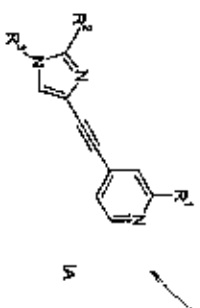
168

The term "heteroaryl" refers to an aromatic 5- or 6-membered ring containing one or more heteroatoms selected from nitrogen, oxygen or sulphur. Preferred are those heteroaryl groups selected from nitrogen. Examples of such heteroaryl groups are pyridinyl, pyrimidinyl, pyrimidinyl or pyridazinyl.

The term "cycloalkyl" denotes a saturated carbocyclic group, containing 3 - 12 carbon atoms, preferably 3-6 carbon atoms.

The term "pharmaceutically acceptable salt" refers to any salt derived from an inorganic or organic acid or base.

Encompassed in formula I are also the compounds of general formula IA:



wherein

R<sup>1</sup> signifies halogen;

R<sup>2</sup> signifies lower alkyl;

R<sup>3</sup> signifies aryl or heteroaryl, which are optionally substituted by one, two or three substituents, selected from the group consisting of halogen, lower alkyl,

lower

alkyl-halogen, cyano, NR<sup>4</sup>R<sup>5</sup> or by 1-morpholinyl, or by

1-pyrrolidinyl, optionally substituted by (CH<sub>2</sub>)<sub>n</sub>OR, or by

piperidinyl, optionally substituted by (CH<sub>2</sub>)<sub>n</sub>OR, or by

1,1-dioxo-thiomorpholinyl or by

piperazinyl, optionally substituted by lower alkyl or (CH<sub>2</sub>)<sub>n</sub>-cycloalkyl;

R is hydrogen, lower alkyl or (CH<sub>2</sub>)<sub>n</sub>-cycloalkyl;

R<sup>4</sup>, R<sup>5</sup> are independently from each other hydrogen, lower alkyl, (CH<sub>2</sub>)<sub>n</sub>-

cycloalkyl or (CH<sub>2</sub>)<sub>n</sub>OR;

n is 1 or 2;

as well as to pharmaceutically acceptable salts thereof.

Preferred compounds of formula I and IA are those, in which R<sup>1</sup> is chloro or fluoro.

Especially preferred are those compounds from this group, in which R<sup>3</sup> is unsubstituted or substituted heteroaryl, wherein the substitution is selected from fluoro, CF<sub>3</sub> and lower alkyl, for example the following compounds:

- 2-[4-(2-chloro-pyridin-4-ylethynyl)-2-methyl-imidazol-1-yl]-4-trifluoromethyl-pyrimidine,
- 2-[4-(2-chloro-pyridin-4-ylethynyl)-2-methyl-imidazol-1-yl]-pyrazine,
- 2-[4-(2-chloro-pyridin-4-ylethynyl)-2-methyl-imidazol-1-yl]-6-trifluoromethyl-pyridine,
- 3-[4-(2-chloro-pyridin-4-ylethynyl)-2-methyl-imidazol-1-yl]-5-fluoro-pyridine,
- 4-[4-(2-chloro-pyridin-4-ylethynyl)-2-methyl-imidazol-1-yl]-2-trifluoromethyl-pyrimidine,
- 2-[4-(2-chloro-pyridin-4-ylethynyl)-2-methyl-imidazol-1-yl]-6-methyl-4-trifluoromethyl-pyridine or
- 2-[4-(2-chloro-pyridin-4-ylethynyl)-2-methyl-imidazol-1-yl]-5-methyl-pyridine.

Especially preferred are further those compounds of this group, wherein R<sup>3</sup> is aryl, substituted by one or more halogen, for example the following compounds:

- 2-Chloro-4-[1-(4-fluoro-phenyl)-2-methyl-1H-imidazol-4-ylethynyl]-pyridine,
  - 2-Fluoro-4-[1-(4-fluoro-phenyl)-2-methyl-1H-imidazol-4-ylethynyl]-pyridine,
  - 2-Chloro-4-[1-(3,5-difluoro-phenyl)-2-methyl-1H-imidazol-4-ylethynyl]-pyridine,
  - 2-Chloro-4-[1-(3,5-difluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine,
- or
- 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

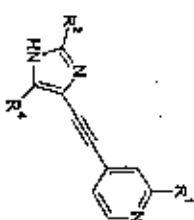
The compounds of formula I or IA of the invention may be prepared according to a process

which comprises reacting

(a) a compound of formula II

169

- 6 -



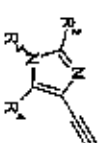
(II)

wherein  $R^1$ ,  $R^2$  and  $R^3$  have the meanings as defined above, with a compound of formula III



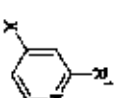
(III)

wherein  $R^3$  has the meanings as defined above and  $Z$  is halogen or  $B(OH)_2$  or (b) a compound of formula IV



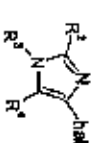
(IV)

wherein  $R^2$ ,  $R^3$  and  $R^4$  have the meanings as defined above, with a compound of formula V



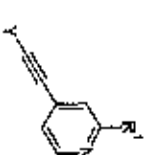
(V)

wherein  $R^1$  has the meanings as defined above and  $X$  is halogen; or (c) a compound of formula VI



(VI)

wherein  $R^2$ ,  $R^3$  and  $R^4$  have the meanings as defined above and  $hal$  is halogen, with a compound of formula VII



(VII)

wherein  $R^1$  has the meaning as defined above and  $Y$  is trimethylsilyl or hydrogen.

- 7 -

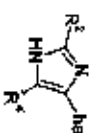
The reaction as described in (a) may be carried out in accordance with standard procedures, e.g. by arylation of a compound of formula II using an aromatic boronic acid and a copper catalyst in a solvent like dichloromethane or tetrahydrofuran [see e.g. Colmann et al., Org. Lett. 2:1233 (2000)] or by heating a compound of formula II and a compound of formula III wherein  $Z$  is halogen with a base like potassium carbonate or cesium carbonate in a solvent like dimethylformamide, or Pd catalyzed according to Buchwald conditions [see e.g. Example 8; Buchwald et al., Tetrahedron Lett. 40:2657 (1999)]. The reaction as described in (b) may be carried out by a Sonogashira coupling of a compound of formula IV and a compound of formula V in the presence of, e.g.,  $CuI$ ,  $(Ph_3P)_2PdCl_2$ ,  $Et_3N$  in a solvent like tetrahydrofuran or dimethylformamide [Sonogashira et al., Synthesis 777 (1977)]. In one embodiment the meaning  $X$  in compounds of formula V is bromine or iodine. The reaction as described in (c) above may, e.g. be carried out in the presence of  $CuI$ ,  $(Ph_3P)_2PdCl_2$ ,  $Et_3N$ ,  $n-Bu_4F$  in a solvent like tetrahydrofuran or dimethylformamide.

The salt forms are made by standard procedures known to the skilled artisan.

The compounds of formulae II, IV, VI und VII are novel and also an embodiment of the present invention.

The compounds of formulae III and V are commercially available or their preparation is known to the skilled artisan.

The compounds of formula II may be prepared by reacting a compound of formula VIII

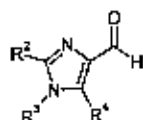


(VIII)

wherein  $R^2$  and  $R^4$  have the above meanings and  $hal$  is halogen, with a compound of formula VII as above.

The compounds of formula VIII may be prepared as described e.g. in Cliff and Pyne [Synthesis 631-632 (1994)].

The compounds of formula IV may be prepared by reacting a compound of formula IX



(IX)

wherein  $R^2$ ,  $R^3$  and  $R^4$  have the meanings as defined above, with dimethyl (3-diazo-2-oxopropyl)phosphonate as described in Ohira [Synth. Comm. 19:561-564 (1989)].

Compounds of formula VI may be prepared by reacting a compound of formula VIII as above with a compound of formula X



(X)

wherein  $R^3$  has the meanings as defined above and Z is halogen or  $B(OH)_2$ .

The reaction may take place by arylation of a compound of formula VIII either by using an aromatic boronic acid (compound of formula X) and a copper catalyst in a solvent like dichloromethane or tetrahydrofuran under an oxygen atmosphere [see e.g. Colmann et al., Org. Lett. 2:1233 (2000)] or by heating with  $R^3-Z$  when Z is halogen with a base like potassium carbonate or cesium carbonate in a solvent like dimethylformamide, or Pd catalyzed according to Buchwald conditions [see e.g. Example 8; Buchwald et al., Tetrahedron Lett. 40:2657 (1999)].

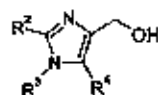
Compounds of formula VII may be prepared by reacting a compound of formula V as above with a compound of formula XI



(XI)

The reaction may take place by a Sonogashira coupling in the presence of e.g.  $CuI$ ,  $(Ph_3P)_2PdCl_2$ ,  $Et_3N$  in a solvent like tetrahydrofuran or dimethylformamide [Sonogashira et al., Synthesis 777 (1977)].

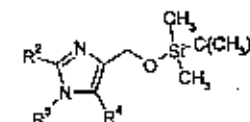
Compounds of formula IX may be prepared by oxidizing a compound of formula XII



(XII)

according to methods known to the skilled artisan.

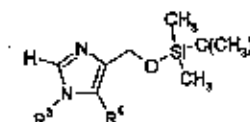
Compounds of formula XII may be prepared by deprotecting a compound of formula XIII



(XIII)

according to methods known to the skilled artisan.

Compounds of formula XIII may be prepared by alkylating a compound of formula XIV



(XIV)

with an alkylating agent of formula XVa

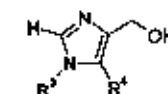


(XVa)

according to methods known to the skilled artisan.

Starting compounds of formula XVa are commercially available.

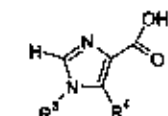
Compounds of formula XIV may be prepared by treating a compound of formula XV



(XV)

with tert-butyl dimethyl silyl chloride according to methods known to the skilled artisan.

Compounds of formula XV may be prepared by treating a compound of formula XVI



(XVI)

with a reducing agent according to methods known to the skilled artisan.

Compounds of formula XVI may be prepared by hydrolysing a compound of formula XVII

121

1177