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SUPERINDUSTRIA Y COMERCIO
Radicacion : 00073351 00000001 Folios: 41
Fecha (AMD): 2000-11-29 17:33:12
Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S D.

Re: P1.-F. HOFFMANN – LA ROCHE A.G.,- Solicitud de Patente de Invención para "DERIVADOS I QUINOLIN-4-IL".- Clase A61 .- Expediente número 00-073.351 .-

1. Me refiero a mi solicitud arriba nombrada de fecha 27 de Noviembre de 2000.

2. Anexos me permito presentar a usted:

(1) Copia autentica, debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad,** a saber la solicitud europea número 99119539.7 de 1 de Octubre de 1999, junto con su traducción Oficial No. 5.768 correspondiente a las legalizaciones y reivindicaciones de dicho documento; y

(2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial de la señora María Luisa Brigard de Restrepo quien elaboró la traducción de la legalizaciones de la solicitud europea número 99119539.7, respecto de la cual se reivindica prioridad en el presente caso.

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

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REPUBLICA DE COLOMBIA
MINISTERIO DE RELACIONES EXTERIORES

EL SUSCRITO JEFE DEL AREA DE LEGALIZACIONES DEL MINISTERIO DE RELACIONES EXTERIORES

C E R T I F I C A

Que revisados los registros que se llevan en la oficina de Legalizaciones aparece la firma de la señora **MARIA LUISA DE BRIGARD DE RESTREPO,** como traductora e intérprete oficial para los idiomas **INGLES - ESPAÑOL, ESPAÑOL-INGLES,** según resolución 0793 del 21 de marzo de 1958

La anterior certificación se expide a solicitud de la interesada quien se identificó con cédula de ciudadanía No. 20.024.691 expedida en Santa Fe de Bogotá.

Dada en Santa Fe de Bogotá, D.C. a los veinticinco (25) días de marzo de 1999

CARLOS GUILLERMO DIAZ BUITRAGO
Jefe Area de Legalizaciones

F-Hoffmann
20469
00.073351 82
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TRADUCCION OFICIAL No. 5.768

de un documento escrito en INGLES, el cual para su identificación se sella con el sello del Traductor al mismo tiempo que la presente. -

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Oficina Europea de Patentes

Certificado

Los documentos anexos son copias exactas de la solicitud de patente europea descrita en las páginas siguientes, tal como fue presentada originalmente.

TRADUCCION OFICIAL No. 5.768
María Luisa Rodrigo
Intérprete Oficial
con ha. 6783 del año de Junio

Solicitud de Patente No. 99119539.7

Por el Presidente de la Oficina Europea de Patentes

(Firma)

I.L.C. HATTEN-HECKMAN

LA HAYA, 9/10/00

PAGINA 2 DEL CERTIFICADO

Solicitud No. 99119539.7 Fecha de Presentación: 1/10/99

Solicitantes:

F. HOFFMANN-LA ROCHE AG

4070 Basilea

SUIZA

Título de la Invención:

Derivados de Quinolin-4-ila

Prioridades reivindicadas:

Estado Fecha No. de Registro:

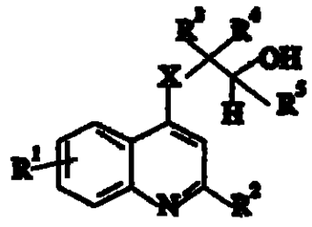
Clasificación Internacional de Patentes:

Estados contratantes designados en la fecha de presentación: AT/BE/CH/CY/DE/ DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE

Anotaciones:

REIVINDICACIONES

1. Compuestos de la fórmula



I

en donde

R^1 es hidrógeno, alquilo inferior, alcoxi inferior, hidroxi, amino, nitro, ciano, amino-alquilo inferior, di-amino-alquilo inferior o halógeno;

R^2 es fenilo, opcionalmente sustituído con alquilo inferior, alcoxi inferior, halógeno, trifluorometilo, amino, amino-alquilo inferior o di-amino-alquilo inferior, 2,3-dihidro-benzofuran-5-ilo, croman-6-ilo, naftalen-2-ilo, indan-5-ilo, alquenilfenilo inferior. 5.6.7.8-tetrahidro-naftalenilo, 2,3-dihidro-isoindol-2-ilo, 1,2,3,4-tetrahidro-naftalenilo, benzofuran-2-ilo, benzo[b]tiofen-2-ilo, alquilfenilo inferior, 3,4-dihidro-1H-isoquinolin-2-ilo o tiofen-3-ilo;

R^3 y R^4 son, independientemente uno del otro, hidrógeno o alquilo inferior;

R^5 es hidrógeno, alquilo inferior, $-CH_2OH$ o $CH_2NR^6R^7$;

R^6 y R^7 son, independientemente uno del otro, hidrógeno, alquilo inferior, $-(CH_2)_n$-fenilo, cicloalquilo, $-(CH_2)_m$-morfolinilo, o forman junto con

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el átomo de N un anillo saturado con 4 a 6 átomos de C;

n es 0 - 3;

m es 2 o 3;

X es $-NR^8-$ u $-O-$; o

X y R^5 son juntos $>N(CH_2)_2-$; o

X y R^3 son juntos $>N(CH_2)_3-$; y

R^8 es hidrógeno o alquilo inferior;

TRADUCCION OFICIAL No. 578
María Luisa Bright de Restrepo
Intérprete Oficial
Cruz del Sur de Justicia

y las sales de adición de ácido farmaceuticamente aceptables de los mismos, con la excepción de los siguientes compuestos:

(6-cloro-2-fenil-4-quinolinil)-(+)-2-aminobutanol;

(6-metil-2-fenil-4-quinolinil)-(+)-2-aminobutanol;

(6-metoxi-2-fenil-4-quinolinil)-(+)-2-aminobutanol; y

(8-metoxi-2-fenil-4-quinolinil)-(+)-2-aminobutanol.

2. Compuestos acordes con la reivindicación 1, en los que X es -NH-.

3. Compuestos acordes con la reivindicación 2 que son:

2-[2-(3,4-dihidro-1H-isoquinolin-2-il)-quinolin-4-ilamino]-etanol;

(RS)-1-amino-3-(2-p-tolil-quinolin-4-ilamino)-propan-2-ol;

(RS)-1-amino-3-[2-(4-metoxi-fenil)-quinolin-4-ilamino]-propan-2-ol;

S(+)-1-[2-(4-metoxi-fenil)-quinolin-4-ilamino]-propan-2-ol;

2-[2-(4-metoxi-fenil)-7-metil-quinolin-4-ilamino]-etanol;

(S)-1-[2-(4-metoxi-3-metil-fenil)-quinolin-4-ilamino]-propan-2-ol;

2-(7-metil-2-p-tolil-quinolin-4-ilamino]-etanol;

(S)-1-[2-(3-cloro-4-metil-fenil)-quinolin-4-ilamino)-propan-2-ol;

(RS)-3-[2-(3,4-dihidro-1H-isoquinolin-2-il)-quinolin-4-ilamino]-propan-2-ol;

(RS)-1-amino-3-[2-(3,4-dihidro-1H-isoquinolin-2-il)-quinolin-4-ilamino]-propan-2-ol;

2-[7-metoxi-2-(4-metoxi-fenil)-quinolin-4-ilamino]-etanol;

(RS)-1-amino-3-[7-metoxi-2-(4-metoxi-fenil)-quinolin-4-ilamino]-propan-2-ol;

y

(RS)-1-amino-3-(7-metoxi-2-p-tolil-quinolin-4-ilamino)-propan-2-ol.

4. Compuestos acordes con la reivindicación 1 en los que X es -O-.

5. Compuestos acordes con la reivindicación 4 que son:

(RS)-1-(7-metoxi-2-fenil-quinolin-4-iloxi)-3-metilamino-propan-2-ol;

(RS)-1-amino-3-(2-fenil-quinolin-4-iloxi)-propan-2-ol;

(RS)-1-isopropilamino-3-(2-fenil-quinolin-4-iloxi)-propan-2-ol;

(RS)-1-ciclopentilamino-3-(2-fenil-quinolin-4-iloxi)-propan-2-ol

(RS)-1-isopropilamino-3-(7-metoxi-2-fenil-quinolin-4-iloxi)-propan-2-ol

(RS)-1-metilamino-3-(2-p-tolil-quinolin-4-iloxi)-propan-2-ol;

(RS)-1-ciclobutilamino-3-(2-fenil-quinolin-4-iloxi)-propan-2-ol;

(RS)-1-[2-(4-metoxi-fenil)-quinolin-4-iloxi]-3-metilamino-propan-2-ol;

(RS)-1-metilamino-3-(7-metil-2-fenil-quinolin-4-iloxi)-propan-2-ol;

(RS)-1-(7-metoxi-2-p-tolil-quinolin-4-iloxi)-3-metilamino-propan-2-ol;

(RS)-1-[7-metoxi-2-(4-metoxi-fenil)-quinolin-4-iloxi]-3-metilamino-propan-2-ol;

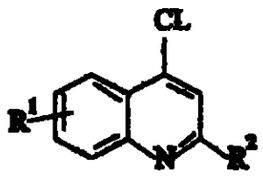
y
(RS)-1-[2-(4-metoxi-fenil)-7-metil-quinolin-4-iloxi)-3-metilamino-propan-2-ol.

6. Un medicamento que contiene uno o varios compuestos de cualquiera de las reivindicaciones 1 a 5 o una sal farmaceuticamente aceptable de los mismos y un portador inerte, para el tratamiento de enfermedades.

7. Un medicamento acorde con la reivindicación 6 para el tratamiento de enfermedades basadas en indicaciones terapéuticas para bloqueadores específicos del subtipo receptor NMDA, que incluyen formas agudas de neurodegeneración causada p.ej. por choque y trauma cerebral, y formas crónicas de degeneración tales como enfermedad de Alzheimer, enfermedad de Parkinson, enfermedad de Huntington, ALS (esclerosis lateral amiotrópica) y neurodegeneración asociada con esclerosis bacteriana) y neurodegeneración asociada con infecciones bacterianas o virales.

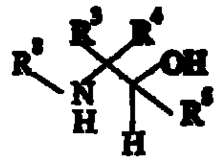
8. Un procedimiento para preparar un compuesto de la fórmula I definida en la reivindicación 1, que comprende:

a) hacer reaccionar un compuesto de la fórmula



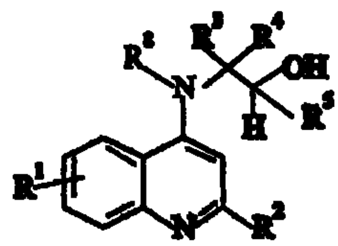
II

con una amina de la fórmula



III

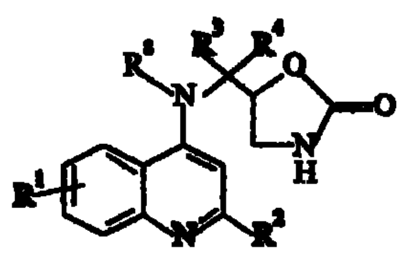
para dar un compuesto de la fórmula



I-1

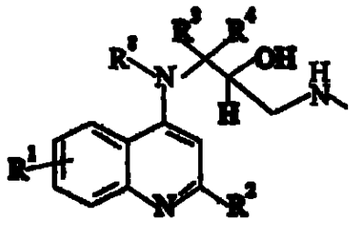
en donde ^{R} - R^5 y R^8 tienen los significados dados arriba, o

b) reducir un compuesto de la fórmula



IV

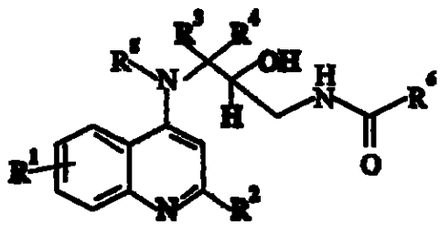
con un agente reductor, para dar un compuesto de la fórmula



I-12

en donde R - R^4 y R^5 tienen los significados dados arriba, o

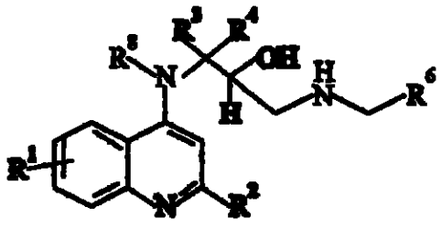
c) reducir un compuesto de la fórmula



V

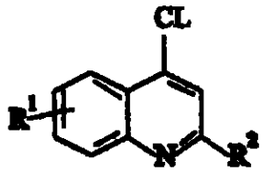
en donde R - R^4 y R^5 tienen los significados dados arriba y R^6 es alquilo inferior-fenilo, alquilo inferior-morfolino o alquilo inferior,

para dar un compuesto de la fórmula



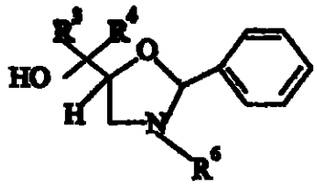
I-13

d) hacer reaccionar un compuesto de la fórmula



II

con un compuesto de la fórmula



VI

para dar un compuesto de la fórmula

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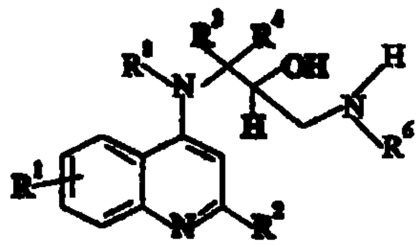
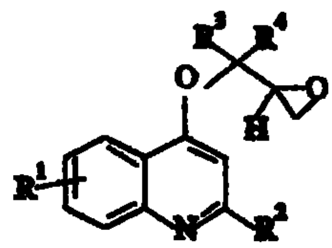


I-2

en donde ^{R} - R^4 y R^6 tienen los significados dados arriba, o

e) hacer reaccionar un compuesto de la fórmula

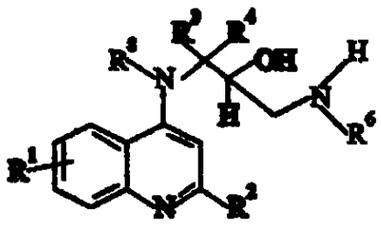


IX

con un compuesto de la fórmula

N-NR^6

para dar un compuesto de la fórmula



I-2

en donde ^{R} - R^4 y R^6 tienen los significados dados arriba, o

si se desea, modificar uno o varios sustitutos dentro de las definiciones dadas arriba, o

si se desea, convertir el compuesto de la fórmula I obtenido en una sal farmacéuticamente aceptable.

9. Un compuesto acorde con cualquiera de las reivindicaciones 1 -5 cuandoquiera que sea preparado mediante un procedimiento como el reivindicado en la reivindicación 8 o por un método equivalente.

10. El uso de un compuesto acorde con cualquiera de las reivindicaciones 1 - 5 para el tratamiento de enfermedades.

11. El uso de un compuesto acorde con la reivindicación 10 para el tratamiento de enfermedades basadas en indicaciones terapéuticas para bloqueadores específicos del subtipo receptor NMDA, que incluyen formas agudas de neurodegeneración causada p.ej. por choque y trauma cerebral, y formas crónicas de degeneración tales como enfermedad

de Alzheimer, enfermedad de Parkinson, enfermedad de Huntington, ALS (esclerosis lateral amiotrópica) y neurodegeneración asociada con esclerosis bacteriana) y neurodegeneración asociada con infecciones bacterianas o virales o para la fabricación de un medicamento que contiene dicho compuesto.

12. La invención descrita aquí antes.

ES TRADUCCION FIEL Y COMPLETA, de la cual queda copia en los archivos de esta oficina de traducciones, para su confrontación y a la que me remito.

Derechos de Traducción: $117.000,oo

BOGOTA, 9 DE NOVIEMBRE DEL 2000.

TRADUCTOR OFICIAL No. 5.748

María Luisa Brigard de Restrepo

Intérprete Oficial

Res. No. 0793 del Min. de Justicia

98.95

Europäisches Patentamt | European Patent Office | Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

5768

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

99119539.7

Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE, 09/10/00
LA HAYE, LE

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Europäisches Patentamt | European Patent Office | Office européen des brevets

Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.: 99119539.7
Demande n°:

Anmeldetag:
Date of filing: 01/10/99
Date de dépôt:

Anmelder:
Applicant(s):
Demandeur(s):
F. HOFFMANN-LA ROCHE AG
4070 Basel
SWITZERLAND

OFICIAL No. 5.763
María Luisa Brigaud de Rodrigo
Intérprete Oficial
Min. de Justicia

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Quinolin-4yl derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat: State: Pays:	Tag: Date: Date:	Aktenzeichen: File no. Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:
/

Am Anmeldetag benannte Vertragstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE
Etats contractants désignés lors du dépôt:

Bemerkungen:
Remarks:
Remarques:

F. Hoffmann-La Roche AG, CH-4070 Basle, Switzerland

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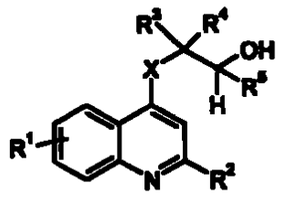
Case 20469

Quinolin-4yl derivatives

The present invention relates to compounds of the general formula



I

wherein

R^1		is hydrogen, lower alkyl, lower alkoxy, hydroxy, amino, nitro, cyano, lower alkyl-amino, di-lower alkyl-amino or halogen;
R^2		is phenyl, optionally substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl, amino, lower alkyl-amino or di-lower alkyl-amino, 2,3-dihydro-benzofuran-5-yl, chroman-6-yl, naphthalen-2-yl, indan-5-yl, lower alkenyl-phenyl, 5,6,7,8-tetrahydro-naphthalenyl, 2,3-dihydro-isoindol-2-yl, 1,2,3,4-tetrahydro-naphthalenyl, benzofuran-2-yl, benzo[b]thiophen-2-yl, lower alkyl-phenyl, 3,4-dihydro-1H-isoquinolin-2-yl or thiophen-3-yl;
R^3 and R^4		are independently from each other hydrogen or lower alkyl;
R^5		is hydrogen, lower alkyl, $-CH_2OH$ or $-CH_2NR^6R^7$;
R^6 and R^7		are independently from each other hydrogen, lower alkyl, $-(CH_2)_n$-phenyl, cycloalkyl, $-(CH_2)_m$-morpholinyl or form together with the N-atom a saturated ring with 4-6 C-atoms;
n		is 0 - 3;

Pop/30.09.1999

m is 2 or 3;

X is $-NR^8-$ or $-O-$; or

X and R^5 are together $>N(CH_2)_2-$; or

X and R^5 are together $>N(CH_2)_3-$; and

R^8 is hydrogen or lower alkyl;

and to pharmaceutically acceptable acid addition salts thereof.

Not encompassed from compounds of formula I are the following specific compounds, which are described in Indian Journal of Chemistry, Vol. 35B, 1996, 871-873 and having an antibacterial activity.

(6-Chloro-2-phenyl-4-quinolinyl)-(+)-2-aminobutanol;

(6-methyl-2-phenyl-4-quinolinyl)-(+)-2-aminobutanol;

(6-methoxy-2-phenyl-4-quinolinyl)-(+)-2-aminobutanol; and

(8-methoxy-2-phenyl-4-quinolinyl)-(+)-2-aminobutanol;

The compounds of formula I and their salts are distinguished by valuable therapeutic properties. Compounds of the present invention are NMDA(N-methyl-D-aspartate)-receptor subtype selective blockers, which have a key function in modulating neuronal activity and plasticity which makes them key players in mediating processes underlying development of CNS as well as learning and memory formation.

Under pathological conditions of acute and chronic forms of neurodegeneration overactivation of NMDA receptors is a key event for triggering neuronal cell death. NMDA receptors are composed of members from two subunit families, namely NR-1 (8 different splice variants) and NR-2 (A to D) originating from different genes. Members from the two subunit families show a distinct distribution in different brain areas. Heteromeric combinations of NR-1 members with different NR-2 subunits result in NMDA receptors displaying different pharmaceutical properties. Possible therapeutic indications for NMDA receptor subtype specific blockers include acute forms of neurodegeneration caused, e.g., by stroke and brain trauma, and chronic forms of neurodegeneration such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS (amyotrophic lateral sclerosis) and neurodegeneration associated with bacterial or viral infections, and, in addition, chronic and acute pain.

Objects of the invention are the compounds of formula I and pharmaceutically acceptable acid addition salts thereof, the preparation of the compounds of formula I and salts thereof, medicaments containing a compound of formula I or a pharmaceutically

acceptable acid addition salt thereof, the manufacture of such medicaments and the use of the compounds of formula I and their pharmaceutically acceptable salts in the control or prevention of illnesses, especially of illnesses and disorders of the kind referred to earlier, and, respectively, for the manufacture of corresponding medicaments.

The present invention embraces racemic mixtures and all their corresponding enantiomers.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl" denotes a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl and the like.

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

The term "lower alkoxy" denotes a group wherein the alkyl residue is as defined above.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

Preferred compounds of formula I in the scope of the present invention are those, wherein X is –NH- and R^5 is hydrogen, $-CH_2NH_2$, $-CH_3$ or- CH_2OH. These are the following compounds:

2-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-quinolin-4-ylamino]-ethanol;

(RS)-1-Amino-3-(2-p-tolyl-quinolin-4-ylamino)-propan-2-ol;

(RS)-1-Amino-3-[2-(4-methoxy-phenyl)-quinolin-4-ylamino]-propan-2-ol;

S(+)-1-[2-(4-Methoxy-phenyl)-quinolin-4-ylamino]-propan-2-ol;

2-[2-(4-Methoxy-phenyl)-7-methyl-quinolin-4-ylamino]-ethanol;

(S)-1-[2-(4-Methoxy-3-methyl-phenyl)-quinolin-4-ylamino]-propan-2-ol;

2-(7-Methyl-2-p-tolyl-quinolin-4-ylamino)-ethanol;

(S)-1-[2-(3-Chloro-4-methyl-phenyl)-quinolin-4-ylamino]-propan-2-ol;

(RS)-3-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-quinolin-4-ylamino]-propane-1,2-diol;

(RS)-1-Amino-3-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-quinolin-4-ylamino]-propan-2-ol;

2-[7-Methoxy-2-(4-methoxy-phenyl)-quinolin-4-ylamino]-ethanol;

(RS)-1-Amino-3-[7-methoxy-2-(4-methoxy-phenyl)-quinolin-4-ylamino]-propan-2-ol; and

(RS)-1-Amino-3-(7-methoxy-2-p-tolyl-quinolin-4-ylamino)-propan-2-ol.

Compounds of the present invention, in which X is –O- and R^5 is $-CH_2NHCH_3$, $-CH_2NH_2$, $-CH_2NHCH(CH_3)_2$ or -CH_2NH-cycloalkyl, are further preferred, for example the following compounds:

(RS)-1-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-3-methylamino-propan-2-ol;

(RS)-1-Amino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol;

(RS)-1-Isopropylamino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol;

(RS)-1-Cyclopentylamino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol;

(RS)-1-Isopropylamino-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-propan-2-ol;

(RS)-1-Methylamino-3-(2-p-tolyl-quinolin-4-yloxy)-propan-2-ol;

(RS)-1-Cyclobutylamino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol;

(RS)-1-[2-(4-Methoxy-phenyl)-quinolin-4-yloxy]-3-methylamino-propan-2-ol;

(RS)-1-Methylamino-3-(7-methyl-2-phenyl-quinolin-4-yloxy)-propan-2-ol;

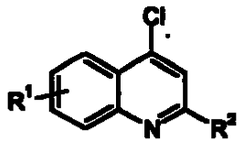
(RS)-1-(7-Methoxy-2-p-tolyl-quinolin-4-yloxy)-3-methylamino-propan-2-ol;

(RS)-1-[7-Methoxy-2-(4-methoxy-phenyl)-quinolin-4-yloxy]-3-methylamino-propan-2-ol; and

(RS)-1-[2-(4-Methoxy-phenyl)-7-methyl-quinolin-4-yloxy]-3-methylamino-propan-2-ol.

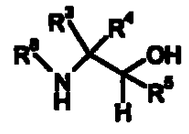
The afore-mentioned compounds of formula I can be manufactured in accordance with the invention by

a) reacting a compound of formula



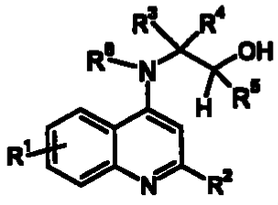
II

with an amine of formula



III

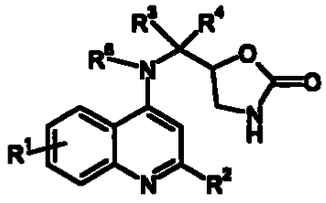
to a compound of formula



I-1

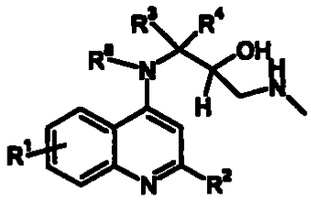
wherein $R^1 - R^5$ and R^8 have the significances given above, or

b) reducing a compound of formula



IV

with a reducing agent to a compound of formula

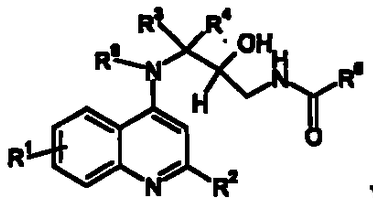


I-12

wherein $R^1 - R^4$ and R^8 have the significances given above,

or

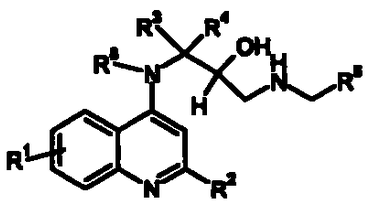
c) reducing a compound of formula



V

wherein R^1 - R^4 and R^5 have the significances given above and R^6 is lower alkyl-phenyl, lower alkyl-morpholino or lower alkyl,

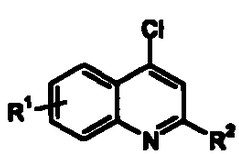
to a compound of formula



I-13

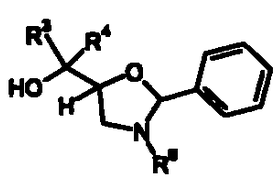
or

d) reacting a compound of formula



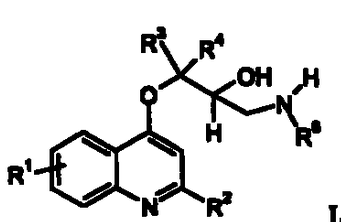
II

with a compound of formula



VI

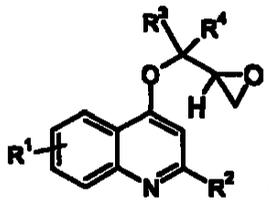
to a compound of formula



I-2

wherein R^1 – R^4 and R^6 have the significances given above, or,

e) reacting a compound of formula

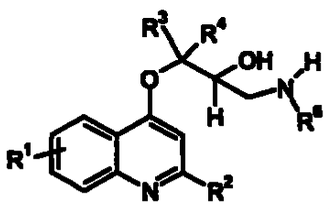


IX

with a compound of formula

$$H\text{-}NR^6$$

to a compound of formula



I-2

wherein R^1 – R^4 and R^6 have the significances given above, or,

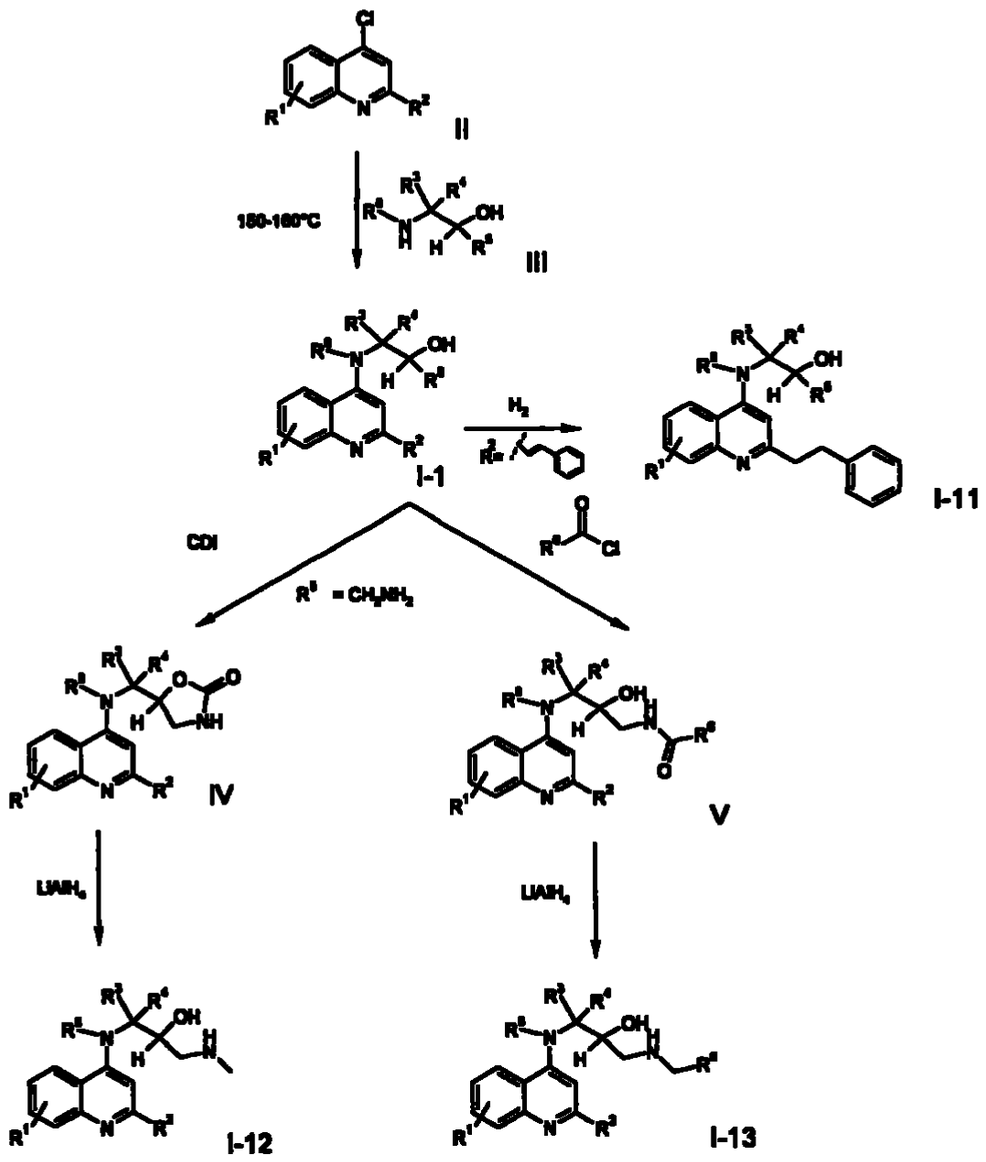
if desired, modifying one or more substituents within the definitions given above, or

if desired, converting the compound of formula I obtained into a pharmaceutically acceptable salt.

In the following the preparation of compounds of formula I are described in more detail:

1. Preparation of compounds of formula I, wherein X is $-NR^8-$:

Scheme 1



The amino group in 4-position is introduced using known procedures[1], for example by reaction at 150°C of a corresponding 4-chloro-quinoline with a primary or secondary amine using the neat amine as solvent (scheme 1).

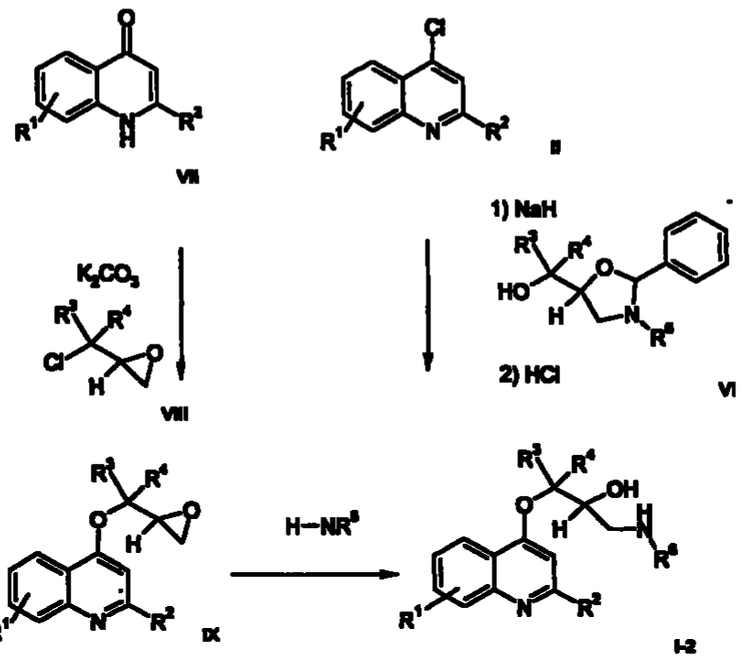
Introduction of the methyl or higher alkyl groups on the primary group of the side chain was performed using known methods by reduction of an oxazolidin-2-one or an amide (scheme 1). Compounds carring a phenethyl substituents at the 2-position were prepared by hydrogenation of the corresponding styryl derivatives.

[1]Field, G. F.; Zally, W. J. (Hoffmann-La Roche, Inc., USA).US 4560692

101

2. Preparation of compounds of formula I, wherein X is –O-:

Scheme 2



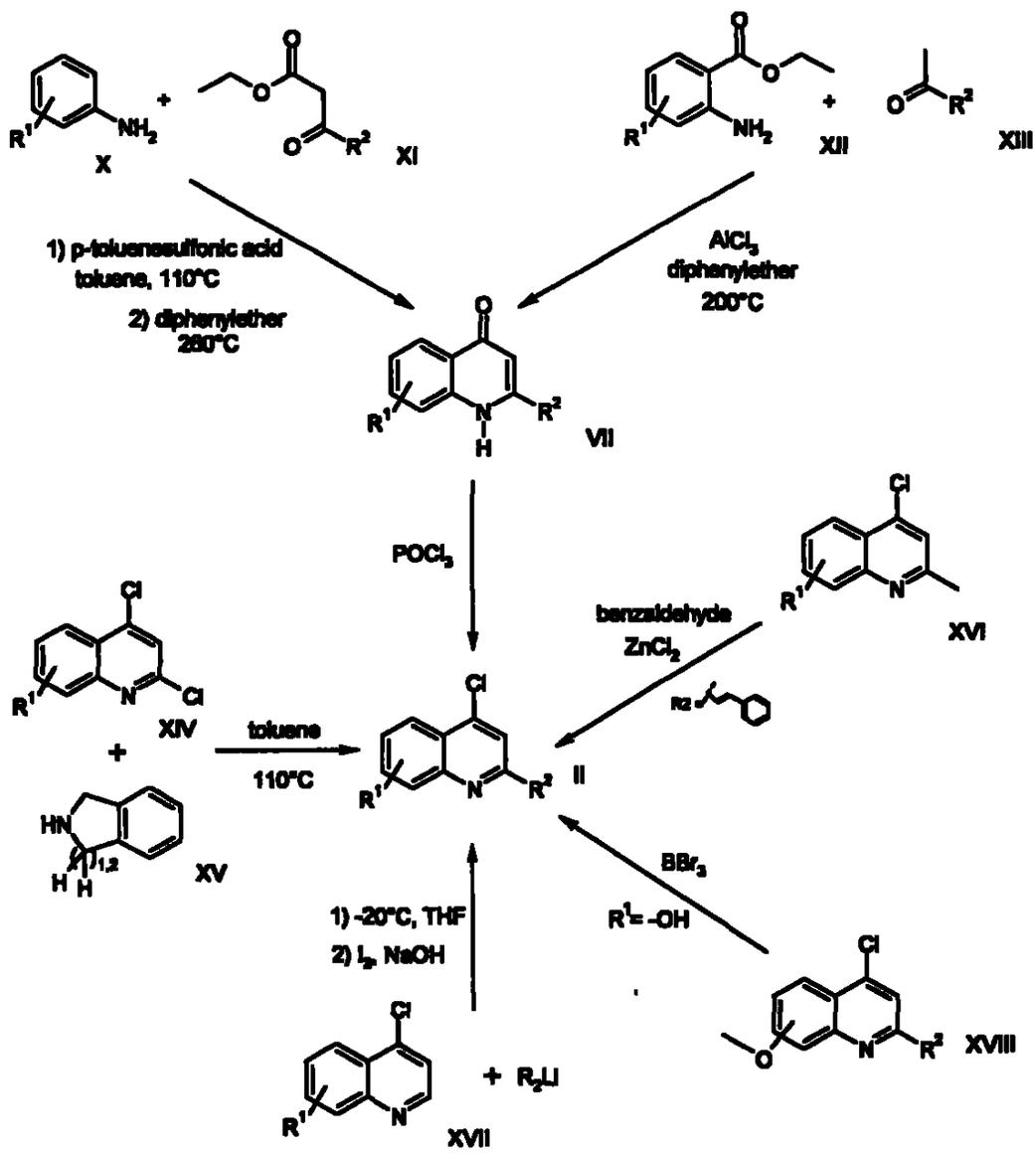
Compounds were made using known procedures either by reacting an amine with an epoxide or by reacting an oxazolidine with a 4-chloro-quinoline in the presence of sodium hydride[2] . Epoxides were prepared using a known procedure by reacting a quinolin-4-one with a chloro epoxide[3] (scheme 2).

[2]Baldwin, J. J.; Lumma, W. C., Jr.; Lundell, G. F.; Ponticello, G. S.; Raab, A. W.; Engelhardt, E. L.; Hirschmann, R.; Sweet, C. S.; Scriabine, A.; J. Med. Chem. (1979), 22(11), 1284-1290.

[3]Asthana, P.; Prasad, M.; R., Shri N.; Indian J.Chem.Sect.B; 26; 1987; 330-334

3. Preparation of the intermediates of formula II

Scheme 3



2-Amino-4-chloro-quinoline have been prepared by reacting of 2,4-dichloro-quinoline with a dialkylamine in refluxing toluene. This reaction was found to be completely regioselective (scheme 3).

Preparation of 2-alkyl; 2-aryl or 2-heteroaryl-4-chloro-quinolines (scheme 3):

Known procedures have been used:

- by adding an aryl or heteroaryl lithium to a 4-chloro-2-unsubstituted-quinoline followed by treatment with an oxidant like iodine[1]

-by converting a quinolin-4-one to the corresponding 4-chloro derivative in the presence of a chlorinating agent like phosphorus oxychloride[1]

Preparation of 2-styryl-4-chloro-quinolines (scheme 3):

By known procedure has been used reaction of a 2-methyl-4-chloro-quinoline with benzaldehyde.[2]

Preparation of hydroxy-4-chloro-quinolines (scheme 3):
By reaction of methoxy substituted-4-chloro-quinoline with BBr_3.
[1]Field, G. F.; Zally, W. J. (Hoffmann-La Roche, Inc., USA).US 4560692
2 I.G. Farbenind.; DE 440008

Preparation of quinolin-4-ones (scheme 3):
Known procedures have been used
-by condensation of an aniline with a β-ketoester[4] or
-by condensation of derivatives of anthranilic acid and aceto phenones[5].

[4] Hauser, C. R.; Reynolds, G. A.; J. Am. Chem. Soc. 1948,70, 2402; Hauser, C. R.; Murray, J. G.; J. Am. Chem. Soc. 1955,77, 2851.
[5] Jones G.; *Quinolines*, The Chemistry of Heterocyclic Compounds, Vol 32, Wiley, New York, 1977, 181-191, 195-207

Pharmaceutically acceptable salts can be manufactured according to methods which are known per se and familiar to any person skilled in the art. The acid addition salts of compounds of formula I are especially well suited for pharmaceutical use.

In schemes 1 – 3 are described processes for preparation of compounds of formula I, starting from known compounds, from commercial products or from compounds, which can be prepared in conventional manner.

The preparation of compounds of formula I are described in more detail in working examples 1 - 103.

As mentioned earlier, the compounds of formula I and their pharmaceutically usable acid addition salts possess valuable pharmacodynamic properties. They are NMDA-receptor subtype selective blockers, which have a key function in modulating neuronal activity and plasticity which makes them key players in mediating processes underlying development of CNS as well as learning and memory formation.

The compounds were investigated in accordance with the test given hereinafter.

Test method

3H-Ro 25-6981 binding (Ro 25-6981 is [R-(R*,S*)]-a-(4-Hydroxy-phenyl)-b-methyl-4-(phenyl-methyl)-1-piperidine propanol)

Male Füllinsdorf albino rats weighing between 150-200 g were used. Membranes were prepared by homogenization of the whole brain minus cerebellum and medulla oblongata with a Polytron (10.000 rpm, 30 seconds), in 25 volumes of a cold Tris-HCl 50 mM, EDTA 10 mM, pH 7.1 buffer. The homogenate was centrifuged at 48.000 g for 10 minutes at 4°C. The pellet was resuspended using the Polytron in the same volume of buffer and the homogenate was incubated at 37°C for 10 minutes. After centrifugation the pellet was homogenized in the same buffer and frozen at -80°C for at least 16 hours but not more than 10 days. For the binding assay the homogenate was thawed at 37°C, centrifuged and the pellet was washed three times as above in a Tris-HCl 5 mM, pH 7.4 cold buffer. The final pellet was resuspended in the same buffer and used at a final concentration of 200 mg of protein/ml.

3H-Ro 25-6981 binding experiments were performed using a Tris-HCl 50 mM, pH 7.4 buffer. For displacement experiments 5 nM of 3H-Ro 25-6981 were used and non specific binding was measured using 10 mM of tetrahydroisoquinoline and usually it accounts for 10% of the total. The incubation time was 2 hours at 4°C and the assay was stopped by filtration on Whatmann GF/B glass fiber filters (Unifilter-96, Packard, Zürich, Switzerland). The filters were washed 5 times with cold buffer. The radioactivity on the filter was counted on a Packard Top-count microplate scintillation counter after addition of 40 mL of microscint 40 (Canberra Packard S.A., Zürich, Switzerland).

The effects of compounds were measured using a minimum of 8 concentrations and repeated at least once. The pooled normalized values were analyzed using a non-linear regression calculation program which provide IC_{50} with their relative upper and lower 95% confidence limits (RS1, BBN, USA).

The IC_{50}(μM) of preferred compounds tested in accordance with the above mentioned methods are in the range of about 0.01. – 0,15.

The compounds of formula I and their salts, as herein described, can be incorporated into standard pharmaceutical dosage forms, for example, for oral or parenteral application with the usual pharmaceutical adjuvant materials, for example, organic or inorganic inert carrier materials, such as, water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkylene-glycols and the like. The pharmaceutical preparations can be employed in a solid form, for example, as tablets, suppositories, capsules, or in liquid form, for example, as solutions, suspensions or

emulsions. Pharmaceutical adjuvant materials can be added and include preservatives stabilizers, wetting or emulsifying agents, salts to change the osmotic pressure or to act as buffers. The pharmaceutical preparations can also contain other therapeutically active substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In the case of oral administration the dosage lies in the range of about 0.1 mg per dosage to about 1000 mg per day of a compound of general formula I although the upper limit can also be exceeded when this is shown to be indicated.

The following examples illustrate the present invention in more detail. However, they are not intended to limit its scope in any manner. All temperatures are given in degree celsius.

Example 1

2-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-quinolin-4-ylamino]-ethanol hydrochloride

4-Chloro-2-(3,4-dihydro-1H-isoquinolin-2-yl)-quinoline (0.5 g, 1.7 mmol) and ethanolamine (0.61 ml, 10.2 mmol) were mixed and heated at 150-160 °C for 16 hours. The reaction mixture was cooled to room temperature and water (20 ml) was added. After decantation of water, the gummy residue was dissolved in ethyl acetate, dried over Na_2SO_4 and the solvent was evaporated. The residue was chromatographed over silica gel (CH_2Cl_2-MeOH, 9:1 then 4:1) to provide a white foam which was dissolved in MeOH (5 ml). HCl-Et_2O was added to provide 2-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-quinolin-4-ylamino]-ethanol hydrochloride (0.16 g, 27%) as a white solid, m.p. 130-140°C and MS: m/e = 320.3 ($M+H^+$).

Following the general method of example 1 the compounds of example 2 to example 74 were prepared.

Example 2

(RS)-1-Amino-3-(2-p-tolyl-quinolin-4-ylamino)-propan-2-ol hydrochloride

The title compound, m.p. 264-272°C and MS: m/e = 308.3 ($M+H^+$), was prepared from 4-chloro-2-p-tolyl-quinoline and 1,3-diamino-2-propanol.

Example 3

(RS)-1-Amino-3-[2-(4-methoxy-phenyl)-quinolin-4-ylamino]-propan-2-ol hydrochloride

The title compound, m.p. 260-264°C and MS: m/e = 324.3 ($M+H^+$), was prepared from 4-chloro-2-(4-methoxy-phenyl)-quinoline and 1,3-diamino-2-propanol.

Example 4

S(+)-1-[2-(4-Methoxy-phenyl)-quinolin-4-ylamino]-propan-2-ol-hydrochloride

The title compound, m.p. 226-227°C, $[\alpha]_D^{20} = +18.1°$ (c = 0.1, methanol) and MS: m/e = 309.2 ($M+H^+$), was prepared from 4-chloro-2-(4-methoxy-phenyl)-quinoline and S(+)-1-amino-2-propanol.

Example 5

2-[2-(4-Methoxy-phenyl)-7-methyl-quinolin-4-ylamino]-ethanol hydrochloride

The title compound, m.p. 233-238°C and MS: m/e = 309.2 ($M+H^+$), was prepared from 4-chloro-2-(4-methoxy-phenyl)-7-methyl-quinoline and ethanolamine.

Example 6

(S)-1-[2-(4-Methoxy-3-methyl-phenyl)-quinolin-4-ylamino]-propan-2-ol hydrochloride

The title compound, m.p. 266-267°C, $[\alpha]_D^{20} = +12.6°$ (c = 0.29, methanol) and MS: m/e = 322 (M^+), was prepared from 4-chloro-2-(4-methoxy-3-methyl-phenyl)-quinoline and S(+)-1-amino-2-propanol.

Example 7

2-(7-Methyl-2-p-tolyl-quinolin-4-ylamino)-ethanol hydrochloride

The title compound, m.p. 260-263°C and MS: m/e = 293.3 ($M+H^+$), was prepared from 4-chloro-7-methyl-2-p-tolyl-quinoline and ethanolamine.

Example 8

(S)-1-[2-(3-Chloro-4-methyl-phenyl)-quinolin-4-ylamino]-propan-2-ol hydrochloride

The title compound, m.p. 249-252°C, MS: m/e = 326 (M^+), was prepared from 4-chloro-2-(3-chloro-4-methyl-phenyl)-quinoline and S(+)-1-amino-2-propanol.

Example 9

(RS)-3-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-quinolin-4-ylamino]-propane-1,2-diol

The title compound, MS: m/e = 349 (M^+), was prepared from 4-chloro-2-(3,4-dihydro-1H-isoquinolin-2-yl)-quinoline and (RS)-3-amino-1,2-propanediol.

Example 10

(RS)-1-Amino-3-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-quinolin-4-ylamino]-propan-2-ol hydrochloride

The title compound, m.p. 265-275°C, MS: m/e = 348 (M^+), was prepared from 4-chloro-2-(3,4-dihydro-1H-isoquinolin-2-yl)-quinoline and 1,3-diamino-2-propanol.

Example 11

2-[7-Methoxy-2-(4-methoxy-phenyl)-quinolin-4-ylamino]-ethanol hydrochloride

The title compound, m.p. 244-245°C and MS: m/e = 325.3 ($M+H^+$), was prepared from 4-chloro-7-methoxy-2-(4-methoxy-phenyl)-quinoline and ethanolamine.

Example 12

(RS)-1-Amino-3-[7-methoxy-2-(4-methoxy-phenyl)-quinolin-4-ylamino]-propan-2-ol hydrochloride

The title compound, m.p. 190-205°C and MS: m/e = 353 (M^+), was prepared from 4-chloro-7-methoxy-2-(4-methoxy-phenyl)-quinoline and 1,3-diamino-2-propanol.

Example 13

(RS)-1-Amino-3-(7-methoxy-2-p-tolyl-quinolin-4-ylamino)-propan-2-ol hydrochloride

The title compound, MS: m/e = 337 (M^+), was prepared from 4-chloro-7-methoxy-2-p-tolyl-quinoline and 1,3-diamino-2-propanol.

Example 14

(S)-1-[2-(4-Methoxy-phenyl)-7-methyl-quinolin-4-ylamino]-propan-2-ol hydrochloride

The title compound, m.p. 189-192°C, MS: m/e = 323.3 ($M+H^+$), was prepared from 4-chloro-2-(4-methoxy-phenyl)-7-methyl-quinoline and S(+)-1-amino-2-propanol.

Example 15

(E)-(RS)-3-(2-Styryl-quinolin-4-ylamino)-propane-1,2-diol fumarate

The title compound, m.p. 220-222°C and MS: m/e = 321.2 ($M+H^+$), was prepared from (E)-4-Chloro-2-styryl-quinoline and (RS)-3-amino-1,2-propandiol.

Example 16

2-(7-Methoxy-2-phenyl-quinolin-4-ylamino)-ethanol hydrochloride

The title compound, m.p. 197°C and MS: m/e = 294 (M^+), was prepared from 4-chloro-7-methoxy-2-phenyl-quinoline and ethanolamine.

Example 17

2-[2-(4-Methoxy-phenyl)-quinolin-4-ylamino]-ethanol hydrochloride

The title compound, m.p. 211-213°C and MS: m/e = 294 (M^+), was prepared from 4-chloro-2-(4-methoxy-phenyl)-quinoline and ethanolamine.

Example 18

2-[2-(5,6,7,8-Tetrahydro-naphthalen-2-yl)-quinolin-4-ylamino]-ethanol hydrochloride

The title compound, m.p. 250-252°C and MS: m/e = 319.4 ($M+H^+$), was prepared from 4-chloro-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-quinoline and ethanolamine.

Example 19

(S)-1-(7-Methyl-2-p-tolyl-quinolin-4-ylamino)-propan-2-ol hydrochloride

The title compound, m.p. 264-267°C, MS: m/e = 307.3 ($M+H^+$), was prepared from 4-chloro-7-methyl-2-p-tolyl-quinoline and S(+)-1-amino-2-propanol.

Example 20

(RS)-3-[2-(3-Chloro-4-methyl-phenyl)-quinolin-4-ylamino]-propane-1,2-diol hydrochloride

The title compound, m.p. 230-231°C and MS: m/e = 343.1 ($M+H^+$), was prepared from 4-chloro-2-(3-chloro-4-methyl-phenyl)-quinoline and (RS)-3-amino-1,2-propandiol.

Example 21

(S)-1-(2-p-Tolyl-quinolin-4-ylamino)-propan-2-ol hydrochloride

The title compound, m.p. 280-281°C, $[\alpha]_D^{20} = +17.0°$ (c = 0.43, methanol) and MS: m/e = 292 (M^+), was prepared from 4-chloro-2-p-tolyl-quinoline and S(+)-1-amino-2-propanol.

Example 22

(RS)-3-[2-(4-Methoxy-phenyl)-quinolin-4-ylamino]-propane-1,2-diol hydrochloride

The title compound, m.p. 216-218°C and MS: m/e = 324 (M^+), was prepared from 4-chloro-2-(4-methoxy-phenyl)-quinoline and (RS)-3-amino-1,2-propandiol.

Example 23

(RS)-1-Amino-3-[2-(4-chloro-phenyl)-7-methoxy-quinolin-4-ylamino]-propan-2-ol hydrochloride

The title compound, m.p. 269-271°C and MS: m/e = 358.1 ($M+H^+$), was prepared from 4-chloro-2-(4-chloro-phenyl)-7-methoxy-quinoline and 1,3-diamino-2-propanol.

Example 24

2-(7-Methoxy-2-p-tolyl-quinolin-4-ylamino)-ethanol hydrochloride

The title compound, m.p. 254-255°C and MS: m/e = 309.2 ($M+H^+$), was prepared from 4-chloro-7-methoxy-2-p-tolyl-quinoline and ethanolamine.

Example 25

(S)-1-[2-(3-Chloro-4-methoxy-phenyl)-quinolin-4-ylamino]-propan-2-ol hydrochloride

The title compound, m.p. 249-251°C, MS: m/e = 342 (M^+), was prepared from 4-chloro-2-(3-chloro-4-methoxy-phenyl)-quinoline and S(+)-1-amino-2-propanol.

Example 26

2-(2-p-Tolyl-quinolin-4-ylamino)-ethanol hydrochloride

The title compound, m.p. 274-276°C and MS: m/e = 278 (M^+), was prepared from 4-chloro-2-p-tolyl-quinoline and ethanolamine.

Example 27

(RS)-3-[2-(3,4-Dimethyl-phenyl)-quinolin-4-ylamino]-propane-1,2-diol hydrochloride

The title compound, m.p. 248°C and MS: m/e = 322 (M^+), was prepared 4-chloro-2-(3,4-dimethyl-phenyl)-quinoline and (RS)-3-amino-1,2-propandiol.

Example 28

(RS)-3-(2-p-Tolyl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

The title compound, m.p. 255-257°C and MS: m/e = 308 (M^+), was prepared from 4-chloro-2-p-tolyl-quinoline and (RS)-3-amino-1,2-propandiol.

Example 29

(RS)-1-Amino-3-(7-methoxy-2-phenyl-quinolin-4-ylamino)-propan-2-ol hydrochloride

The title compound, m.p. 184-186°C and MS: m/e = 323 (M^+), was prepared from 4-chloro-7-methoxy-2-phenyl-quinoline and 1,3-diamino-2-propanol.

Example 30

(RS)-3-[2-(5,6,7,8-Tetrahydro-naphthalen-2-yl)-quinolin-4-ylamino]-propane-1,2-diol hydrochloride

The title compound, m.p. 210-230°C and MS: m/e = 348 (M^+), was prepared from 4-chloro-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-quinoline and (RS)-3-amino-1,2-propandiol.

Example 31

(S)-1-[2-(2,3-Dihydro-benzofuran-5-yl)-quinolin-4-ylamino]-propan-2-ol hydrochloride

The title compound, m.p. 236-242°C, MS: m/e = 321.3 ($M+H^+$), was prepared from 4-chloro-2-(2,3-dihydro-benzofuran-5-yl)-quinoline and S(+)-1-amino-2-propanol.

Example 32

(RS)-3-[2-(2,3-Dihydro-benzofuran-5-yl)-quinolin-4-ylamino]-propane-1,2-diol hydrochloride

The title compound, m.p. 267-270°C and MS: m/e = 336 (M^+), was prepared from 4-chloro-2-(2,3-dihydro-benzofuran-5-yl)-quinoline and (RS)-3-amino-1,2-propandiol.

Example 33

(S)-1-(7-Methoxy-2-phenyl-quinolin-4-ylamino)-propan-2-ol hydrochloride

The title compound, m.p. 139-141°C, $[\alpha]_D^{20}$ = +19.7° (c = 0.5, methanol) and MS: m/e = 308 (M^+), was prepared from 4-chloro-7-methoxy-2-phenyl-quinoline and S(+)-1-amino-2-propanol.

Example 34

(RS)-3-[2-(4-Methoxy-3-methyl-phenyl)-quinolin-4-ylamino]-propane-1,2-diol hydrochloride

The title compound, m.p. 166-171°C, and MS: m/e = 338 (M^+), was prepared from 4-chloro-2-(4-methoxy-3-methyl-phenyl)-quinoline and (RS)-3-amino-1,2-propandiol.

Example 35

(RS)-3-(7-Methoxy-2-phenyl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

The title compound, m.p. 218-222°C, and MS: m/e = 325.3 ($M+H^+$), was prepared from 4-chloro-7-methoxy-2-phenyl-quinoline and (RS)-3-amino-1,2-propandiol.

Example 36

(RS)-3-[2-(3,4-Dichloro-phenyl)-quinolin-4-ylamino]-propane-1,2-diol hydrochloride

The title compound, m.p. 234-236°C, and MS: m/e = 362 (M^+), was prepared from 4-chloro-2-(3,4-dichloro-phenyl)-quinoline and (RS)-3-amino-1,2-propandiol.

Example 37

2-[2-(4-Chloro-phenyl)-7-methoxy-quinolin-4-ylamino]-ethanol hydrochloride

The title compound, m.p. 271-272°C, and MS: m/e = 328 (M^+), was prepared from 4-chloro-2-(4-chloro-phenyl)-7-methoxy-quinoline and ethanolamine.

Example 38

(RS)-3-[2-(3-Chloro-4-methoxy-phenyl)-quinolin-4-ylamino]-propane-1,2-diol hydrochloride

The title compound, m.p. 205-210°C, and MS: m/e = 358 (M^+), was prepared from 4-chloro-2-(3-chloro-4-methoxy-phenyl)-quinoline and (RS)-3-amino-1,2-propandiol.

Example 39

2-[2-(4-Chloro-phenyl)-quinolin-4-ylamino]-ethanol hydrochloride

The title compound, m.p. 262-264°C, and MS: m/e = 299.2 ($M+H^+$), was prepared from 4-chloro-2-(4-chloro-phenyl)-quinoline and ethanolamine.

Example 40

(RS)-1-Amino-3-[2-(3,4-dichloro-phenyl)-quinolin-4-ylamino]-propan-2-ol hydrochloride

The title compound, m.p. 230-240°C, and MS: m/e = 362.1 ($M+H^+$), was prepared from 4-chloro-2-(3,4-dichloro-phenyl)-quinoline and 1,3-diamino-2-propanol.

Example 41

2-[2-(3,4-Dichloro-phenyl)-7-methoxy-quinolin-4-ylamino]-ethanol hydrochloride

The title compound, m.p. 268-270°C, and MS: m/e = 363.0 ($M+H^+$), was prepared from 4-chloro-2-(3,4-dichloro-phenyl)-7-methoxy-quinoline and ethanolamine.

Example 42

(RS)-1-Amino-3-[2-(3,4-dichloro-phenyl)-7-methoxy-quinolin-4-ylamino]-propan-2-ol hydrochloride

The title compound, m.p. 230-233°C, and MS: m/e = 391 (M^+), was prepared from 4-chloro-2-(3,4-dichloro-phenyl)-7-methoxy-quinoline and 1,3-diamino-2-propanol.

Example 43

(R)-1-[2-(4-Methoxy-phenyl)-quinolin-4-yl]-pyrrolidin-3-ol hydrochloride

The title compound, m.p. 266-267°C, and MS: m/e = 321.3 ($M+H^+$), was prepared from 4-chloro-2-(4-methoxy-phenyl)-quinoline and (R)-3-hydroxypyrrolidine.

Example 44

(RS)-1-Amino-3-[[2-(4-chlorophenyl)-4-quinolinyl]amino]-2-propanol dihydrochloride

The title compound, m.p. 283-287°C, and MS: m/e = 328.2 ($M+H^+$), was prepared from 4-chloro-2-(4-chloro-phenyl)-quinoline and 1,3-diamino-2-propanol.

Example 45

(RS)-3-(2-Chroman-6-yl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

The title compound, MS: m/e = 351.3 ($M+H^+$), was prepared from 4-chloro-2-chroman-6-yl-quinoline and (RS)-3-amino-1,2-propandiol.

Example 46

2-{[2-(4-Methoxy-phenyl)-quinolin-4-yl]-methyl-amino}-ethanol hydrochloride

The title compound, m.p. 201-204°C, and MS: m/e = 309.2 ($M+H^+$), was prepared from 4-chloro-2-(4-methoxy-phenyl)-quinoline and 2-(Methylamino)-ethanol.

Example 47

(RS)-1-Amino-3-(2-naphthalen-2-yl-quinolin-4-ylamino)-propan-2-ol hydrochloride

The title compound, m.p. 288-291°C, MS: m/e = 343 (M^+), was prepared 4-chloro-2-naphthalen-2-yl-quinoline and 1,3-diamino-2-propanol.

Example 48

(RS)-3-(2-Indan-5-yl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

The title compound, m.p. 157-160°C, MS: m/e = 334 (M^+), was prepared from 4-chloro-2-indan-5-yl-quinoline and (RS)-3-amino-1,2-propandiol.

Example 49

2-(7-Methyl-2-phenyl-quinolin-4-ylamino)-ethanol hydrochloride

The title compound, m.p. 234-236°C, and MS: m/e = 278 (M^+), was prepared from 4-chloro-7-methyl-2-phenyl-quinoline and ethanolamine.

Example 50

(R)-{1-[2-(4-Methoxy-phenyl)-quinolin-4-yl]-pyrrolidin-2-yl}-methanol hydrochloride

The title compound, m.p. 148-160°C, $[\alpha]_D^{20} = -62.6°$ (c = 0.51, methanol) and MS: m/e = 334 (M^+), was prepared from 4-chloro-2-(4-methoxy-phenyl)-quinoline and D-prolinol.

Example 51

2-(8-Methoxy-2-phenyl-quinolin-4-ylamino)-ethanol hydrochloride

The title compound, m.p. 205-209°C, and MS: m/e = 295.3 ($M+H^+$), was prepared from 4-chloro-8-methoxy-2-phenyl-quinoline and ethanolamine.

Example 52

2-[2-(3,4-Dichloro-phenyl)-quinolin-4-ylamino]-ethanol hydrochloride

The title compound, m.p. 256-258°C, and MS: m/e = 333.1 ($M+H^+$), was prepared from 4-chloro-2-(3,4-dichloro-phenyl)-quinoline and ethanolamine.

Example 53

(RS)-1-Dimethylamino-3-[2-(4-methoxy-phenyl)-quinolin-4-ylamino]-propan-2-ol hydrochloride

The title compound, m.p. 226-228°C, and MS: m/e = 352.3 ($M+H^+$), was prepared from 4-chloro-2-(4-methoxy-phenyl)-quinoline and (RS)-1-amino-3-dimethylamino-propan-2-ol.

(RS)-1-amino-3-dimethylamino-propan-2-ol is a known compound and has been prepared as described in the following reference: I.G. Farbenind. DE 479354.

Example 54

(RS)-3-[2-(1,3-Dihydro-isoindol-2-yl)-quinolin-4-ylamino]-propane-1,2-diol hydrochloride

The title compound, m.p. 295-301°C, and MS: m/e = 336.2 ($M+H^+$), was prepared from 4-chloro-2-(1,3-dihydro-isoindol-2-yl)-quinoline and (RS)-3-amino-1,2-propandiol.

Example 55

(RS)-1-Amino-3-(2-phenyl-quinolin-4-ylamino)-propan-2-ol hydrochloride

The title compound, m.p. 291-294°C, MS: m/e = 294.3 ($M+H^+$), was prepared from 4-chloro-2-phenyl-quinoline and 1,3-diamino-2-propanol.

Example 56

(RS)-3-[2-(4-Trifluoromethyl-phenyl)-quinolin-4-ylamino]-propane-1,2-diol hydrochloride

The title compound, m.p. 243-247°C, and MS: m/e = 362 (M^+), was prepared from 4-chloro-2-(4-trifluoromethyl-phenyl)-quinoline and (RS)-3-amino-1,2-propandiol.

Example 57

(S)-1-(2-Phenyl-quinolin-4-ylamino)-propan-2-ol hydrochloride

The title compound, m.p. 251-252°C, $[\alpha]_D^{20} = +20.3°$ (c = 0.43, methanol) and MS: m/e = 278 (M^+), was prepared from 4-chloro-2-phenyl-quinoline and S(+)-1-amino-2-propanol.

Example 58

(RS)- and (SR)-3-[2-[(RS)-1,2,3,4-Tetrahydro-naphthalen-2-yl]-quinolin-4-ylamino]-propane-1,2-diol hydrochloride

The title compound, m.p. 212-218°C, and MS: m/e = 348 (M^+), was prepared from (RS)-4-chloro-2-(1,2,3,4-tetrahydro-naphthalen-2-yl)-quinoline and (RS)-3-amino-1,2-propandiol.

Example 59

(RS)-3-[2-(4-Chloro-phenyl)-quinolin-4-ylamino]-propane-1,2-diol hydrochloride

The title compound, m.p. 232-236°C, and MS: m/e = 328 (M^+), was prepared from 4-chloro-2-(4-chloro-phenyl)-quinoline and (RS)-3-amino-1,2-propandiol.

Example 60

2-(2-Phenyl-quinolin-4-ylamino)-ethanol hydrochloride

The title compound, m.p. 258-260°C, MS: m/e = 264 (M^+), was prepared from 4-chloro-2-phenyl-quinoline and ethanolamine.

Example 61

(RS)-3-(8-Methoxy-2-phenyl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

The title compound, m.p. 110-116 °C, and MS: m/e = 325.3 ($M+H^+$), was prepared from 4-chloro-8-methoxy-2-phenyl-quinoline and (RS)-3-amino-1,2-propandiol.

Example 62

(RS)-3-(7-Hydroxy-2-phenyl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

The title compound, m.p. 267-268 °C, and MS: m/e = 310 (M^+), was prepared from 4-chloro-2-phenyl-quinolin-7-ol and (RS)-3-amino-1,2-propandiol.

Example 63

(RS)-3-(2-Benzofuran-2-yl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

The title compound, m.p. 263-265 °C, and MS: m/e = 335.2($M+H^+$), was prepared from 2-benzofuran-2-yl-4-chloro-quinoline and (RS)-3-amino-1,2-propandiol.

Example 64

(RS)-3-(2-m-Tolyl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

The title compound, m.p. 208-215 °C, and MS: m/e = 309.2 ($M+H^+$), was prepared from 4-chloro-2-m-tolyl-quinoline and (RS)-3-amino-1,2-propandiol.

Example 65

(RS)-1-Amino-3-[[2-(4-chlorophenyl)-4-quinolinyl]amino]-2-propanol

The title compound, m.p. 283-287°C and MS: m/e = 328.2 ($M+H^+$), was prepared from 4-chloro-2-(4-chloro-phenyl)-quinoline and 1,3-diamino-2-propanol.

Example 66

(S)-1-[2-(4-Methoxy-phenyl)-quinolin-4-yl]-pyrrolidin-3-ol hydrochloride

The title compound, m.p. 270-271°C, MS: m/e = 321.3 ($M+H^+$), was prepared 4-chloro-2-(4-methoxy-phenyl)-quinoline and (S)-3-hydroxypyrrolidine.

Example 67

(RS)-3-[2-(4-Dimethylamino-phenyl)-quinolin-4-ylamino]-propane-1,2-diol hydrochloride

The title compound, m.p. 250-260 °C, and MS: m/e = 338.2 ($M+H^+$), was prepared from [4-(4-chloro-quinolin-2-yl)-phenyl]-dimethyl-amine and (RS)-3-amino-1,2-propandiol.

Example 68

(RS)-3-(6-Hydroxy-2-phenyl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

The title compound, m.p. 303-304 °C, and MS: m/e = 310 (M^+), was prepared from 4-chloro-2-phenyl-quinolin-6-ol and (RS)-3-amino-1,2-propandiol.

Example 69

(RS)-3-(2-Phenyl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

The title compound, m.p. 225-227 °C, and MS: m/e = 295.3 ($M+H^+$), was prepared from 4-chloro-2-phenyl-quinolin and (RS)-3-amino-1,2-propandiol.

Example 70

(RS)-1-(2-Phenyl-quinolin-4-ylamino)-propan-2-ol hydrochloride

The title compound, m.p. 251-253 °C, and MS: m/e = 279.2 ($M+H^+$), was prepared from 4-chloro-2-phenyl-quinolin and (RS)-1-amino-2-propanol.

Example 71

R-(+)-1-(2-Phenyl-quinolin-4-yl)-pyrrolidin-3-ol-hydrochloride

The title compound, m.p. 291-293, $[\alpha]_D^{20}$ = +54.4° (c = 0.11, methanol) and MS: m/e = 291.2 ($M+H^+$), was prepared from 4-chloro-2-phenyl-quinolin and (R)-3-hydroxypyrrolidine.

Example 72

(RS)-3-(2-Benzo[b]thiophen-2-yl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

The title compound, m.p. 253-255 °C, and MS: m/e = 386 (M^+), was prepared from 2-benzo[b]thiophen-2-yl-4-chloro-quinoline and (RS)-3-amino-1,2-propandiol.

Example 73

(RS)-3-(7-Chloro-2-phenyl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

The title compound, m.p. 234-236 °C, and MS: m/e = 328 (M^+), was prepared from 4,7-dichloro-2-phenyl-quinoline and (RS)-3-amino-1,2-propandiol.

Example 74

(RS)-1-[2-(4-Methoxy-phenyl)-quinolin-4-ylamino]-3-piperidin-1-yl-propan-2-ol hydrochloride

The title compound, m.p. 269-272°C, and MS: m/e = 392.3 ($M+H^+$), was prepared from 4-chloro-2-(4-methoxy-phenyl)-quinoline and (RS)-1-amino-3-piperidin-1-yl-propan-2-ol.

(RS)-1-Amino-3-piperidin-1-yl-propan-2-ol is a known compound and has been prepared as described in the following reference: I. G. Farbenind. ; DE 479354.

Example 75

(RS)-3-(2-Phenethyl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

(E)-(RS)-3-(2-Styryl-quinolin-4-ylamino)-propane-1,2-diol (0.23 g, 0.718 mmol) was dissolved in MeOH (25 ml) and acidified with HCl/Et_2O. The reaction mixture was refluxed for 2 hours in the presence of 10% Pd/C (0.02 g) under an atmospheric pressure of hydrogen. The mixture was cooled to room temperature, the catalyst was filtered, and the filtrate was concentrated. Addition of EtOH provided (RS)-3-(2-phenethyl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride (0.075 g, 29%) as a light yellow solid, m. p. 143-145 °C, MS: m/e = 323.3 ($M+H^+$).

Following the method of example 75 the compound of example 76 was prepared.

Example 76

(RS)-3-(6-Amino-2-phenyl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride

The title compound, m. p. 239-241 °C, MS: m/e = 309 (M^+), was prepared from (RS)-3-(6-nitro-2-phenyl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride.

(RS)-3-(6-Nitro-2-phenyl-quinolin-4-ylamino)-propane-1,2-diol hydrochloride was prepared according to the general procedure described in example 1 from 4-chloro-6-nitro-2-phenyl-quinoline and (RS)-3-amino-1,2-propandiol.

Example 77

(RS)-1-[2-(4-Methoxy-phenyl)-quinolin-4-ylamino]-3-methylamino-propan-2-ol hydrochloride

(RS)-5-{[2-(4-Methoxy-phenyl)-quinolin-4-ylamino]-methyl}-oxazolidin-2-one (0.1g, 0.286 mmol) in THF (3 ml) was added dropwise to a suspension of $LiAlH_4$ (0.054g, 1.43 mmol) in THF at 0°C. Reaction mixture was refluxed for 1 hour, cooled to 0°C, treated sucessively with H_2O (50 µl), 5N NaOH (50 µl), H_2O (150 µl), filtered, and concentrated. The residue was chromatographed over silica gel (CH_2Cl_2-MeOH, 9:1 then 4:1 +1% aqueous NH_3) to provide an oil which was dissolved in MeOH . HCl-Et_2O was added to provide (RS)-1-[2-(4-methoxy-phenyl)-quinolin-4-ylamino]-3-methylamino-propan-2-ol hydrochloride (0.085 g, 72%) as a white foam, MS: m/e = 337 (M^+).

Following the general method of Example 77, the compounds of Example 78 to Example 82 were prepared.

Example 78

(RS)-1-(7-Methoxy-2-p-tolyl-quinolin-4-ylamino)-3-methylamino-propan-2-ol hydrochloride

The title compound, MS: m/e = 352.3 ($M+H^+$), was prepared from (RS)-5-[(7-methoxy-2-p-tolyl-quinolin-4-ylamino)-methyl]-oxazolidin-2-one.

Example 79

(RS)-1-[2-(4-Chloro-phenyl)-7-methoxy-quinolin-4-ylamino]-3-methylamino-propan-2-ol hydrochloride

The title compound, MS: m/e = 372.2 ($M+H^+$), was prepared from (RS)-5-{[2-(4-chloro-phenyl)-7-methoxy-quinolin-4-ylamino]-methyl}-oxazolidin-2-one.

Example 80

(RS)-1-Methylamino-3-(2-phenyl-quinolin-4-ylamino)-propan-2-ol hydrochloride

The title compound, m.p. 256-259 °C MS: m/e = 307 (M^+), was prepared from (RS)-5-[(2-phenyl-quinolin-4-ylamino)-methyl]-oxazolidin-2-one.

Example 81

(RS)-1-Phenethylamino-3-(2-phenyl-quinolin-4-ylamino)-propan-2-ol

The title compound, MS: m/e =398 ($M+H^+$), was prepared from (RS)-N-[2-hydroxy-3-(2-phenyl-quinolin-4-ylamino)-propyl]-2-phenyl-acetamide.

Example 82

(RS)-1-(3-Phenyl-propylamino)-3-(2-phenyl-quinolin-4-ylamino)-propan-2-ol hydrochloride

The title compound, MS: m/e = 412.3 ($M+H^+$), was prepared from (RS)-N-[2-hydroxy-3-(2-phenyl-quinolin-4-ylamino)-propyl]-3-phenyl-propionamide.

Example 83

(RS)-1-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-3-methylamino-propan-2-ol hydrochloride

(RS)-7-Methoxy-4-oxiranylmethoxy-2-phenyl-quinoline (0.2 g, 0.65 mmol) in MeOH (4 ml) was refluxed for 1.2 hour in the presence of a 33% solution of methylamine in EtOH (0.4 ml, 3.3 mmol). The reaction mixture was concentrated and the residue was chromatographed over silica gel (CH_2Cl_2-MeOH, 9:1 then 4:1 +1% aqueous NH_3) to provide a foam which was dissolved in MeOH . HCl-Et_2O was added to provide (RS)-1-(7-methoxy-2-phenyl-quinolin-4-yloxy)-3-methylamino-propan-2-ol hydrochloride (0.120 g, 45%) as a white solide, m. p. 175-185 ^{0}C, MS: m/e = 338 (M^+).

Following the general method of example 83 the compounds of example 84 to example 95 were prepared.

Example 84

(RS)-1-Amino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol hydrochloride

The title compound, m. p. 175-178 °C, MS: m/e =294 (M^+), was prepared from (RS)-4-oxiranylmethoxy-2-phenyl-quinoline and a 25% solution of NH_3 in H_2O.

Example 85

(RS)-1-Isopropylamino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol

The title compound, m. p. 109-111 °C, MS: m/e =337.2 ($M+H^+$), was prepared from (RS)-4-oxiranylmethoxy-2-phenyl-quinoline and isopropylamine.

Example 86

(RS)-1-Cyclopentylamino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol hydrochloride

The title compound, m. p. 109-111 °C, MS: m/e =363.2 ($M+H^+$), was prepared from (RS)-4-oxiranylmethoxy-2-phenyl-quinoline and cyclopentylamine.

Example 87

(RS)-1-Isopropylamino-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-propan-2-ol hydrochloride

The title compound, m. p. 115-125 °C, MS: m/e =366 (M^+), was prepared from (RS)-7-methoxy-4-oxiranylmethoxy-2-phenyl-quinoline and isopropylamine.

Example 88

(RS)-1-Methylamino-3-(2-p-tolyl-quinolin-4-yloxy)-propan-2-ol hydrochloride

The title compound, m. p. 203-208 °C, MS: m/e =322 (M^+), was prepared from (RS)-4-oxiranylmethoxy-2-p-tolyl-quinoline and a 33% solution of methylamine in EtOH.

Example 89

(RS)-1-Cyclobutylamino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol hydrochloride

The title compound, m. p. 190-195 °C, MS: m/e =349.4 ($M+H^+$), was prepared from (RS)-4-oxiranylmethoxy-2-phenyl-quinoline and cyclobutylamine.

Example 90

(RS)-1-[2-(4-Methoxy-phenyl)-quinolin-4-yloxyl-3-methylamino-propan-2-ol hydrochloride

The title compound, m. p. 230-232 °C, MS: m/e =338 (M^+), was prepared from (RS)-2-(4-methoxy-phenyl)-4-oxiranylmethoxy-quinoline and a 33% solution of methylamine in EtOH.

Example 91

1-(6-Fluoro-2-phenyl-quinolin-4-yloxy)-3-methylamino-propan-2-ol hydrochloride

The title compound, m. p. 218-219 °C, MS: m/e =326 (M^+), was prepared from (RS)-6-fluoro-4-oxiranylmethoxy-2-phenyl-quinoline and a 33% solution of methylamine in EtOH.

Example 92

(RS)-(3-Morpholin-4-yl-propylamino)-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol hydrochloride

The title compound, m. p. 151-154 °C, MS: m/e =422.4 ($M+H^+$), was prepared from (RS)-4-oxiranylmethoxy-2-phenyl-quinoline and 4-(3-aminopropyl)-morpholine.

Example 93

(RS)-1-Ethylamino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol hydrochloride

The title compound, m. p. 170-174 °C, MS: m/e =323.3 ($M+H^+$), was prepared from (RS)-4-oxiranylmethoxy-2-phenyl-quinoline and ethylamine.

Example 94

(RS)-1-Cyclopropylamino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol hydrochloride

The title compound, m. p. 145-152 °C, MS: m/e = 334 ($M+H^+$), was prepared from (RS)-4-oxiranylmethoxy-2-phenyl-quinoline and cyclopropylamine.

Example 95

(RS)-1-Butylamino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol hydrochloride

The title compound, MS: m/e = 351 ($M+H^+$), was prepared from (RS)-4-oxiranylmethoxy-2-phenyl-quinoline and n-butylamine.

Example 96

(RS)-1-Methylamino-3-(7-methyl-2-phenyl-quinolin-4-yloxy)-propan-2-ol hydrochloride

To a 0°C suspension of NaH (0.11g, 2.5 mmol, 55% in mineral oil) in DMF (3 ml) was added dropwise a DMF solution (3 ml) of a mixture of (2RS,5RS) and (2RS,5SR) (3-methyl-2-phenyl-oxazolidin-5-yl)-methanol (0.46 g, 2.4 mmol) in DMF (3 ml). After 15 min. at 0 °C and 2 hours at room temperature, reaction mixture was cooled to 0 °C and treated with a solution of 4-chloro-7-methyl-2-phenyl-quinoline (0.3 g, 1.2 mmol) in DMF (3 ml). After 5 min. at 0 °C and 21 hours at room temperature, the reaction mixture was cooled to 0 °C, quenched with H_2O (0.5 ml), and concentrated. The residue was treated with 1N HCl (6 ml). The so obtained yellow aqueous solution was extracted with CH_2Cl_2 (3x 20 ml). Organic phases were washed with 1N HCl (2 x 10 ml). Combined aqueous phases were basified to pH 11 with 2N NaOH, and extracted with CH_2Cl_2 (3 x 20

ml). Combined organic phases were dried over Na_2SO_4 and concentrated. The residue was crystallized with Et_2O to provide after filtration 95 mg of a white solid which was dissolved in MeOH . HCl-Et_2O was added to provide (RS)-1-methylamino-3-(7-methyl-2-phenyl-quinolin-4-yloxy)-propan-2-ol hydrochloride (0.075 g, 16%) as a white solid, MS: m/e = 323.3 ($M+H^+$).

Following the general method of Example 96 the compounds of Example 97 to Example 103 were prepared.

Example 97

(RS)-1-(7-Methoxy-2-p-tolyl-quinolin-4-yloxy)-3-methylamino-propan-2-ol hydrochloride

The title compound m. p. 240 °C, MS: m/e = 352 (M^+), was prepared from 4-chloro-7-methoxy-2-p-tolyl-quinoline.

Example 98

(RS)-1-[7-Methoxy-2-(4-methoxy-phenyl)-quinolin-4-yloxyl-3-methylamino-propan-2-ol hydrochloride

The title compound m. p. 245 °C, MS: m/e = 368 (M^+), was prepared from 4-chloro-7-methoxy-2-(4-methoxy-phenyl)-quinoline.

Example 99

(RS)-1-[2-(4-Methoxy-phenyl)-7-methyl-quinolin-4-yloxyl-3-methylamino-propan-2-ol

The title compound m. p. 140-142 °C, MS: m/e = 353.3 ($M+H^+$), was prepared from 4-chloro-2-(4-methoxy-phenyl)-7-methyl-quinoline.

Example 100

(RS)-1-Methylamino-3-(7-methyl-2-p-tolyl-quinolin-4-yloxy)-propan-2-ol

The title compound m. p. 146-150 °C, MS: m/e = 337.2 ($M+H^+$), was prepared from 4-chloro-7-methyl-2-p-tolyl-quinoline.

Example 101

(RS)-1-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-quinolin-4-yloxyl-3-methylamino-propan-2-ol hydrochloride

The title compound MS: m/e = 364.2 ($M+H^+$), was prepared from 4-chloro-2-(3,4-dihydro-1H-isoquinolin-2-yl)-quinoline.

Example 102

(RS)-1-(7-Chloro-2-phenyl-quinolin-4-yloxy)-3-methylamino-propan-2-ol hydrochloride

The title compound m. p. 192-193°C, MS: m/e = 343.2 ($M+H^+$), was prepared from 4,7-dichloro-2-phenyl-quinoline.

Example 103

(RS)-1-Methylamino-3-(2-thiophen-3-yl-quinolin-4-yloxy)-propan-2-ol hydrochloride

The title compound m. p. 236-238 °C MS: m/e = 315.2 ($M+H^+$), was prepared from 4-chloro-2-thiophen-3-yl-quinoline.

Preparation of intermediates

Preparation of oxazolidin-2-ones, precursors of examples 77-80

Example 104

(RS)-5-{[2-(4-Methoxy-phenyl)-quinolin-4-ylamino]-methyl}-oxazolidin-2-one

To a 0°C solution of (RS)-1-amino-3-[2-(4-methoxy-phenyl)-quinolin-4-ylamino]-propan-2-ol (0.139 g, 0.429 mmol) in DMF (2.5 ml) was added dropwise a solution of 1,1-carbonyldiimidazole (0.076 g, 0.472 mmol) in DMF (1 ml). After 20 min. at 0°C, and 1.5 hours at 60°C, the reaction mixture was cooled to room temperature and concentrated. Addition of H_2O provided (RS)-5-{[2-(4-methoxy-phenyl)-quinolin-4-ylamino]-methyl}-oxazolidin-2-one (0.110 g, 73%) as yellowish solid, MS: m/e = 349 (M^+).

Following the general method of Example 104, the compounds of Example 105 to Example 107 were prepared.

Example 105

(RS)-5-[(7-Methoxy-2-p-tolyl-quinolin-4-ylamino)-methyl]-oxazolidin-2-one

The title compound, MS: m/e = 364.1 ($M+H^+$), was prepared from (RS)-1-amino-3-(7-methoxy-2-p-tolyl-quinolin-4-ylamino)-propan-2-ol.

Example 106

(RS)-5-{[2-(4-Chloro-phenyl)-7-methoxy-quinolin-4-ylamino]-methyl}-oxazolidin-2-one

The title compound, MS: m/e = 383 (M^+), was prepared from (RS)-1-amino-3-[2-(4-chloro-phenyl)-7-methoxy-quinolin-4-ylamino]-propan-2-ol.

Example 107

(RS)-5-[(2-Phenyl-quinolin-4-ylamino)-methyl]-oxazolidin-2-one

The title compound, MS: m/e = 320.3 ($M+H^+$), was prepared from (RS)-1-amino-3-(2-phenyl-quinolin-4-ylamino)-propan-2-ol.

Preparation of the amides, precursors of examples 81-82

Example 108

(RS)-N-[2-Hydroxy-3-(2-phenyl-quinolin-4-ylamino)-propyl]-2-phenyl-acetamide hydrochloride

To a room temperature solution of (RS)-1-amino-3-(2-phenyl-quinolin-4-ylamino)-propan-2-ol (0.293 g, 1 mmol) and triethylamine (0.42 ml,3 mmol) in dioxane (6 ml) was added a solution of phenylacetylchloride (0.198 ml, 1.5 mmol) in dioxane (1 ml). After stirring for 3 hours at room temperature, the reaction mixture was quenched with H_2O and 1N NaOH. The aqueous phase was extracted with CH_2Cl_2 (5 x 10 ml). The combined organic phases were dried over Na_2SO_4, concentrated and chromatographed over silica gel (CH_2Cl_2-MeOH, 19:1 then 9:1) to provide a yellow oil which was dissolved in MeOH. HCl-Et_2O was added to provide (RS)-N-[2-hydroxy-3-(2-phenyl-quinolin-4-ylamino)-propyl]-2-phenyl-acetamide hydrochloride (0.113 g, 25 %) as a light yellow foam, MS: m/e = 412.3 ($M+H^+$).

Following the general method of Example 108, the compound of Example 109 was prepared.

Example 109

(RS)-N-[2-Hydroxy-3-(2-phenyl-quinolin-4-ylamino)-propyl]-3-phenyl-propionamide

The title compound, MS: m/e = 426.4 ($M+H^+$), was prepared from (RS)-1-amino-3-(2-phenyl-quinolin-4-ylamino)-propan-2-ol.

Preparation of the epoxides, precursors of examples 83-95

Example 110

(RS)-7-Methoxy-4-oxiranylmethoxy-2-phenyl-quinoline

To a solution of 7-methoxy-2-phenyl-1H-quinolin-4-one (1.5 g, 6 mmol) in DMF (11 ml) were added successively K_2CO_3 (1.66 g, 12 mmol) and (RS)-epichlorohydrin (1.9 ml, 24 mmol). The reaction mixture was stirred at 65°C for 3 hours, then cooled to room temperature and diluted with CH_2Cl_2 (25 ml). Solid was filtrated, and filtrate was

concentrated. The residue was chromatographed over silica gel (hexane-ethyl acetate, 4:1) to provide (RS)-7-methoxy-4-oxiranylmethoxy-2-phenyl-quinoline (1.05 g, 57 %) as a colorless oil, MS: m/e = 307 (M^+).

Following the general method of example 110, the compounds of example 111 to 114 were prepared.

Example 111

(RS)-4-Oxiranylmethoxy-2-phenyl-quinoline

The title compound, MS: m/e = 277 (M^+), was prepared from 2-phenyl-1H-quinolin-4-one.

Example 112

(RS)-4-Oxiranylmethoxy-2-p-tolyl-quinoline

The title compound, m. p. 100-102°C, MS: m/e = 292.2 ($M+H^+$), was prepared from 2-p-tolyl-1H-quinolin-4-one.

Example 113

(RS)-2-(4-Methoxy-phenyl)-4-oxiranylmethoxy-quinoline

The title compound, m. p. 100-106°C, MS: m/e = 307 (M^+), was prepared from 2-(4-methoxy-phenyl)-1H-quinolin-4-one.

Example 114

(RS)-6-Fluoro-4-oxiranylmethoxy-2-phenyl-quinoline

The title compound, m. p. 118-120°C, MS: m/e = 295.9 (M^+), was from 6-fluoro-2-phenyl-1H-quinolin-4-one.

Preparation of 4- and 2-chloro-quinolines, precursors of examples 1-74 and 96-103

a) Preparation of the 2-amino-4-chloro-quinolines and 2-chloro-4-amino-quinolines

Example 115

4-Chloro-2-(3,4-dihydro-1H-isoquinolin-2-yl)-quinoline

A solution of 2,4-dichloroquinoline (0.2 g, 1 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.282 ml, 2.2 mmol) in toluene (2 ml) was refluxed during 18 hours then cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2 and quenched with a saturated solution of $NaHCO_3$. Aqueous phase was extracted with CH_2Cl_2 (2 x). Combined organic phases were washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was chromatographed over silica gel (hexane-ethyl acetate, 97:3) to provide 4-chloro-2-(3,4-dihydro-1H-isoquinolin-2-yl)-quinoline (0.235 g, 79 %) as a yellow oil, MS: m/e = 295.3 ($M+H^+$).

Following the general method of example 115 the compound of example 116 was prepared.

Example 116

4-Chloro-2-(1,3-dihydro-isoindol-2-yl)-quinoline

The title compound, m. p. 172-173°C, MS: m/e = 281.1 ($M+H^+$), was prepared from 2,3-dihydro-1H-isoindole.

Example 117

2-Chloro-4-(3,4-dihydro-1H-isoquinolin-2-yl)-quinoline

A mixture of 2,4-quinolinediol (1 g, 6.2 mmol) and 1,2,3,4-tetrahydroisoquinoline (1.57 ml, 12.4 mmol) was heated overnight under argon at 200 °C. Reaction mixture was cooled to room temperature, diluted with MeOH, stirred for 30 min. and filtered. The solid obtained was refluxed overnight in the presence of $POCl_3$ (3 ml). The reaction mixture was cooled to room temperature and poured into a 0°C stirring mixture of 5N NaOH (50 ml) and CH_2Cl_2 (50 ml). After 15 min., aqueous phase was extracted with CH_2Cl_2 (2 x), combined organic phases were washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was chromatographed over silica gel (hexane-ethyl acetate, 97:3 then 9:1) to provide 2-chloro-4-(3,4-dihydro-1H-isoquinolin-2-yl)-quinoline (0.1 g, 5 %) as a colorless oil, MS: m/e = 295.3 ($M+H^+$).

4-Chloro-quinolin-2-ylamine, precursor of example 111, is a known compound and has been prepared as described in the following reference: R.Hardman, M.W. Partridge, J.C.S., 1958, 614.

b) Preparation of 2-unsubstituted; 2-styryl; 2-alkyl; 2-aryl or 2-heteroaryl-4-chloro-quinolines

(E)-4-Chloro-2-styryl-quinoline, precursor of example 15, is a known compound and has been prepared as described in the following reference: I.G. Farbenind.; DE 440008.

Preparation of hydroxylated-4-chloro-quinolines

4-Chloro-quinolin-6-ol is a known compound and has been prepared as described in the following reference: C. Ramsey; J. Am. Chem. Soc.; 69; 1947; 1659-1660

Example 118

4-Chloro-2-phenyl-quinolin-6-ol

To a –78°C solution of 4-chloro-6-methoxy-2-phenyl-quinoline (1.0 g, 3.7 mmol) in CH_2Cl_2 (25 ml) was added dropwise BBr_3 (11.1 ml, 11.1 mmol, 1M in CH_2Cl_2). Reaction mixture was then allowed to warm to room temperature. After 4.5 hours,

mixture was cooled to –10°C and quenched slowly with a saturated solution of $NaHCO_3$ (70 ml). The aqueous phase was extracted with ethyl acetate (3 x 100 ml). Combined organic phases were dried over Na_2SO_4 and concentrated. The solid residue was refluxed during 1 hour in ethyl acetate (30 ml), cooled to room temperature, and filtered. Filtrate was concentrated and chromatographed over silica gel (hexane-ethyl acetate, 4:1) to provide 4-chloro-2-phenyl-quinolin-6-ol (0.375 g, 40 %) as a yellow solid, m. p. 180-181°C, MS: m/e = 255 (M^+).

Following the general method of Example 118, the compound of Example 119 was prepared.

Example 119

4-Chloro-2-phenyl-quinolin-7-ol

The title compound, m. p. 190-192°C, MS: m/e = 255 ($M+H^+$), was prepared from 4-chloro-7-methoxy-2-phenyl-quinoline

Preparation of 4-chloro-quinolines by reaction of an aryl lithium on a 4-chloro-2-unsubstituted quinoline

Example 120

4-Chloro-2-m-tolyl-quinoline

To a –25°C solution of 3-bromo-toluene (2.1 ml , 17.4 mmol) in Et_2O (20 ml) was added dropwise nBuLi (13.4 ml, 21.4 mmol, 1.6 M in hexane). After 30 min. stirring at -20°C and 30 min. at 0°C, reaction mixture was cooled to –20°C. A suspension of 4-chloroquinoline (2.5 g, 15.3 mmol) in Et_2O (15 ml) was added slowly (15 min.). After 10 min. at –20°C, and 20 min. at 10°C, reaction mixture was quenched slowly with H_2O (4 ml). I_2 (3.9 g, 15.3 mmol) was then added portionwise. After 2 hours stirring at room temperature, reaction mixture was treated successively with 2N NaOH (18 ml) and H_2O (50 ml). The aqueous phase was extracted with ethyl acetate (3 x 80 ml). Combined organic phases were dried over Na_2SO_4 and concentrated. The residue was chromatographed over silica gel (hexane-ethyl acetate, 9:1) to provide 3.4 g of a yellow oil. Addition of n-pentane provided 4-chloro-2-m-tolyl-quinoline (1.58 g, 41 %) as a white solid, m. p. 75-77°C, MS: m/e = 253 (M^+).

The following 4-chloroquinolines, which are known in the literature, have been prepared according to the general method of example 120:

4-chloro-2-p-tolyl-quinoline; 4-chloro-2-(4-methoxy-phenyl)-quinoline;
4-chloro-2-(4-methoxy-phenyl)-7-methyl-quinoline;
4-chloro-7-methoxy-2-phenyl-quinoline;

4-chloro-2-(4-chloro-phenyl)-quinoline;
4-chloro-2-naphthalen-2-yl-quinoline;
4-chloro-7-methyl-2-phenyl-quinoline; and
4,7-dichloro-2-phenyl-quinoline.

The following compounds of example 121 to 137, which are not known in the literature, have been prepared according to the general method of example 120

Example 121

4-Chloro-2-(4-methoxy-3-methyl-phenyl)-quinoline

The title compound, m. p. 90-92°C, MS: m/e = 283 (M^+), was prepared from 4-chloro-quinoline and 4-bromo-1-methoxy-2-methyl-benzene.

4-Bromo-1-methoxy-2-methyl-benzene is a known compound and has been prepared as described in the following reference: M. J. S. Dewar; N. A. Puttnam, J. Chem. Soc. 1960, 959-963.

Example 122

4-Chloro-7-methyl-2-p-tolyl-quinoline

The title compound, m. p. 110-111°C, MS: m/e = 267 (M^+), was prepared from 4-chloro-7-methyl-quinoline and 4-bromotoluene.

4-Chloro-7-methyl-quinoline is a known compound and has been prepared as described in the following reference: Breslow; J. Am. Chem. Soc, 68, 1946, 1232-1236

Example 123

4-Chloro-2-(3-chloro-4-methyl-phenyl)-quinoline

The title compound, m. p. 115-116°C, MS: m/e = 288 (M^+), was prepared from 4-chloroquinoline and 2-chloro-4-iodo-toluene.

Example 124

4-Chloro-7-methoxy-2-(4-methoxy-phenyl)-quinoline

The title compound, m. p. 99-101°C, MS: m/e = 299 (M^+), was prepared from 4-chloro-7-methoxy-quinoline and 4-bromoanisole.

4-Chloro-7-methoxy-quinoline is a known compound and has been prepared as described in the following reference: Lauer; J. Am. Chem. Soc, 68, 1946, 1268

Example 125

4-Chloro-7-methoxy-2-p-tolyl-quinoline

The title compound, m. p. 129-131°C, MS: m/e = 283 (M^+), was prepared from 4-chloro-7-methoxy-quinoline and 4-bromotoluene.

Example 126

4-Chloro-2-(4-chloro-phenyl)-7-methoxy-quinoline

The title compound, m. p. 153-155°C, MS: m/e = 305 ($M+H^+$), was prepared from 4-chloro-7-methoxy-quinoline and 1-bromo-4-chlorobenzene.

Example 127

4-Chloro-2-(3-chloro-4-methoxy-phenyl)-quinoline

The title compound, m. p. 113-116°C, MS: m/e = 304 (M^+), was prepared from 4-chloro-quinoline and 4-bromo-2-chloro-1-methoxy-benzene.

4-Bromo-2-chloro-1-methoxy-benzene is a known compound and has been prepared as described in the following reference: E. A. Nodiff; J. Het. Chem.; 5, 1968, 165-167.

Example 128

4-Chloro-2-(3,4-dimethyl-phenyl)-quinoline

The title compound, MS: m/e = 267 (M^+), was prepared from 4-chloro-quinoline and 4-bromo-o-xylene.

Example 129

4-Chloro-2-(2,3-dihydro-benzofuran-5-yl)-quinoline

The title compound, m. p. 130-132°C, MS: m/e = 281 (M^+), was prepared from 4-chloro-quinoline and 5-iodo-2,3-dihydrobenzofuran.

5-Iodo-2,3-dihydrobenzofuran is a known compound and has been prepared as described in the following reference: A. Walser, T. Flynn, C. Mason, H. Crowley, C. Maresca, M. O'Donnell, J. Med. Chem., 34, 4, 1991, 1440-1446

Example 130

4-Chloro-2-(3,4-dichloro-phenyl)-quinoline

The title compound, m. p. 138-140°C, MS: m/e = 308 (M^+), was prepared from 4-chloro-quinoline and 3,4-dichloroiodobenzene.

Example 131

4-Chloro-2-(3,4-dichloro-phenyl)-7-methoxy-quinoline

The title compound, m. p. 122-131°C, MS: m/e = 338 (M^+), was prepared from 4-chloro-7-methoxyquinoline and 3,4-dichloroiodobenzene.

Example 132

4-Chloro-2-chroman-6-yl-quinoline

The title compound, MS: m/e = 295 (M^+), was prepared from 4-chloro-quinoline and 6-bromo-chroman.

6-Bromo-chroman is a known compound and has been prepared as described in the following reference: Maitte, Ann. Chim. (Paris), 9, 1954, 431, 446, 450

Example 133

4-Chloro-2-(4-trifluoromethyl-phenyl)-quinoline

The title compound, m. p. 53-55°C, MS: m/e = 307 (M^+), was prepared from 4-chloro-quinoline and 4-bromo-benzotrifluoride.

Example 134

2-Benzofuran-2-yl-4-chloro-quinoline

The title compound, m. p. 148-149°C, MS: m/e = 279 (M^+), was prepared from 4-chloro-quinoline and benzofuran.

Example 135

[4-(4-Chloro-quinolin-2-yl)-phenyl]-dimethyl-amine

The title compound, MS: m/e = 282 (M^+), was prepared from 4-chloro-quinoline and 4-bromo-N,N-dimethylaniline.

Example 136

2-Benzo[b]thiophen-2-yl-4-chloro-quinoline

The title compound, m. p. 142-145°C, MS: m/e = 295 (M^+), was prepared from 4-chloro-quinoline and 1-benzothiophene.

Example 137

4-Chloro-2-thiophen-3-yl-quinoline

The title compound, MS: m/e = 245 (M^+), was prepared from 4-chloro-quinoline and 3-bromothiophene.

By reaction of a quinolin-4-one with phophorus oxychloride

Example 138

2-Indan-5-yl-1H-quinolin-4-one

A mixture of 2-indan-5-yl-1H-quinolin-4-one (4.2 g, 16.1 mmol) and $POCl_3$ (6.3 ml, 67.5 mmol) was refluxed during 30 min. The reaction mixture was cooled to room temperature and added slowly to 2N NaOH (210 ml). After 2 hours of stirring, ethyl acetate was added. Aqueous phase was extracted with ethyl acetate (3 x 100 ml). Combined organic phases were dried over Na_2SO_4 and concentrated. The solid residue was stirred at 0°C in the presence of Et_2O (10 ml) and then filtered to provide (2.0 g, 45 %) as a light green solid, m. p. 92-93°C, MS: m/e = 279 (M^+).

The following 4-chloro-quinolines, which are known in the literature, have been prepared according to the general method of example 138:

4-Chloro-8-methoxy-2-phenyl-quinoline: D.Bangdiwala;J. Indian Chem. Soc.; 31; 1954; 43-46;

4-Chloro-6-methoxy-2-phenyl-quinoline: Staskun; J. S. Afr. Chem. Inst.; 9; 1956; 89;

4-Chloro-6-methoxy-quinoline: Riegel; J. Am. Chem. Soc.; 68; 1946; 2685);

4-Chloro-7-methoxyquinoline and 4-Chloro-8-methoxy-quinoline: Lauer; J. Am. Chem. Soc.; 68; 1946; 1268);

4-Chloro-7-methyl-quinoline: Breslow; J. Am. Chem. Soc.; 68; 1946; 1232-1236);

4-Chloro-6-fluoroquinoline: Snyder; J. Am. Chem. Soc.; 69; 1947; 371-373);

4-Chloro-8-fluoroquinoline: Renault; Eur. J. Med. Chem. Chim. Ther.; 11; 1976; 555-559

4-Chloro-6-nitro-2-phenyl-quinoline: I. Stasku; J. Org. Chem.; 26; 1961; 3191

The following compounds of example 139 to 140, which are not known in the literature, have been prepared according to the general method of example 138.

Example 139

4-Chloro-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-quinoline

The title compound, MS: m/e = 293 (M^+), was prepared from 2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-1H-quinolin-4-one.

Example 140

(RS)-4-Chloro-2-(1,2,3,4-tetrahydro-naphthalen-2-yl)-quinoline

The title compound, MS: m/e = 293 (M^+), was prepared from (RS)-2-(1,2,3,4-tetrahydro-naphthalen-2-yl)-1H-quinolin-4-one.

Preparation of the quinolin-4-ones

By condensation of derivatives of anthranilic acid and acetophenone

Example 141

2-Indan-5-yl-1H-quinolin-4-one

To a mixture of 5-acetylindane (3.0 g, 18.7 mmol) and anthranilic acid ethyl ester (2.8 ml, 18.7 mmol) in diphenylether (47 g) was added portionwise $AlCl_3$ (3.5 g, 26.2 mmol). The reaction mixture was stirred at 200°C for 2.5 hours and cooled to room temperature. Hexane (100 ml) and MeOH (3 ml) were then added. The so obtained solid was filtered, washed with hexane and stirred in the presence of 5N HCl (85 ml) and acetone (10 ml). After filtration, the solid was again washed with H_2O, and stirred with MeOH (15 ml) for 30 min. Filtration provided 2-indan-5-yl-1H-quinolin-4-one (4.35 g, 89 %) as a light yellow solid, MS: m/e = 261 (M^+).

The following quinolin-4-ones, which are known in the literature, have been prepared according to the general method of example 141:

2-p-Tolyl-1H-quinolin-4-one;
2-(4-methoxy-phenyl)-1H-quinolin-4-one;

The compound of example 142 has been prepared according to the general method of example 141.

Example 142

2-(5,6,7,8-Tetrahydro-naphthalen-2-yl)-1H-quinolin-4-one

The title compound, m. p. 241-250°C, MS: m/e = 276.3 ($M+H^+$), was prepared from 6-acetyltetraline.

By condensation of an aniline with a β-ketoester.

Example 143

(RS)-2-(1,2,3,4-Tetrahydro-naphthalen-2-yl)-1H-quinolin-4-one

A mixture containing aniline (0.7 ml, 7.7 mmol), p-toluene sulfonic acid (0.037 g, 0.19 mmol) and (RS)-3-oxo-3-(1,2,3,4-tetrahydro-naphthalen-2-yl)-propionic acid ethyl ester (1.9 g, 7.7 mmol) in toluene (10 ml) was refluxed for 2.5 hours, and water was removed azeotropically. Reaction mixture was concentrated, diluted with diphenylether (8 ml), refluxed for 45 min., cooled to room temperature and diluted with Et_2O (150 ml). The resulting solid was filtered, washed with Et_2O and CH_2Cl_2 to provide (RS)-2-(1,2,3,4-

Tetrahydro-naphthalen-2-yl)-1H-quinolin-4-one (0.67 g, 32%) as a light yellow solid, mp.>300°C, MS: m/e = 275 (M^+).

The following quinolin-4-ones, which are known in the literature, have been prepared according to the general method of example 143:

7-Methoxy-2-phenyl-1H-quinolin-4-one;
8-methoxy-2-phenyl-1H-quinolin-4-one;
2-phenyl-1H-quinolin-4-one;
6-fluoro-2-phenyl-1H-quinolin-4-one; and
6-methoxy-2-phenyl-1H-quinolin-4-one.

Preparation of other intermediates

Example 144

(2RS,5RS) and (2RS,5SR) (3-Methyl-2-phenyl-oxazolidin-5-yl)-methanol

A mixture containing benzaldehyde (21.2 g, 0.2 mol) and (RS)-3-methylamino-1,2-propandiol (17.6 g, 0.167 mol) in toluene (110 ml) was refluxed for 3.5 hours. Mixture was then cooled to room temperature, concentrated and residue was distilled at 135 °C under 0.7 mbar pressure to provide a mixture of (2RS,5RS) and (2RS,5SR) (3-methyl-2-phenyl-oxazolidin-5-yl)-methanol (28.7 g, 89 %) as a colorless oil, MS: m/e = 193 (M^+).

Example 145

(RS)-3-Oxo-3-(1,2,3,4-tetrahydro-naphthalen-2-yl)-propionic acid ethyl ester

A solution of malonic acid monoethyl ester (3.8 g, 29 mmol) in THF (80 ml) was cooled to –78°C. n-BuLi (36 ml, 58 mmol, 1.6 M in hexane) was added dropwise so that the temperature of the reaction mixture at the end the addition was –5°C. After 5 min. stirring at –5°C, reaction mixture was cooled to –65°C and treated with a solution of (RS)-1,2,3,4-tetrahydro-naphthalene-2-carbonyl chloride (3.2 g, 16.5 mmol) in THF. Mixture was stirred for 10 min. at –65°C and then added to a stirring mixture containing Et_2O (200 ml) and 1N HCl (100 ml). Aqueous phase was extracted with Et_2O (2 x 150 ml). Combined organic phases were washed successively with a saturated solution of $NaHCO_3$ (100 ml) and NaCl (100 ml), dried over Na_2SO_4 and concentrated to provide (RS)-3-oxo-3-(1,2,3,4-tetrahydro-naphthalen-2-yl)-propionic acid ethyl ester (3.8 g, 93%) as a light brown oil, MS: m/e = 246 (M^+).

(RS)-1,2,3,4-Tetrahydro-naphthalene-2-carbonyl chloride is a known compound and has been prepared as described in the following reference: *J. C. Morris; L. N. Mander; D. C. R. Hockless; Synthesis; 1998; 455-467*

Example A

Tablet Formulation (Wet Granulation)

Item	Ingredients	mg/tablet			
		5 mg	25 mg	100mg	500mg
1.	Compound of formula 1	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	835

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granulation at 50°C.
3. Pass the granulation through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Example B

Capsule Formulation

Item	Ingredients	mg/tablet			
		5 mg	25mg	100mg	500mg
1.	Compound of formula 1	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure

1 Mix items 1, 2, and 3 in a suitable mixer for 30 minutes.

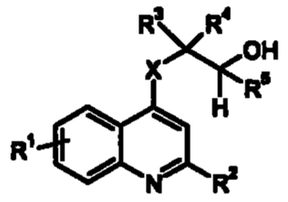
2. Add items 4 and 5 and mix for 3 minutes.

3. Fill into a suitable capsule.

4. Add item 5 and mix for three minutes; compress on a suitable press.

Claims

1. Compounds of formula



I

wherein

R^1		is hydrogen, lower alkyl, lower alkoxy, hydroxy, amino, nitro, cyano, lower alkyl-amino, di-lower alkyl-amino or halogen;
R^2		is phenyl, optionally substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl, amino, lower alkyl-amino or di-lower alkyl-amino, 2,3-dihydro-benzofuran-5-yl, chroman-6-yl, naphthalen-2-yl, indan-5-yl, lower alkenyl-phenyl, 5,6,7,8-tetrahydro-naphthalenyl, 2,3-dihydro-isoindol-2-yl, 1,2,3,4-tetrahydro-naphthalenyl, benzofuran-2-yl, benzo[b]thiophen-2-yl, lower alkyl-phenyl, 3,4-dihydro-1H-isoquinolin-2-yl or thiophen-3-yl;
R^3 and R^4		are independently from each other hydrogen or lower alkyl;
R^5		is hydrogen, lower alkyl, $-CH_2OH$ or $-CH_2NR^6R^7$;
R^6 and R^7		are independently from each other hydrogen, lower alkyl, $-(CH_2)_n$-phenyl, cycloalkyl, $-(CH_2)_m$-morpholinyl or form together with the N-atom a saturated ring with 4-6 C-atoms;
n		is 0 - 3;
m		is 2 or 3;
X		is $-NR^8-$ or $-O-$; or
X and R^5 are together		$>N(CH_2)_2-$; or
X and R^3 are together		$>N(CH_2)_3-$; and
R^8		is hydrogen or lower alkyl;

and to pharmaceutically acceptable acid addition salts thereof, with the exception of the following compounds

(6-chloro-2-phenyl-4-quinolinyl)-(+)-2-aminobutanol;

(6-methyl-2-phenyl-4-quinolinyl)-(+)-2-aminobutanol;

(6-methoxy-2-phenyl-4-quinolinyl)-(+)-2-aminobutanol; and
(8-methoxy-2-phenyl-4-quinolinyl)-(+)-2-aminobutanol.

2. Compounds according to claim 1, wherein X is –NH-.

3. Compounds according to claim 2, which are

2-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-quinolin-4-ylamino]-ethanol;
(RS)-1-Amino-3-(2-p-tolyl-quinolin-4-ylamino)-propan-2-ol;
(RS)-1-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-quinolin-4-ylamino]-3-[2-(4-methoxy-phenyl)-quinolin-4-ylamino]-propan-2-ol;
(S)-1-[2-(4-Methoxy-phenyl)-quinolin-4-ylamino]-propan-2-ol;
2-[2-(4-Methoxy-phenyl)-7-methyl-quinolin-4-ylamino]-ethanol;
(S)-1-[2-(4-Methoxy-3-methyl-phenyl)-quinolin-4-ylamino]-propan-2-ol;
2-(7-Methyl-2-p-tolyl-quinolin-4-ylamino)-ethanol;
(S)-1-[2-(3-Chloro-4-methyl-phenyl)-quinolin-4-ylamino]-propan-2-ol;
(RS)-3-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-quinolin-4-ylamino]-propane-1,2-diol;
(RS)-1-Amino-3-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-quinolin-4-ylamino]-propan-2-ol;
2-[7-Methoxy-2-(4-methoxy-phenyl)-quinolin-4-ylamino]-ethanol;
(RS)-1-Amino-3-[7-methoxy-2-(4-methoxy-phenyl)-quinolin-4-ylamino]-propan-2-ol; and
(RS)-1-Amino-3-(7-methoxy-2-p-tolyl-quinolin-4-ylamino)-propan-2-ol.

4. Compounds according to claim 1, wherein X is –O-.

5. Compounds according to claim 4, which are

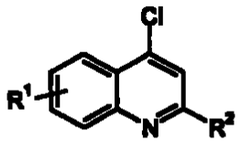
(RS)-1-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-3-methylamino-propan-2-ol;
(RS)-1-Amino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol;
(RS)-1-Isopropylamino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol;
(RS)-1-Cyclopentylamino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol;
(RS)-1-Isopropylamino-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-propan-2-ol;
(RS)-1-Methylamino-3-(2-p-tolyl-quinolin-4-yloxy)-propan-2-ol;
(RS)-1-Cyclobutylamino-3-(2-phenyl-quinolin-4-yloxy)-propan-2-ol;
(RS)-1-[2-(4-Methoxy-phenyl)-quinolin-4-yloxy]-3-methylamino-propan-2-ol;
(RS)-1-Methylamino-3-(7-methyl-2-phenyl-quinolin-4-yloxy)-propan-2-ol;
(RS)-1-(7-Methoxy-2-p-tolyl-quinolin-4-yloxy)-3-methylamino-propan-2-ol;
(RS)-1-[7-Methoxy-2-(4-methoxy-phenyl)-quinolin-4-yloxy]-3-methylamino-propan-2-ol; and
(RS)-1-[2-(4-Methoxy-phenyl)-7-methyl-quinolin-4-yloxy]-3-methylamino-propan-2-ol.

6. A medicament containing one or more compounds of any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof and an inert carrier for the treatment of diseases.

7. A medicament according to claim 6 for the treatment of diseases based on therapeutic indications for NMDA receptor subtype specific blockers, which include acute forms of neurodegeneration caused, e.g., by stroke and brain trauma, and chronic forms of neurodegeneration such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS (amyotrophic lateral sclerosis) and neurodegeneration associated with bacterial sclerosis) and neurodegeneration associated with bacterial or viral infections.

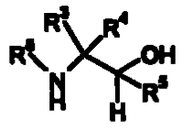
8. A process for preparing a compound of formula I as defined in claim 1, which process comprises

a) reacting a compound of formula



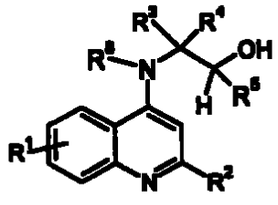
II

with an amine of formula



III

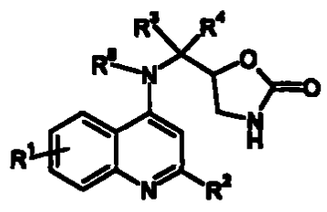
to a compound of formula



I-1

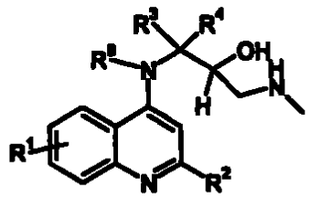
wherein $R^1 - R^5$ and R^8 have the significances given above, or

b) reducing a compound of formula



IV

with a reducing agent to a compound of formula

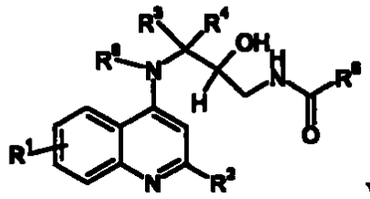


I-12

wherein R^1 –R^4 and R^5 have the significances given above,

or

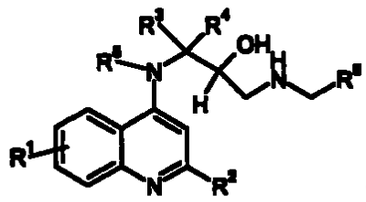
c) reducing a compound of formula



V

wherein R^1–R^4 and R^5 have the significances given above and R^6 is lower alkyl-phenyl, lower alkyl-morpholino or lower alkyl,

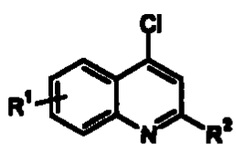
to a compound of formula



I-13

or

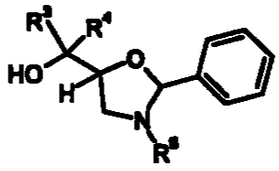
d) reacting a compound of formula



II

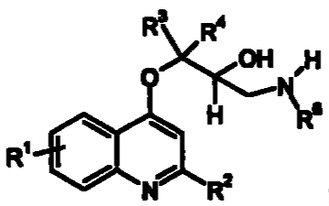
123
120

with a compound of formula



VI

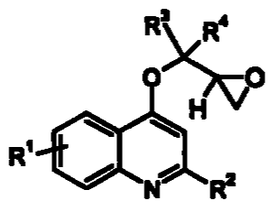
to a compound of formula



I-2

wherein $R^1 - R^4$ and R^6 have the significances given above, or,

e) reacting a compound of formula

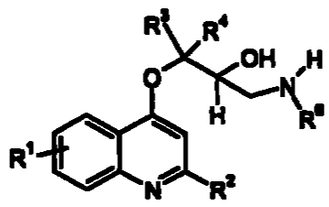


IX

with a compound of formula

$$H\text{-}NR^6$$

to a compound of formula



I-2

wherein $R^1 - R^4$ and R^6 have the significances given above, or,

if desired, modifying one or more substituents within the definitions given above, or

if desired, converting the compound of formula I obtained into a pharmaceutically acceptable salt.

4)

9. A compound according to any one of claims 1-5 whenever prepared by a process as claimed in claim 8 or by an equivalent method.

10. The use of a compound in accordance with any one of claims 1 - 5 for the treatment of diseases.

11. The use of a compound in accordance with claim 14 for the treatment of diseases based on therapeutic indications for NMDA receptor subtype specific blockers, which include acute forms of neurodegeneration caused e.g. by stroke and brain trauma, and chronic forms of neurodegeneration such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS (amyotrophic lateral sclerosis) and neurodegeneration associated with bacterial or viral infections, and chronic or acute pain, or for the manufacture of a medicament containing such a compound.

12. The invention as hereinbefore described.

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