

07-128153



Industria y Comercio

SUPERINTENDENCIA

Organización CSA Ltda

13T ✓

Delegatura de propiedad Industrial

División de Nuevas Creaciones



DVN
OK

PCT

SOLICITUD

PATENTE DE INVENCION

07-128153

21. EXPEDIENTE No.

54. TÍTULO

TETRAHIDROQUINOLINONAS Y SU USO COMO MODULADORES DE RECEPTORES

DE GLUTAMATO METABOTROPICOS

51. CLASIFICACIÓN INTERNACIONAL

71. SOLICITANTE

MERZ PHARMA GMBH & CO. KGAA

DOMICILIO

FRANKFURT (MAIN) ALEMANIA

74. APODERADO

DILIA RODRIGUEZ D ALEMAN

22. BOGOTÁ, D. C.,

DI. 4, 2007



FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT

ENTRADA EN FASE NACIONAL 24 marzo 2008

1) SOLICITUD DE:			
☒ Patente de invención		☐ Patente de Modelo de Utilidad	
☒ Capitulo I.		☐ Capitulo II.	
2) SOLICITANTE (71)	Nombre: MERZ PHARMA GMBH & CO. KGAA . Dirección: 100 Eckenheimer Landstrasse, 60318 Frankfurt (Main), Alemania Nacionalidad o domicilio: Frankfurt (Main) Alemania Lugar de constitución: Alemania		IDENTIFICACIÓN C.C. ☐ NIT: ☐ C.E. ☐ OTRO ☐ Cual _____ NÚMERO _____
	Teléfono: _____ Fax: _____ E. Mail: _____		
3) REPRESENTANTE O APODERADO	Nombre: DILIA MARÍA RODRÍGUEZ D'ALEMAN Dirección: Carrera 11 N°. 86-53 Piso 6 Bogotá D.C. Teléfono: 6181088 Fax: 6350824 E. Mail: info@clarkemodet.com.co		IDENTIFICACIÓN C.C. ☒ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO: 41.654.882 TP: 20824 CSJ
4) INVENTOR (ES) (72)	Nombre: VER LISTA ADJUNTA Dirección: VER LISTA ADJUNTA Nacionalidad o Domicilio: VER LISTA ADJUNTA		
5) PCT (86) Solicitud Internacional No. PCT/GB2006/003170 Fecha: AGOSTO 24, 2006 Publicación Internacional No. WO2007/023290 A1 Fecha: Marzo 1, 2007			
6) Título (54) TETRAHIDROQUINOLINONAS Y SU USO COMO MODULADORES DE RECEPTORES DE GLUTAMATO METABOTRÓPICOS			
7) Clasificación Internacional:			
8) PRIORIDAD SI ☒ NO ☐	33) País de Origen	(32) Fecha	(31) Número de Solicitud
	GRAN BRETAÑA	AGOSTO 24, 2005	PCT/GB2005/003285
9) Comprobante de pago N°			
Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina			

10)

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☒ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12 y 6 x 6 cm
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☒ Otros:
 - 1. Informe de búsqueda
 - 2. Request
 - 3. Opinión escrita,

11) FIGURA CARACTERÍSTICA:

12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D'ALEMAN

FIRMA:

C.C. 41.654.882 de Bogotá TP 20824 CSJ

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina

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Nacionalidad: Polaco

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 98,474
FECHA : DICIEMBRE 3 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Tra. 11 PATENTEIYII
Act. 411 PRESENTACION
Dep. 2020 NUECREACION
Eve: 378 FASENACIONALI
Folios: 239

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	64177535	03/12/2007	22,680,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	72,000.00
		31 PRORROGA DE TERMINOS	72,000.00
		TOTAL :	\$ 72,000.00

MON: SETENTA Y DOS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

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 FECHA : DICIEMBRE 3 DE 2007

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	64177535	03/12/2007	22,680,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	5,000.00
		TOTAL :	\$ 5,000.00

ON: CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	53267311	26/11/2007	28,480,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		82 INVOCACION DE UNA PRIORIDAD EN NU	135,000.00
		TOTAL :	\$ 135,000.00

SON: CIENTO TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

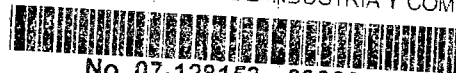
P 1062 8

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 96,300
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DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	53267311	26/11/2007	28,480,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		82 INVOCACION DE UNA PRIORIDAD EN NU	135,000.00
		TOTAL :	\$ 135,000.00

SON: CIENTO TREINTA Y CINCO MIL PESOS

RESPONSABLE :

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7

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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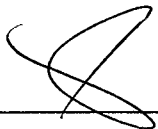
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	53267311	26/11/2007	28,480,000.00

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		82 INVOCACION DE UNA PRIORIDAD EN NU	135,000.00
		TOTAL :	\$ 135,000.00

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KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT,
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ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: TETRAHYDROQUINOLINONES AND THEIR USE AS MODULATORS OF METABOTROPIC GLUTAMATE RE-
CEPTORS

(57) Abstract: The invention relates to ethynyl-substituted tetrahydroquinolinone derivatives as well as their pharmaceutically ac-
ceptable salts. The invention further relates to a process for the preparation of such compounds. The compounds of the invention are
group I mGluR modulators and are therefore useful for the control and prevention of acute and/or chronic neurological disorders.

WO 2007/023290 A1

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**TETRAHYDROQUINOLINONES AND THEIR USE AS MODULATORS OF
METABOTROPIC GLUTAMATE RECEPTORS**

FIELD OF THE INVENTION

5 [0001] The present invention is concerned with novel metabotropic glutamate receptor (mGluR) modulators, methods for their synthesis and the treatment and/or prevention of neurological disorders by administration of such substances.

10 **BACKGROUND OF THE INVENTION**

[0002] Neuronal stimuli are transmitted by the central nervous system (CNS) through the interaction of a neurotransmitter released by a neuron, which neurotransmitter has a specific effect on a neuroreceptor of another neuron.

15 [0003] L-glutamic acid is considered to be the major excitatory neurotransmitter in the mammalian CNS, consequently playing a critical role in a large number of physiological processes. Glutamate-dependent stimulus receptors are divided into two main groups. The first group comprises ligand-controlled ion channels whereas the second comprises metabotropic
20 glutamate receptors (mGluR). Metabotropic glutamate receptors are a subfamily of G-protein-coupled receptors (GPCR). There is increasing evidence for a peripheral role of both ionotropic and metabotropic glutamate receptors outside of the CNS e.g., in chronic pain states.

25 [0004] At present, eight different members of these mGluRs are known. On the basis of structural parameters such as sequence homology, the second messenger system utilized by these receptors and their different affinity to low-molecular weight compounds, these eight receptors can be divided into three groups: mGluR1 and mGluR5 belong to group I which couple to
30 phospholipase C and their activation leads to intracellular calcium-ion mobilization. Both mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III, which couple to adenylyl

cyclase with their activation causing a reduction in second messenger cAMP and as such a dampening of the neuronal activity.

5 [0005] Group I mGluR modulators have been shown to modulate the effects of the presynaptically released neurotransmitter glutamate via postsynaptic mechanisms. Moreover, as these modulators can be both positive and/or negative Group I mGluR modulators, such modulators may increase or inhibit the effects of these metabotropic receptors. Since a variety of pathophysiological processes and disease states affecting the CNS are
10 thought to be related to abnormal glutamate neurotransmission and group I mGluRs are shown to be expressed in several areas of the CNS, modulators of these receptors could be therapeutically beneficial in the treatment of CNS diseases.

15 [0006] Therefore, group I mGluR modulators may be administered to provide neuroprotection in acute and chronic pathological conditions such as: AIDS-related dementia, Alzheimer's disease, Creutzfeld-Jakob's syndrome, bovine spongiform encephalopathy (BSE) or other prion related infections, diseases involving mitochondrial dysfunction, diseases involving β -amyloid and/or
20 tauopathy such as Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), olivoponto-cerebellar atrophy, post-operative cognitive deficit (POCD), Parkinson's disease, Parkinson's dementia, mild cognitive impairment, dementia pugilistica, vascular and frontal lobe
25 dementia, cognitive impairment, eye injuries or diseases (e.g. glaucoma, retinopathy, macular degeneration), head and spinal cord injuries / trauma, hypoglycaemia, hypoxia (e.g. perinatal), ischaemia (e.g. resulting from cardiac arrest, stroke, bypass operations or transplants), convulsions, glioma and other tumours, inner ear insult (e.g. in tinnitus, sound or drug-induced), L-
30 dopa-induced and tardive dyskinesias.

[0007] Other indications in this context include a symptomatological effect on the following conditions: addiction (nicotine, alcohol, opiate, cocaine,

amphetamine, obesity and others), amyotrophic lateral sclerosis (ALS), anxiety and panic disorders, attention deficit hyperactivity disorder (ADHD), restless leg syndrome and hyperactive children, autism, convulsions / epilepsy, dementia (e.g. in Alzheimer's disease, Korsakoff syndrome, vascular dementia, HIV infections), major depressive disorder or depression (including that resulting from Borna virus infection) and bipolar manic-depressive disorder, drug tolerance e.g. to opioids, movement disorders, dystonia, dyskinesia (e.g. L-Dopa-induced, tardive dyskinesia or in Huntington's disease), fragile-X syndrome, Huntington's chorea, irritable bowel syndrome (IBS), migraine, multiple sclerosis, muscle spasms, pain (chronic and acute, e.g. inflammatory pain, neuropathic pain, allodynia, hyperalgesia, nociceptive pain), Parkinson's disease, post traumatic stress disorder, schizophrenia (positive and negative symptoms), spasticity, tinnitus, Tourette's syndrome, urinary incontinence and vomiting, pruritic conditions (e.g. pruritis), sleep disorders, micturition disorders, neuromuscular disorder in the lower urinary tract, gastroesophageal reflux disease (GERD), lower esophageal sphincter (LES), functional gastrointestinal disorders, dyspepsia, regurgitation, respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma (e.g. reflux-related asthma), lung disease, eating disorders, obesity and obesity-related disorders.

[0008] Yet further indications for Group I mGluR modulators include those indications wherein a particular condition does not necessarily exist but wherein a particular physiological parameter may be improved through administration of the instant compounds, for example cognitive enhancement.

[0009] Positive modulators may be particularly useful in the treatment of positive and negative symptoms in schizophrenia and cognitive deficits in various forms of dementia and mild cognitive impairment.

[0010] Among the Group I mGluR modulators, those which exhibit a modulatory effect on mGluR5 receptors and thus may affect conditions or diseases associated with the function of those mGluR5 receptors are of

particular interest. In addition to the utility of mGluR5 modulators in preventing and/or treating the conditions and/or diseases mentioned above, mGluR5 positive modulators or agonists may be particularly useful for preventing and/or treating conditions or diseases that are associated with an insufficient stimulation or activity of mGluR5 receptors. mGluR5 modulators and especially mGluR5 positive modulators or agonists may be particularly useful for preventing and/or treating addiction, neuropathic pain, L-dopa-induced and tardive dyskinesias, ALS, fragile-X syndrome, Parkinson's disease, anxiety disorders, epilepsy, positive and/or negative symptoms of schizophrenia, cognitive impairment, or for cognitive enhancement and neuroprotection.

THE PRESENT INVENTION

[0011] We have determined that certain ethynyl-substituted tetrahydroquinolones within the genus of compounds disclosed in our copending International Patent Application No. PCT/GB2005/000717 are Group I mGluR modulators and in particular mGluR5 modulators. Therefore, these substances may be therapeutically beneficial in the treatment of conditions which involve abnormal glutamate neurotransmission or in which modulation of Group I mGluR receptors results in therapeutic benefit. These substances are preferably administered in the form of a pharmaceutical composition, wherein they are present together with one or more pharmaceutically acceptable diluents, carriers, or excipients.

OBJECTS OF THE INVENTION

[0012] It is an object of the present invention to provide novel pharmaceutical compounds which are tetrahydroquinolone Group I mGluR modulators and pharmaceutical compositions thereof. It is a further object of the invention to provide a novel method of treating, eliminating, alleviating, palliating, or ameliorating undesirable CNS disorders which involve abnormal glutamate neurotransmission by employing a compound of the invention or a pharmaceutical composition containing the same. An additional object of the

invention is the provision of a process for producing the tetrahydroquinolone active principles. Yet additional objects will become apparent hereinafter, and still further objects will be apparent to one skilled in the art.

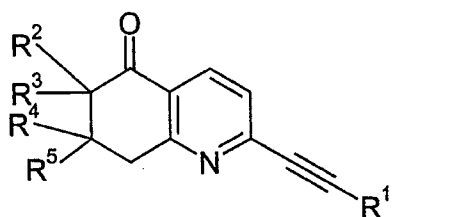
5

SUMMARY OF THE INVENTION

[0013] What we therefore believe to be comprised by our invention may be summarized inter alia in the following words:

[0014] A compound of Formula I

10



wherein

15

R¹ represents aryl or heteroaryl;

R² and R³, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

20

R⁴ and R⁵, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

it being understood that:

25

aryl represents an unsubstituted phenyl ring or a phenyl ring that is substituted with 1, 2, 3, 4 or 5 substituents, that may be the same or different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted

with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, 4-C₁₋₆alkyl-piperazinyl, tetrazolyl, oxazolyl, furyl, pyrrolyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and phenyl;

heteroaryl represents a (hetero)aromatic 5-, 6- or 7-membered ring having from 1 to 4 heteroatoms said heteroatoms being independently selected from oxygen, nitrogen and sulfur, wherein said ring is unsubstituted or substituted with 1, 2 or 3 substituents, that may be the same or different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, 4-C₁₋₆alkyl-piperazinyl, tetrazolyl, oxazolyl, furyl, pyrrolyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and phenyl;

and that the compounds of Formula I may not represent:

2-Phenylethynyl-7,8-dihydro-6H-quinolin-5-one
 2-Pyridin-3-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 2-m-Tolylethynyl-7,8-dihydro-6H-quinolin-5-one
 2-(3-Hydroxy-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
 2-(3-Methoxy-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
 2-(3-Fluoro-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
 2-(3-Chloro-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
 2-(3-Bromo-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
 3-(5-Oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile
 2-Thiazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one

2-Oxazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
7,7-Dimethyl-2-pyridin-3-ylethynyl-7,8-dihydro-6H-quinolin-5-one
7,7-Dimethyl-2-m-tolylethynyl-7,8-dihydro-6H-quinolin-5-one
2-(3-Hydroxy-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-
5 one
2-(3-Methoxy-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-
one
2-(3-Fluoro-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
2-(3-Chloro-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
10 2-(3-Bromo-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
3-(7,7-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-
benzonitrile
7,7-Dimethyl-2-thiazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
7,7-Dimethyl-2-oxazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
15 2-(2-Phenyl-oxazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one or
2-(2-Phenyl-thiazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one;

and optical isomers, pharmaceutically acceptable salts, hydrates, solvates
and polymorphs thereof.

20

[0015] Such a compound of Formula I, wherein
 R^2 and R^3 , which may be the same or different, represent methyl, ethyl,
n-propyl, 2-propyl, n-butyl or tert-butyl and
25 R^4 and R^5 represent hydrogen.

[0016] Such a compound of Formula I, wherein
 R^2 and R^3 represent hydrogen and
 R^4 and R^5 , which may be the same or different, represent methyl, ethyl,
30 n-propyl, 2-propyl, n-butyl or tert-butyl.

[0017] Such a compound of Formula I, wherein

R^2 , R^3 , R^4 and R^5 , which may be the same or different, represent hydrogen, methyl or ethyl.

[0018] Such a compound of Formula I, wherein

5 R^1 represents aryl;

it being understood that:

aryl represents unsubstituted phenyl or phenyl that is mono- or di-substituted with the same or different substituents that are selected from the group consisting of methyl, ethyl, n-propyl, 2-propyl, n-butyl, 10 tert-butyl, hydroxyl, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, CF_3 , CH_2F , CH_2F , C_2F_5 , OCF_3 , OC_2F_5 , F, Cl, Br, CN, piperidinyl, morpholinyl, tetrazolyl, oxazolyl, furyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and phenyl.

15 [0019] Such a compound of Formula I, wherein aryl represents unsubstituted phenyl or a phenyl ring that is mono- or di-substituted with the substituent(s) in the meta-position.

[0020] Such a compound of Formula I, wherein the phenyl ring is di-substituted in the meta-position and the substituents are different.

20

[0021] Such a compound of Formula I, wherein the substituents are selected from F, CN, pyridinyl, tetrazolyl and unsubstituted phenyl.

25 [0022] Such a compound of Formula I, wherein

R^1 represents heteroaryl;

it being understood that:

30 heteroaryl represents pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, oxazol-5-yl, thiazol-5-yl, wherein each of these rings may be unsubstituted or mono or di-substituted with phenyl, methyl, ethyl, n-propyl, 2-propyl, n-butyl, tert-butyl, hydroxyl, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy,

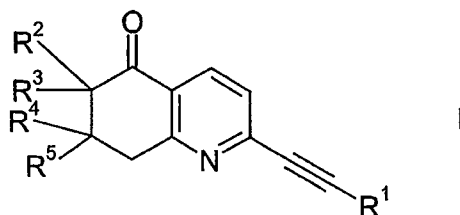
tert-butoxy, CF₃, CH₂F, CH₂F, C₂F₅, OCF₃, OC₂F₅, F, Cl, Br, CN, piperidinyl, morpholinyl, tetrazolyl, oxazolyl, furyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl or pyrimidyl.

- 5 [0023] Such a compound of Formula I, wherein heteroaryl represents unsubstituted heteroaryl or an heteroaryl ring that is mono- or di-substituted with the substituent(s) in the meta-position.

- 10 [0024] Such a compound of Formula I, wherein the heteroaryl ring is di-substituted in the meta-position and the substituents are different.

[0025] Such a compound of Formula I, wherein the substituents are selected from F, CN, pyridinyl, tetrazolyl and unsubstituted phenyl.

- 15 [0026] Moreover, a method-of-treating a living animal, including a human, for a condition or a disease associated with abnormal glutamate neurotransmission or in which modulation of Group I mGluR receptors results in therapeutic benefit comprising the step of administering to the living animal, including a human, an amount of a Group I mGluR modulator selected from
20 those of Formula I



- 25 wherein
R¹ represents aryl or heteroaryl;
R² and R³, which may be the same or different, represent hydrogen or C₁₋₆alkyl;
R⁴ and R⁵, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

it being understood that:

5 aryl represents an unsubstituted phenyl ring or a phenyl ring that is substituted with 1, 2, 3, 4 or 5 substituents, that may be the same of different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-
10 C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholiny, 4-C₁₋₆alkyl-piperaziny, tetrazoly, oxazoly, furyl, pyrroly, thiophenyl, isoxazoly, thiazoly, imidazoly, oxadiazoly, pyridiny, pyrimidyl and phenyl;

15 heteroaryl represents a (hetero)aromatic 5-, 6- or 7-membered ring having from 1 to 4 heteroatoms said heteroatoms being independently selected from oxygen, nitrogen and sulfur, wherein said ring is unsubstituted or substituted with 1, 2 or 3 substituents, that may be the same or different, which substituents are selected from the group
20 consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N- C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholiny, 4-C₁₋₆alkyl-piperaziny, tetrazoly, oxazoly, furyl, pyrroly, thiophenyl, isoxazoly, thiazoly, imidazoly, oxadiazoly, pyridiny, pyrimidyl and phenyl;
25

30 and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof;

which is effective for alleviation of the condition or disease or for enhancing cognition.

[0027] Such a method wherein the condition associated with abnormal glutamate neurotransmission, or wherein modulation of mGluR receptors results in therapeutic benefit, is selected from: AIDS-related dementia, Alzheimer's disease, Creutzfeld-Jakob's syndrome, bovine spongiform encephalopathy (BSE) or other prion related infections, diseases involving mitochondrial dysfunction, diseases involving β -amyloid and/or tauopathy such as Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), olivoponto-cerebellar atrophy, post-operative cognitive deficit (POCD), Parkinson's disease, Parkinson's dementia, mild cognitive impairment, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, eye injuries or diseases (e.g. glaucoma, retinopathy, macular degeneration), head and spinal cord injuries / trauma, hypoglycaemia, hypoxia (e.g. perinatal), ischaemia (e.g. resulting from cardiac arrest, stroke, bypass operations or transplants), convulsions, glioma and other tumours, inner ear insult (e.g. in tinnitus, sound or drug-induced), L-dopa-induced and tardive dyskinesias, addiction (nicotine, alcohol, opiate, cocaine, amphetamine, obesity and others), anxiety and panic disorders, attention deficit hyperactivity disorder (ADHD), restless leg syndrome and hyperactive children, autism, convulsions / epilepsy, dementia (e.g. in Alzheimer's disease, Korsakoff syndrome, vascular dementia, HIV infections), major depressive disorder or depression (including that resulting from Borna virus infection) and bipolar manic-depressive disorder, drug tolerance e.g. to opioids, movement disorders, dystonia, dyskinesia (e.g. L-Dopa-induced, tardive dyskinesia or in Huntington's disease), fragile-X syndrome, Huntington's chorea, irritable bowel syndrome (IBS), migraine, multiple sclerosis, muscle spasms, pain (chronic and acute, e.g. inflammatory pain, neuropathic pain, allodynia, hyperalgesia, nociceptive pain), Parkinson's disease, post traumatic stress disorder, schizophrenia (positive and negative symptoms), spasticity, Tourette's syndrome, urinary incontinence and vomiting, pruritic conditions (e.g. pruritis), sleep disorders, micturition disorders, neuromuscular disorder in the lower urinary tract,

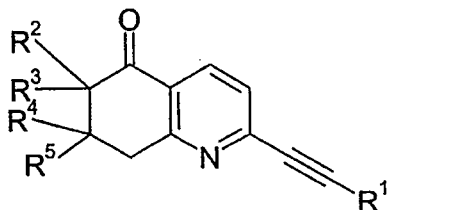
gastroesophageal reflux disease (GERD), lower esophageal sphincter (LES), functional gastrointestinal disorders, dyspepsia, regurgitation, respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma (e.g. reflux-related asthma), lung disease, eating disorders, obesity and obesity-related disorders, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia, substance-induced anxiety disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder, substance-induced psychotic disorder, delirium, or for cognitive enhancement or neuroprotection.

10

[0028] Such a method wherein the compound is administered in the form of a pharmaceutical composition thereof comprising the compound of Formula I in combination with one or more pharmaceutically-acceptable diluents, excipients, or carriers.

15

[0029] Further, the use of at least one compound of Formula I



wherein

20

R¹ represents aryl or heteroaryl;

R² and R³, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

25

R⁴ and R⁵, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

it being understood that:

aryl represents an unsubstituted phenyl ring or a phenyl ring that is substituted with 1, 2, 3, 4 or 5 substituents, that may be the same or different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholiny, 4-C₁₋₆alkyl-piperaziny, tetrazoly, oxazolyl, furyl, pyrroly, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridiny, pyrimidyl and phenyl;

heteroaryl represents a (hetero)aromatic 5-, 6- or 7-membered ring having from 1 to 4 heteroatoms said heteroatoms being independently selected from oxygen, nitrogen and sulfur, wherein said ring is unsubstituted or substituted with 1, 2 or 3 substituents, that may be the same or different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholiny, 4-C₁₋₆alkyl-piperaziny, tetrazoly, oxazolyl, furyl, pyrroly, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridiny, pyrimidyl and phenyl;

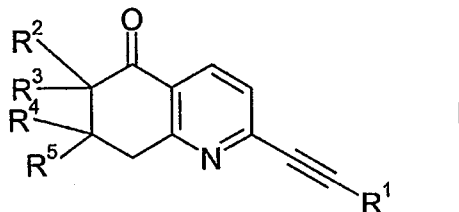
and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof;

for the manufacturing of a medicament for the prevention and/or treatment of a condition or disease in an animal including a human being which condition or disease is affected or facilitated by the

modulatory effect of Group I mGluR1 modulators and in particular of mGluR5 modulators.

[0030] The compounds of Formula I used according to the present invention for the manufacturing of a medicament have been found to be modulators of Group I mGluR receptors. In particular, these compounds are modulators of mGluR5 receptors. Surprisingly it has been found that they show at least partially agonistic or positive modulatory effects on the mGluR5 receptors.

[0031] Consequently, one aspect of the present invention is the use of one or more compounds of formula I



wherein

R¹ represents aryl or heteroaryl;

R² and R³, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

R⁴ and R⁵, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

it being understood that:

aryl represents an unsubstituted phenyl ring or a phenyl ring that is substituted with 1, 2, 3, 4 or 5 substituents, that may be the same or different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine,

chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholiny, 4-C₁₋₆alkyl-piperaziny, tetrazoly, oxazoly, furyl, pyrroly, thiophenyl, isoxazoly, thiazoly, imidazoly, oxadiazoly, pyridiny, pyrimidyl and phenyl;

heteroaryl represents a (hetero)aromatic 5-, 6- or 7-membered ring having from 1 to 4 heteroatoms said heteroatoms being independently selected from oxygen, nitrogen and sulfur, wherein said ring is unsubstituted or substituted with 1, 2 or 3 substituents, that may be the same or different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholiny, 4-C₁₋₆alkyl-piperaziny, tetrazoly, oxazoly, furyl, pyrroly, thiophenyl, isoxazoly, thiazoly, imidazoly, oxadiazoly, pyridiny, pyrimidyl and phenyl;

and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof;

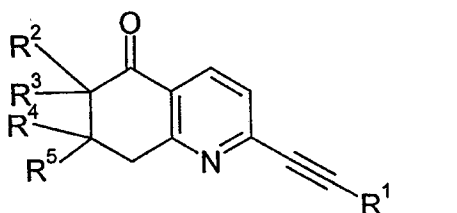
for the manufacturing of a medicament for the prevention and/or treatment of AIDS-related dementia, Alzheimer's disease, Creutzfeld-Jakob's syndrome, bovine spongiform encephalopathy (BSE) or other prion related infections, diseases involving mitochondrial dysfunction, diseases involving β -amyloid and/or tauopathy such as Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), olivoponto-cerebellar atrophy, post-operative cognitive

deficit (POCD), Parkinson's disease, Parkinson's dementia, mild cognitive impairment, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, eye injuries or diseases (e.g. glaucoma, retinopathy, macular degeneration), head and spinal cord injuries / trauma, hypoglycaemia, hypoxia (e.g. perinatal), ischaemia (e.g. resulting from cardiac arrest, stroke, bypass operations or transplants), convulsions, glioma and other tumours, inner ear insult (e.g. in tinnitus, sound or drug-induced), L-dopa-induced and tardive dyskinesias, addiction (nicotine, alcohol, opiate, cocaine, amphetamine, obesity and others), anxiety and panic disorders, attention deficit hyperactivity disorder (ADHD), restless leg syndrome and hyperactive children, autism, convulsions / epilepsy, dementia (e.g. in Alzheimer's disease, Korsakoff syndrome, vascular dementia, HIV infections), major depressive disorder or depression (including that resulting from Borna virus infection) and bipolar manic-depressive disorder, drug tolerance e.g. to opioids, movement disorders, dystonia, dyskinesia (e.g. L-Dopa-induced, tardive dyskinesia or in Huntington's disease), fragile-X syndrome, Huntington's chorea, irritable bowel syndrome (IBS), migraine, multiple sclerosis, muscle spasms, pain (chronic and acute, e.g. inflammatory pain, neuropathic pain, allodynia, hyperalgesia, nociceptive pain), Parkinson's disease, post traumatic stress disorder, schizophrenia (positive and negative symptoms), spasticity, Tourette's syndrome, urinary incontinence and vomiting, pruritic conditions (e.g. pruritis), sleep disorders, micturition disorders, neuromuscular disorder in the lower urinary tract, gastroesophageal reflux disease (GERD), lower esophageal sphincter (LES), functional gastrointestinal disorders, dyspepsia, regurgitation, respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma (e.g. reflux-related asthma), lung disease, eating disorders, obesity and obesity-related disorders, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia, substance-induced anxiety disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder, substance-induced

psychotic disorder, delirium, or for cognitive enhancement or neuroprotection.

5 [0032] Such a medicament wherein the medicament is for the prevention and/or treatment of addiction, neuropathic pain, L-dopa-induced and tardive dyskinesias, ALS, fragile-X syndrome, Parkinson's disease, anxiety disorders, epilepsy, positive and/or negative symptoms of schizophrenia, cognitive impairment, or for cognitive enhancement and neuroprotection.

10 [0033] Further, a pharmaceutical composition comprising, together with one or more pharmaceutically acceptable excipients or vehicles, a compound of Formula I



15

wherein

R¹ represents aryl or heteroaryl;

20

R² and R³, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

R⁴ and R⁵, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

25

it being understood that:

aryl represents an unsubstituted phenyl ring or a phenyl ring that is substituted with 1, 2, 3, 4 or 5 substituents, that may be the same of

different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholinyl, 4-C₁₋₆alkyl-piperazinyl, tetrazolyl, oxazolyl, furyl, pyrrolyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and phenyl;

heteroaryl represents a (hetero)aromatic 5-, 6- or 7-membered ring having from 1 to 4 heteroatoms said heteroatoms being independently selected from oxygen, nitrogen and sulfur, wherein said ring is unsubstituted or substituted with 1, 2 or 3 substituents, that may be the same or different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholinyl, 4-C₁₋₆alkyl-piperazinyl, tetrazolyl, oxazolyl, furyl, pyrrolyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and phenyl;

and that the compounds of Formula I may not represent:

2-Phenylethynyl-7,8-dihydro-6H-quinolin-5-one
2-Pyridin-3-ylethynyl-7,8-dihydro-6H-quinolin-5-one
2-m-Tolylethynyl-7,8-dihydro-6H-quinolin-5-one
2-(3-Hydroxy-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
2-(3-Methoxy-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
2-(3-Fluoro-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
2-(3-Chloro-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one

25
27

- 2-(3-Bromo-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
 3-(5-Oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile
 2-Thiazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 2-Oxazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 5 7,7-Dimethyl-2-pyridin-3-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 7,7-Dimethyl-2-m-tolylethynyl-7,8-dihydro-6H-quinolin-5-one
 2-(3-Hydroxy-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
 10 2-(3-Methoxy-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
 2-(3-Fluoro-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
 2-(3-Chloro-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
 2-(3-Bromo-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
 15 3-(7,7-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile
 7,7-Dimethyl-2-thiazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 7,7-Dimethyl-2-oxazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 2-(2-Phenyl-oxazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one or
 2-(2-Phenyl-thiazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one;
 20 and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

- [0034] Specific compounds of Formula I within the present invention include
 25 but are not limited to:
 6,6-Dimethyl-2-pyridin-3-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 2-(3-Fluoro-phenylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one
 2-(3-Chloro-phenylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one
 2-(3-Methoxy-phenylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one
 30 2-(3-Hydroxy-phenylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one
 3-(6,6-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile
 6,6-Dimethyl-2-thiazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 6,6-Dimethyl-2-(3-piperidin-1-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one

- 7,7-Dimethyl-2-(3-piperidin-1-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
2-(3-Piperidin-1-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
2-(3-Morpholin-4-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
7,7-Dimethyl-2-(3-morpholin-4-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-
5 one
6,6-Dimethyl-2-(3-morpholin-4-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-
one
6,6-Dimethyl-2-[3-(1H-tetrazol-5-yl)-phenylethynyl]-7,8-dihydro-6H-quinolin-5-
one
10 7,7-Dimethyl-2-[3-(1H-tetrazol-5-yl)-phenylethynyl]-7,8-dihydro-6H-quinolin-5-
one
2-[3-(1H-Tetrazol-5-yl)-phenylethynyl]-7,8-dihydro-6H-quinolin-5-one
2-[3-Fluoro-5-(1H-tetrazol-5-yl)-phenylethynyl]-6,6-dimethyl-7,8-dihydro-6H-
quinolin-5-one
15 2-[3-Fluoro-5-(1H-tetrazol-5-yl)-phenylethynyl]-7,7-dimethyl-7,8-dihydro-6H-
quinolin-5-one
2-[3-Fluoro-5-(1H-tetrazol-5-yl)-phenylethynyl]-7,8-dihydro-6H-quinolin-5-one
2-(3-Trifluoromethyl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
7,7-Dimethyl-2-(3-trifluoromethyl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-
20 one
6,6-Dimethyl-2-(3-trifluoromethyl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-
one
7,7-Dimethyl-2-phenylethynyl-7,8-dihydro-6H-quinolin-5-one
6,6-Dimethyl-2-phenylethynyl-7,8-dihydro-6H-quinolin-5-one
25 2-(4-Methyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
7,7-Dimethyl-2-(4-methyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
6,6-Dimethyl-2-(4-methyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
2-(4-Fluoro-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
2-(4-Fluoro-thiazol-2-ylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
30 2-(4-Fluoro-thiazol-2-ylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one
2-(2-Phenyl-thiazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
2-(5-Fluoro-pyridin-3-ylethynyl)-7,8-dihydro-6H-quinolin-5-one

- 3-Fluoro-5-(7,7-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile
- 2-(4-Fluoro-5-phenyl-oxazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
- 2-(4-Fluoro-5-pyridin-3-yl-oxazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
- 5 2-(4-Fluoro-5-pyridin-3-yl-oxazol-2-ylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
- 2-(4-Fluoro-5-pyridin-3-yl-oxazol-2-ylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one
- 7,7-Dimethyl-2-pyridin-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one
- 10 2-Pyridin-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one
- 6,6-Dimethyl-2-pyridin-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one
- 6,6-Dimethyl-2-(4-methyl-oxazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
- 7,7-Dimethyl-2-(4-methyl-oxazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
- 2-(4-Fluoro-5-pyridin-3-yl-1H-imidazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
- 15 one
- 2-(4-Fluoro-5-pyridin-3-yl-1H-imidazol-2-ylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
- 2-(4-Fluoro-5-pyridin-3-yl-1H-imidazol-2-ylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one
- 20 6,6-Dimethyl-2-(4-pyridin-3-yl-imidazol-1-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
- 7,7-Dimethyl-2-(4-pyridin-3-yl-imidazol-1-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
- 2-(4-Pyridin-3-yl-imidazol-1-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
- 25 2-Thiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one
- 2-[1,3,4]Thiadiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one
- 2-[1,3,4]Oxadiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one
- 2-(1H-Tetrazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
- 6,6-Dimethyl-2-[1,3,4]thiadiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one
- 30 7,7-Dimethyl-2-[1,3,4]thiadiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one
- 7,7-Dimethyl-2-(1H-tetrazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
- 6,6-Dimethyl-2-(1H-tetrazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
- 6,6-Dimethyl-2-oxazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one

- 2-Oxazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 6,6-Dimethyl-2-oxazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 7,7-Dimethyl-2-oxazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 6,6-Dimethyl-2-m-tolylethynyl-7,8-dihydro-6H-quinolin-5-one
 5 7,7-Dimethyl-2-(2-phenyl-oxazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
 6,6-Dimethyl-2-(2-phenyl-oxazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
 7,7-Dimethyl-2-(5-phenyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
 6,6-Dimethyl-2-(5-phenyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
 2-(5-Fluoro-pyridin-3-ylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
 10 2-(5-Fluoro-pyridin-3-ylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one
 3-Fluoro-5-(5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile
 3-(6,6-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-5-fluoro-
 benzonitrile
 2-(4-Fluoro-5-phenyl-oxazol-2-ylethynyl)-7,7-dimethyl-7,8-dihydro-6H-
 15 quinolin-5-one
 2-(4-Fluoro-5-phenyl-oxazol-2-ylethynyl)-6,6-dimethyl-7,8-dihydro-6H-
 quinolin-5-one
 6,6-Dimethyl-2-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-ylethynyl)-7,8-dihydro-6H-
 quinolin-5-one
 20 7,7-Dimethyl-2-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-ylethynyl)-7,8-dihydro-6H-
 quinolin-5-one
 2-(5-Pyridin-3-yl-[1,3,4]oxadiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one
- and optical isomers, pharmaceutically acceptable salts, hydrates, solvates,
 25 and polymorphs thereof.

DETAILED DESCRIPTION OF THE INVENTION

- [0035] For the purpose of the present invention, the carbon atom content of
 various hydrocarbon-containing moieties is indicated by a prefix designating
 30 the minimum and maximum number of carbon atoms in the moiety, i.e., the
 prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms,
 inclusive. Thus, for example, (C₁₋₃)alkyl refers to alkyl of one to three carbon

atoms, inclusive, (i.e., methyl, ethyl, propyl, and isopropyl), straight and branched forms thereof.

[0036] As used herein, the term "C₁₋₆alkyl" comprises straight or branched chain alkyl groups having 1, 2, 3, 4, 5 or 6 carbon atoms. Said alkyl groups may be unsubstituted and include, e.g., methyl, ethyl, n-propyl, 2-propyl, n-butyl, tert-butyl. Further, these alkyl groups may optionally be substituted by one or more fluorine, chlorine and/or bromine atoms; examples of these halogenated alkyl moieties include -CF₃, -C₂F₅, -CBr₃, and -CCl₃. The term "C₁₋₆alkoxy" comprises straight or branched chain -O-C₁₋₆alkyl groups wherein "C₁₋₆alkyl" is defined as given hereinbefore. Examples of "C₁₋₆alkoxy" include methoxy, ethoxy, n-propoxy, i-propoxy. A C₁₋₆alkoxy group optionally may be substituted by one or more fluorine, chlorine and/or bromine atoms thereby forming, for instance, -OCF₃, -OC₂F₅, -CBr₃. The term "cycloC₃₋₁₂alkyl" represents monocyclic, bicyclic or tricyclic alkyl groups having 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl and adamantyl. A cycloC₃₋₁₂alkyl group optionally may be substituted with one or more fluorine, chlorine and/or bromine atoms. In the context of the present invention the term "di-C₁₋₆alkylamino" refers to an amino moiety in which the nitrogen atom of the amino group is substituted with two C₁₋₆alkyl groups, that may be the same or different, as defined above. Examples of di-C₁₋₆alkylamino groups include dimethylamino, diethylamino and N-methyl-N-isopropylamino. The term "N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino" comprises amino groups in which the nitrogen atom of the amino group is substituted by one C₁₋₆alkyl group and one N-cycloC₃₋₁₂alkyl group. Both the C₁₋₆alkyl group and the N-cycloC₃₋₁₂alkyl group are defined as given hereinbefore. The term "4-C₁₋₆alkyl-piperazinyl" comprises piperazinyl radicals bearing a C₁₋₆alkyl moiety at the nitrogen atom in 4-position of the piperazine ring, said "C₁₋₆alkyl" having the same meaning as given hereinbefore. The term "(hetero)aromatic 5-, 6- or 7-membered ring" refers to heterocyclic rings having up to 4 oxygen, nitrogen and/or sulfur atoms in the ring that comprises 5, 6 or 7 carbon and hetero atoms, said heterocyclic ring being an aromatic ring system. Examples of such

(hetero)aromatic 5-, 6- or 7-membered rings include unsubstituted or appropriately substituted pyrroles, oxazoles, thiophens, furans, isoxazoles, imidazoles, oxazoles, oxadiazoles, thiazoles, imidazolines, pyrazoles, oxazolidines, isoxazolidines, thiazolidines, pyridines, pyridazines, pyrimidines, pyrazines, azepines. The term "halogen" represents fluorine, chlorine, bromine and iodine.

[0037] The compounds of the present invention are named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for hour or hours, and "rt" for room temperature).

[0038] The term "analog" or "derivative" is used herein in the conventional pharmaceutical sense, to refer to a molecule that structurally resembles a reference molecule (such as 7,8-dihydro-6H-quinolin-5-one), but has been modified in a targeted and controlled manner to replace one or more specific substituents of the referent molecule with an alternate substituent, thereby generating a molecule which is structurally similar to the reference molecule. Synthesis and screening of analogs (e.g., using structural and/or biochemical analysis), to identify slightly modified versions of a known compound which may have improved or biased traits (such as higher potency and/or selectivity at a specific targeted receptor type, greater ability to penetrate mammalian blood-brain barriers, fewer side effects, etc.) is a drug design approach that is well known in pharmaceutical chemistry.

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[0039] In addition, using methods known to those skilled in the art, analogs and derivatives of the compounds of the invention can be created which have improved therapeutic efficacy in controlling dementia, *i.e.*, higher potency and/or selectivity at a specific targeted receptor type, either greater or lower ability to penetrate mammalian blood-brain barriers (e.g., either higher or lower blood-brain barrier permeation rate), fewer side effects, etc.

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[0040] The phrase "pharmaceutically acceptable", as used in connection with compositions of the invention, refers to molecular entities and other ingredients of such compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (e.g., human). Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals, and more particularly in humans.

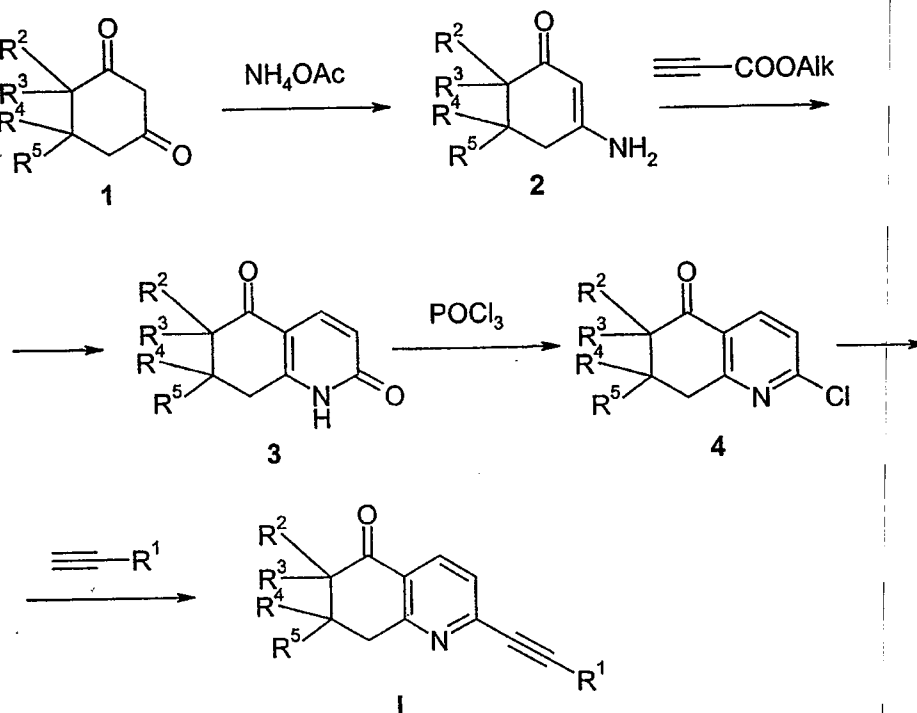
[0041] Compounds of the present invention may be in the form of pharmaceutically acceptable salts. "Pharmaceutically acceptable salts" refers to those salts which possess the biological effectiveness and properties of the parent compound and which are not biologically or otherwise undesirable. The nature of the salt or isomer is not critical, provided that it is non-toxic and does not substantially interfere with the desired pharmacological activity.

[0042] It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, tautomeric, or stereoisomeric form, or mixture thereof, of a compound of the invention, which possesses the useful properties described herein.

[0043] The following Scheme 1 describes the preparation of compounds of Formula I of the present invention. All of the starting materials are prepared by procedures described in the scheme, by procedures well known to one of ordinary skill in organic chemistry or can be obtained commercially. All of the final compounds of the present invention are prepared by procedures described in this chart or by procedures analogous thereto, which would be well known to one of ordinary skill in organic chemistry. All of the variables used in the scheme are as defined below or as in the claims.

[0044] A synthetic procedure toward 2-substituted-ethynyl-7,8-dihydro-6H-quinolin-5-ones with the general Formula I is given in **Scheme 1**. The reaction of appropriately functionalized cyclohexane-1,3-dione derivatives **1** with ammonium acetate / acetic acid in benzene gave the corresponding 3-amino-cyclohex-2-enone derivatives **2**. Compound **2** were then reacted with alkyl propiolate and cyclization was achieved at elevated temperatures to form the quinoline-2,5-dione **3**. Subsequent reaction with phosphoryl chloride gave the 2-chloro-substituted quinolin-5-one derivative **4**. Substitution of the chloro-substituent with appropriate acetylene derivative under palladium (0) catalysis in the presence of base yielded compounds of Formula I.

Scheme 1 Synthesis of 2-substituted-ethynyl-7,8-dihydro-6H-quinolin-5-ones



[0045] It will be apparent to those skilled in the art that the described synthetic procedures are merely representative in nature and that alternative synthetic processes are known to one of ordinary skill in organic chemistry.

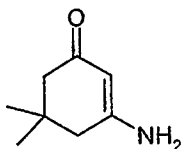
EXPERIMENTAL PART

[0046] The compounds and their preparation of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

[0047] Hereinafter, "DMF" is defined as N,N-dimethylformamide, "HCl" as hydrochloric acid, "DMSO" as dimethylsulfoxide and "TMS" as tetramethylsilane.

Preparation 1

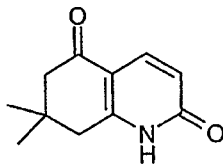
3-Amino-5,5-dimethylcyclohex-2-en-1-one



[0048] The title compound was prepared according to (Baraldi, P. G.; Simoni, D.; Manfredini, S.; *Synthesis* 1983, (11) 902-903.) as a colorless solid in 76% yield.

Preparation 2

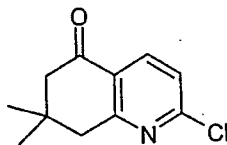
7,7-Dimethyl-7,8-dihydro-1H,6H-quinoline-2,5-dione



[0049] In analogy to (Pettit, G. R.; Fleming, W. C.; Paull, K. D. *J. Org. Chem.* 1968, 33 (3) 1089-1092.), 3-amino-5,5-dimethylcyclohex-2-en-1-one was reacted with ethyl propiolate to give the title compound as a light brown solid in 78.5% yield.

Physical characteristics are as follows:

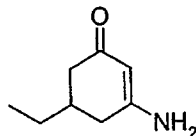
^1H NMR (CDCl_3 , TMS) δ : 1.14, 2.42, 2.82, 6.47, and 8.04.

Preparation 3**2-Chloro-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one**

- 5 [0050] In analogy to (Shanazarov, A. K.; Kuzovkin, V. A.; Chistjakov, V. V.; Granik, V. G. *Khim. Geterotsikl. Soedin.* 1991, (1) 86-92.) 7,7-dimethyl-7,8-dihydro-1H,6H-quinoline-2,5-dione was treated with phosphoryl chloride (POCl_3) to give the title compound as a gray solid in 60% yield.

Physical characteristics are as follows:

- 10 ^1H NMR (CDCl_3 , TMS) δ : 1.11, 2.54, 3.01, 7.30, and 8.30.

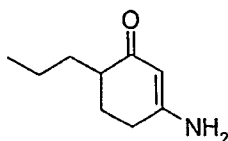
Preparation 4**3-Amino-5-ethylcyclohex-2-en-1-one**

15

[0051] In close analogy to (Baraldi, P. G.; Simoni, D.; Manfredini, S.; *Synthesis* 1983, (11) 902-903) 5-ethylcyclohexane-1,3-dione was reacted with ammonium acetate to give the title compound.

Physical characteristics are as follows:

- 20 ^1H NMR (CDCl_3 , TMS) δ : 0.93 (t, 6.5 Hz, 3H); 1.42 (m, 2H); 1.88 – 2.44 (m, 5H); 4.62 (br s, 2H) and 5.23 ppm (s, 1H).

Preparation 5**3-Amino-6-propylcyclohex-2-en-1-one**

25

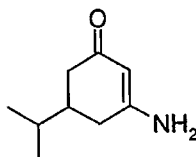
[0052] In close analogy to (Baraldi, P. G.; Simoni, D.; Manfredini, S.; *Synthesis* 1983, (11) 902-903) 4-propylcyclohexane-1,3-dione was reacted with ammonium acetate to give the title compound as a colorless solid.

Physical characteristics are as follows:

- 5 ^1H NMR (CDCl_3 , TMS) δ : 0.91 (t, 7 Hz, 3H); 1.25 – 1.90 (m, 5H); 1.98 – 2.18 (m, 2H); 2.35 (t, 6 Hz, 2H); 4.50 (br s, 2H) and 5.19 ppm (s, 1H).

Preparation 6

3-Amino-5-isopropylcyclohex-2-en-1-one



10

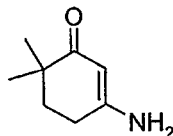
[0053] In analogy to (Baraldi, P. G.; Simoni, D.; Manfredini, S.; *Synthesis* 1983, (11) 902-903) 5-isopropylcyclohexane-1,3-dione was reacted with ammonium acetate to give the title compound as a colorless solid.

- 15 Physical characteristics are as follows:

^1H NMR (CDCl_3 , TMS) δ : 0.91 (d, 6.5 Hz); 1.48 – 1.65 (m, 1H); 1.84 – 2.39 (m, 5H); 5.04 (br s, 2H) and 5.22 ppm (s, 1H).

Preparation 7

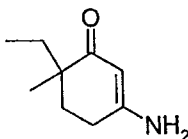
- 20 **3-Amino-6,6-dimethylcyclohex-2-en-1-one**



- 25 [0054] In analogy to (Baraldi, P. G.; Simoni, D.; Manfredini, S.; *Synthesis* 1983, (11) 902-903) 4,4-dimethylcyclohexane-1,3-dione was reacted with ammonium acetate to give the title compound as a colorless solid.

Physical characteristics are as follows:

Mp 153-154 $^{\circ}\text{C}$; ^1H NMR ($\text{DMSO}-d_6$, TMS) δ : 0.94 (s, 6H); 1.64 (t, 6.5 Hz, 2H); 2.28 (t, 6.5 Hz, 2H); 4.79 (s, 1H) and 6.58 ppm (br s, 2H).

Preparation 8**3-Amino-6-ethyl-6-methylcyclohex-2-en-1-one**

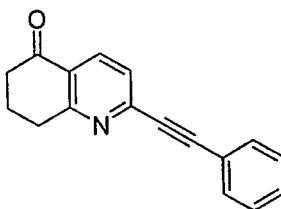
- 5 [0055] In analogy to (Baraldi, P. G.; Simoni, D.; Manfredini, S.; Synthesis 1983, (11) 902-903) 4-ethyl-4-methylcyclohexane-1,3-dione was reacted with ammonium acetate to give the title compound as a colorless solid.

Physical characteristics are as follows:

- 10 ^1H NMR (CDCl_3 , TMS) δ : 0.83 (t, 6.5 Hz, 3H); 1.06 (s, 3H); 1.40 – 1.80 (m, 3H); 1.85 – 2.00 (m, 1H); 2.35 (t, 6.5 Hz, 2H); 4.31 (br s, 2H) and 5.14 ppm (s, 1H).

Mp 99-100 °C; ^1H NMR (CDCl_3 , TMS) δ : 1.08, 1.73, 2.45, 2.79, 3.91, and 8.33; Anal. Found ($\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}$) (%): C, 71.6; H, 7.5; N, 14.4

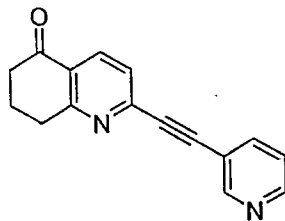
15

Preparation 9**2-Phenylethynyl-7,8-dihydro-6H-quinolin-5-one**

- 20 [0056] To a solution of 2-chloro-7,8-dihydro-6H-quinolin-5-one (0.2 g, 1.1 mmol) and ethynylbenzene (0.17 g, 1.6 mmol) in triethylamine (7 ml) under an argon atmosphere was added tetrakis (triphenylphosphine) palladium (0.02 g, 0.062 mmol). The mixture was heated at reflux for 3 h. Then it was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to give the title compound (0.04 g, 15%).

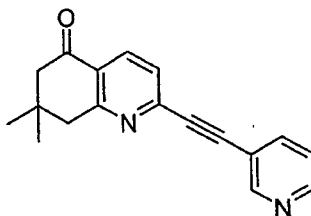
- 25 Physical characteristics are as follows:

Mp 121-122 °C; ^1H NMR (CDCl_3 , TMS) δ : 2.20 (2H); 2.68 (2H); 3.17 (2H); 7.22-7.38 (3H); 7.46 (1H); 7.60 (2H); 8.24 (1H); MS 248 (M+1).

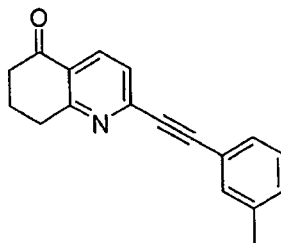
Preparation 10**2-Pyridin-3-ylethynyl-7,8-dihydro-6H-quinolin-5-one**

5

[0057] In analogy to the procedure described in **Preparation 9**, the title compound was obtained in moderate yield (120 mg, 15%, MP: 120-122.1°C).

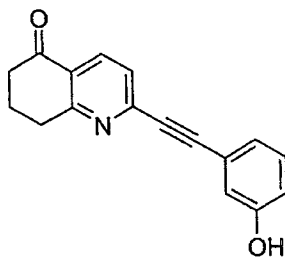
Preparation 11**7,7-Dimethyl-2-pyridin-3-ylethynyl-7,8-dihydro-6H-quinolin-5-one**

[0058] In analogy to the procedure described in **Preparation 9**, the title compound was obtained in moderate yield (50 mg, 12 %, MP: 108-109.2°C).

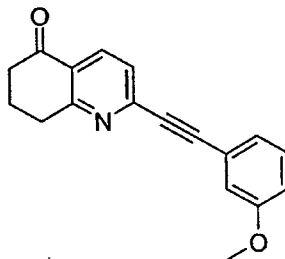
Preparation 12**2-m-Tolylethynyl-7,8-dihydro-6H-quinolin-5-one**

[0059] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

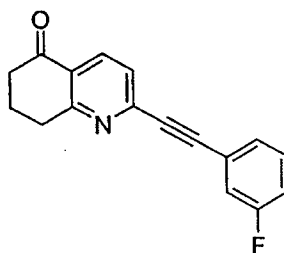
20

Preparation 13**2-(3-Hydroxy-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one**

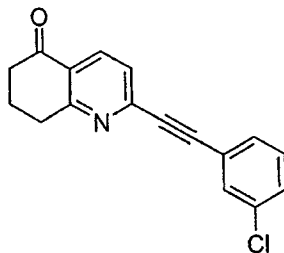
- 5 [0060] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Preparation 14**2-(3-Methoxy-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one**

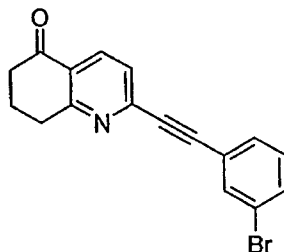
- 10 [0061] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Preparation 15**2-(3-Fluoro-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one**

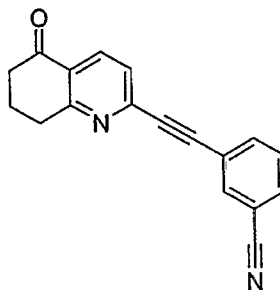
- 15 [0062] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Preparation 16**2-(3-Chloro-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one**

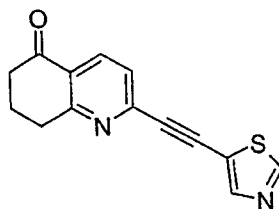
5 [0063] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Preparation 17**2-(3-Bromo-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one**

10 [0064] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Preparation 18**3-(5-Oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile**

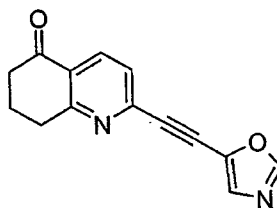
15 [0065] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Preparation 19**2-Thiazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one**

- 5 [0066] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

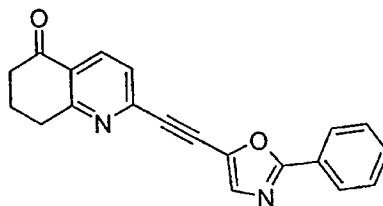
Preparation 20

10 **2-Oxazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one**

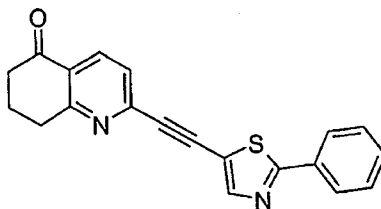


- [0067] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

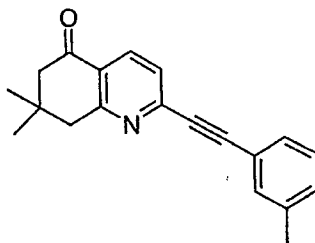
15 **Preparation 21**

2-(2-Phenyl-oxazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one

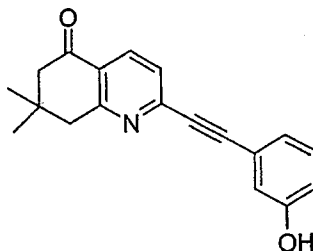
- 20 [0068] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Preparation 22**2-(2-Phenyl-thiazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one**

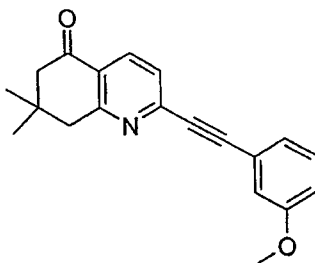
- 5 [0069] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Preparation 23**7,7-Dimethyl-2-m-tolyethynyl-7,8-dihydro-6H-quinolin-5-one**

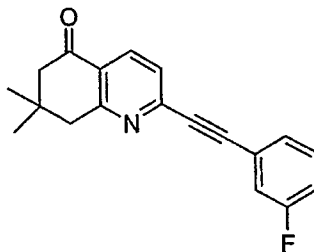
- 10 [0070] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Preparation 24**2-(3-Hydroxy-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one**

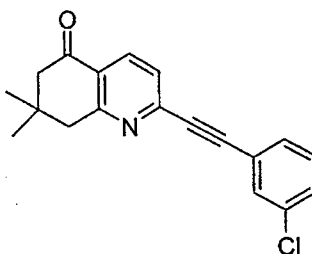
- [0071] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Preparation 25**2-(3-Methoxy-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one**

5 [0072] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

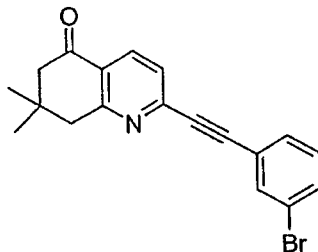
Preparation 26**2-(3-Fluoro-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one**

10 [0073] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

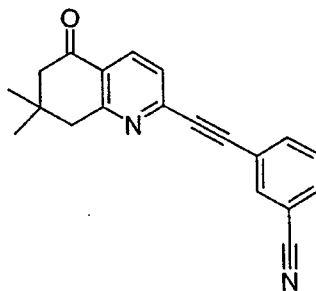
Preparation 27**2-(3-Chloro-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one**

15 [0074] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

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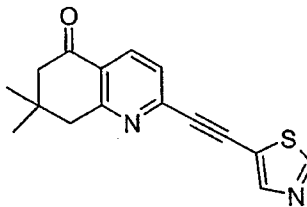
Preparation 28**2-(3-Bromo-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one**

5 [0075] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Preparation 29**3-(7,7-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile**

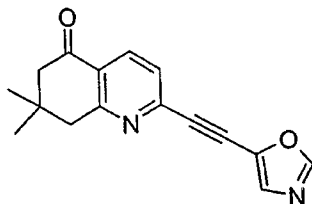
10

[0076] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

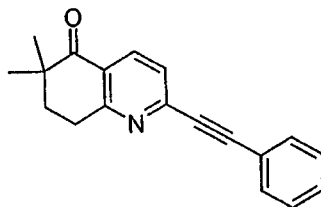
Preparation 30**7,7-Dimethyl-2-thiazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one**

15

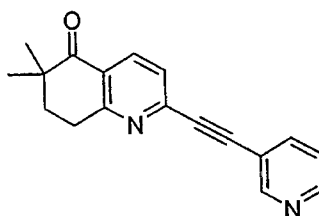
[0077] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Preparation 31**7,7-Dimethyl-2-oxazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one**

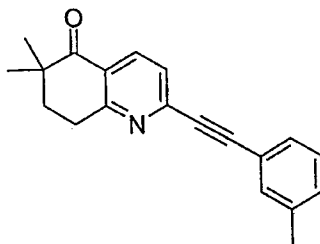
5 [0078] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 1**6,6-Dimethyl-2-phenylethynyl-7,8-dihydro-6H-quinolin-5-one**

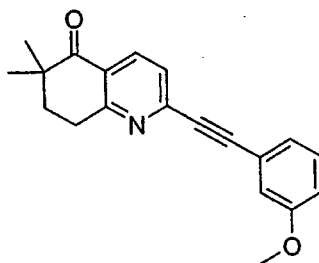
10 [0079] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 2**6,6-Dimethyl-2-pyridin-3-ylethynyl-7,8-dihydro-6H-quinolin-5-one**

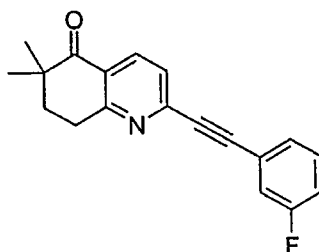
15 [0080] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 3**6,6-Dimethyl-2-m-tolylethynyl-7,8-dihydro-6H-quinolin-5-one**

5 [0081] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield

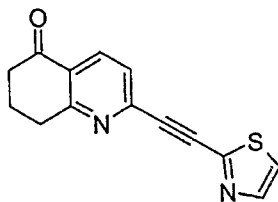
Example 4**2-(3-Methoxy-phenylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one**

10 [0082] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

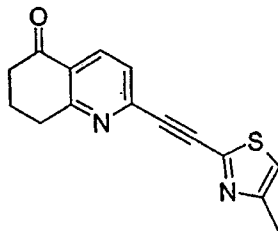
Example 5**2-(3-Fluoro-phenylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one**

15

[0083] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 6**2-Thiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one**

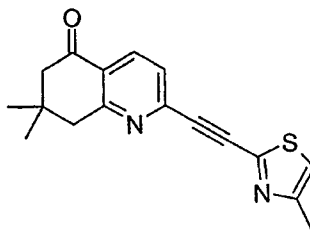
- 5 [0084] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 7**2-(4-Methyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one**

- 10 [0085] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 8

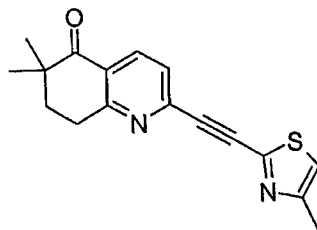
- 15 **7,7-Dimethyl-2-(4-methyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one**



- 20 [0086] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 9

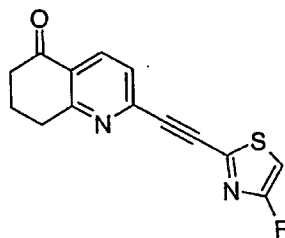
6,6-Dimethyl-2-(4-methyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one



- 5 [0087] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 10

2-(4-Fluoro-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one

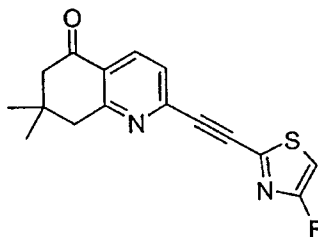


10

- [0088] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

15 **Example 11**

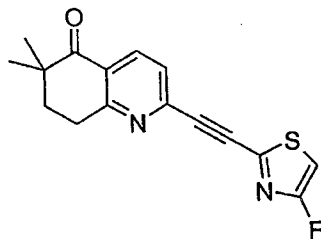
2-(4-Fluoro-thiazol-2-ylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one



- 20 [0089] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 12

2-(4-Fluoro-thiazol-2-ylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one

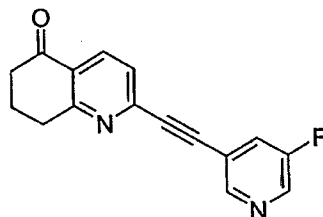


5

[0090] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 13

2-(5-Fluoro-pyridin-3-ylethynyl)-7,8-dihydro-6H-quinolin-5-one

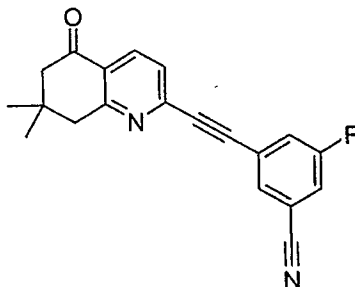


10

[0091] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 14

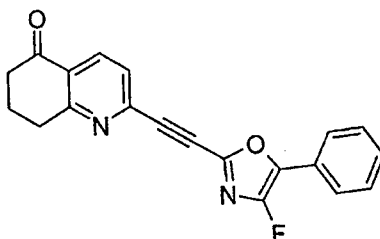
3-Fluoro-5-(7,7-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile



[0092] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 15

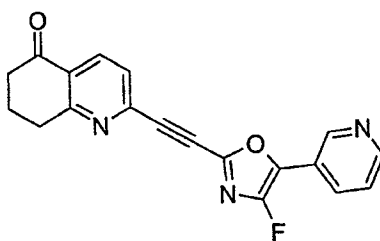
5 2-(4-Fluoro-5-phenyl-oxazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one



[0093] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

10 Example 16

2-(4-Fluoro-5-pyridin-3-yl-oxazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one

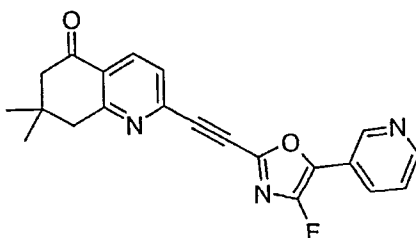


[0094] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

15

Example 17

2-(4-Fluoro-5-pyridin-3-yl-oxazol-2-ylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one

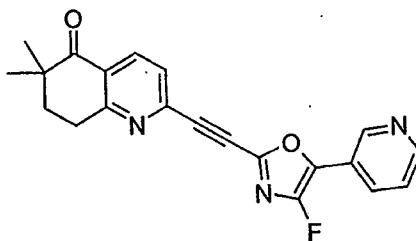


20

[0095] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 18

- 5 **2-(4-Fluoro-5-pyridin-3-yl-oxazol-2-ylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one**

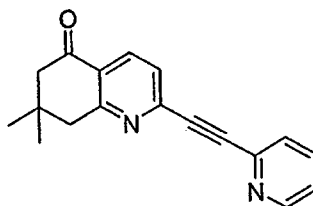


[0096] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

10

Example 19

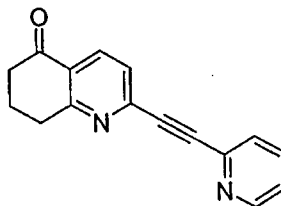
- 7,7-Dimethyl-2-pyridin-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one**



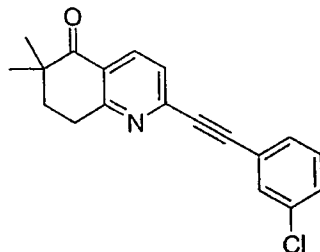
- 15 [0097] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 20

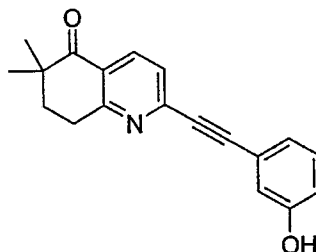
- 2-Pyridin-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one**



- 20 [0098] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 21**2-(3-Chloro-phenylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one**

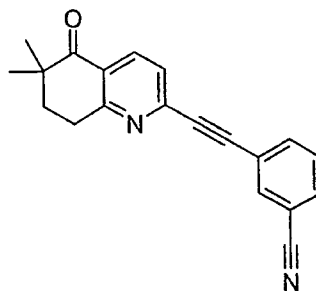
- 5 [0099] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 22**2-(3-Hydroxy-phenylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one**

- 10 [00100] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 23

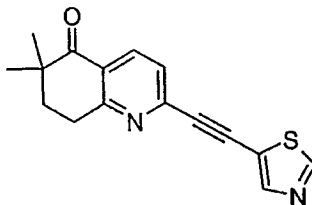
- 15 **3-(6,6-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile**

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5.4

[00101] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 24

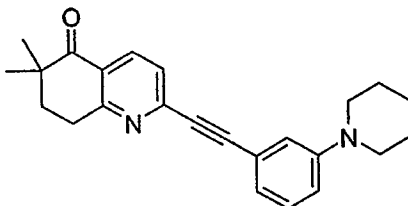
5 **6,6-Dimethyl-2-thiazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one**



[00102] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

10 **Example 25**

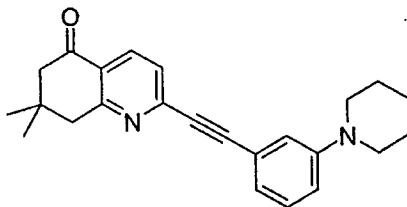
6,6-Dimethyl-2-(3-piperidin-1-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one



15 [00103] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 26

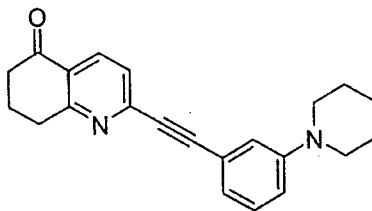
7,7-Dimethyl-2-(3-piperidin-1-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one



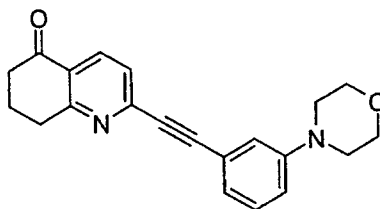
20

[00104] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

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Example 27**2-(3-Piperidin-1-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one**

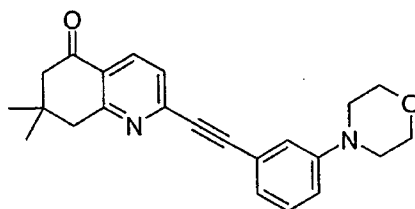
- 5 [00105] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 28**2-(3-Morpholin-4-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one**

- 10 [00106] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 29

- 15 **7,7-Dimethyl-2-(3-morpholin-4-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one**

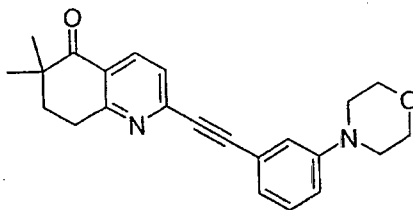


- [00107] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

20

Example 30

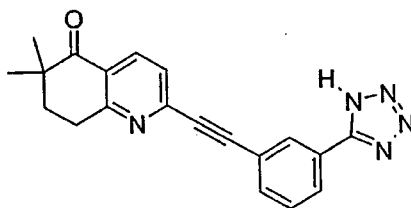
6,6-Dimethyl-2-(3-morpholin-4-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one



- 5 [00108] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 31

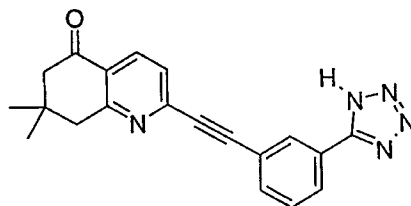
6,6-Dimethyl-2-[3-(1H-tetrazol-5-yl)-phenylethynyl]-7,8-dihydro-6H-quinolin-5-one



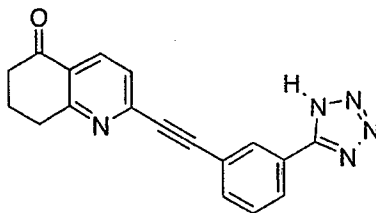
- [00109] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

15 **Example 32**

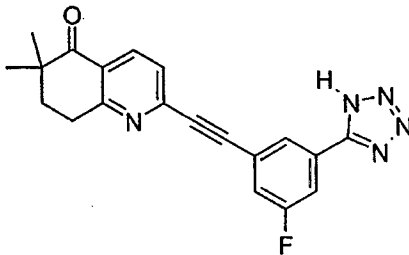
7,7-Dimethyl-2-[3-(1H-tetrazol-5-yl)-phenylethynyl]-7,8-dihydro-6H-quinolin-5-one



- 20 [00110] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

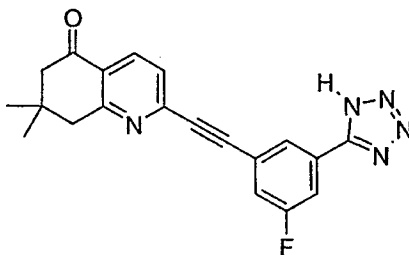
Example 33**2-[3-(1H-Tetrazol-5-yl)-phenylethynyl]-7,8-dihydro-6H-quinolin-5-one**

[00111] In analogy to the procedure described in **Preparation 9**, the title
5 compound is obtained in moderate yield.

Example 34**2-[3-Fluoro-5-(1H-tetrazol-5-yl)-phenylethynyl]-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one**

10

[00112] In analogy to the procedure described in **Preparation 9**, the title
compound is obtained in moderate yield.

Example 35**2-[3-Fluoro-5-(1H-tetrazol-5-yl)-phenylethynyl]-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one**

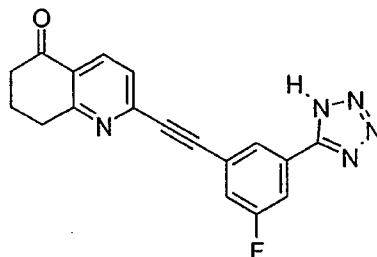
20

[00113] In analogy to the procedure described in **Preparation 9**, the title
compound is obtained in moderate yield.

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58

Example 36

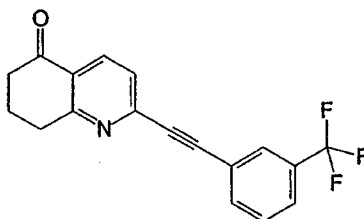
2-[3-Fluoro-5-(1H-tetrazol-5-yl)-phenylethynyl]-7,8-dihydro-6H-quinolin-5-one



- 5 [00114] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 37

2-(3-Trifluoromethyl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one

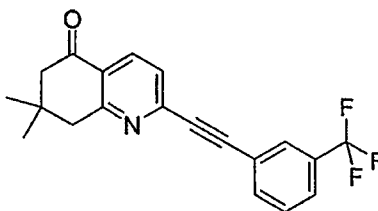


10

- [00115] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 38

- 15 **7,7-Dimethyl-2-(3-trifluoromethyl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one**

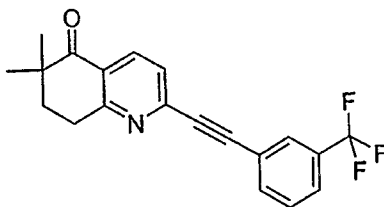


- [00116] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

20

Example 39

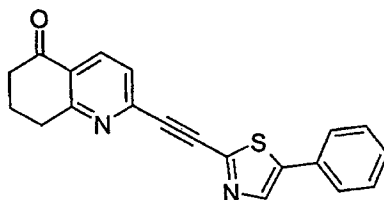
6,6-Dimethyl-2-(3-trifluoromethyl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one



- 5 [00117] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 40

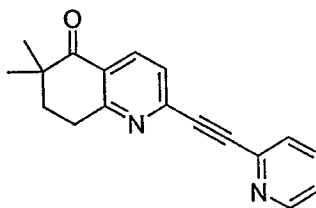
2-(2-Phenyl-thiazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one



- 10 [00118] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 41

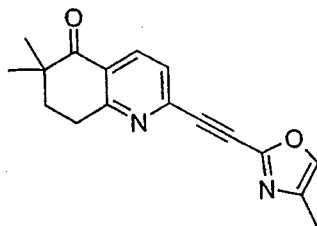
15 **6,6-Dimethyl-2-pyridin-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one**



- [00119] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 42

6,6-Dimethyl-2-(4-methyl-oxazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one

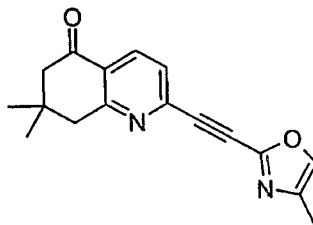


- 5 [00120] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 43

7,7-Dimethyl-2-(4-methyl-oxazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one

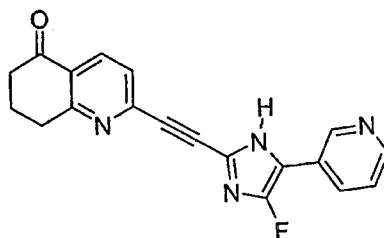
10 one



- [00121] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

15 **Example 44**

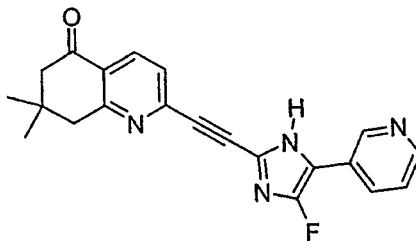
2-(4-Fluoro-5-pyridin-3-yl-1H-imidazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one



- 20 [00122] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 45

2-(4-Fluoro-5-pyridin-3-yl-1H-imidazol-2-ylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one

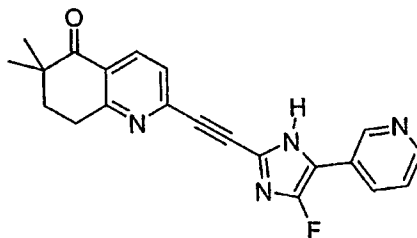


5

[00123] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 46

10 **2-(4-Fluoro-5-pyridin-3-yl-1H-imidazol-2-ylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one**

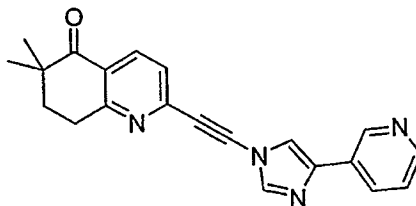


[00124] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

15

Example 47

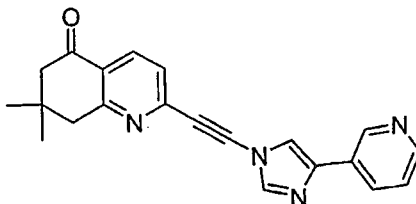
6,6-Dimethyl-2-(4-pyridin-3-yl-imidazol-1-ylethynyl)-7,8-dihydro-6H-quinolin-5-one



20 [00125] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 48

7,7-Dimethyl-2-(4-pyridin-3-yl-imidazol-1-ylethynyl)-7,8-dihydro-6H-quinolin-5-one

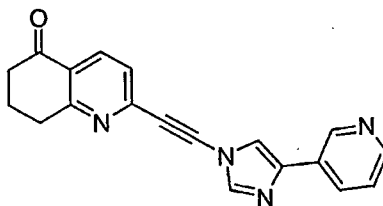


5

[00126] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 49

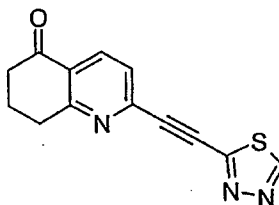
10 **2-(4-Pyridin-3-yl-imidazol-1-ylethynyl)-7,8-dihydro-6H-quinolin-5-one**



[00127] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

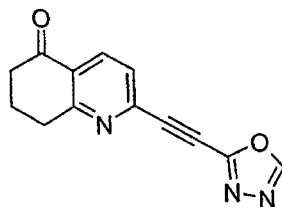
15 **Example 50**

2-[1,3,4]Thiadiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one

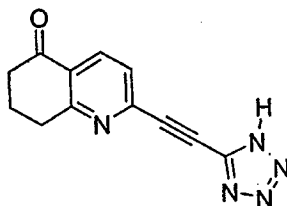


[00128] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

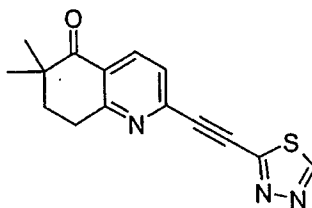
20

Example 51**2-[1,3,4]Oxadiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one**

[00129] In analogy to the procedure described in **Preparation 9**, the title
5 compound is obtained in moderate yield.

Example 52**2-(1H-Tetrazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one**

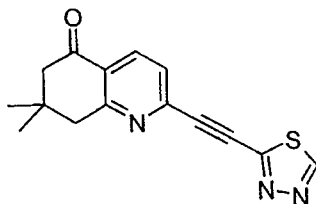
10 [00130] In analogy to the procedure described in **Preparation 9**, the title
compound is obtained in moderate yield.

Example 53**6,6-Dimethyl-2-[1,3,4]thiadiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one**
15 one

[00131] In analogy to the procedure described in **Preparation 9**, the title
compound is obtained in moderate yield.

Example 54

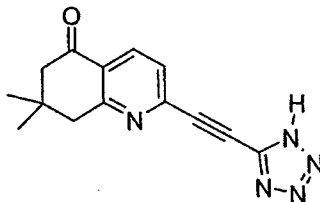
7,7-Dimethyl-2-[1,3,4]thiadiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one



- 5 [00132] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 55

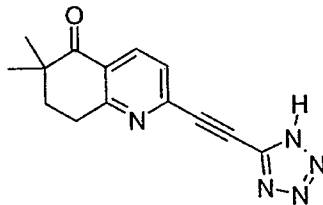
7,7-Dimethyl-2-(1H-tetrazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one



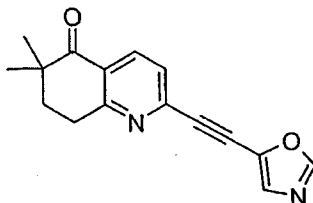
- 10 [00133] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 56

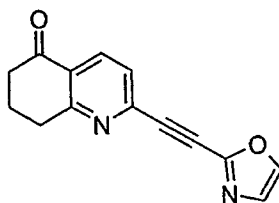
15 **6,6-Dimethyl-2-(1H-tetrazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one**



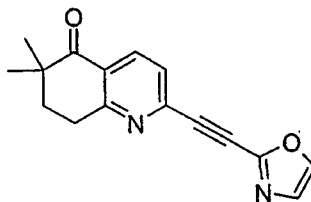
- [00134] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 57**6,6-Dimethyl-2-oxazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one**

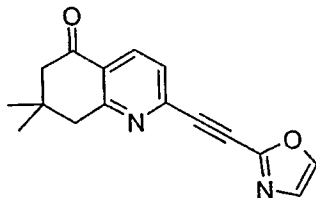
5 [00135] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 58**2-Oxazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one**

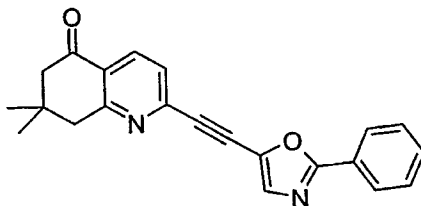
10 [00136] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 59**6,6-Dimethyl-2-oxazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one**

15 [00137] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 60**7,7-Dimethyl-2-oxazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one**

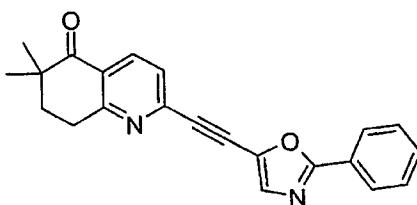
5 [00138] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 61**7,7-Dimethyl-2-(2-phenyl-oxazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one**

10 [00139] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 62

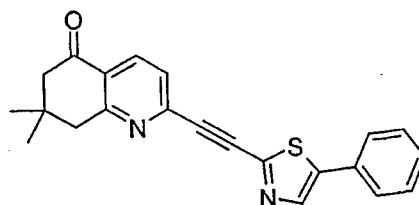
15 **6,6-Dimethyl-2-(2-phenyl-oxazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one**



20 [00140] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 63

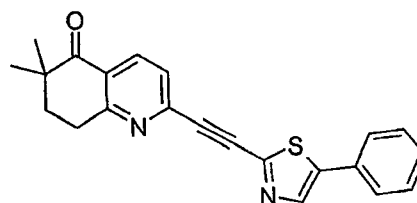
7,7-Dimethyl-2-(5-phenyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one



- 5 [00141] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 64

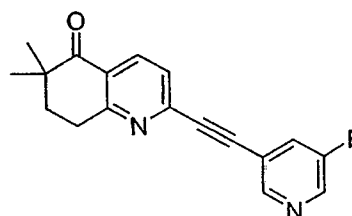
10 **6,6-Dimethyl-2-(5-phenyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one**



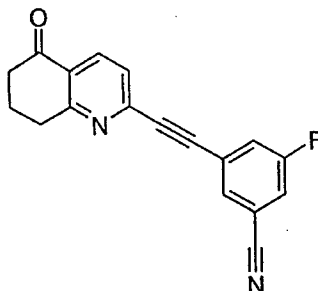
- [00142] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

15 **Example 65**

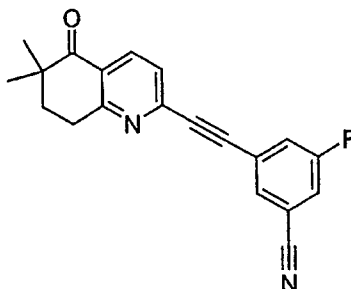
2-(5-Fluoro-pyridin-3-ylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one



- 20 [00143] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 66**3-Fluoro-5-(5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile**

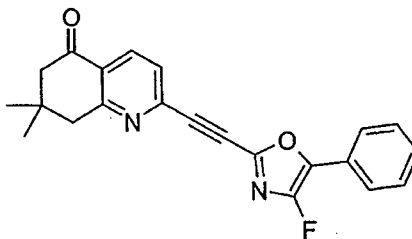
5 [00144] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 67**3-(6,6-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-5-fluorobenzonitrile**

10 [00145] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 68

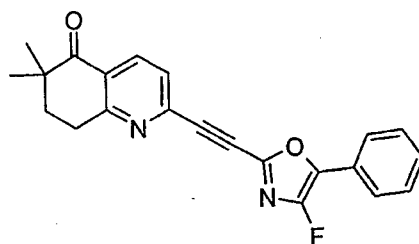
15 **2-(4-Fluoro-5-phenyl-oxazol-2-ylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one**



[00146] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 69

- 5 **2-(4-Fluoro-5-phenyl-oxazol-2-ylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one**

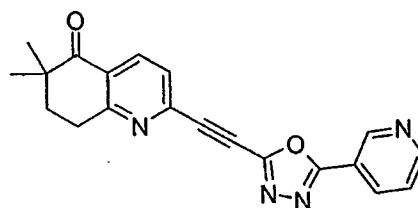


[00147] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

10

Example 70

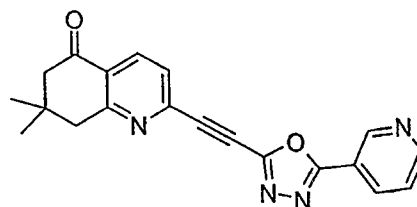
- 6,6-Dimethyl-2-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one**



- 15 [00148] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 71

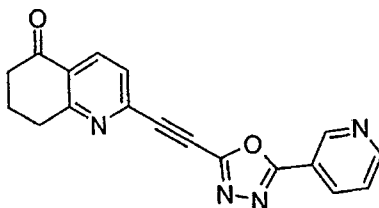
- 20 **7,7-Dimethyl-2-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one**



[00149] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

Example 72

5 **2-(5-Pyridin-3-yl-[1,3,4]oxadiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one**

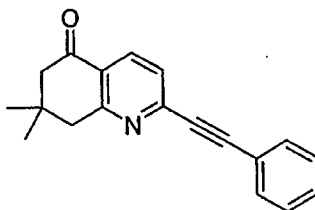


[00150] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

10

Example 73

7,7-Dimethyl-2-phenylethynyl-7,8-dihydro-6H-quinolin-5-one



[00151] In analogy to the procedure described in **Preparation 9**, the title compound is obtained in moderate yield.

15

[00152] Pure stereoisomeric forms of the compounds and the intermediates of this invention may be obtained by the application of art-known procedures. Diastereomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g. liquid chromatography using chiral stationary phases. Enantiomers may be separated from each other by selective crystallization of their diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases.

20

25 Said pure stereoisomeric forms may also be derived from the corresponding

pure stereoisomeric form of appropriate starting materials, provided that the reaction occurs stereoselectively. Stereoisomeric forms of Formula I are obviously intended to be included within the scope of this invention.

5 **ADDITION SALTS**

[00153] For therapeutic use, salts of the compounds of Formula I are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation and purification of pharmaceutically acceptable compounds. All salts whether pharmaceutically acceptable or not are included within the ambit of the present invention. The pharmaceutically acceptable salts as mentioned above are meant to comprise the therapeutically active non-toxic salt forms which the compounds of Formula I are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, e.g. hydrohalic acids such as hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids such as acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfonic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely, the salt form can be converted by treatment with alkali into the free base form.

25 **PHARMACEUTICAL COMPOSITIONS**

[00154] The active ingredients of the invention, together with one or more conventional adjuvants, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as coated or uncoated tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use; in the form of suppositories or capsules for rectal administration or in the form of sterile injectable solutions for parenteral (including intravenous or subcutaneous) use. Such

pharmaceutical compositions and unit dosage forms thereof may comprise conventional or new ingredients in conventional or special proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing one (1) to one hundred (100) milligrams of active ingredient or, more broadly, zero point five (0.5) to five hundred (500) milligrams per tablet, are accordingly suitable representative unit dosage forms.

10 [00155] The term "carrier" applied to pharmaceutical compositions of the invention refers to a diluent, excipient, or vehicle with which an active compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water, saline solutions, aqueous dextrose solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable or
15 synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin, 18th Edition.

METHOD OF TREATING

20 [00156] Due to their high degree of activity and their low toxicity, together presenting a most favorable therapeutic index, the active principles of the invention may be administered to a subject, e.g., a living animal (including a human) body, in need thereof, for the treatment, alleviation, or amelioration, palliation, or elimination of an indication or condition which is susceptible
25 thereto, or representatively of an indication or condition set forth elsewhere in this application, preferably concurrently, simultaneously, or together with one or more pharmaceutically-acceptable excipients, carriers, or diluents, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parental (including intravenous and subcutaneous)
30 or in some cases even topical route, in an effective amount. Suitable dosage ranges are 1-1000 milligrams daily, preferably 10-500 milligrams daily, and especially 50-500 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the

administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

5 [00157] The term "therapeutically effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical composition that is sufficient to result in a desired activity upon administration to a living animal body in need thereof.

10 [00158] The active agents of the present invention may be administered orally, topically, parenterally, or mucosally (e.g., buccally, by inhalation, or rectally) in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers. It is usually desirable to use the oral route. The active agents may be administered orally in the form of a capsule,
15 a tablet, or the like (see Remington: The Science and Practice of Pharmacy, 20th Edition (2000), Philadelphia, PA). The orally administered medicaments may be administered in the form of a time-controlled release vehicle, including diffusion-controlled systems, osmotic devices, dissolution-controlled matrices, and erodible/degradable matrices.

20 [00159] For oral administration in the form of a tablet or capsule, the active drug component can be combined with a non-toxic, pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g.,
25 lactose, sucrose, glucose, mannitol, sorbitol and other reducing and non-reducing sugars, microcrystalline cellulose, calcium sulfate, or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc, or silica, steric acid, sodium stearyl fumarate, glyceryl behenate, calcium stearate, and the like); disintegrants (e.g., potato starch or sodium starch glycolate); or
30 wetting agents (e.g., sodium lauryl sulphate), coloring and flavoring agents, gelatin, sweeteners, natural and synthetic gums (such as acacia, tragacanth or alginates), buffer salts, carboxymethylcellulose, polyethyleneglycol, waxes, and the like. For oral administration in liquid form, the drug components can

be combined with non-toxic, pharmaceutically acceptable inert carriers (e.g., ethanol, glycerol, water), suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (e.g., lecithin or acacia), non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or
5 fractionated vegetable oils), preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid), and the like. Stabilizing agents such as antioxidants (BHA, BHT, propyl gallate, sodium ascorbate, citric acid) can also be added to stabilize the dosage forms.

10 [00160] The tablets can be coated by methods well known in the art. The compositions of the invention can be also introduced in microspheres or microcapsules, e.g., fabricated from polyglycolic acid/lactic acid (PGLA). Liquid preparations for oral administration can take the form of, for example, solutions, syrups, emulsions or suspensions, or they can be presented as a
15 dry product for reconstitution with water or other suitable vehicle before use. Preparations for oral administration can be suitably formulated to give controlled or postponed release of the active compound.

[00161] The active drugs can also be administered in the form of
20 liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines, as is well known.

25 [00162] Drugs of the invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drugs may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl methacrylamide-phenol,
30 polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic

and polyglycolic acid, polyepsilon caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polyhydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

- 5 [00163] For administration by inhalation, the therapeutics according to the present invention can be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. In the case of
- 10 a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.
- 15 [00164] The formulations of the invention can be delivered parenterally, i.e., by intravenous (i.v.), intracerebroventricular (i.c.v.), subcutaneous (s.c.), intraperitoneal (i.p.), intramuscular (i.m.), subdermal (s.d.), or intradermal (i.d.) administration, by direct injection, via, for example, bolus injection or continuous infusion. Formulations for injection can be presented in unit
- 20 dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as excipients, suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form for
- 25 reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.
- [00165] Compositions of the present invention can also be formulated for rectal administration, e.g., as suppositories or retention enemas (e.g.,
- 30 containing conventional suppository bases such as cocoa butter or other glycerides).

[00166] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient and/or may contain different dosage levels to facilitate dosage titration. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

10

[00167] As disclosed herein, the dose of the components in the compositions of the present invention is determined to ensure that the dose administered continuously or intermittently will not exceed an amount determined after consideration of the results in test animals and the individual conditions of a patient. A specific dose naturally varies depending on the dosage procedure, the conditions of a patient or a subject animal such as age, body weight, sex, sensitivity, feed, dosage period, drugs used in combination, seriousness of the disease. The appropriate dose and dosage times under certain conditions can be determined by the test based on the above-described indices but may be refined and ultimately decided according to the judgment of the practitioner and each patient's circumstances (age, general condition, severity of symptoms, sex, etc.) according to standard clinical techniques.

15

20

[00168] Toxicity and therapeutic efficacy of the compositions of the invention can be determined by standard pharmaceutical procedures in experimental animals, e.g., by determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index and it can be expressed as the ratio ED₅₀/LD₅₀. Compositions that exhibit large therapeutic indices are preferred.

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EXAMPLES OF REPRESENTATIVE PHARMACEUTICAL COMPOSITIONS

[00169] With the aid of commonly used solvents, auxiliary agents and carriers, the reaction products can be processed into tablets, coated tablets, capsules, drip solutions, suppositories, injection and infusion preparations, and the like and can be therapeutically applied by the oral, rectal, parenteral, and additional routes. Representative pharmaceutical compositions follow.

(a) Tablets suitable for oral administration which contain the active ingredient may be prepared by conventional tableting techniques.

(b) For suppositories, any usual suppository base may be employed for incorporation therein by usual procedure of the active ingredient, such as a polyethyleneglycol which is a solid at normal room temperature but which melts at or about body temperature.

(c) For parental (including intravenous and subcutaneous) sterile solutions, the active ingredient together with conventional ingredients in usual amounts are employed, such as for example sodium chloride and double-distilled water q.s., according to conventional procedure, such as filtration, aseptic filling into ampoules or IV-drip bottles, and autoclaving for sterility.

[00170] Other suitable pharmaceutical compositions will be immediately apparent to one skilled in the art.

FORMULATION EXAMPLES

[00171] The following examples are again given by way of illustration only and are not to be construed as limiting.

25

EXAMPLE 1**Tablet Formulation**

A suitable formulation for a tablet containing 10 milligrams of active ingredient is as follows:

	mg
69	

75
78

Active Ingredient	10
Lactose	61
Microcrystalline Cellulose	25
Talcum	2
Magnesium stearate	1
Colloidal silicon dioxide	1

EXAMPLE 2

Tablet Formulation

- 5 Another suitable formulation for a tablet containing 100 mg is as follows:

	mg
Active Ingredient	100
Polyvinylpyrrolidone, crosslinked	10
Potato starch	20
Polyvinylpyrrolidone	19
Magnesium stearate	1
Microcrystalline Cellulose	50
Film coated and colored.	
The film coating material consists of:	
Hypromellose	10
Microcryst. Cellulose	5
Talcum	5
Polyethylene glycol	2

Color pigments

5

EXAMPLE 3

Capsule Formulation

5 A suitable formulation for a capsule containing 50 milligrams of active ingredient is as follows:

	mg
Active Ingredient	50
Corn starch	26
Dibasic calcium phosphate	50
Talcum	2
Colloidal silicon dioxide	2

filled in a gelatin capsule.

EXAMPLE 4

10

Solution for injection

A suitable formulation for an injectable solution is as follows:

Active Ingredient	mg	10
Sodium chloride	mg	q.s.
Water for Injection	mL	add 1.0

EXAMPLE 5

15

Liquid oral formulation

A suitable formulation for 1 liter of a an oral solution containing 2 milligrams of active ingredient in one milliliter of the mixture is as follows:

	mg
Active Ingredient	2
Saccharose	250
Glucose	300
Sorbitol	150
Orange flavor	10
Colorant	q.s.
Purified water	add 1000 mL

5

EXAMPLE 6

Liquid oral formulation

Another suitable formulation for 1 liter of a liquid mixture containing 20 milligrams of active ingredient in one milliliter of the mixture is as follows:

	G
Active Ingredient	20.00
Tragacanth	7.00
Glycerol	50.00
Saccharose	400.00
Methylparaben	0.50
Propylparaben	0.05

Black currant-flavor	10.00
Soluble Red color	0.02
Purified water	add 1000 mL

EXAMPLE 7

Liquid oral formulation

Another suitable formulation for 1 liter of a liquid mixture containing 2
5 milligrams of active ingredient in one milliliter of the mixture is as follows:

	G
Active Ingredient	2
Saccharose	400
Bitter orange peel tincture	20
Sweet orange peel tincture	15
Purified water	add 1000 mL

EXAMPLE 8

Aerosol formulation

10 180 g aerosol solution contain:

	G
Active Ingredient	10
Oleic acid	5
Ethanol	81
Purified Water	9

Tetrafluoroethane

75

15 ml of the solution are filled into aluminum aerosol cans, capped with a dosing valve, purged with 3.0 bar.

5

EXAMPLE 9

TDS formulation

100 g solution contain:

	G
Active Ingredient	10.0
Ethanol	57.5
Propyleneglycol	7.5
Dimethylsulfoxide	5.0
Hydroxyethylcellulose	0.4
Purified water	19.6

10 1.8 ml of the solution are placed on a fleece covered by an adhesive backing foil. The system is closed by a protective liner which will be removed before use.

EXAMPLE 10

Nanoparticle formulation

15 10 g of polybutylcyanoacrylate nanoparticles contain:

	G

Active Ingredient	1.00
Poloxamer	0.10
Butylcyanoacrylate	8.75
Mannitol	0.10
Sodium chloride	0.05

5 Polybutylcyanoacrylate nanoparticles are prepared by emulsion polymerization in a water/0.1 N HCl/ethanol mixture as polymerization medium. The nanoparticles in the suspension are finally lyophilized under vacuum.

PHARMACOLOGY - SUMMARY

10 [00172] The active principles of the present invention, and pharmaceutical compositions thereof and method of treating therewith, are characterized by unique and advantageous properties, rendering the "subject matter as a whole", as claimed herein, unobvious. The compounds and pharmaceutical compositions thereof exhibit, in standard accepted reliable test procedures, the following valuable properties and characteristics:

15 METHODS

BINDING ASSAYS FOR THE CHARACTERIZATION OF MGLUR5 ANTAGONIST PROPERTIES

20 [³H]MPEP (2-methyl-6-(phenylethynyl)pyridine) binding to transmembrane allosteric modulatory sites of mGluR5 receptors in cortical membranes

Preparation of rat cortical membranes:

[00173] Male Sprague-Dawley rats (200-250 g) are decapitated and their brains are removed rapidly. The cortex is dissected and homogenized in 20 volumes of ice-cold 0.32 M sucrose using a glass-Teflon homogenizer. The homogenate is centrifuged at 1000xg for 10 min. The pellet is discarded and
5 the supernatant centrifuged at 20,000xg for 20 min. The resulting pellet is resuspended in 20 volumes of distilled water and centrifuged for 20 min at 8000xg. Then the supernatant and the buffy coat are centrifuged at 48,000xg for 20 min in the presence of 50 mM Tris-HCl, pH 8.0. The pellet is then resuspended and centrifuged two to three more times at 48,000xg for 20 min in
10 the presence of 50 mM Tris-HCl, pH 8.0. All centrifugation steps are carried out at 4°C. After resuspension in 5 volumes of 50 mM Tris-HCl, pH 8.0 the membrane suspension is frozen rapidly at -80°C.

[00174] On the day of assay the membranes are thawed and washed
15 four times by resuspension in 50 mM Tris-HCl, pH 8.0 and centrifugation at 48,000xg for 20 min. and finally re-suspended in 50 mM Tris-HCl, pH 7.4. The amount of protein in the final membrane preparation (250-500 µg/ml) is determined according to the method of Lowry (Lowry O. H. et al., 1951. J. Biol. Chem. 193, 256-275).

20

[³H]MPEP Assay

[00175] Incubations are started by adding (³H)-MPEP (50.2 Ci/mmol, 5nM, Tocris) to vials with 125-250µg protein (total volume 0.5 ml) and various concentrations of the agents. The incubations are continued at room
25 temperature for 60 min (equilibrium was achieved under the conditions used). Non-specific binding is defined by the addition of unlabeled MPEP (10 µM). Incubations are terminated using a Millipore filter system. The samples are rinsed twice with 4 ml of ice cold assay buffer over glass fibre filters (Schleicher & Schuell) under a constant vacuum. Following separation and
30 rinse, the filters are placed into scintillation liquid (5 ml Ultima Gold) and radioactivity retained on the filters is determined with a conventional liquid scintillation counter (Hewlett Packard, Liquid Scintillation Analyser).

Characterization

[00176] Specific binding is extremely high i.e. normally > 85% and essentially independent of buffer (Tris or HEPES oth 50 mM) and pH (6.8-8.9). There is a clear saturable protein dependence and the chosen protein concentration used for subsequent assays (250-500 µg/ml) is within the linear portion of this dependence. Cold MPEP displaces hot ligand with an IC₅₀ of 18.8 ± 4.1 nM. The K_d of (³H)-MPEP of 13.6 nM is determined by Scatchard analysis and used according to the Cheng Prusoff relationship to calculate the affinity of displacers as K_d values (IC₅₀ of cold MPEP equates to a K_i of 13.7 nM). B_{max} was 0.56 pm / mg protein. Compounds of the present invention exhibit specific affinity for transmembrane modulatory sites of mGluR5 receptors in cortical/cerebellar membrane preparations.

FUNCTIONAL ASSAY OF MGLUR5 RECEPTORS

Materials and Methods

Astrocyte culture

[00177] Primary astrocyte cultures were prepared from cortices of newborn rats as described by Booher and Sensenbrenner (1972). Briefly, Sprague-Dawley rat pups (2 - 4 d old) were decapitated and neocortices were dissected, disintegrated with a nylon filter (poresize 80 µm) and carefully triturated. The cell suspension was plated on poly-D-lysine precoated flasks (Costar) and cultivated in Dulbecco's Modified Eagle's Medium (DMEM, InVitrogen) supplemented with 10% heat inactivated fetal calf serum (FCS_i, Sigma), 4 mM glutamine (Biochrom) and 50 µg/mL gentamycin (Biochrom) at 37°C in a humidified atmosphere of 5% CO₂/95% air for 7 d with exchanging the medium at day 2.

[00178] After 7 DIV, cells were shaken overnight at 250 rpm to remove oligodendrocytes and microglia. The next day, astrocytes were rinsed twice with CMF-PBS, trypsinized and subplated on poly-D-lysine precoated 96-well plates (Becton Dickinson #6516 or #6640) at a density of 40,000 – 45,000 cells/well. 24 h after establishing the secondary culture the astrocytes were

rinsed with PBS⁺⁺ and fed with astrocyte-defined medium (ADM) consisting of DMEM containing 1x G5-supplement (Invitrogen), 0.5 µg/mL heparan sulfate (Sigma), and 1.5 µg/mL fibronectin (Sigma) (Miller et al., 1993). 3 d later the medium was exchanged and the cells incubated for another 2-3 d, so that at the time of experiments astrocytes were 14-15 DIV.

Immunocytochemistry

[00179] Immunostaining was performed to confirm the presence of classical astrocytic markers such as GFAP as well the expression of mGluR5 receptors.

Accumulation of [³H]-Inositol Phosphates

[00180] After astrocytes were cultured for 12 d ADM was removed and inositol-free DMEM (MP Biomedicals) supplemented with [³H]myo-inositol (0.5 µCi / well; Perkin Elmer), and the ADM chemicals was added. After 48 h the medium was replaced with 100 µL Locke's buffer (plus 20 mM Li⁺, pH 7.4) and incubated for 15 min at 37°C before replacement with agonists / antagonists in Locke's buffer. The incubation (45 min at 37 °C) was terminated by replacing the Locke's solutions with 100 µL 0.1 M HCl (10 min on ice). The 96 well plates can be frozen at -20°C at this stage until further analysis. Home made resin exchange columns (AG1-X8 Biorad, 140-14444) were used to separate labeled inositol phosphates by elution with 1 mL of 1 M ammonium formate / 0.1 M formic acid into 24-well visiplates (Perkin Elmer). Scintillation liquid (UltimaFlow AF, Perkin Elmer) was added, the plate sealed and vortexed before radioactivity was determined by conventional liquid scintillation counting (Microbeta, Perkin Elmer) as disintegration per minute (DPM).

Calcium FLIPR studies

[00181] Cultured astrocytes expressed mGluR5 receptors as shown by immunostaining. The increase of intracellular calcium after stimulation with the mGluR5 agonist DHPG or L-quisqualate was measured using the fluorometric imaging plate reader (FLIPR) and the Ca-Kit (both Molecular Devices, CA).

Prior to addition of agonist or antagonist the medium was aspirated and cells were loaded for 2 h at RT with 150 μ L of loading buffer consisting of Ca-sensitive dye (MD # R8033) reconstituted in sodium chloride (123 mM), potassium chloride (5.4 mM), magnesium chloride (0.8 mM), calcium chloride (1.8 mM), D-glucose (15 mM), and HEPES (20 mM), pH 7.3. Subsequently, plates were transferred to FLIPR to detect calcium increase with the addition of DHPG (300 μ M) or L-quisqualate (100 nM) measured as relative fluorescence units (RFU). If antagonists were tested, these compounds were pre-incubated for 10 min at RT before addition of the respective agonist.

10

[00182] For positive modulators, concentration-response curves for quisqualate were performed in the presence and absence of 10 μ M modulator to determine the extent of potentiation / agonist potency increase. Thereafter, concentration-response curves for the positive modulator were performed in the presence of a fixed concentration of quisqualate showing the biggest window for potentiation (normally 10-30 nM).

15

Data analysis

[00183] The fluorescence signal increase after addition of agonist reflects the increase of intracellular calcium. Inconsistencies in the amount of cells per well were normalised by using the spatial uniformity correction of the FLIPR software. The mean of replicated temporal data (n=5) was calculated and used for graphical representation. For the evaluation of the pharmacology, the calcium changes in response to different concentrations of agonist or antagonist were determined using a maximum minus minimum (MaxMin) calculation.

20

25

[00184] All responses (DPM- or RFU-values) were determined as percentage of control (= maximum response at 100 nM quisqualate).

EC₅₀ and IC₅₀ were calculated according the logistic equation using GraFit 5.0 (Erithacus Software).

30

Chemicals

[00185] Unless otherwise stated all chemicals were purchased from Sigma.

5 References

Booher and Sensenbrenner (1972) *Neurobiology* **2(3)**:97-105
Miller et al., (1993) *Brain Res.* **618(1)**:175-8

10 [00186] Compounds of the present invention have an EC₅₀ range of about 0.5 nM to about 100 μ M.

CONCLUSIONS

[00187] In conclusion, from the foregoing, it is apparent that the present invention provides novel, valuable, and unpredictable applications and uses of the compounds of the present invention, which compounds comprise the active principle according to the present invention, as well as novel pharmaceutical compositions thereof and methods of preparation thereof and of treating therewith, all possessed of the foregoing more specifically-enumerated characteristics and advantages.

20

[00188] The high order of activity of the active agent of the present invention and compositions thereof, as evidenced by the tests reported, is indicative of utility based on its valuable activity in human beings as well as in lower animals. Clinical evaluation in human beings has not been completed, however. It will be clearly understood that the distribution and marketing of any compound or composition falling within the scope of the present invention for use in human beings will of course have to be predicated upon prior approval by governmental agencies, such as the U.S. Federal Food and Drug Administration, which are responsible for and authorized to pass judgment on such questions.

30

[00189] The instant ethynyl-substituted tetrahydroquinolinone derivatives represent a novel class of Group I mGluR modulators. They are especially useful as mGluR 5 positive modulators or agonists. In view of their potency, they will be useful therapeutics in a wide range of CNS disorders which involve abnormal glutamate induced excitation.

[00190] These compounds accordingly find application in the treatment of the following disorders of a living animal body, especially a human: AIDS-related dementia, Alzheimer's disease, Creutzfeld-Jakob's syndrome, bovine spongiform encephalopathy (BSE) or other prion related infections, diseases involving mitochondrial dysfunction, diseases involving β -amyloid and/or tauopathy such as Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), olivoponto-cerebellar atrophy, post-operative cognitive deficit (POCD), Parkinson's disease, Parkinson's dementia, mild cognitive impairment, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, eye injuries or diseases (e.g. glaucoma, retinopathy, macular degeneration), head and spinal cord injuries / trauma, hypoglycaemia, hypoxia (e.g. perinatal), ischaemia (e.g. resulting from cardiac arrest, stroke, bypass operations or transplants), convulsions, glioma and other tumours, inner ear insult (e.g. in tinnitus, sound or drug-induced), L-dopa-induced and tardive dyskinesias.

[00191] These compounds also find application in the treatment of the following disorders of a living animal body, especially a human: addiction (nicotine, alcohol, opiate, cocaine, amphetamine, obesity and others), amyotrophic lateral sclerosis (ALS), anxiety and panic disorders, attention deficit hyperactivity disorder (ADHD), restless leg syndrome and hyperactive children, autism, convulsions / epilepsy, dementia (e.g. in Alzheimer's disease, Korsakoff syndrome, vascular dementia, HIV infections), major depressive disorder or depression (including that resulting from Borna virus infection) and bipolar manic-depressive disorder, drug tolerance e.g. to opioids, movement disorders, dystonia, dyskinesia (e.g. L-Dopa-induced,

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5 tardive dyskinesia or in Huntington's disease), fragile-X syndrome, Huntington's chorea, irritable bowel syndrome (IBS), migraine, multiple sclerosis, muscle spasms, pain (chronic and acute, e.g. inflammatory pain, neuropathic pain, allodynia, hyperalgesia, nociceptive pain), Parkinson's
10 disease, post traumatic stress disorder, schizophrenia (positive and negative symptoms), spasticity, tinnitus, Tourette's syndrome, urinary incontinence and vomiting, pruritic conditions (e.g. pruritis), sleep disorders, micturition disorders, neuromuscular disorder in the lower urinary tract, gastroesophageal reflux disease (GERD), lower esophageal sphincter (LES),
15 functional gastrointestinal disorders, dyspepsia, regurgitation, respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma (e.g. reflux-related asthma), lung disease, eating disorders, obesity and obesity-related disorders.

20 [00192] These compounds also find application in the treatment of indications in of a living animal body, especially a human, wherein a particular condition does not necessarily exist but wherein a particular physiological parameter may be improved through administration of the instant compounds, including cognitive enhancement.

25 [00193] The method-of-treating a living animal body with a compound of the invention, for the inhibition of progression or alleviation of the selected ailment therein, is as previously stated by any normally-accepted pharmaceutical route, employing the selected dosage which is effective in the alleviation of the particular ailment desired to be alleviated.

30 [00194] Use of the compounds of the present invention in the manufacture of a medicament for the treatment of a living animal for inhibition of progression or alleviation of selected ailments or conditions, particularly ailments or conditions susceptible to treatment with a Group I mGluR modulator, in particular an mGluR 5 modulator, especially an mGluR 5

positive modulator or agonist, is carried out in the usual manner comprising the step of admixing an effective amount of a compound of the invention with a pharmaceutically-acceptable diluent, excipient, or carrier, and the method-of-treating, pharmaceutical compositions, and use of a compound of the
5 present invention in the manufacture of a medicament.

[00195] Representative pharmaceutical compositions prepared by admixing the active ingredient with a suitable pharmaceutically-acceptable excipient, diluent, or carrier, include tablets, capsules, solutions for injection,
10 liquid oral formulations, aerosol formulations, TDS formulations, and nanoparticle formulations, thus to produce medicaments for oral, injectable, or dermal use, also in accord with the foregoing.

* * * * *

15

[00196] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description.

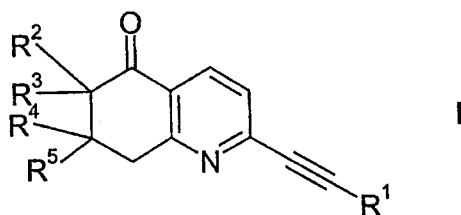
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[00197] All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference.

CLAIMS

We claim: -

- 5 1. A compound of Formula I



wherein

10

R¹ represents aryl or heteroaryl;

R² and R³, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

15

R⁴ and R⁵, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

it being understood that:

20

aryl represents an unsubstituted phenyl ring or a phenyl ring that is substituted with 1, 2, 3, 4 or 5 substituents, that may be the same or different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholinyl, 4-C₁₋₆alkyl-piperazinyl, tetrazolyl, oxazolyl, furyl, pyrrolyl, thiophenyl,

25

isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and phenyl;

heteroaryl represents a (hetero)aromatic 5-, 6- or 7-membered ring
 5 having from 1 to 4 heteroatoms said heteroatoms being independently
 selected from oxygen, nitrogen and sulfur, wherein said ring is
 unsubstituted or substituted with 1, 2 or 3 substituents, that may be the
 same or different, which substituents are selected from the group
 consisting of C₁₋₆alkyl, which is optionally substituted with one or more
 10 fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally
 substituted with one or more fluorine, chlorine or bromine atoms,
 cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino,
 N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidinyl, piperidinyl,
 morpholinyl, 4-C₁₋₆alkyl-piperazinyl, tetrazolyl, oxazolyl, furyl, pyrrolyl,
 15 thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl,
 pyrimidyl and phenyl;

and that the compounds of Formula I may not represent:

20 2-Phenylethynyl-7,8-dihydro-6H-quinolin-5-one
 2-Pyridin-3-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 2-m-Tolylethynyl-7,8-dihydro-6H-quinolin-5-one
 2-(3-Hydroxy-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
 2-(3-Methoxy-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
 25 2-(3-Fluoro-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
 2-(3-Chloro-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
 2-(3-Bromo-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
 3-(5-Oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile
 2-Thiazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 30 2-Oxazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 7,7-Dimethyl-2-pyridin-3-ylethynyl-7,8-dihydro-6H-quinolin-5-one
 7,7-Dimethyl-2-m-tolylethynyl-7,8-dihydro-6H-quinolin-5-one

- 2-(3-Hydroxy-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
- 2-(3-Methoxy-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
- 5 2-(3-Fluoro-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
- 2-(3-Chloro-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
- 2-(3-Bromo-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
- 3-(7,7-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile
- 10 7,7-Dimethyl-2-thiazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
- 7,7-Dimethyl-2-oxazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
- 2-(2-Phenyl-oxazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one or
- 2-(2-Phenyl-thiazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one;
- 15 and optical isomers, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof.
2. A compound according to Claim 1, wherein
- R^2 and R^3 , which may be the same or different, represent methyl, ethyl,
- 20 n-propyl, 2-propyl, n-butyl or tert-butyl and
- R^4 and R^5 represent hydrogen.
3. A compound according to Claim 1, wherein
- R^2 and R^3 represent hydrogen and
- 25 R^4 and R^5 , which may be the same or different, represent methyl, ethyl, n-propyl, 2-propyl, n-butyl or tert-butyl.
4. A compound according to Claim 1, wherein
- R^2 , R^3 , R^4 and R^5 , which may be the same or different represent
- 30 hydrogen, methyl or ethyl.
5. A compound according to any one of the preceding claims, wherein R^1 represents aryl;

it being understood that:

5 aryl represents unsubstituted phenyl or phenyl which is mono- or di-substituted with the same or different substituents which are selected from the group consisting of methyl, ethyl, n-propyl, 2-propyl, n-butyl, tert-butyl, hydroxyl, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, CF₃, CH₂F, CH₂Cl, C₂F₅, OCF₃, OC₂F₅, F, Cl, Br, CN, piperidinyl, morpholinyl, tetrazolyl, oxazolyl, furyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and phenyl.

6. A compound according to Claim 5, wherein aryl represents unsubstituted phenyl or phenyl that is mono- or di-substituted bearing the substituent(s) in the meta-position.

15 7. A compound according to any one of Claims 1 to 4, wherein R¹ represents heteroaryl;

it being understood that:

20 heteroaryl represents pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, oxazol-5-yl, thiazol-5-yl, wherein each of these rings may be unsubstituted or mono or di-substituted with phenyl, methyl, ethyl, n-propyl, 2-propyl, n-butyl, tert-butyl, hydroxyl, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, CF₃, CH₂F, CH₂Cl, C₂F₅, OCF₃, OC₂F₅, F, Cl, Br, CN, piperidinyl, morpholinyl, tetrazolyl, oxazolyl, furyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl or pyrimidyl.

8. A compound according to Claim 1 which is selected from:
30 6,6-Dimethyl-2-pyridin-3-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
2-(3-Fluoro-phenylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one,
2-(3-Chloro-phenylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one,

- 2-(3-Methoxy-phenylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one,
2-(3-Hydroxy-phenylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one,
5 3-(6,6-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile,
6,6-Dimethyl-2-thiazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
6,6-Dimethyl-2-(3-piperidin-1-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one,
10 7,7-Dimethyl-2-(3-piperidin-1-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one,
2-(3-Piperidin-1-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one,
2-(3-Morpholin-4-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one,
7,7-Dimethyl-2-(3-morpholin-4-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one,
15 6,6-Dimethyl-2-(3-morpholin-4-yl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one,
6,6-Dimethyl-2-[3-(1H-tetrazol-5-yl)-phenylethynyl]-7,8-dihydro-6H-quinolin-5-one,
20 7,7-Dimethyl-2-[3-(1H-tetrazol-5-yl)-phenylethynyl]-7,8-dihydro-6H-quinolin-5-one,
2-[3-(1H-Tetrazol-5-yl)-phenylethynyl]-7,8-dihydro-6H-quinolin-5-one,
2-[3-Fluoro-5-(1H-tetrazol-5-yl)-phenylethynyl]-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one,
25 2-[3-Fluoro-5-(1H-tetrazol-5-yl)-phenylethynyl]-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one,
2-[3-Fluoro-5-(1H-tetrazol-5-yl)-phenylethynyl]-7,8-dihydro-6H-quinolin-5-one,
2-(3-Trifluoromethyl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one,
30 7,7-Dimethyl-2-(3-trifluoromethyl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one,
6,6-Dimethyl-2-(3-trifluoromethyl-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one,

- 7,7-Dimethyl-2-phenylethynyl-7,8-dihydro-6H-quinolin-5-one,
6,6-Dimethyl-2-phenylethynyl-7,8-dihydro-6H-quinolin-5-one,
2-(4-Methyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
7,7-Dimethyl-2-(4-methyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-
5 one,
6,6-Dimethyl-2-(4-methyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-
one,
2-(4-Fluoro-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
2-(4-Fluoro-thiazol-2-ylethynyl)-7, 7-dimethyl-7,8-dihydro-6H-quinolin-5-
10 one,
2-(4-Fluoro-thiazol-2-ylethynyl)-6, 6-dimethyl-7,8-dihydro-6H-quinolin-5-
one,
2-(2-Phenyl-thiazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
2-(5-Fluoro-pyridin-3-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
15 3-Fluoro-5-(7,7-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-
benzonitrile,
2-(4-Fluoro-5-phenyl-oxazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-
one,
2-(4-Fluoro-5-pyridin-3-yl-oxazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-
20 5-one,
2-(4-Fluoro-5-pyridin-3-yl-oxazol-2-ylethynyl)-7,7-dimethyl-7,8-dihydro-
6H-quinolin-5-one,
2-(4-Fluoro-5-pyridin-3-yl-oxazol-2-ylethynyl)-6,6-dimethyl-7,8-dihydro-
6H-quinolin-5-one,
25 7,7-Dimethyl-2-pyridin-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
2-Pyridin-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
6,6-Dimethyl-2-pyridin-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
6,6-Dimethyl-2-(4-methyl-oxazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-
one,
30 7,7-Dimethyl-2-(4-methyl-oxazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-
one,
2-(4-Fluoro-5-pyridin-3-yl-1H-imidazol-2-ylethynyl)-7,8-dihydro-6H-
quinolin-5-one,

- 2-(4-Fluoro-5-pyridin-3-yl-1H-imidazol-2-ylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one,
2-(4-Fluoro-5-pyridin-3-yl-1H-imidazol-2-ylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one,
5 6,6-Dimethyl-2-(4-pyridin-3-yl-imidazol-1-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
7,7-Dimethyl-2-(4-pyridin-3-yl-imidazol-1-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
2-(4-Pyridin-3-yl-imidazol-1-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
10 2-Thiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
2-[1,3,4]Thiadiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
2-[1,3,4]Oxadiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
2-(1H-Tetrazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
6,6-Dimethyl-2-[1,3,4]thiadiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
15 one,
7,7-Dimethyl-2-[1,3,4]thiadiazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
7,7-Dimethyl-2-(1H-tetrazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
6,6-Dimethyl-2-(1H-tetrazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
20 6,6-Dimethyl-2-oxazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
2-Oxazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
6,6-Dimethyl-2-oxazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
7,7-Dimethyl-2-oxazol-2-ylethynyl-7,8-dihydro-6H-quinolin-5-one,
6,6-Dimethyl-2-m-tolyethynyl-7,8-dihydro-6H-quinolin-5-one,
25 7,7-Dimethyl-2-(2-phenyl-oxazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
6,6-Dimethyl-2-(2-phenyl-oxazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
7,7-Dimethyl-2-(5-phenyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
30 one,
6,6-Dimethyl-2-(5-phenyl-thiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,
one,

2-(5-Fluoro-pyridin-3-ylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one,

2-(5-Fluoro-pyridin-3-ylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one,

5 3-Fluoro-5-(5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile,
3-(6,6-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-5-fluoro-benzonitrile,

2-(4-Fluoro-5-phenyl-oxazol-2-ylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one,

10 2-(4-Fluoro-5-phenyl-oxazol-2-ylethynyl)-6,6-dimethyl-7,8-dihydro-6H-quinolin-5-one,

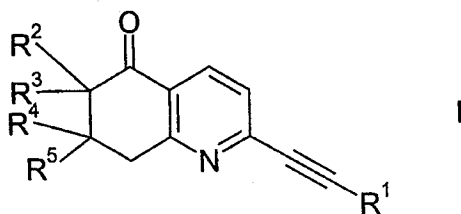
6,6-Dimethyl-2-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,

7,7-Dimethyl-2-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,

15 2-(5-Pyridin-3-yl-[1,3,4]oxadiazol-2-ylethynyl)-7,8-dihydro-6H-quinolin-5-one,

and optical isomers, pharmaceutically acceptable salts, hydrates,
20 solvates and polymorphs thereof.

9. A medicament comprising at least one of the compounds of Formula I



wherein

25

R¹ represents aryl or heteroaryl;

R² and R³, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

R⁴ and R⁵, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

5 it being understood that:

aryl represents an unsubstituted phenyl ring or a phenyl ring that is substituted with 1, 2, 3, 4 or 5 substituents, that may be the same of different, which substituents are selected from the group consisting of
10 C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholinyl, 4-C₁₋₆
15 alkyl-piperazinyl, tetrazolyl, oxazolyl, furyl, pyrrolyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and phenyl;

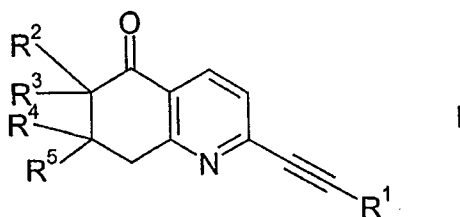
heteroaryl represents a (hetero)aromatic 5-, 6- or 7-membered ring
20 having from 1 to 4 heteroatoms said heteroatoms being independently selected from oxygen, nitrogen and sulfur, wherein said ring is unsubstituted or substituted with 1, 2 or 3 substituents, that may be the same or different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more
25 fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholinyl, 4-C₁₋₆alkyl-piperazinyl, tetrazolyl, oxazolyl, furyl, pyrrolyl,
30 thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and phenyl;

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and optical isomers, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

- 5 with the exception of the following compounds and optical isomers, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof:
- 2-Phenylethynyl-7,8-dihydro-6H-quinolin-5-one
2-Pyridin-3-ylethynyl-7,8-dihydro-6H-quinolin-5-one
2-m-Tolyethynyl-7,8-dihydro-6H-quinolin-5-one
10 2-(3-Hydroxy-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
2-(3-Methoxy-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
2-(3-Fluoro-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
2-(3-Chloro-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
2-(3-Bromo-phenylethynyl)-7,8-dihydro-6H-quinolin-5-one
15 3-(5-Oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile
2-Thiazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
2-Oxazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
7,7-Dimethyl-2-pyridin-3-ylethynyl-7,8-dihydro-6H-quinolin-5-one
7,7-Dimethyl-2-m-tolyethynyl-7,8-dihydro-6H-quinolin-5-one
20 2-(3-Hydroxy-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
2-(3-Methoxy-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
2-(3-Fluoro-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
25 2-(3-Chloro-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
2-(3-Bromo-phenylethynyl)-7,7-dimethyl-7,8-dihydro-6H-quinolin-5-one
3-(7,7-Dimethyl-5-oxo-5,6,7,8-tetrahydro-quinolin-2-ylethynyl)-benzonitrile
7,7-Dimethyl-2-thiazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
30 7,7-Dimethyl-2-oxazol-5-ylethynyl-7,8-dihydro-6H-quinolin-5-one
2-(2-Phenyl-oxazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one and
2-(2-Phenyl-thiazol-5-ylethynyl)-7,8-dihydro-6H-quinolin-5-one.

10. Use of a compound of Formula I



wherein

5 R^1 represents aryl or heteroaryl;

R^2 and R^3 , which may be the same or different, represent hydrogen or C_{1-6} alkyl;

10 R^4 and R^5 , which may be the same or different, represent hydrogen or C_{1-6} alkyl;

it being understood that:

15 aryl represents an unsubstituted phenyl ring or a phenyl ring that is substituted with 1, 2, 3, 4 or 5 substituents, that may be the same or different, which substituents are selected from the group consisting of C_{1-6} alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C_{1-6} alkoxy, which is optionally substituted
 20 with one or more fluorine, chlorine or bromine atoms, cyclo C_{3-12} alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di- C_{1-6} alkylamino, N-cyclo C_{3-12} alkyl-N- C_{1-6} alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholinyl, 4- C_{1-6} alkyl-piperazinyl, tetrazolyl, oxazolyl, furyl, pyrrolyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and
 25 phenyl;

heteroaryl represents a (hetero)aromatic 5-, 6- or 7-membered ring having from 1 to 4 heteroatoms said heteroatoms being independently selected from oxygen, nitrogen and sulfur, wherein said ring is

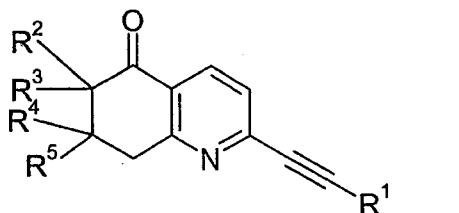
unsubstituted or substituted with 1, 2 or 3 substituents, that may be the same or different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholinyl, 4-C₁₋₆alkyl-piperaziny, tetrazolyl, oxazolyl, furyl, pyrrolyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridiny, pyrimidyl and phenyl;

and optical isomers, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

for the manufacturing of a medicament for the prevention and/or treatment of a condition or disease in an animal including a human being which condition or disease is affected or facilitated by the modulatory effect of mGluR5 modulators.

11. Use according to Claim 10, wherein the mGluR5 modulators are positive mGluR5 modulators or mGluR5 agonists.

12. Use of a compound of Formula I



wherein

R¹ represents aryl or heteroaryl;

R² and R³, which may be the same or different, represent hydrogen or

C₁₋₆alkyl;

R⁴ and R⁵, which may be the same or different, represent hydrogen or C₁₋₆alkyl;

5

it being understood that:

10

aryl represents an unsubstituted phenyl ring or a phenyl ring that is substituted with 1, 2, 3, 4 or 5 substituents, that may be the same or different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholiny, 4-C₁₋₆alkyl-piperaziny, tetrazoly, oxazolyl, furyl, pyrrolyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridiny, pyrimidyl and phenyl;

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20

heteroaryl represents a (hetero)aromatic 5-, 6- or 7-membered ring having from 1 to 4 heteroatoms said heteroatoms being independently selected from oxygen, nitrogen and sulfur, wherein said ring is unsubstituted or substituted with 1, 2 or 3 substituents, that may be the same or different, which substituents are selected from the group consisting of C₁₋₆alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C₁₋₆alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC₃₋₁₂alkyl, hydroxyl, F, Cl, Br, I, CN, nitro, di-C₁₋₆alkylamino, N-cycloC₃₋₁₂alkyl-N-C₁₋₆alkylamino, azetidiny, pyrrolidiny, piperidiny, morpholiny, 4-C₁₋₆alkyl-piperaziny, tetrazoly, oxazolyl, furyl, pyrrolyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridiny, pyrimidyl and phenyl;

25

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and optical isomers, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

5 for the manufacturing of a medicament for the prevention and/or treatment of AIDS-related dementia, Alzheimer's disease, Creutzfeld-Jakob's syndrome, bovine spongiform encephalopathy (BSE) or other prion related infections, diseases involving mitochondrial dysfunction, diseases involving β -amyloid and/or tauopathy such as Down's syndrome, hepatic encephalopathy, Huntington's disease, motor
10 neuron diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), olivoponto-cerebellar atrophy, post-operative cognitive deficit (POCD), Parkinson's disease, Parkinson's dementia, mild cognitive impairment, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, eye injuries or diseases (e.g.
15 glaucoma, retinopathy, macular degeneration), head and spinal cord injuries / trauma, hypoglycaemia, hypoxia (e.g. perinatal), ischaemia (e.g. resulting from cardiac arrest, stroke, bypass operations or transplants), convulsions, glioma and other tumours, inner ear insult (e.g. in tinnitus, sound or drug-induced), L-dopa-induced and tardive
20 dyskinesias, addiction (nicotine, alcohol, opiate, cocaine, amphetamine, obesity and others), anxiety and panic disorders, attention deficit hyperactivity disorder (ADHD), restless leg syndrome and hyperactive children, autism, convulsions / epilepsy, dementia (e.g. in Alzheimer's disease, Korsakoff syndrome, vascular dementia, HIV
25 infections), major depressive disorder or depression (including that resulting from Borna virus infection) and bipolar manic-depressive disorder, drug tolerance e.g. to opioids, movement disorders, dystonia, dyskinesia (e.g. L-Dopa-induced, tardive dyskinesia or in Huntington's disease), fragile-X syndrome, Huntington's chorea, irritable bowel
30 syndrome (IBS), migraine, multiple sclerosis, muscle spasms, pain (chronic and acute, e.g. inflammatory pain, neuropathic pain, allodynia, hyperalgesia, nociceptive pain), Parkinson's disease, post traumatic stress disorder, schizophrenia (positive and negative symptoms),

- 5 spasticity, Tourette's syndrome, urinary incontinence and vomiting,
pruritic conditions (e.g. pruritis), sleep disorders, micturition disorders,
neuromuscular disorder in the lower urinary tract, gastroesophageal
reflux disease (GERD), lower esophageal sphincter (LES), functional
gastrointestinal disorders, dyspepsia, regurgitation, respiratory tract
infection, bulimia nervosa, chronic laryngitis, asthma (e.g. reflux-related
asthma), lung disease, eating disorders, obesity and obesity-related
disorders, agoraphobia, generalized anxiety disorder, obsessive-
compulsive disorder, panic disorder, posttraumatic stress disorder,
10 social phobia, substance-induced anxiety disorder, delusional disorder,
schizoaffective disorder, schizophreniform disorder, substance-induced
psychotic disorder, delirium, or for cognitive enhancement and/or
neuroprotection.
- 15 13. Use according to Claim 12, wherein the medicament is for the
prevention and/or treatment of addiction, neuropathic pain, L-dopa-
induced and tardive dyskinesias, ALS, fragile-X syndrome, Parkinson's
disease, anxiety disorders, epilepsy, positive and/or negative
symptoms of schizophrenia, cognitive impairment, or for cognitive
20 enhancement and/or neuroprotection.
14. A pharmaceutical composition comprising as active ingredient a
compound of Claim 1 together with one or more pharmaceutically
acceptable excipients or vehicles.

25

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2006/003170

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D215/00 A61K31/4709 A61P25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/28837 A (JANSSEN PHARMACEUTICA N.V.; MABIRE, DOMINIQUE, JEAN-PIERRE; VENET, MARC) 11 April 2002 (2002-04-11) claim 1	1-14
A	SCHOEPP D D ET AL: "Pharmacological agents acting at subtypes of metabotropic glutamate receptors" NEUROPHARMACOLOGY, PERGAMON PRESS, OXFORD, GB, vol. 38, no. 10, 1999, pages 1431-1476, XP002345330 ISSN: 0028-3908 the whole document	1-14

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

17 November 2006

Date of mailing of the international search report

01/12/2006

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Wolf, Claudia

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2006/003170

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TETRAHIDROQUINOLINONAS Y SU USO COMO MODULADORES DE

RECEPTORES DE GLUTAMATO METABOTRÓPICOS

CAMPO DE LA INVENCION

[0001] La presente invención se relaciona con nuevos moduladores del receptor de glutamato metabotrópico (mGluR), con métodos para sintetizarlos, y con el tratamiento y/o la prevención de trastornos neurológicos mediante la administración de estas sustancias.

ANTECEDENTES DE LA INVENCION

[0002] Los estímulos neuronales son transmitidos por el sistema nervioso central (CNS) a través de la interacción de un neurotransmisor liberado por una neurona, donde el neurotransmisor presenta un efecto específico sobre un neuroreceptor en otra neurona.

[0003] Se considera que el ácido L-glutámico es el neurotransmisor de mayor capacidad excitativa en el CNS de los mamíferos, por lo que tiene una participación crítica en una gran cantidad de procesos fisiológicos. Los receptores de estímulos dependientes de glutamato se dividen en dos grupos principales. El primer grupo comprende canales de iones controlados por ligandos, mientras que el segundo grupo comprende receptores de glutamato metabotrópicos (mGluR). Los receptores de glutamato metabotrópicos son una subfamilia de los receptores unidos a proteína G (GPCR). Existe una evidencia creciente de una función periférica de los receptores de glutamato ionotrópicos y metabotrópicos fuera del CNS, por ejemplo, en estados de dolor crónico.

[0004] En la actualidad, se conocen ocho miembros diferentes de estos mGluR. Sobre la base de parámetros estructurales, tales como la homología de secuencia, el sistema de segundo mensajero utilizado por estos receptores y

su afinidad diferente con compuestos de bajo peso molecular, estos ocho receptores pueden dividirse en tres grupos: mGluR1 y mGluR5 pertenecen al grupo I, cuyos miembros se unen a la fosfolipasa C y cuya activación conduce a la movilización de iones de calcio intracelulares. mGluR2 y mGluR3 pertenecen al grupo II, y mGluR4, mGluR6, mGluR7 y mGluR8 pertenecen al grupo III, cuyos miembros se une a la adenil ciclasa, y cuya activación provoca una reducción en el APMc segundo mensajero, lo que provoca una atenuación de la actividad neuronal.

[0005] Se ha demostrado que los moduladores de mGluR del Grupo I modulan los efectos del neurotransmisor glutamato liberado antes de la sinapsis mediante mecanismos post-sinápticos. Más aún, como estos moduladores pueden ser moduladores de mGluR del Grupo I positivos y/o negativos, estos moduladores pueden incrementar o inhibir los efectos de estos receptores metabotrópicos. Como se cree que una variedad de procesos patofisiológicos y estados de enfermedad que afectan el CNS se relacionan con la neurotransmisión anormal de glutamato, y se ha demostrado que los mGluR del Grupo I se expresan en diversas áreas del CNS, los moduladores de estos receptores podrían presentar un beneficio terapéutico en el tratamiento de las enfermedades del CNS.

[0006] Por consiguiente, es posible administrar moduladores de mGluR del Grupo I para proporcionar neuroprotección en condiciones patológicas agudas y crónicas, tales como: demencia relacionada con SIDA, enfermedad de Alzheimer, síndrome de Creutzfeld-Jakob, encefalopatía espongiforme bovina (BSE) u otras infecciones relacionadas con priones, enfermedades que comprenden la disfunción mitocondrial, enfermedades que comprenden β

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amiloides y/o tauopatía, tales como síndrome de Down, encefalopatía hepática, enfermedad de Huntington, enfermedades de las neuronas motoras, tales como esclerosis lateral amiotrófica (ALS), esclerosis múltiple (MS), atrofia olivoponto-cerebelar, déficit cognitivo post-operatorio (POCD), enfermedad de Parkinson, demencia de Parkinson, alteración cognitiva leve, demencia pugilística, demencia vascular y del lóbulo frontal, alteración cognitiva, lesiones o enfermedades oculares (por ejemplo, glaucoma, retinopatía, degeneración macular), lesiones/traumas cefálicos y espinales, hipoglucemia, hipoxia (por ejemplo, perinatal), isquemia (por ejemplo, como resultado de una detención del corazón, apoplejía, operaciones de bypass o trasplantes), convulsiones, glioma y otros tumores, lesiones en el oído interno (por ejemplo, en el tinitus, inducido por sonido o drogas), discinecias inducidas por L-dopa y tardías.

[0007] Otras indicaciones en este contexto incluyen un efecto sintomatológico de las siguientes condiciones: adicción (nicotina, alcohol, opiáceos, cocaína, anfetaminas, obesidad y otras), esclerosis lateral amiotrófica (ALS), trastornos de ansiedad y pánico, trastorno de hiperactividad con déficit de atención (ADHD), síndrome de piernas inquietas y niños hiperactivos, autismo, convulsiones/epilepsia, demencia (por ejemplo, en la enfermedad de Alzheimer, el síndrome de Korsakoff, la demencia vascular, las infecciones de HIV), trastorno depresivo mayor o depresión (incluyendo la que resulta de una infección del virus Borna) y trastorno bipolar maniaco-depresivo, tolerancia a drogas, por ejemplo, a opiáceos, trastornos del movimiento, distonia, discinesia (por ejemplo, inducida por L-Dopa, discinesia tardía o en la enfermedad de Huntington), síndrome de X frágil, corea de Huntington, síndrome de intestino irritable (IBS), migraña, esclerosis múltiple, espasmos musculares, dolor

(crónico y agudo, por ejemplo, dolor inflamatorio, dolor neuropático, alodinia, hiperalgesia, dolor nociceptivo), enfermedad de Parkinson, trastorno de estrés post-traumático, esquizofrenia (síntomas positivos y negativos), espasticidad, tinitus, síndrome de Tourette, incontinencia urinaria y vómitos, condiciones pruríticas (por ejemplo, pruritis), trastornos del sueño, trastornos de la micción, trastorno neuromuscular en el tracto urinario inferior, enfermedad de reflujo gastroesofágico (GERD), esfínter esofágico inferior (LES), trastornos gastrointestinales funcionales, dispepsia, regurgitación, infección del tracto respiratorio, bulimia nerviosa, laringitis crónica, asma (por ejemplo, asma relacionado con reflujo), enfermedad pulmonar, trastornos de la alimentación, obesidad y trastornos relacionados con la obesidad.

[0008] Aún otras indicaciones para los moduladores de mGluR del Grupo I incluyen aquellas indicaciones donde no existe una necesariamente una condición particular, sino que es posible mejorar un parámetro fisiológico particular mediante la administración de los presentes compuestos, por ejemplo, mejoramiento cognitivo.

[0009] Los moduladores positivos pueden ser particularmente útiles en el tratamiento de los síntomas positivos y negativos en la esquizofrenia, y los déficits cognitivos en diversas formas de demencia y alteración cognitiva leve.

[0010] Entre los moduladores de mGluR del Grupo I, aquellos que presentan un efecto modulador sobre los receptores mGluR5, por lo que pueden afectar condiciones o enfermedades asociadas con la función de aquellos receptores mGluR5, son de interés particular. Además de la utilidad de los moduladores de mGluR5 en la prevención y/o el tratamiento de las condiciones y/o las enfermedades mencionadas previamente, los moduladores positivos o los

agonistas de mGluR5 pueden ser particularmente útiles para prevenir y/o tratar condiciones o enfermedades asociadas con una estimulación o una actividad insuficiente de los receptores mGluR5. los moduladores de mGluR5, y los moduladores positivos o los agonistas de mGluR5, pueden ser particularmente útiles para prevenir y/o tratar la adicción, el dolor neuropático, las discinecias inducidas por L-dopa y tardías, la ALS, el síndrome de X frágil, la enfermedad de Parkinson, los trastornos de ansiedad, la epilepsia, los síntomas positivos y/o negativos de la esquizofrenia, la alteración cognitiva, o para el mejoramiento cognitivo y la neuroprotección.

LA PRESENTE INVENCION

[0011] Se ha determinado que determinadas tetrahydroquinolonas sustituidas con etinilo dentro del género de los compuestos descritos en la Solicitud de Patente Internacional copendiente N° PCT/GB2005/000717 son moduladores de mGluR del Grupo I, y en particular, moduladores de mGluR5. Por consiguiente, estas sustancias pueden presentar un beneficio terapéutico en el tratamiento de condiciones que comprenden la neurotransmisión anormal de glutamato, o donde la modulación de los receptores mGluR del Grupo I resulta en un beneficio terapéutico. Estas sustancias se administran preferiblemente bajo la forma de una composición farmacéutica, donde están presentes en combinación con uno o más diluyentes, vehículos o excipientes aceptables para el uso farmacéutico.

OBJETOS DE LA INVENCION

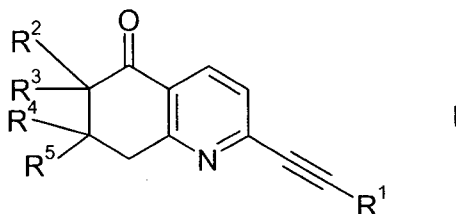
[0012] Un objeto de la presente invención es proporcionar nuevos compuestos farmacéuticos que son moduladores de tetrahydroquinolona de mGluR del Grupo I, y composiciones farmacéuticas que los contienen. Otro objeto de la

invención es proporcionar un nuevo método para tratar, eliminar, aliviar, paliar o mejorar trastornos indeseables del CNS, que comprenden la neurotransmisión anormal de glutamato, mediante el uso de un compuesto de la invención, o una composición farmacéutica que lo contiene. Otro objeto de la invención es la provisión de un proceso para producir los principios activos de tetrahydroquinolona. Aún otros objetos serán evidentes posteriormente en la presente documentación, y aún otros objetos serán evidentes para aquellos entrenados en la técnica.

RESUMEN DE LA INVENCION

[0013] Lo que se consideramos como objeto de nuestra invención, puede ser resumido, entre otros, en los siguientes términos:

[0014] Un compuesto de Fórmula I



donde

R¹ representa arilo o heteroarilo;

R² y R³, que pueden ser iguales o diferentes entre sí, representan hidrógeno o C₁₋₆alquilo;

R⁴ y R⁵, que pueden ser iguales o diferentes entre sí, representan hidrógeno o C₁₋₆alquilo;

entendiéndose que:

arilo representa un anillo fenilo no sustituido o un anillo fenilo que está sustituido con 1, 2, 3, 4 o 5 sustituyentes, que pueden ser iguales o

distintos entre sí, que se seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino, azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 4-C₁₋₆alquil-piperazinilo, tetrazolilo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo; heteroarilo representa un anillo (hetero)aromático de 5, 6 o 7 miembros con entre 1 y 4 heteroátomos donde dichos heteroátomos se seleccionan en forma independiente entre oxígeno, nitrógeno y azufre, donde dicho anillo no está sustituido o está sustituido con 1, 2 o 3 sustituyentes, que pueden ser iguales o diferentes entre sí, que se seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino, azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 4-C₁₋₆alquil-piperazinilo, tetrazolilo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo;

y que los compuestos de Fórmula I no pueden representar:

2-Feniletinil-7,8-dihidro-6H-quinolin-5-ona

2-Piridin-3-iletinil-7,8-dihidro-6H-quinolin-5-ona

2-m-Toliletinil-7,8-dihidro-6H-quinolin-5-ona

2-(3-Hidroxi-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Metoxi-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Fluoro-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Cloro-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Bromo-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 3-(5-Oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo
 2-Tiazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 2-Oxazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-piridin-3-iletinil-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-m-toliletinil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Hidroxi-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Metoxi-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Fluoro-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Cloro-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Bromo-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 3-(7,7-Dimetil-5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo
 7,7-Dimetil-2-tiazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-oxazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 2-(2-Fenil-oxazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona o
 2-(2-Fenil-tiazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona;

e isómeros ópticos, sales, hidratos, solvatos y polimorfos de éste aceptables para uso farmacéutico.

[0015] El compuesto de Fórmula I, donde

R^2 y R^3 , que pueden ser iguales o diferentes entre sí, representan metilo, etilo, n-propilo, 2-propilo, n-butilo o tert-butilo y

R^4 y R^5 representan hidrógeno.

[0016] El compuesto de Fórmula I, donde

R^2 y R^3 representan hidrógeno y

R^4 y R^5 , que pueden ser iguales o diferentes entre sí, representan metilo, etilo, n-propilo, 2-propilo, n-butilo o tert-butilo.

[0017] El compuesto de Fórmula I, donde

R^2 , R^3 , R^4 y R^5 , que pueden ser iguales o diferentes entre sí, representan hidrógeno, metilo o etilo.

[0018] El compuesto de Fórmula I, donde

R^1 representa arilo;

entendiéndose que:

arilo representa fenilo no sustituido o fenilo que esta mono o disustituido con sustituyentes iguales o diferentes entre sí que se seleccionan entre el grupo que consiste en metilo, etilo, n-propilo, 2-propilo, n-butilo, tert-butilo, hidroxilo, metoxi, etoxi, n-propoxi, iso-propoxi, n-butoxi, tert-butoxi, CF_3 , CH_2F , CH_2F , C_2F_5 , OCF_3 , OC_2F_5 , F, Cl, Br, CN, piperidinilo, morfolinilo, tetrazolilo, oxazolilo, furilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo.

[0019] En este compuesto de fórmula I, arilo representa fenilo no sustituido o un anillo de fenilo que está mono o disustituido con el o los sustituyentes en la posición meta.

[0020] En este compuesto de fórmula I, el anillo de fenilo está disustituido en la posición meta, y los sustituyentes son diferentes.

[0021] En este compuesto de fórmula I, los sustituyentes se seleccionan entre F, CN, piridinilo, tetrazolilo y fenilo no sustituido.

[0022] El compuesto de Fórmula I, donde

R^1 representa heteroarilo;

entendiéndose que:

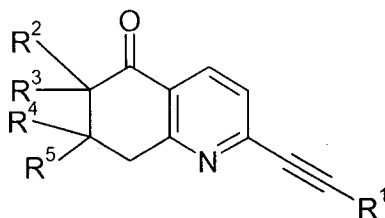
heteroarilo representa piridin-2-ilo, piridin-3-ilo, piridin-4-ilo, oxazol-5-ilo, tiazol-5-ilo, donde cada uno de estos anillos puede no estar sustituido o estar mono o disustituido con fenilo, metilo, etilo, n-propilo, 2-propilo, n-butilo, tert-butilo, hidroxilo, metoxi, etoxi, n-propoxi, iso-propoxi, n-butoxi, tert-butoxi, CF_3 , CH_2F , CH_2F , C_2F_5 , OCF_3 , OC_2F_5 , F, Cl, Br, CN, piperidinilo, morfolinilo, tetrazolilo, oxazolilo, furilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo o pirimidilo.

[0023] En este compuesto de fórmula I, heteroarilo representa heteroarilo no sustituido, o un anillo de heteroarilo que esta mono o disustituido con el o los sustituyentes en la posición meta.

[0024] En este compuesto de fórmula I, el anillo de heteroarilo está disustituido en la posición meta y los sustituyentes son diferentes.

[0025] En este compuesto de fórmula I, los sustituyentes se seleccionan entre F, CN, piridinilo, tetrazolilo y fenilo no sustituido.

[0026] Más aún, un método para tratar un animal vivo, incluyendo un ser humano human, por una condición o una enfermedad asociada con la neurotransmisión anormal de glutamato, o donde la modulación de los receptores mGluR del Grupo I resulta en un beneficio terapéutico, comprende el paso de administrarle al animal vivo, incluyendo un ser humano, una cantidad de un modulador de mGluR del Grupo I seleccionado entre aquellos de fórmula I



donde

R^1 representa arilo o heteroarilo;

R^2 y R^3 , que pueden ser iguales o diferentes entre sí, representan hidrógeno o C_{1-6} alquilo;

R^4 y R^5 , que pueden ser iguales o diferentes entre sí, representan hidrógeno o C_{1-6} alquilo;

entendiéndose que:

arilo representa un anillo fenilo no sustituido o un anillo fenilo que está sustituido con 1, 2, 3, 4 o 5 sustituyentes, que pueden ser iguales o distintos entre sí, que se seleccionan del grupo que consiste en C_{1-6} alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C_{1-6} alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, ciclo C_{3-12} alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di- C_{1-6} alquilamino, N-ciclo C_{3-12} alquil-N- C_{1-6} alquilamino, azetidino, pirrolidino, piperidino, morfolino, 4- C_{1-6} alquil-piperazino, tetrazolo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo; heteroarilo representa un anillo (hetero)aromático de 5, 6 o 7 miembros con entre 1 y 4 heteroátomos donde dichos heteroátomos se seleccionan en forma independiente entre oxígeno, nitrógeno y azufre, donde dicho anillo no está sustituido o está sustituido con 1, 2 o 3 sustituyentes, que pueden ser iguales o diferentes entre sí, que se

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seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N- C₁₋₆alquilamino, azetidino, pirrolidinilo, piperidinilo, morfolinilo, 4-C₁₋₆alquil-piperazinilo, tetrazolilo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo;

e isómeros ópticos, sales, hidratos, solvatos y polimorfos de éste aceptables para el uso farmacéutico;

que es efectivo para aliviar la condición o la enfermedad, o para mejorar la cognición.

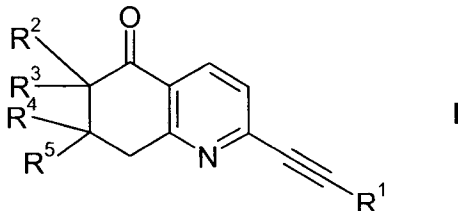
[0027] En este método, la condición asociada con la neurotransmisión anormal de glutamato, o donde la modulación de mGluR receptores resulta en un beneficio terapéutico, se selecciona entre: demencia relacionada con SIDA, enfermedad de Alzheimer, síndrome de Creutzfeld-Jakob, encefalopatía espongiiforme bovina (BSE) u otras infecciones relacionadas con priones, enfermedades que comprenden la disfunción mitocondrial, enfermedades que comprenden β amiloides y/o tauopatía, tales como síndrome de Down, encefalopatía hepática, enfermedad de Huntington, enfermedades de las neuronas motoras, tales como esclerosis lateral amiotrófica (ALS), esclerosis múltiple (MS), atrofia olivoponto-cerebelar, déficit cognitivo post-operatorio (POCD), enfermedad de Parkinson, demencia de Parkinson, alteración cognitiva leve, demencia pugilística, demencia vascular y del lóbulo frontal, alteración cognitiva, lesiones o enfermedades oculares (por ejemplo, glaucoma,

retinopatía, degeneración macular), lesiones/traumas cefálicos y espinales, hipoglucemia, hipoxia (por ejemplo, perinatal), isquemia (por ejemplo, como resultado de una detención del corazón, apoplejía, operaciones de bypass o transplantes), convulsiones, glioma y otros tumores, lesiones en el oído interno (por ejemplo, en el tinnitus, inducido por sonido o drogas), discinecias inducidas por L-dopa y tardías, adicción (nicotina, alcohol, opiáceos, cocaína, amfetaminas, obesidad y otras), trastornos de ansiedad y pánico, trastorno de hiperactividad con déficit de atención (ADHD), síndrome de piernas inquietas y niños hiperactivos, autismo, convulsiones/epilepsia, demencia (por ejemplo, en la enfermedad de Alzheimer, el síndrome de Korsakoff, la demencia vascular, las infecciones de HIV), trastorno depresivo mayor o depresión (incluyendo la que resulta de una infección del virus Borna) y trastorno bipolar maníaco-depresivo, tolerancia a drogas, por ejemplo, a opiáceos, trastornos del movimiento, distonia, discinesia (por ejemplo, inducida por L-Dopa, discinesia tardía o en la enfermedad de Huntington), síndrome de X frágil, corea de Huntington, síndrome de intestino irritable (IBS), migraña, esclerosis múltiple, espasmos musculares, dolor (crónico y agudo, por ejemplo, dolor inflamatorio, dolor neuropático, alodinia, hiperalgesia, dolor nociceptivo), enfermedad de Parkinson, trastorno de estrés post-traumático, esquizofrenia (síntomas positivos y negativos), espasticidad, síndrome de Tourette, incontinencia urinaria y vómitos, condiciones pruríticas (por ejemplo, pruritis), trastornos del sueño, trastornos de la micción, trastorno neuromuscular en el tracto urinario inferior, enfermedad de reflujo gastroesofágico (GERD), esfínter esofágico inferior (LES), trastornos gastrointestinales funcionales, dispepsia, regurgitación, infección del tracto respiratorio, bulimia nerviosa, laringitis

crónica, asma (por ejemplo, asma relacionado con reflujo), enfermedad pulmonar, trastornos de la alimentación, obesidad y trastornos relacionados con la obesidad, agorafobia, trastorno de ansiedad generalizada, trastorno obsesivo-compulsivo, trastorno de pánico, trastorno de estrés post-traumático, fobia social, trastorno de ansiedad inducida por sustancias, trastorno alucinatorio, trastorno esquizoafectivo, trastorno esquizofreniforme, trastorno psicótico inducido por sustancias, delirio, o para el mejoramiento cognitivo o la neuroprotección.

[0028] Un método tal que cuando el compuesto se administra en la forma de una composición farmacéutica del mismo que comprende el compuesto de Fórmula I en combinación con uno o más diluyentes, excipientes o vehículos aceptables para uso farmacéutico;

[0029] Además, el uso de al menos un compuesto de fórmula I



donde

R¹ representa arilo o heteroarilo;

R² y R³, que pueden ser iguales o diferentes entre sí, representan hidrógeno o

C₁₋₆alquilo;

R⁴ y R⁵, que pueden ser iguales o diferentes entre sí, representan hidrógeno o

C₁₋₆alquilo;

entendiéndose que:

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arilo representa un anillo fenilo no sustituido o un anillo fenilo que está sustituido con 1, 2, 3, 4 o 5 sustituyentes, que pueden ser iguales o distintos entre sí, que se seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino, azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 4-C₁₋₆alquil-piperazinilo, tetrazolilo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo;

heteroarilo representa un anillo (hetero)aromático de 5, 6 o 7 miembros con entre 1 y 4 heteroátomos donde dichos heteroátomos se seleccionan en forma independiente entre oxígeno, nitrógeno y azufre, donde dicho anillo no está sustituido o está sustituido con 1, 2 o 3 sustituyentes, que pueden ser iguales o diferentes entre sí, que se seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino, azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 4-C₁₋₆alquil-piperazinilo, tetrazolilo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo;

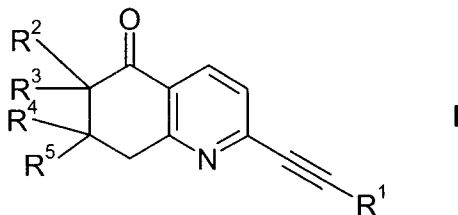
e isómeros ópticos, sales, hidratos, solvatos y polimorfos de éste aceptables para el uso farmacéutico;

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para fabricar un medicamento para la prevención y/o el tratamiento de una condición o una enfermedad, incluyendo un ser humano, donde la condición o la enfermedad es afectada o facilitada por el efecto modulador de los moduladores de mGluR1 del Grupo I, y en particular, de moduladores mGluR5.

[0030] Se ha descubierto que los compuestos de fórmula I, usados de acuerdo con la presente invención para fabricar un medicamento, son moduladores de receptores mGluR del Grupo I. En particular, estos compuestos son moduladores de receptores mGluR5. Sorprendentemente, se ha descubierto al menos que presentan efectos parcialmente agonísticos o moduladores positivos sobre los receptores mGluR5.

[0031] En consecuencia, un aspecto de la presente invención comprende el uso de uno o más compuestos de fórmula I



donde

R¹ representa arilo o heteroarilo;

R² y R³, que pueden ser iguales o diferentes entre sí, representan hidrógeno o C₁₋₆alquilo;

R⁴ y R⁵, que pueden ser iguales o diferentes entre sí, representan hidrógeno o C₁₋₆alquilo;

entendiéndose que:

arilo representa un anillo fenilo no sustituido o un anillo fenilo que está sustituido con 1, 2, 3, 4 o 5 sustituyentes, que pueden ser iguales o distintos entre sí, que se seleccionan del grupo que consiste en C₁.

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₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino, azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 4-C₁₋₆alquil-piperazinilo, tetrazolilo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo; heteroarilo representa un anillo (hetero)aromático de 5, 6 o 7 miembros con entre 1 y 4 heteroátomos donde dichos heteroátomos se seleccionan en forma independiente entre oxígeno, nitrógeno y azufre, donde dicho anillo no está sustituido o está sustituido con 1, 2 o 3 sustituyentes, que pueden ser iguales o diferentes entre sí, que se seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino, azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 4-C₁₋₆alquil-piperazinilo, tetrazolilo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo; e isómeros ópticos, sales, hidratos, solvatos y polimorfos de éste aceptables para el uso farmacéutico;

para fabricar de un medicamento para la prevención y/o el tratamiento de las siguientes condiciones: demencia relacionada con SIDA, enfermedad de Alzheimer, síndrome de Creutzfeld-Jakob, encefalopatía espongiforme bovina (BSE) u otras infecciones relacionadas con priones, enfermedades que


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comprenden la disfunción mitocondrial, enfermedades que comprenden β amiloides y/o tauopatía, tales como síndrome de Down, encefalopatía hepática, enfermedad de Huntington, enfermedades de las neuronas motoras, tales como esclerosis lateral amiotrófica (ALS), esclerosis múltiple (MS), atrofia olivoponto-cerebelar, déficit cognitivo post-operatorio (POCD), enfermedad de Parkinson, demencia de Parkinson, alteración cognitiva leve, demencia pugilística, demencia vascular y del lóbulo frontal, alteración cognitiva, lesiones o enfermedades oculares (por ejemplo, glaucoma, retinopatía, degeneración macular), lesiones/traumas cefálicos y espinales, hipoglucemia, hipoxia (por ejemplo, perinatal), isquemia (por ejemplo, como resultado de una detención del corazón, apoplejía, operaciones de bypass o transplantes), convulsiones, glioma y otros tumores, lesiones en el oído interno (por ejemplo, en el tinitus, inducido por sonido o drogas), discinesias inducidas por L-dopa y tardías, adicción (nicotina, alcohol, opiáceos, cocaína, anfetaminas, obesidad y otras), trastornos de ansiedad y pánico, trastorno de hiperactividad con déficit de atención (ADHD), síndrome de piernas inquietas y niños hiperactivos, autismo, convulsiones/epilepsia, demencia (por ejemplo, en la enfermedad de Alzheimer, el síndrome de Korsakoff, la demencia vascular, las infecciones de HIV), trastorno depresivo mayor o depresión (incluyendo la que resulta de una infección del virus Borna) y trastorno bipolar maniaco-depresivo, tolerancia a drogas, por ejemplo, a opiáceos, trastornos del movimiento, distonia, discinesia (por ejemplo, inducida por L-Dopa, discinesia tardía o en la enfermedad de Huntington), síndrome de X frágil, corea de Huntington, síndrome de intestino irritable (IBS), migraña, esclerosis múltiple, espasmos musculares, dolor (crónico y agudo, por ejemplo, dolor inflamatorio, dolor neuropático, alodinia,

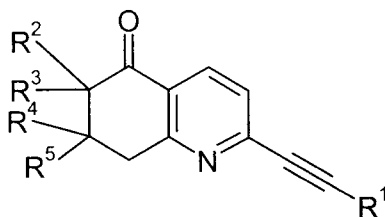
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hiperalgesia, dolor nociceptivo), enfermedad de Parkinson, trastorno de estrés post-traumático, esquizofrenia (síntomas positivos y negativos), espasticidad, síndrome de Tourette, incontinencia urinaria y vómitos, condiciones pruríticas (por ejemplo, pruritis), trastornos del sueño, trastornos de la micción, trastorno neuromuscular en el tracto urinario inferior, enfermedad de reflujo gastroesofágico (GERD), esfínter esofágico inferior (LES), trastornos gastrointestinales funcionales, dispepsia, regurgitación, infección del tracto respiratorio, bulimia nerviosa, laringitis crónica, asma (por ejemplo, asma relacionado con reflujo), enfermedad pulmonar, trastornos de la alimentación, obesidad y trastornos relacionados con la obesidad, agorafobia, trastorno de ansiedad generalizada, trastorno obsesivo-compulsivo, trastorno de pánico, trastorno de estrés post-traumático, fobia social, trastorno de ansiedad inducida por sustancias, trastorno alucinatorio, trastorno esquizoafectivo, trastorno esquizofreniforme, trastorno psicótico inducido por sustancias, delirio, o para el mejoramiento cognitivo o la neuroprotección.

[0032] Este medicamento sirve para la prevención y/o el tratamiento de adicción, dolor neuropático, discinecias inducidas por L-dopa y tardías, ALS, síndrome de X frágil, enfermedad de Parkinson, trastornos de ansiedad, epilepsia, los síntomas positivos y/o negativos de la esquizofrenia, alteración cognitiva, o para el mejoramiento cognitivo y la neuroprotection.

[0033] Además, una composición farmacéutica que comprende, junto con uno o más excipientes o vehículos aceptables para uso farmacéutico, un compuesto de Fórmula I

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donde

R^1 representa arilo o heteroarilo;

R^2 y R^3 , que pueden ser iguales o diferentes entre sí, representan hidrógeno o C_{1-6} alquilo;

R^4 y R^5 , que pueden ser iguales o diferentes entre sí, representan hidrógeno o C_{1-6} alquilo;

entendiéndose que:

arilo representa un anillo fenilo no sustituido o un anillo fenilo que está sustituido con 1, 2, 3, 4 o 5 sustituyentes, que pueden ser iguales o distintos entre sí, que se seleccionan del grupo que consiste en C_{1-6} alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C_{1-6} alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, ciclo C_{3-12} alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di- C_{1-6} alquilamino, N-ciclo C_{3-12} alquil-N- C_{1-6} alquilamino, azetidino, pirrolidino, piperidino, morfolino, 4- C_{1-6} alquil-piperazino, tetrazolo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo; heteroarilo representa un anillo (hetero)aromático de 5, 6 o 7 miembros con entre 1 y 4 heteroátomos donde dichos heteroátomos se seleccionan en forma independiente entre oxígeno, nitrógeno y azufre, donde dicho anillo no está sustituido o está sustituido con 1, 2 o 3 sustituyentes, que pueden ser iguales o diferentes entre sí, que se

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seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino, azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 4-C₁₋₆alquil-piperazinilo, tetrazolilo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo;

y que los compuestos de Fórmula I no pueden representar:

2-Feniletinil-7,8-dihidro-6H-quinolin-5-ona
 2-Piridin-3-iletinil-7,8-dihidro-6H-quinolin-5-ona
 2-m-Toliletinil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Hidroxi-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Metoxi-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Fluoro-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Cloro-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Bromo-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 3-(5-Oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo
 2-Tiazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 2-Oxazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-piridin-3-iletinil-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-m-toliletinil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Hidroxi-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Metoxi-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Fluoro-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona

2-(3-Cloro-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Bromo-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 3-(7,7-Dimetil-5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo
 7,7-Dimetil-2-tiazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-oxazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 2-(2-Fenil-oxazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona o
 2-(2-Fenil-tiazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona;

e isómeros ópticos, sales aceptables para uso farmacéutico, hidratos, solvatos y polimorfos del mismo.

[0034] Los compuestos de Fórmula I de la presente invención incluyen sin que esto constituya limitación alguna:

6,6-Dimetil-2-piridin-3-iletinil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Fluoro-feniletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Cloro-feniletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Metoxi-feniletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Hidroxi-feniletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona
 3-(6,6-Dimetil-5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo
 6,6-Dimetil-2-tiazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 6,6-Dimetil-2-(3-piperidin-1-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-(3-piperidin-1-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Piperidin-1-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Morfolin-4-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-(3-morfolin-4-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 6,6-Dimetil-2-(3-morfolin-4-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 6,6-Dimetil-2-[3-(1H-tetrazol-5-il)-feniletinil]-7,8-dihidro-6H-quinolin-5-ona

7,7-Dimetil-2-[3-(1H-tetrazol-5-il)-feniletinil]-7,8-dihidro-6H-quinolin-5-ona
 2-[3-(1H-Tetrazol-5-il)-feniletinil]-7,8-dihidro-6H-quinolin-5-ona
 2-[3-Fluoro-5-(1H-tetrazol-5-il)-feniletinil]-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-[3-Fluoro-5-(1H-tetrazol-5-il)-feniletinil]-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-[3-Fluoro-5-(1H-tetrazol-5-il)-feniletinil]-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Trifluorometil-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-(3-trifluorometil-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 6,6-Dimetil-2-(3-trifluorometil-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-feniletinil-7,8-dihidro-6H-quinolin-5-ona
 6,6-Dimetil-2-feniletinil-7,8-dihidro-6H-quinolin-5-ona
 2-(4-Metil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-(4-metil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 6,6-Dimetil-2-(4-metil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(4-Fluoro-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(4-Fluoro-tiazol-2-iletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(4-Fluoro-tiazol-2-iletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(2-Fenil-tiazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(5-Fluoro-piridin-3-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 3-Fluoro-5-(7,7-Dimetil-5-oxo-5,6,7,8-tetraidro-quinolin-2-iletinil)-benzonitrilo
 2-(4-Fluoro-5-fenil-oxazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(4-Fluoro-5-piridin-3-il-oxazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(4-Fluoro-5-piridin-3-il-oxazol-2-iletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona

2-(4-Fluoro-5-piridin-3-il-oxazol-2-iletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona
7,7-Dimetil-2-piridin-2-iletinil-7,8-dihidro-6H-quinolin-5-ona
2-Piridin-2-iletinil-7,8-dihidro-6H-quinolin-5-ona
6,6-Dimetil-2-piridin-2-iletinil-7,8-dihidro-6H-quinolin-5-ona
6,6-Dimetil-2-(4-metil-oxazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona
7,7-Dimetil-2-(4-metil-oxazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona
2-(4-Fluoro-5-piridin-3-il-1H-imidazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona
2-(4-Fluoro-5-piridin-3-il-1H-imidazol-2-iletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
2-(4-Fluoro-5-piridin-3-il-1H-imidazol-2-iletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona
6,6-Dimetil-2-(4-piridin-3-il-imidazol-1-iletinil)-7,8-dihidro-6H-quinolin-5-ona
7,7-Dimetil-2-(4-piridin-3-il-imidazol-1-iletinil)-7,8-dihidro-6H-quinolin-5-ona
2-(4-Piridin-3-il-imidazol-1-iletinil)-7,8-dihidro-6H-quinolin-5-ona
2-Tiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona
2-[1,3,4]Tiadiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona
2-[1,3,4]Oxadiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona
2-(1H-Tetrazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona
6,6-Dimetil-2-[1,3,4]tiadiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona
7,7-Dimetil-2-[1,3,4]tiadiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona
7,7-Dimetil-2-(1H-tetrazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona
6,6-Dimetil-2-(1H-tetrazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona
6,6-Dimetil-2-oxazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
2-Oxazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona

6,6-Dimetil-2-oxazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-oxazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona
 6,6-Dimetil-2-m-toliletinil-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-(2-fenil-oxazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 6,6-Dimetil-2-(2-fenil-oxazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-(5-fenil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 6,6-Dimetil-2-(5-fenil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(5-Fluoro-piridin-3-iletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(5-Fluoro-piridin-3-iletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona
 3-Fluoro-5-(5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo
 3-(6,6-Dimetil-5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-5-fluoro-benzonitrilo
 2-(4-Fluoro-5-fenil-oxazol-2-iletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(4-Fluoro-5-fenil-oxazol-2-iletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona
 6,6-Dimetil-2-(5-piridin-3-il-[1,3,4]oxadiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-(5-piridin-3-il-[1,3,4]oxadiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona

2-(5-Piridin-3-il-[1,3,4]oxadiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona
 e isómeros ópticos, sales, hidratos, solvatos y polimorfos de éste aceptables para el uso farmacéutico.

DESCRIPCIÓN DETALLADA DE LA INVENCION

[0035] Para el propósito de la presente invención, se indica el contenido de átomos de carbono de las diversas porciones que contienen hidrocarburos con un prefijo, que designa la cantidad mínima y máxima de átomos de carbono en la porción, es decir, el prefijo C_{i-j} designa una porción que contiene entre "i" e "j"

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(i y j son números enteros) átomos de carbono, inclusive. Por consiguiente, por ejemplo, un (C₁₋₃)alquilo designa un alquilo con entre uno y tres átomos de carbono, inclusive, (es decir, metilo, etilo, propilo e isopropilo), donde se abarcan las formas de cadenas rectas y ramificadas.

[0036] Como se lo usa en la presente documentación, el término "C₁₋₆alquilo" comprende grupos de cadena recta o ramificada que tienen 1, 2, 3, 4, 5 ó 6 átomos de carbono. Estos grupos alquilo pueden no estar sustituidos, e incluyen, por ejemplo, metilo, etilo, n-propilo, 2-propilo, n-butilo, ter-butilo. Además, estos grupos alquilo pueden estar opcionalmente sustituidos con uno o más átomos de flúor, cloro y/o bromo; los ejemplos de estas porciones de alquilo halogenado incluyen -CF₃, -C₂F₅, -CBr₃, y -CCl₃. El término "C₁₋₆alcoxilo" comprende grupos -O-C₁₋₆alquilo de cadena recta o ramificada, donde "C₁₋₆alquilo" se define como se indicó previamente en la presente documentación. Los ejemplos de "C₁₋₆alcoxilo" incluyen metoxilo, etoxilo, n-propoxilo, i-propoxilo. Un grupo C₁₋₆alcoxilo puede estar opcionalmente sustituido con uno o más átomos de flúor, cloro y/o bromo, por lo que forma, por ejemplo, -OCF₃, -OC₂F₅, -CBr₃. El término "cicloC₃₋₁₂ alquilo" representa grupos alquilo monocíclicos, bicíclicos o tricíclicos que tienen 3, 4, 5, 6, 7, 8, 9, 10, 11 ó 12 átomos de carbono, e incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, biciclo[2,2,1]heptilo y adamantilo. Un grupo cicloC₃₋₁₂alquil puede estar opcionalmente sustituido con uno o más átomos de flúor, cloro y/o bromo. En el contexto de la presente invención, el término "di-C₁₋₆alquilamino" hace referencia a una porción de amino en la que el átomo de nitrógeno del grupo amino está sustituido con dos grupos C₁₋₆alquilo, que pueden ser iguales o diferentes, como se definió previamente. Los ejemplos de grupos di-

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C₁₋₆alquilamino incluyen dimetilamino, dietilamino y N-metil-N-isopropilamino. El término "N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino" comprende grupos amino en los que el átomo de nitrógeno está sustituido por un grupo C₁₋₆alquilo y un grupo N-cicloC₃₋₁₂alquilo. El grupo C₁₋₆alquilo y el grupo N-cicloC₃₋₁₂alquilo se definen como se indicó previamente en la presente documentación. El término "4-C₁₋₆alquil-piperazinilo" comprende radicales piperazinilo que tienen una porción C₁₋₆alquilo en el átomo de nitrógeno en la posición 4 del anillo de piperazina, donde dicho "C₁₋₆alquilo" tiene el mismo significado que se indicó previamente en la presente documentación. El término "anillo (hetero)aromático de 5, 6 ó 7 miembros" hace referencia a anillos heterocíclicos que tienen hasta 4 átomos de oxígeno, nitrógeno y/o azufre en el anillo que comprende 5, 6 ó 7 átomos de carbono y otros, donde dicho anillo heterocíclico es un sistema de anillos aromáticos. Los ejemplos de estos anillos (hetero)aromáticos de 5, 6 ó 7 miembros incluyen pirroles, oxazoles, tiofenos, furanos, isoxazoles, imidazoles, oxazoles, oxadiazoles, tiazoles, imidazolidinas, pirazoles, oxazolidinas, isoxazolidinas, tiazolidinas, piridinas, piridazinas, pirimidinas, pirazinas, azepinas no sustituidas o sustituidas apropiadamente. El término "halógeno" representa flúor, cloro, bromo e iodo.

[0037] Los compuestos de la presente invención se denominan de acuerdo con el sistema de nomenclatura IUPAC o CAS. Pueden usarse abreviaturas bien conocidas por aquellos entrenados en la técnica (por ejemplo, "Ph" para fenilo, "Me" para metilo, "Et" para etilo, "h" para hora u horas, y "rt" para temperatura ambiente).

[0038] El término "análogo" o "derivado" se usa en la presente documentación en el sentido farmacéutico convencional, para designar una molécula que

presenta una similitud estructural con una molécula de referencia (tal como 7,8-dihidro-6H-quinolin-5-ona), pero que ha sido modificada de una forma deliberada y controlada para reemplazar uno o más sustituyentes de la molécula de referencia por un sustituyente alternativo, con el fin de generar una molécula que presenta una similitud estructural con la molécula de referencia. La síntesis y el análisis de análogos (por ejemplo, usando análisis estructural y/o bioquímico) para identificar versiones ligeramente modificadas de un compuesto conocido, que puedan presentar caracteres mejorados o sesgados (tales como mayor potencia y/o selectividad por un tipo de receptor deseado, mayor capacidad de penetrar las barreras hematoencefálicas de los mamíferos, menos efectos colaterales, etcétera) es un abordaje de diseño de drogas bien conocido en la química farmacéutica.

[0039] Además, usando métodos conocidos por aquellos entrenados en la técnica, pueden crearse análogos y derivados de los compuestos de la invención que presenten una eficacia terapéutica mejorada para controlar la demencia, es decir, mayor potencia y/o selectividad por un tipo de receptor deseado, mayor o menor capacidad de penetrar las barreras hematoencefálicas de los mamíferos (por ejemplo, mayor o menor velocidad de permeabilidad de la barrera hematoencefálica), menos efectos colaterales, etcétera.

[0040] La frase "aceptable para el uso farmacéutico", como se usa en conexión con las composiciones de la invención, hace referencia a entidades moleculares y otros ingredientes de estas composiciones que pueden ser tolerados en el ámbito fisiológico, y que típicamente no producen reacciones indeseadas cuando se administran a un mamífero (por ejemplo, un ser

humano). Preferiblemente, como se lo usa en la presente documentación, el término "aceptable para el uso farmacéutico" significa que está aprobado por la agencia reguladora del gobierno federal o de un gobierno estatal, o que está indicado en la Farmacopea de los EEUU o en otra farmacopea de generalmente reconocida, como aceptable para usar en mamíferos, y más particularmente en seres humanos.

[0041] Los compuestos de la presente invención pueden tomar la forma de sales aceptables para el uso farmacéutico. Las "sales aceptables para el uso farmacéutico" designan aquellas sales que poseen la efectividad biológica y las propiedades del compuesto original, y que no son indeseables desde el punto de vista biológico o desde otro punto de vista. La naturaleza de la sal o el isómero no es crítica, siempre que no sea tóxico y no interfiera sustancialmente con la actividad farmacológica deseada.

[0042] Aquellos entrenados en la técnica apreciarán que los compuestos de la invención que contienen un centro quiral podrán existir y podrán aislarse en formas con actividad óptica y racémicas. Algunos compuestos pueden presentar polimorfismo. Debe comprenderse que la presente invención comprende cualquier forma racémica, con actividad óptica, polimórfica, tautomérica o estereoisomérica, o mezclas de éstas, de un compuesto de la invención, que posea las propiedades útiles descritas en la presente documentación.

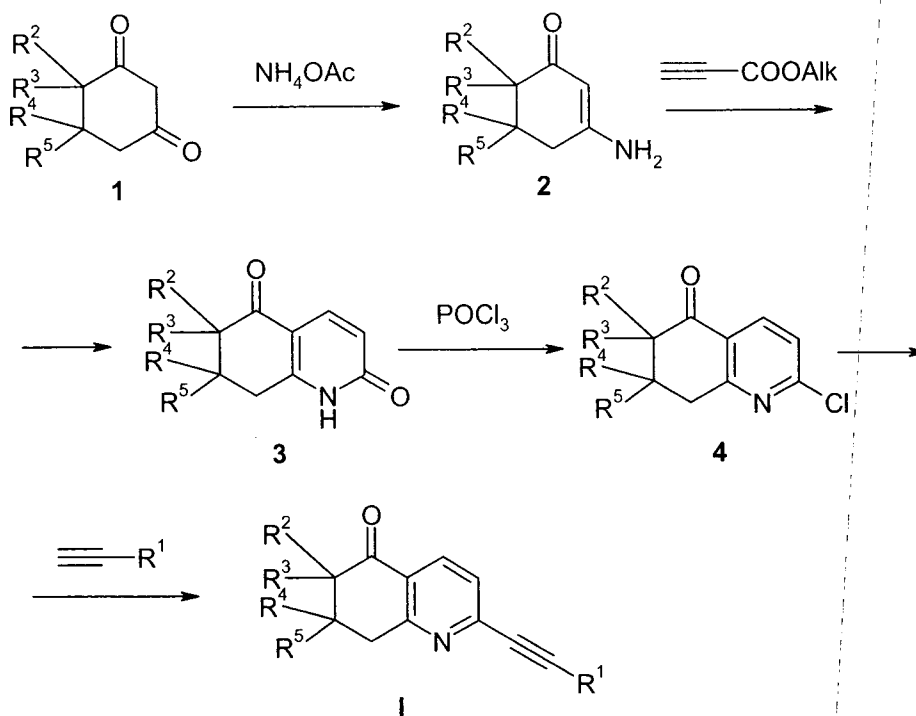
[0043] El siguiente esquema 1 describe la preparación de los compuestos de fórmula I de la presente invención. Todos los materiales iniciales se preparan de acuerdo con los procedimientos descritos en el esquema, empleando procedimientos bien conocidos por aquellos con conocimiento de química

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orgánica, o pueden obtenerse en los comercios. Todos los compuestos finales de la presente invención se preparan de acuerdo con los procedimientos descritos en este cuadro, o procedimientos análogos a éstos, que serán bien conocidos por aquellos con conocimiento de química orgánica. Todas las variables usadas en el esquema son como se las define más adelante o en las reivindicaciones.

[0044] En el Esquema 1 se proporciona un procedimiento sintético para obtener etinil-7,8-dihidro-6H-quinolin-5-onas 2-sustituidas con la fórmula general I. La reacción de los derivados de ciclohexan-1,3-diona funcionalizados apropiadamente **1** con acetato de amonio/ácido acético en benceno proporcionó los derivados de 3-amino-ciclohex-2-enona **2** correspondientes. Luego se hizo reaccionar el compuesto **2** con propiolato de alquilo, y se efectuó el ciclado a temperaturas elevadas para formar la quinolin-2,5-diona **3**. La reacción subsiguiente con cloruro de fosforilo proporcionó el derivado de quinolin-5-ona 2-cloro-sustituida **4**. La sustitución del sustituyente de cloro por el derivado de acetileno apropiado bajo catálisis con paladio (0), en presencia de una base, proporcionó los compuestos de fórmula I.

Esquema 1 Síntesis de etinil-7,8-dihidro-6H-quinolin-5-onas 2-sustituidas



[0045] Será evidente para aquellos entrenados en la técnica que los procedimientos de síntesis descriptos son meramente de naturaleza representativa, y aquellos con conocimiento de química orgánica conocen procesos de síntesis alternativos.

PARTE EXPERIMENTAL

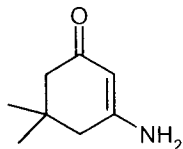
[0046] Los compuestos de la presente invención, y su preparación, se comprenderán mejor en conexión con los siguientes ejemplos, que se incluyen a modo ilustrativo y no limitan el alcance de la invención.

[0047] En adelante, "DMF" se define como N,N-dimetilformamida, "HCl" es ácido clorhídrico, "DMSO" es dimetilsulfóxido y "TMS" es tetrametilsilano.

Preparación 1

3-Amino-5,5-dimetilciclohex-2-en-1-ona

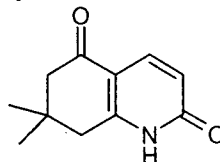
140



[0048] El compuesto del título se preparó de acuerdo con (Baraldi, P. G.; Simoni, D.; Manfredini, S.; *Synthesis* 1983, (11) 902-903.) como un sólido incoloro con 76% de rendimiento.

Preparación 2

7,7-Dimetil-7,8-dihidro-1H,6H-quinolin-2,5-diona



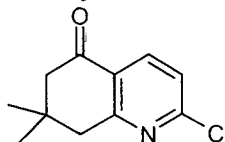
[0049] De manera análoga a (Pettit, G. R.; Fleming, W. C.; Paull, K. D. *J. Org. Chem.* 1968, 33 (3) 1089-1092.), se hizo reaccionar 3-amino-5,5-dimetilciclohex-2-en-1-ona con propiolato de etilo para dar el compuesto del título como un sólido color marrón con 78,5% de rendimiento.

Las características físicas son las siguientes:

^1H RMN (CDCl_3 , TMS) δ : 1,14, 2,42, 2,82, 6,47, y 8,04.

Preparación 3

2-Cloro-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona



[0050] De manera análoga a (Shanazarov, A. K.; Kuzovkin, V. A.; Chistjakov, V. V.; Granik, V. G. *Khim. Geterotsikl. Soedin.* 1991, (1) 86-92.) se trató 7,7-dimetil-7,8-dihidro-1H,6H-quinolin-2,5-diona con cloruro de fosforilo (POCl_3) para dar el compuesto del título como un sólido color gris con 60% de

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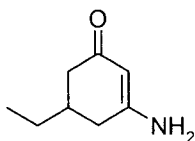
rendimiento.

Las características físicas son las siguientes:

^1H RMN (CDCl_3 , TMS) δ : 1,11, 2,54, 3,01, 7,30, y 8,30.

Preparación 4

3-Amino-5-etilciclohex-2-en-1-ona



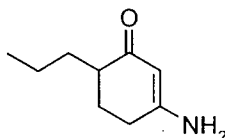
[0051] De manera análoga a (Baraldi, P. G.; Simoni, D.; Manfredini, S.; *Synthesis* 1983, (11) 902-903) se hizo reaccionar 5-etilciclohexan-1,3-diona con acetato de amonio para dar el compuesto del título.

Las características físicas son las siguientes:

^1H RMN (CDCl_3 , TMS) δ : 0,93 (t, 6,5 Hz, 3H); 1,42 (m, 2H); 1,88 – 2,44 (m, 5H); 4,62 (br s, 2H) y 5,23 ppm (s, 1H).

Preparación 5

3-Amino-6-propilciclohex-2-en-1-ona

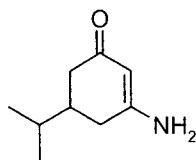


[0052] De manera análoga a (Baraldi, P. G.; Simoni, D.; Manfredini, S.; *Synthesis* 1983, (11) 902-903) se hizo reaccionar 4-propilciclohexan-1,3-diona con acetato de amonio para dar el compuesto del título como un sólido incoloro.

Las características físicas son las siguientes:

^1H RMN (CDCl_3 , TMS) δ : 0,91 (t, 7 Hz, 3H); 1,25 – 1,90 (m, 5H); 1,98 – 2,18 (m, 2H); 2,35 (t, 6 Hz, 2H); 4,50 (br s, 2H) y 5,19 ppm (s, 1H).

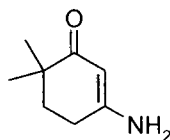
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Preparación 6**3-Amino-5-isopropilciclohex-2-en-1-ona**

[0053] De manera análoga a (Baraldi, P. G.; Simoni, D.; Manfredini, S.; *Synthesis* 1983, (11) 902-903) se hizo reaccionar 5-isopropilciclohexan-1,3-diona con acetato de amonio para dar el compuesto del título como un sólido incoloro.

Las características físicas son las siguientes:

^1H RMN (CDCl_3 , TMS) δ : 0,91 (d, 6,5 Hz); 1,48 – 1,65 (m, 1H); 1,84 – 2,39 (m, 5H); 5,04 (br s, 2H) y 5,22 ppm (s, 1H).

Preparación 7**3-Amino-6,6-dimetilciclohex-2-en-1-ona**

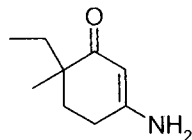
[0054] De manera análoga a (Baraldi, P. G.; Simoni, D.; Manfredini, S.; *Synthesis* 1983, (11) 902-903) se hizo reaccionar 4,4-dimetilciclohexan-1,3-diona con acetato de amonio para dar el compuesto del título como un sólido incoloro.

Las características físicas son las siguientes:

Mp 153-154 $^{\circ}\text{C}$; ^1H RMN ($\text{DMSO}-d_6$, TMS) δ : 0,94 (s, 6H); 1,64 (t, 6,5 Hz, 2H); 2,28 (t, 6,5 Hz, 2H); 4,79 (s, 1H) y 6,58 ppm (br s, 2H).

Preparación 8**3-Amino-6-etil-6-metilciclohex-2-en-1-ona**

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[0055] De manera análoga a (Baraldi, P. G.; Simoni, D.; Manfredini, S.; Synthesis 1983, (11) 902-903) se hizo reaccionar 4-etil-4-metilciclohexan-1,3-diona con acetato de amonio para dar el compuesto del título como un sólido incoloro.

Las características físicas son las siguientes:

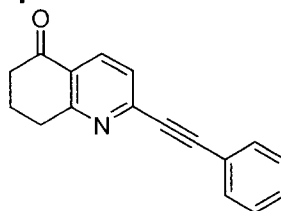
¹H RMN (CDCl₃, TMS) δ: 0,83 (t, 6,5 Hz, 3H); 1,06 (s, 3H); 1,40 – 1,80 (m, 3H); 1,85 – 2,00 (m, 1H); 2,35 (t, 6,5 Hz, 2H); 4,31 (br s, 2H) y 5,14 ppm (s, 1H).

Mp 99-100 °C; ¹H RMN (CDCl₃, TMS) δ: 1,08, 1,73, 2,45, 2,79, 3,91, y 8,33;

Anal. Hallado (C₁₇H₂₁N₃O) (%): C, 71,6; H, 7,5; N, 14,4

Preparación 9

2-Feniletinil-7,8-dihidro-6H-quinolin-5-ona



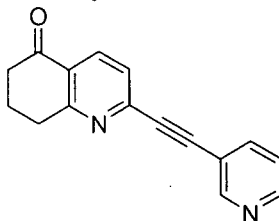
[0056] A una solución de 2-cloro-7,8-dihidro-6H-quinolin-5-ona (0,2 g, 1,1 mmol) y etinilbenceno (0,17 g, 1,6 mmol) en trietilamina (7 ml) bajo una atmósfera de argón se agregó tetrakis (trifenilfosfin) paladio (0,02 g, 0,062 mmol). La mezcla se calentó a reflujo durante 3 h. Luego se concentró bajo presión reducida y el residuo se purificó por cromatografía en columna sobre gel de sílice para dar el compuesto del título (0,04 g, 15%).

Las características físicas son las siguientes:

Mp 121-122 °C; ^1H RMN (CDCl_3 , TMS) δ : 2,20 (2H); 2,68 (2H); 3,17 (2H); 7,22-7,38 (3H); 7,46 (1H); 7,60 (2H); 8,24 (1H); MS 248 (M+1).

Preparación 10

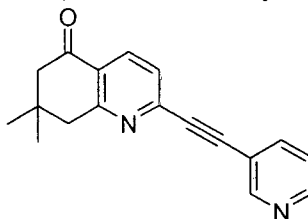
2-Piridin-3-iletinil-7,8-dihidro-6H-quinolin-5-ona



[0057] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado (120 mg, 15%, PF: 120-122,1°C).

Preparación 11

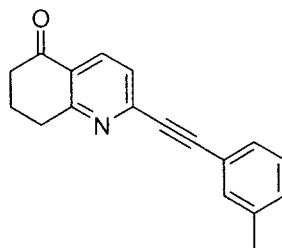
7,7-Dimetil-2-piridin-3-iletinil-7,8-dihidro-6H-quinolin-5-ona



[0058] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado (50 mg, 12 %, PF: 108-109,2°C).

Preparación 12

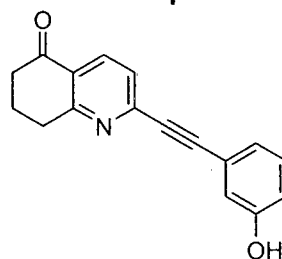
2-m-Toliletinil-7,8-dihidro-6H-quinolin-5-ona



[0059] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 13

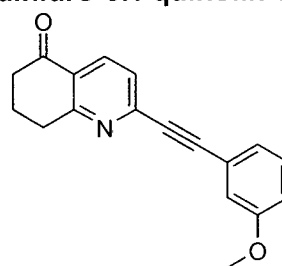
2-(3-Hidroxifeniletinil)-7,8-dihidro-6H-quinolin-5-ona



[0060] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 14

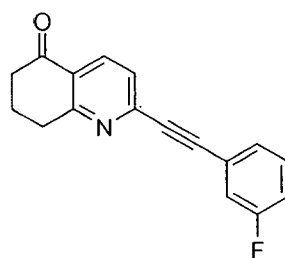
2-(3-Metoxifeniletinil)-7,8-dihidro-6H-quinolin-5-ona



[0061] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 15

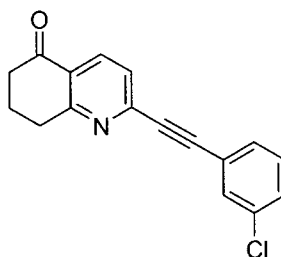
2-(3-Fluorofeniletinil)-7,8-dihidro-6H-quinolin-5-ona



[0062] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 16

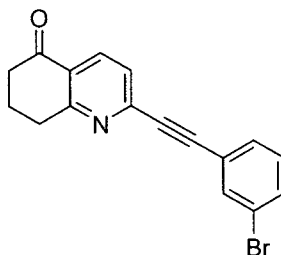
2-(3-Cloro-feniletinil)-7,8-dihidro-6H-quinolin-5-ona



[0063] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 17

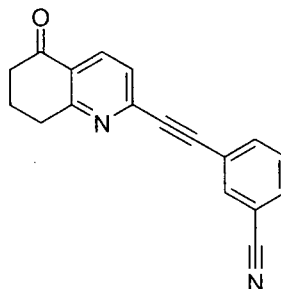
2-(3-Bromo-feniletinil)-7,8-dihidro-6H-quinolin-5-ona



[0064] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 18

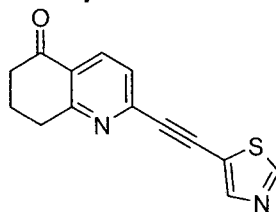
3-(5-Oxo-5,6,7,8-tetrahydro-quinolin-2-iletinil)-benzonitrilo



[0065] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 19

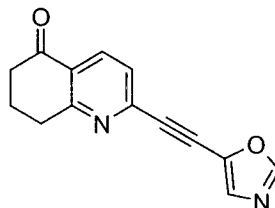
2-Tiazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona



[0066] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 20

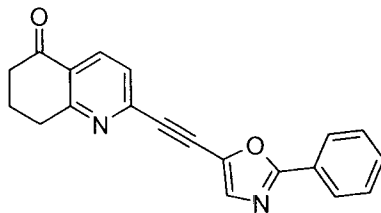
2-Oxazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona



[0067] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 21

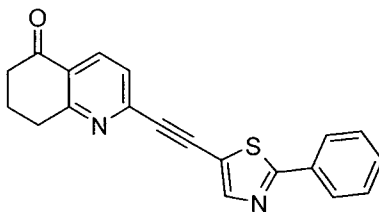
2-(2-Fenil-oxazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona



[0068] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 22

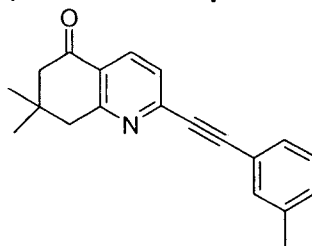
2-(2-Fenil-tiazol-5-iletilinil)-7,8-dihidro-6H-quinolin-5-ona



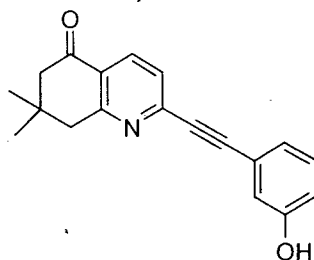
[0069] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 23

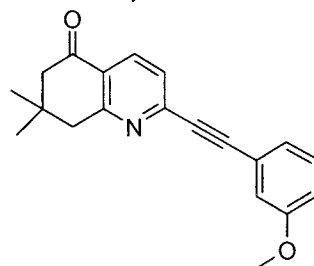
7,7-Dimetil-2-m-toliletilinil-7,8-dihidro-6H-quinolin-5-ona



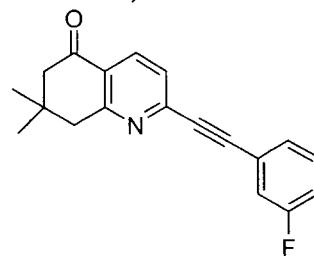
[0070] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 24**2-(3-Hidroxi-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona**

[0071] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

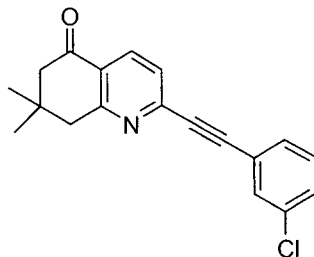
Preparación 25**2-(3-Metoxi-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona**

[0072] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

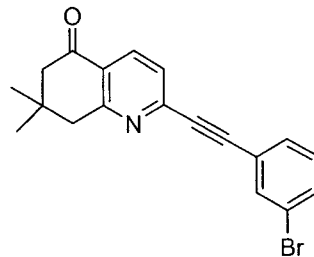
Preparación 26**2-(3-Fluoro-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona**

[0073] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

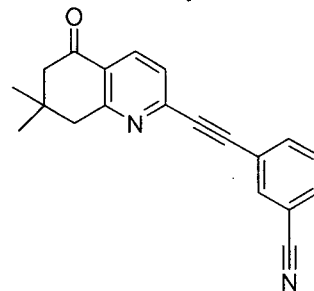
157
150

Preparación 27**2-(3-Cloro-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona**

[0074] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 28**2-(3-Bromo-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona**

[0075] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 29**3-(7,7-Dimetil-5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo**

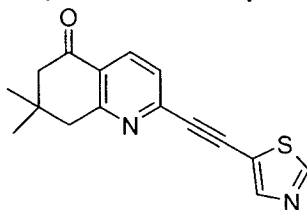
[0076] De manera análoga al procedimiento descrito en la **Preparación 9**, se

148
151

obtuvo el compuesto del título con rendimiento moderado.

Preparación 30

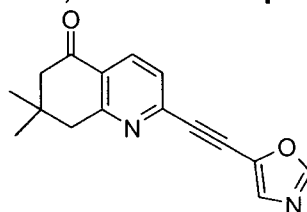
7,7-Dimetil-2-tiazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona



[0077] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Preparación 31

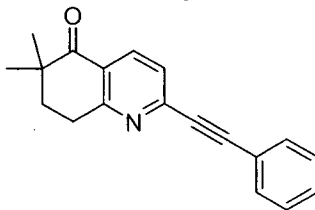
7,7-Dimetil-2-oxazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona



[0078] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 1

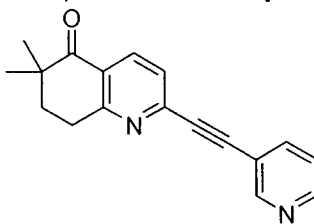
6,6-Dimetil-2-feniletinil-7,8-dihidro-6H-quinolin-5-ona



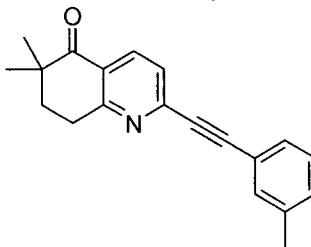
[0079] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 2

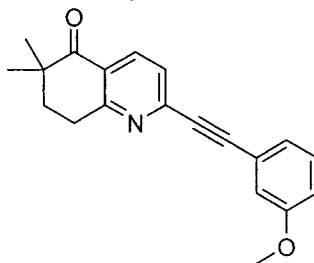
147
152

6,6-Dimetil-2-piridin-3-iletinil-7,8-dihidro-6H-quinolin-5-ona

[0080] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 3**6,6-Dimetil-2-m-toliletinil-7,8-dihidro-6H-quinolin-5-ona**

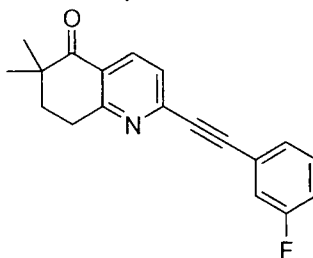
[0081] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 4**2-(3-Metoxi-feniletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona**

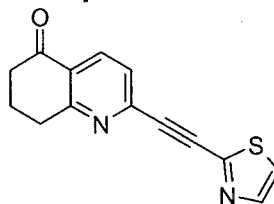
[0082] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 5

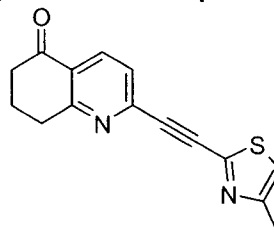
150
153

2-(3-Fluoro-feniletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona

[0083] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

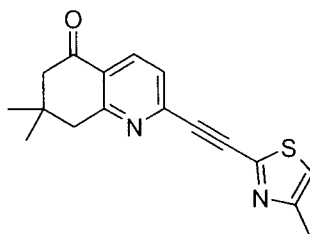
Ejemplo 6**2-Tiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona**

[0084] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 7**2-(4-Metil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona**

[0085] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

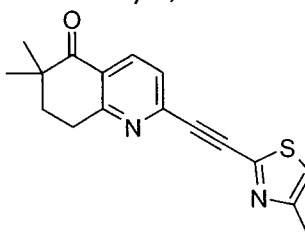
Ejemplo 8**7,7-Dimetil-2-(4-metil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona**



[0086] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 9

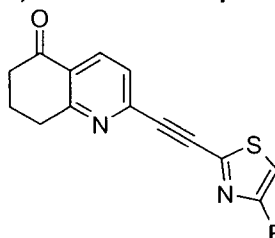
6,6-Dimetil-2-(4-metil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona



[0087] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 10

2-(4-Fluoro-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona

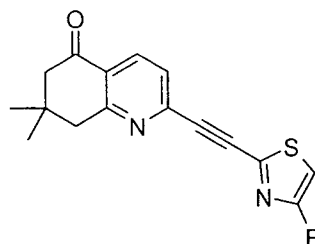


[0088] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 11

2-(4-Fluoro-tiazol-2-iletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona

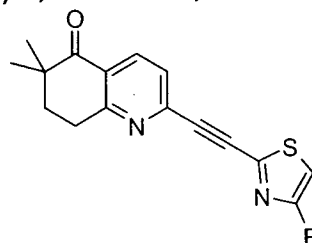
152
155



[0089] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 12

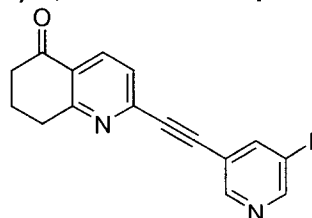
2-(4-Fluoro-tiazol-2-iletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona



[0090] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 13

2-(5-Fluoro-piridin-3-iletinil)-7,8-dihidro-6H-quinolin-5-ona

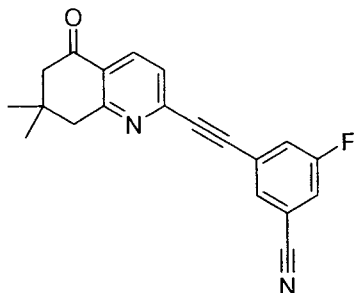


[0091] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 14

3-Fluoro-5-(7,7-Dimetil-5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo

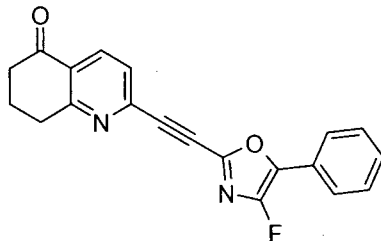
153
156



[0092] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 15

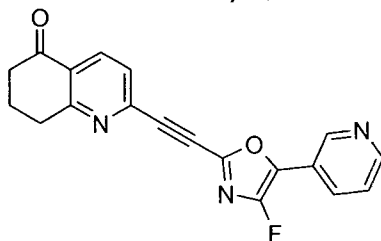
2-(4-Fluoro-5-fenil-oxazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona



[0093] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 16

2-(4-Fluoro-5-piridin-3-il-oxazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona

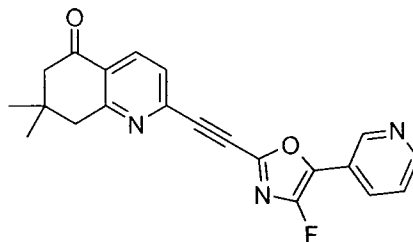


[0094] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 17

2-(4-Fluoro-5-piridin-3-il-oxazol-2-iletinil)-7,7-dimetil-7,8-dihidro-6H-

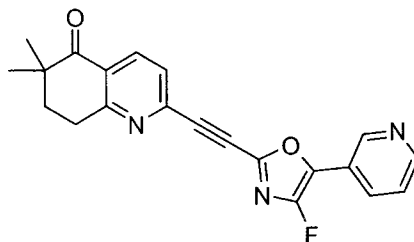
157
157

quinolin-5-ona

[0095] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 18

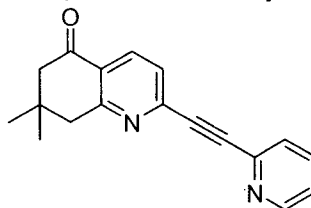
2-(4-Fluoro-5-piridin-3-il-oxazol-2-iletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona



[0096] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 19

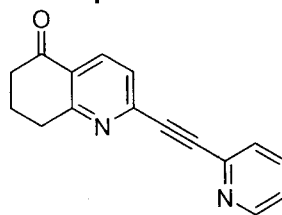
7,7-Dimetil-2-piridin-2-iletinil-7,8-dihidro-6H-quinolin-5-ona



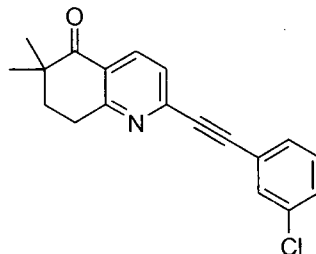
[0097] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 20

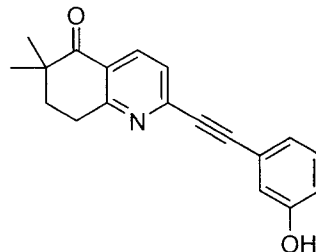
158
158

2-Piridin-2-iletinil-7,8-dihidro-6H-quinolin-5-ona

[0098] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 21**2-(3-Cloro-feniletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona**

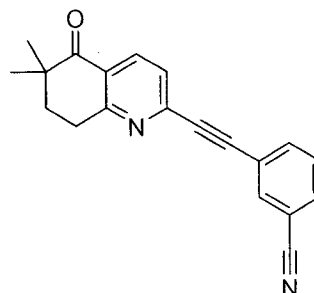
[0099] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 22**2-(3-Hidroxi-feniletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona**

[00100] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 23**3-(6,6-Dimetil-5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo**

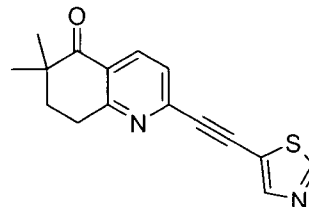
158
159



[00101] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 24

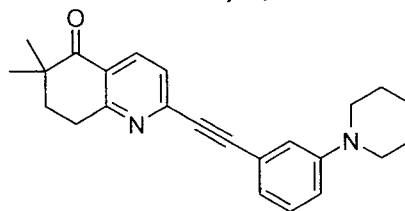
6,6-Dimetil-2-tiazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona



[00102] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 25

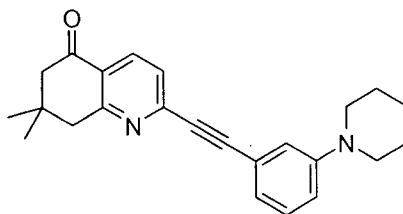
6,6-Dimetil-2-(3-piperidin-1-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona



[00103] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 26

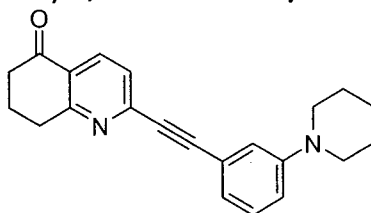
7,7-Dimetil-2-(3-piperidin-1-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona



[00104] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 27

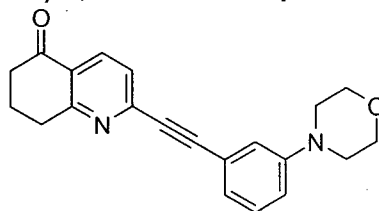
2-(3-Piperidin-1-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona



[00105] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 28

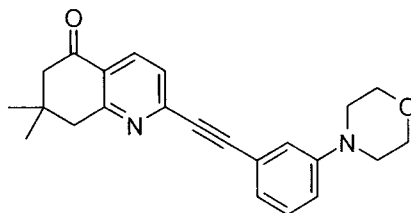
2-(3-Morfolin-4-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona



[00106] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 29

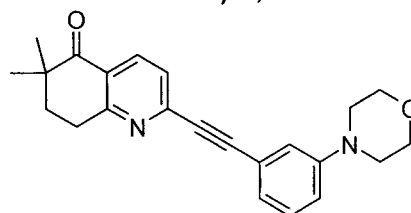
7,7-Dimetil-2-(3-morfolin-4-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona



[00107] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 30

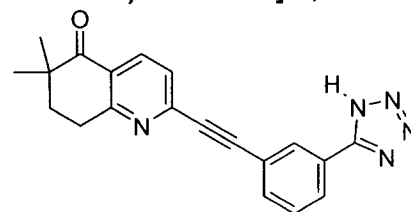
6,6-Dimetil-2-(3-morfolin-4-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona



[00108] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 31

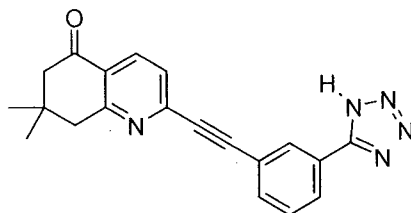
6,6-Dimetil-2-[3-(1H-tetrazol-5-il)-feniletinil]-7,8-dihidro-6H-quinolin-5-ona



[00109] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 32

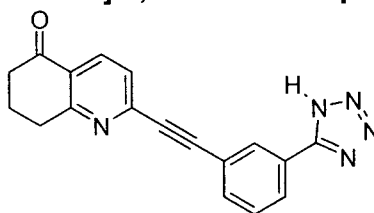
7,7-Dimetil-2-[3-(1H-tetrazol-5-il)-feniletinil]-7,8-dihidro-6H-quinolin-5-ona



[00110] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 33

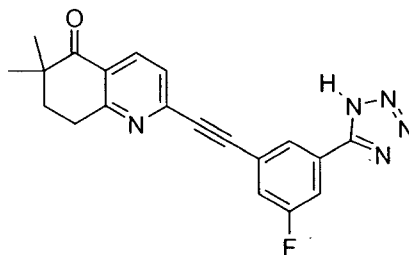
2-[3-(1H-Tetrazol-5-yl)-feniletinil]-7,8-dihidro-6H-quinolin-5-ona



[00111] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 34

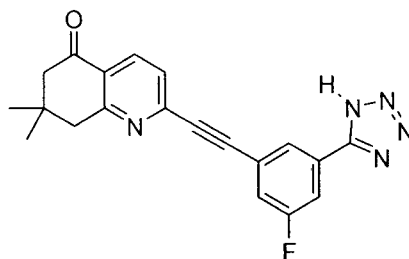
2-[3-Fluoro-5-(1H-tetrazol-5-yl)-feniletinil]-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona



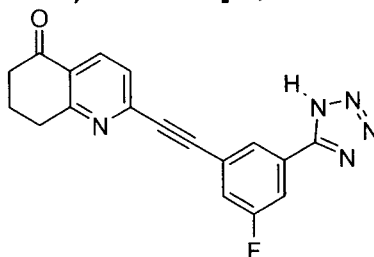
[00112] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 35

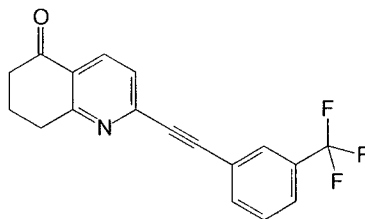
2-[3-Fluoro-5-(1H-tetrazol-5-yl)-feniletinil]-7,7-dimetil-7,8-dihidro-6H-

quinolin-5-ona

[00113] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

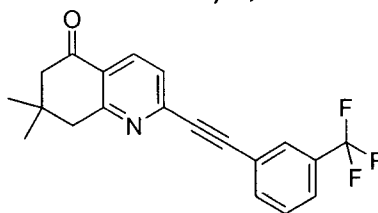
Ejemplo 36**2-[3-Fluoro-5-(1H-tetrazol-5-il)-feniletinil]-7,8-dihidro-6H-quinolin-5-ona**

[00114] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

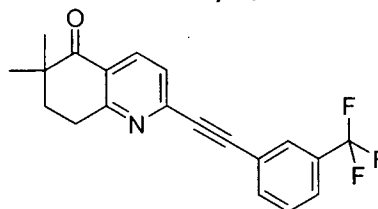
Ejemplo 37**2-(3-Trifluorometil-feniletinil)-7,8-dihidro-6H-quinolin-5-ona**

[00115] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

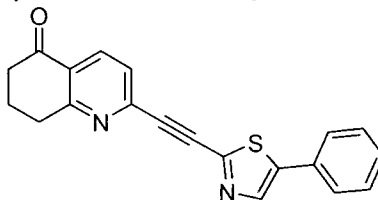
Ejemplo 38

7,7-Dimetil-2-(3-trifluorometil-feniletinil)-7,8-dihidro-6H-quinolin-5-ona

[00116] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 39**6,6-Dimetil-2-(3-trifluorometil-feniletinil)-7,8-dihidro-6H-quinolin-5-ona**

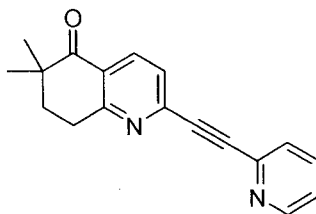
[00117] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 40**2-(2-Fenil-tiazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona**

[00118] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 41**6,6-Dimetil-2-piridin-2-iletinil-7,8-dihidro-6H-quinolin-5-ona**

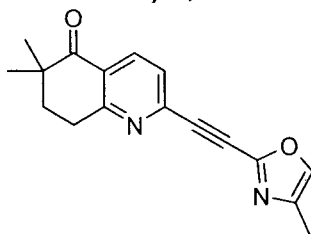
167
165



[00119] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 42

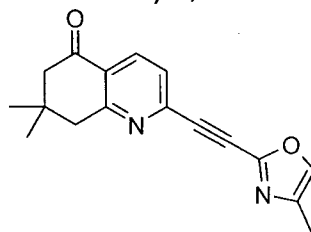
6,6-Dimetil-2-(4-metil-oxazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona



[00120] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 43

7,7-Dimetil-2-(4-metil-oxazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona

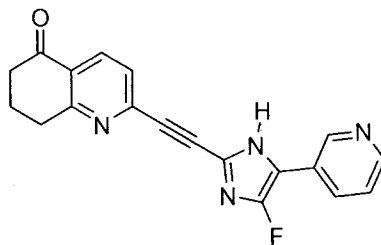


[00121] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 44

2-(4-Fluoro-5-piridin-3-il-1H-imidazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona

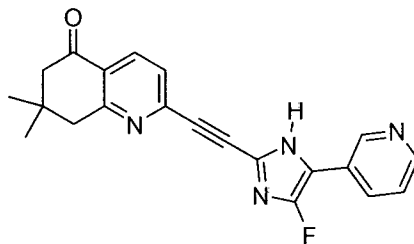
163
166



[00122] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 45

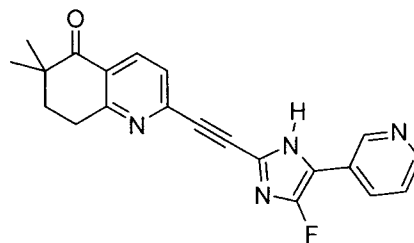
2-(4-Fluoro-5-piridin-3-il-1H-imidazol-2-iletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona



[00123] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 46

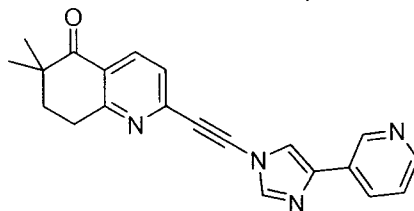
2-(4-Fluoro-5-piridin-3-il-1H-imidazol-2-iletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona



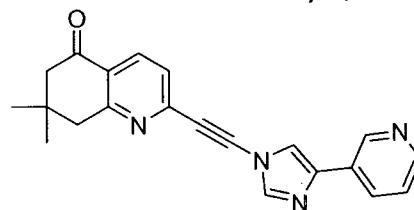
[00124] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 47

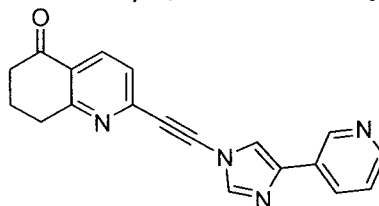
164
167

6,6-Dimetil-2-(4-piridin-3-il-imidazol-1-iletinil)-7,8-dihidro-6H-quinolin-5-ona

[00125] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 48**7,7-Dimetil-2-(4-piridin-3-il-imidazol-1-iletinil)-7,8-dihidro-6H-quinolin-5-ona**

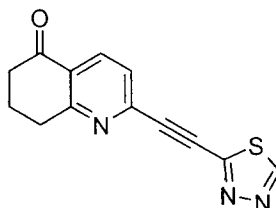
[00126] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 49**2-(4-Piridin-3-il-imidazol-1-iletinil)-7,8-dihidro-6H-quinolin-5-ona**

[00127] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 50**2-[1,3,4]Tiadiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona**

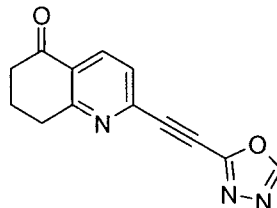
165
168



[00128] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 51

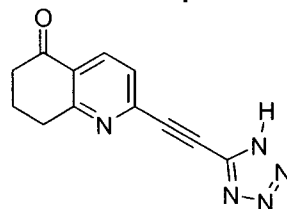
2-[1,3,4]Oxadiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona



[00129] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 52

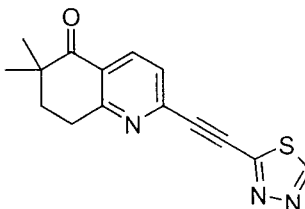
2-(1H-Tetrazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona



[00130] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 53

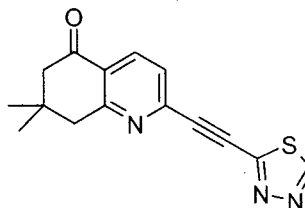
6,6-Dimetil-2-[1,3,4]tiadiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona



[00131] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 54

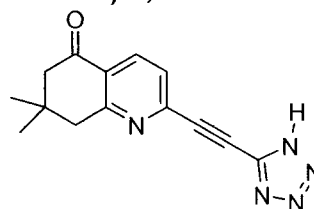
7,7-Dimetil-2-[1,3,4]tiadiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona



[00132] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 55

7,7-Dimetil-2-(1H-tetrazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona

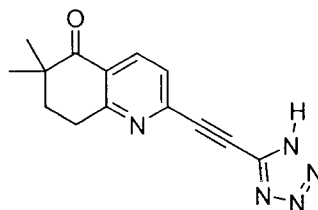


[00133] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 56

6,6-Dimetil-2-(1H-tetrazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona

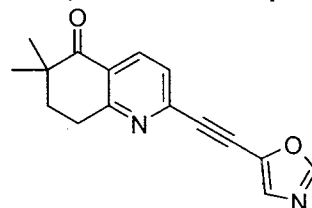
167
170



[00134] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 57

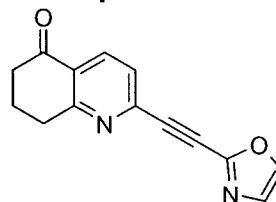
6,6-Dimetil-2-oxazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona



[00135] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 58

2-Oxazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona

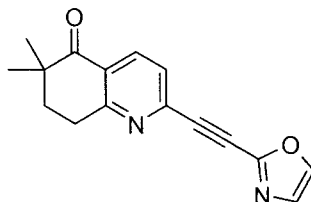


[00136] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 59

6,6-Dimetil-2-oxazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona

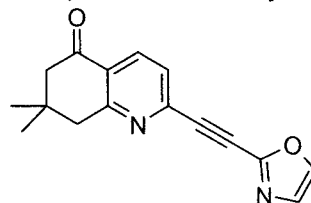
168
171



[00137] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 60

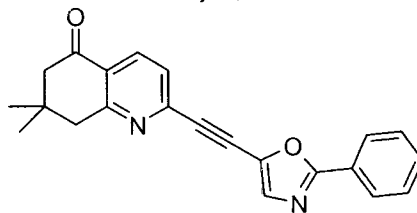
7,7-Dimetil-2-oxazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona



[00138] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 61

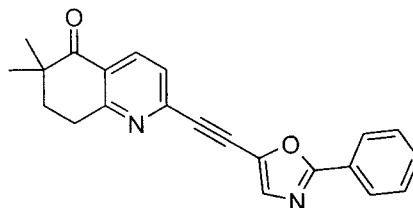
7,7-Dimetil-2-(2-fenil-oxazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona



[00139] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 62

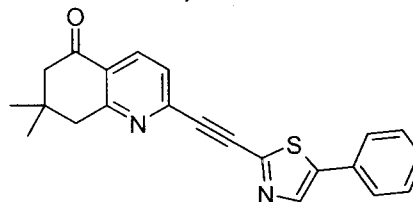
6,6-Dimetil-2-(2-fenil-oxazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona



[00140] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 63

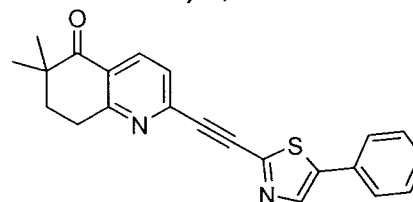
7,7-Dimetil-2-(5-fenil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona



[00141] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 64

6,6-Dimetil-2-(5-fenil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona

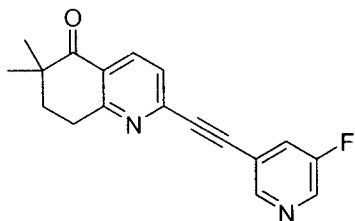


[00142] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 65

2-(5-Fluoro-piridin-3-iletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona

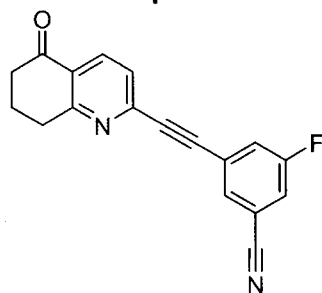
170
173



[00143] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 66

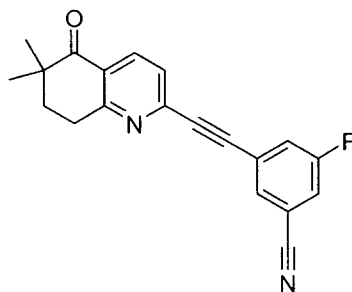
3-Fluoro-5-(5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo



[00144] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 67

3-(6,6-Dimetil-5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-5-fluoro-benzonitrilo

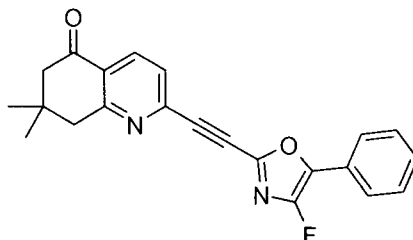


[00145] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

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Ejemplo 68

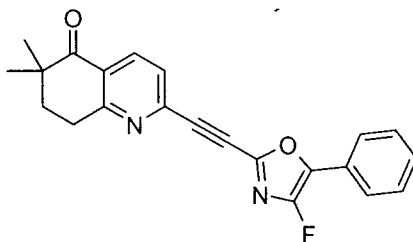
2-(4-Fluoro-5-fenil-oxazol-2-iletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona



[00146] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 69

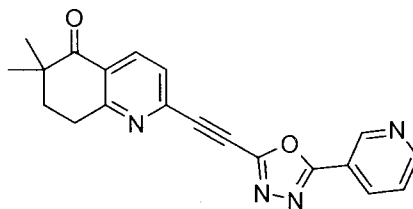
2-(4-Fluoro-5-fenil-oxazol-2-iletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona



[00147] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 70

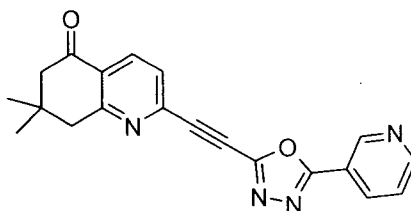
6,6-Dimetil-2-(5-piridin-3-il-[1,3,4]oxadiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona



[00148] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 71

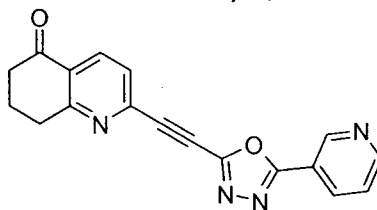
7,7-Dimetil-2-(5-piridin-3-il-[1,3,4]oxadiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona



[00149] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 72

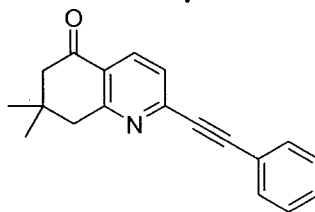
2-(5-Piridin-3-il-[1,3,4]oxadiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona



[00150] De manera análoga al procedimiento descrito en la **Preparación 9**, se obtuvo el compuesto del título con rendimiento moderado.

Ejemplo 73

7,7-Dimetil-2-feniletinil-7,8-dihidro-6H-quinolin-5-ona



[00151] De manera análoga al procedimiento descrito en la **Preparación**

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9, se obtuvo el compuesto del título con rendimiento moderado.

[00152] Pueden obtenerse formas estereoisoméricas puras de los compuestos y los intermediarios de esta invención aplicando procedimientos conocidos en la técnica. Pueden separarse los diastereómeros empleando métodos de separación física, tales como cristalización selectiva y procedimientos de cromatografía, por ejemplo, cromatografía líquida con fases quirales estacionarias. Pueden separarse los enantiómeros unos de otros mediante la cristalización selectiva de sus sales diastereoméricas con ácidos con actividad óptica. Como alternativa, pueden separarse los enantiómeros empleando procedimientos de cromatografía con fases quirales estacionarias. Estas formas estereoisoméricas puras también pueden derivar de la forma estereoisomérica pura de los materiales iniciales apropiados, siempre y cuando la reacción ocurra en forma estereoselectiva. Las formas estereoisoméricas de fórmula I están obviamente incluidas dentro del alcance de esta invención.

Sales de adición

[00153] Para el uso terapéutico, las sales de adición de los compuestos de fórmula I son aquellas donde el contraión es aceptable para el uso farmacéutico. Sin embargo, también pueden usarse sales de ácidos y bases que no son aceptables para el uso farmacéutico, por ejemplo, en la preparación y la purificación de compuestos aceptables para el uso farmacéutico. Todas las sales, aceptables para el uso farmacéutico o no, se incluyen dentro del ámbito de la presente invención. Las sales aceptables para el uso farmacéutico mencionadas previamente comprenden las formas de sales no tóxicas con actividad terapéutica que pueden formar los compuestos de fórmula I. Estos últimos pueden convertirse tratando la forma de base con ácidos apropiados,

tales como ácidos inorgánicos, por ejemplo, ácidos halhídricos, tales como ácido clorhídrico, ácido bromhídrico y semejantes; ácido sulfúrico; ácido nítrico; ácido fosfórico y semejantes; o ácidos orgánicos, tales como ácido acético, propanoico, hidroxiacético, 2-hidroxipropanoico, oxopropanoico, oxálico, malónico, succínico, maleico, fumárico, málico, tartárico, 2-hidroxi-1,2,3-propantricarboxílico, metansulfónico, etansulfónico, bencensulfónico, 4-metilbencensulfónico, ciclohexansulfónico, 2-hidroxibenzoico, 4-amino-2-hidroxibenzoico y semejantes. Por otro lado, puede convertirse la forma de sal empleando un tratamiento con álcali sobre la forma de base libre.

COMPOSICIONES FARMACÉUTICAS

[00154] Los ingredientes activos de la invención, en combinación con uno o más coadyuvantes, vehículos o diluyentes convencionales, pueden presentarse bajo la forma de composiciones farmacéuticas y dosificaciones unitarias de éstas, y pueden emplearse en esta forma como sólidos, tales como tabletas recubiertas o no recubiertas, o cápsulas rellenas, o líquidos, tales como soluciones, suspensiones, emulsiones, elíxires o cápsulas rellenas con éstos, todas para uso oral; bajo la forma de supositorios o cápsulas para administración rectal, o bajo la forma de soluciones estériles inyectables para uso parenteral (incluyendo intravenoso o subcutáneo). Estas composiciones farmacéuticas y las formas de dosificación unitarias de éstas pueden comprender ingredientes convencionales o novedosos en proporciones convencionales o especiales, con o sin compuestos o principios activos adicionales, y estas formas de dosificación unitarias pueden contener cualquier cantidad efectiva apropiada de ingrediente activo, de acuerdo con el rango de dosificación diaria que se desea emplear. Por consiguiente, las tabletas que

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contienen entre uno (1) y cien (100) miligramos de ingrediente activo, o más ampliamente, entre cero coma cinco (0,5) y quinientos (500) miligramos por tableta, son formas de dosificación unitarias representativas apropiadas.

[00155] El término "vehículo", aplicado a las composiciones farmacéuticas de la invención, hace referencia a un diluyente, un excipiente o un vehículo con el que se administra el compuesto activo. Estos vehículos farmacéuticos pueden ser líquidos estériles, tales como agua, soluciones salinas, soluciones de dextrosa acuosa, soluciones de glicerol acuoso y aceites, incluyendo aquellos de petróleo, animales, vegetales o de origen sintético, tales como aceite de maní, aceite de soja, aceite mineral, aceite de sésamo y semejantes. Se describen vehículos farmacéuticos apropiados en "Remington's Pharmaceutical Sciences", por E.W. Martin, 18ª edición.

MÉTODO DE TRATAMIENTO

[00156] Debido a su alto grado de actividad y su baja toxicidad, en combinación con un índice terapéutico muy favorable, pueden administrarse los principios de la invención en el cuerpo de un sujeto, por ejemplo, un animal vivo (incluyendo un ser humano), para tratar, aliviar, paliar o eliminar una indicación a una condición susceptible, o representativa de una indicación o una condición detallada en otra sección de esta solicitud, preferiblemente en forma concurrente o simultánea, o en combinación con uno o más excipientes, vehículos o diluyentes aceptables para el uso farmacéutico, especial y preferiblemente bajo la forma de una composición farmacéutica, a través de una ruta oral, rectal o parenteral (incluyendo intravenosa y subcutánea), o, en algunos casos, aún una ruta tópica, en una cantidad efectiva. Los rangos de dosificación apropiados son de 1-1000 miligramos por día, preferiblemente 10-

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500 miligramos por día y especialmente 50-500 miligramos por día, donde la cantidad depende comúnmente del modo exacto de administración, la forma que se administra, la indicación a la que se dirige la administración, el sujeto a tratar y el peso corporal de dicho sujeto, y la preferencia y la experiencia del médico o el veterinario a cargo.

[00157] El término “efectiva para el uso terapéutico”, aplicado a una dosis u una cantidad, hace referencia a aquella cantidad de un compuesto o una composición farmacéutica que es suficiente para obtener una actividad deseada al administrarla en el cuerpo de un animal vivo que la necesita.

[00158] Los agentes activos de la presente invención pueden administrarse por vía oral, tópica, parenteral o a través de las mucosas (por ejemplo, por vía bucal, por inhalación o por vía rectal), en formulaciones en dosis individuales que contienen vehículos convencionales no tóxicos aceptables para el uso farmacéutico. Es comúnmente deseable usar la ruta oral. Los agentes activos pueden administrarse por vía oral, bajo la forma de una cápsula, una tableta o semejantes (véase Remington: The Science and Practice of Pharmacy, 20ª edición (2000), Filadelfia, PA). Los medicamentos de administración oral pueden administrarse bajo la forma de un vehículo de liberación controlada por tiempo, incluyendo sistemas de difusión controlada, dispositivos osmóticos, matrices de disolución controlada y matrices erosionables/degradables.

[00159] Para la administración oral bajo la forma de una tableta o una cápsula, puede combinarse el componente de droga activa con excipientes no tóxicos aceptables para el uso farmacéutico, tales como agentes aglutinantes (por ejemplo, almidón de maíz pregelificado, polivinilpirrolidona o hidroxipropil

metilcelulosa); rellenos (por ejemplo, lactosa, sacarosa, glucosa, manitol, sorbitol y otros azúcares reductores y no reductores, celulosa microcristalina, sulfato de calcio, o hidrógeno fosfato de calcio); lubricantes (por ejemplo, estearato de magnesio, talco o sílice, ácido esteárico, estearil fumarato de sodio, behenato de glicerilo, estearato de calcio y semejantes); desintegradores (por ejemplo, almidón de papa o almidón de glicolato de sodio); o agentes humectantes (por ejemplo, lauril sulfato de sodio), agentes colorantes y saborizantes, gelatina, edulcorantes, gomas naturales y sintéticas (tales como acacia, tragacanto o alginatos), sales amortiguadoras, carboximetilcelulosa, polietilenglicol, ceras y semejantes. Para la administración oral en forma líquida, pueden combinarse los componentes de droga con vehículos inertes no tóxicos aceptables para el uso farmacéutico (por ejemplo, etanol, glicerol, agua), agentes de suspensión (por ejemplo, jarabe de sorbitol, derivados de celulosa o grasas comestibles hidrogenadas), agentes emusificantes (por ejemplo, lecitina o acacia), vehículos no acuosos (por ejemplo, aceite de almendra, ésteres oleosos, alcohol etílico o aceites vegetales fraccionados), preservadores (por ejemplo, p-hidroxibenzoatos de metilo o propilo, o ácido sórbico), y semejantes. También pueden agregarse agentes estabilizadores, tales como antioxidantes (BHA, BHT, galato de propilo, ascorbato de sodio, ácido cítrico) para estabilizar las formas de dosificación.

[00160] Pueden recubrirse las tabletas empleando métodos bien conocidos en la técnica. Las composiciones de la invención también pueden introducirse en microesferas o microcápsulas, por ejemplo, fabricadas con ácido poliglicólico/ácido láctico (PGLA). Las preparaciones líquidas para administración oral pueden tomar la forma, por ejemplo, de soluciones, jarabes,

emulsiones o suspensiones, o pueden presentarse como un producto seco para reconstituir con agua u otro vehículo apropiado antes de usarlo. Las preparaciones para administración oral pueden formularse apropiadamente para obtener una liberación controlada o pospuesta del compuesto activo.

[00161] También pueden administrarse las drogas activas bajo la forma de sistemas de administración de liposomas, tales como vesículas unilamelares pequeñas y vesículas multilamelares. Pueden formarse liposomas a partir de una variedad de fosfolípidos, tales como colesterol, estearilamina o fosfatidilcolinas, como es bien conocido.

[00162] Las drogas de la invención también pueden administrarse usando anticuerpos monoclonales, como vehículos individuales con los cuales unir las moléculas de compuesto. También pueden unirse las drogas activas con polímeros solubles como vehículos de direccionamiento de drogas. Estos polímeros pueden incluir polivinil-pirrolidona, copolímero de pirano, polihidroxi-propil-metacrilamida-fenol, polihidroxi-etil-aspartamida-fenol, u óxido de polietileno-polilisina sustituida con residuos de palmitoilo. Además, puede unirse la droga activa con una clase de polímeros biodegradables, útil para obtener una liberación controlada de una droga, por ejemplo, ácido poliláctico, ácido poliglicólico, copolímeros de ácido poliláctico y ácido poliglicólico, poliépsilon caprolactona, ácido polihidroxibutírico, poliortoésteres, poliacetales, polihidropiranos, policianoacrilatos, y copolímeros en bloque de hidrogeles reticulados o anfipáticos.

[00163] Para una administración por inhalación, las sustancias terapéuticas de acuerdo con la presente invención pueden administrarse convenientemente bajo la forma de una presentación como rocío en aerosol, a

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partir de envases presurizados o un nebulizador, con el uso de un propelente apropiado, por ejemplo, diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, dióxido de carbono u otro gas apropiado. En el caso de un aerosol presurizado, puede determinarse la unidad de dosificación proporcionando una válvula para administrar una cantidad medida. Pueden formularse cápsulas y cartuchos, por ejemplo, de gelatina, para usar en un inhalador o un insuflador que contenga una mezcla en polvo del compuesto y una base en polvo apropiada, tal como lactosa o almidón.

[00164] Las formulaciones de la invención pueden administrarse por vía parenteral, es decir, por administración intravenosa (i.v.), intracerebroventricular (i.c.v.), subcutánea (s.c.), intraperitoneal (i.p.), intramuscular (i.m.), subdérmica (s.d.) o intradérmica (i.d.), por inyección directa, por ejemplo, a través de una inyección en bolo o una infusión continua. Las formulaciones para inyección pueden presentarse en una forma de dosificación individual, por ejemplo, en ampollas o recipientes con dosificaciones múltiples, con un preservador adicional. Las composiciones pueden tomar formas tales como excipientes, suspensiones, soluciones o emulsiones en vehículos oleosos o acuosos, y pueden contener agentes de formulación, tales como agentes de suspensión, estabilizadores y/o dispersantes. Como alternativa, el ingrediente activo puede tomar la forma de un polvo, que puede reconstituirse con un vehículo apropiado, por ejemplo, agua estéril libre de pirógenos, antes de usarse.

[00165] Las composiciones de la presente invención también pueden formularse para administración rectal, por ejemplo, como supositorios o enemas de retención (por ejemplo, que contienen bases convencionales para

supositorios, tales como manteca de cacao u otros glicéridos).

[00166] Si se lo desea, pueden presentarse las composiciones en un envase o un dispositivo de administración que puede contener una o más formas de dosificación individuales, cada una de las cuales contiene el ingrediente activo, y/o pueden contener niveles de dosificación diferentes para facilitar la titulación de las dosis. El envase puede comprender, por ejemplo, láminas metálicas o plásticas, tal como un envase con ampollas. El envase o el dispositivo de administración puede estar acompañado por instrucciones de administración. También pueden prepararse composiciones de la invención formuladas en un vehículo farmacéutico compatible, puede colocárselas en un recipiente apropiado y puede etiquetárselas para el tratamiento de una condición indicada.

[00167] Como se describe en la presente documentación, se determina la dosis de los componentes en las composiciones de la presente invención con el fin de asegurar que la dosis administrada en forma continua o intermitente no exceda una cantidad determinada, después de considerar los resultados en animales de prueba y las condiciones individuales del paciente. Naturalmente, una dosis específica varía dependiendo del procedimiento de dosificación, las condiciones de un paciente o un sujeto animal, tales como la edad, el peso corporal, el sexo, la sensibilidad, la alimentación, el período de dosificación, las drogas usadas en combinación y la severidad de la enfermedad. Puede determinarse la dosis apropiada y el cronograma de dosificación bajo determinadas condiciones realizando una prueba basada en los índices descriptos previamente, pero también puede refinarse y finalmente decidirse de acuerdo con el juicio del médico y las circunstancias de cada paciente (la edad,

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la condición general, la severidad de los síntomas, el sexo, etcétera), de acuerdo con procedimientos clínicos convencionales.

[00168] Puede determinarse la toxicidad y la eficacia terapéutica de las composiciones de la invención empleando procedimientos farmacéuticos convencionales en animales experimentales, por ejemplo, determinando la LD₅₀ (la dosis letal para 50% de la población) y la ED₅₀ (la dosis con efectividad terapéutica en 50% de la población). La relación de dosis entre los efectos terapéuticos y tóxicos es el índice terapéutico, y puede expresarse como la relación ED₅₀/LD₅₀. Se prefieren las composiciones con mayores índices terapéuticos.

EJEMPLOS DE COMPOSICIONES FARMACÉUTICAS REPRESENTATIVAS

[00169] Con la ayuda de solventes, agentes auxiliares y vehículos de uso común, pueden procesarse los productos de reacción para obtener tabletas, tabletas recubiertas, cápsulas, soluciones de goteo, supositorios, preparaciones de inyección e infusión, y semejantes, y puede aplicárselos como terapia a través de una ruta oral, rectal, parenteral y otras. A continuación se detallan composiciones farmacéuticas representativas.

Pueden prepararse tabletas apropiadas para administración oral que contienen el ingrediente activo empleando técnicas convencionales para fabricar tabletas.

Para los supositorios, puede emplearse cualquier base apropiada para supositorios para incorporarla en éstos, empleando procedimientos convencionales, en combinación con el ingrediente activo, tal como un polietilenglicol, que es sólido a temperatura ambiente normal, pero que se funde a la temperatura del cuerpo o cerca de ella.

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Para las soluciones estériles parenterales (incluyendo intravenosas y subcutáneas), se emplea el ingrediente activo en combinación con ingredientes convencionales en cantidades usuales, tales como, por ejemplo, cloruro de sodio y agua doblemente destilada q.s., de acuerdo con procedimientos convencionales, tales como filtración, relleno aséptico en ampollas o botellas de goteo IV, y autoclavado para lograr la esterilidad.

[00170] Otras composiciones farmacéuticas apropiadas serán inmediatamente evidentes para aquellos entrenados en la técnica.

EJEMPLOS DE FORMULACIÓN

[00171] Nuevamente, los siguientes ejemplos se proporcionan solamente a modo de ilustración, y no deben interpretarse como limitaciones.

EJEMPLO 1

Formulación en tableta

Una formulación apropiada para una tableta que contiene 10 miligramos de ingrediente activo es como se indica a continuación:

	mg
Ingrediente activo	10
Lactosa	61
Celulosa microcristalina	25
Talco	2
Esterarato de magnesio	1

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Dióxido de silicio coloidal

1

EJEMPLO 2

Formulación en tableta

Otra formulación apropiada para un comprimido que contiene 100 mg es como se indica a continuación:

	mg
Ingrediente activo	100
Polivinilpirrolidona, reticulada	10
Almidón de papa	20
Polivinilpirrolidona	19
Esterarato de magnesio	1
Celulosa microcristalina	50
Recubrimiento con película y coloración.	
El material de recubrimiento con película consiste en:	
Hipromelosa	10
Celulosa microcristalina	5
Talco	5
Polietilenglicol	2

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Pigmentos colorantes

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EJEMPLO 3

Formulación en cápsula

Una formulación apropiada para una cápsula que contiene 50 miligramos de ingrediente activo es como se indica a continuación:

	mg
Ingrediente activo	50
Almidón de maíz	26
Fosfato de calcio dibásico	50
Talco	2
Dióxido de silicio coloidal	2

Se introduce en una cápsula de gelatina.

EJEMPLO 4

Solución para inyección

Una formulación apropiada para una solución inyectable es como se indica a continuación:

Ingrediente activo	mg	10
Cloruro de sodio	mg	q.s.
Agua para inyección	ml	Se agrega 1,0

EJEMPLO 5

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Formulación oral líquida

Una formulación apropiada para 1 litro de una solución oral que contiene 2 miligramos de ingrediente activo en un mililitro de mezcla es como se indica a continuación:

	mg
Ingrediente activo	2
Sacarosa	250
Glucosa	300
Sorbitol	150
Sabor a naranja	10
Colorante	q.s.
Agua purificada	Se agregan 1000
	ml

EJEMPLO 6

Formulación oral líquida

Otra formulación apropiada para 1 litro de una mezcla líquida que contiene 20 miligramos de ingrediente activo en un mililitro de mezcla es como se indica a continuación:

	G
Ingrediente activo	20,00

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Tragacanto	7,00
Glicerol	50,00
Sacarosa	400,00
Metilparaben	0,50
Propilparaben	0,05
Sabor a grosella negra	10,00
Color rojo soluble	0,02
Agua purificada	Se agregan 1000 ml

EJEMPLO 7

Formulación oral líquida

Otra formulación apropiada para 1 litro de una mezcla líquida que contiene 2 miligramos de ingrediente activo en un mililitro de mezcla es como se indica a continuación:

	G
Ingrediente activo	2
Sacarosa	400
Tintura de cáscara de naranja amarga	20

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Tintura de cáscara de naranja dulce	15
Agua purificada	Se agregan 1000 ml

EJEMPLO 8

Formulación en aerosol

Una solución de 180 g de aerosol contiene:

	G
Ingrediente activo	10
Ácido oleico	5
Etanol	81
Agua purificada	9
Tetrafluoroetano	75

Se introducen 15 ml de la solución en recipientes para aerosol, se tapa con una válvula de dosificación, se purga con 3,0 bar.

EJEMPLO 9

Formulación TDS

100 g de solución contienen:

	G
Ingrediente activo	10,0

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Etanol	57,5
Propilenglicol	7,5
Dimetilsulfóxido	5,0
Hidroxietilcelulosa	0,4
Agua purificada	19,6

Se introducen 1,8 ml de la solución en un lienzo recubierto con una lámina de respaldo adhesiva. Se cierra el sistema con un recubrimiento protector, que se eliminará antes de usarlo.

EJEMPLO 10

Formulación nanoparticulada

10 g de nanopartículas de cianoacrilato depolibutilo contienen:

	G
Ingrediente activo	1,00
Poloxámero	0,10
Cianoacrilato de butilo	8,75
Manitol	0,10
Cloruro de sodio	0,05

Se preparan nanopartículas de cianoacrilato de polibutilo a través de una polimerización en emulsión, en una mezcla de agua/HCl 0,1 N/etanol como medio de polimerización. Las nanopartículas en la suspensión finalmente se liofilizan al vacío.

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Farmacología – resumen

[00172] Los principios activos de la presente invención, las composiciones farmacéuticas de éstos y el método de tratamiento con éstas se caracterizan por propiedades únicas y ventajosas, lo que hace que el "sujeto en cuestión como un todo", como se reivindica en la presente documentación, no sea obvio. Los compuestos y las composiciones farmacéuticas de éstos presentan, en procedimientos de prueba confiables de aceptación convencional, las siguientes propiedades y características valiosas:

MÉTODOS

ENSAYOS DE UNIÓN PARA CARACTERIZAR LAS PROPIEDADES DEL ANTAGONISTA MGLUR5

Unión de [³H]MPEP (2-metil-6-(feniletinil)piridina) a sitios moduladores alostéricos transmembrana de receptores mGluR5 en membranas corticales

Preparación de membranas corticales de rata:

[00173] Se decapitan ratas Sprague-Dawley macho (200-250 g) y se extraen rápidamente los cerebros. Se disecta la corteza, y se homogeniza en 20 volúmenes de sacarosa helada 0,32 M, usando un homogenizador de vidrio-teflón. Se centrifuga el homogenato a 1000 x G por 10 minutos. Se descarta el precipitado y se centrifuga el sobrenadante a 20000 x G por 20 minutos. Se suspende nuevamente el precipitado resultante en 20 volúmenes de agua destilada, y se centrifuga por 20 minutos a 8000 x G. Luego se centrifuga el sobrenadante y el recubrimiento a 48000 x G por 20 minutos, en presencia de Tris-HCl 50 mM, pH 8,0. Luego se suspende nuevamente el precipitado y se centrifuga dos o tres veces más a 48000 x G por 20 minutos, en presencia de

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Tris-HCl 50 mM, pH 8,0. Todos los pasos de centrifugación se efectúan a 4°C. Después de suspender nuevamente en 5 volúmenes de Tris-HCl 50 mM, pH 8,0, la suspensión de membrana se congela rápidamente a -80°C.

[00174] El día del ensayo, se descongelan las membranas y se lava cuatro veces, suspendiéndolas nuevamente en Tris-HCl 50 mM, pH 8,0, y centrifugando a 48000 x G por 20 minutos, y finalmente suspendiendo nuevamente en Tris-HCl 50 mM, pH 7,4. La cantidad de proteínas en la preparación de membrana final (250-500 µg/ml) se determina de acuerdo con el método de Lowry (Lowry O. H. et al., 1951. J. Biol. Chem. 193, 256-275).

Ensayo de [³H]MPEP

[00175] Se comienzan las incubaciones introduciendo (³H)-mPEP (50,2 Ci/mmol, 5 nM, Tocris) en recipientes con 125-250 µg de proteínas (con un volumen total de 0,5 ml) y varias concentraciones de los agentes. Se continúan las incubaciones a temperatura ambiente por 60 minutos (se logró el equilibrio bajo las condiciones usadas). Se define la unión no específica mediante la adición de MPEP sin marcar (10 µM). Se terminan las incubaciones usando un sistema de filtro Millipore. Se lavan las muestras dos veces con 4 ml de amortiguador de ensayo helado sobre filtros de fibra de vidrio (Scleicher & Schuell) bajo un vacío constante. Después de la separación y el lavado, se colocan los filtros en fluido de centelleo (5 ml de Ultima Gold) y se determina la radiactividad retenida en los filtros con un contador de centelleo líquido convencional (Hewlett Packard, analizador de centelleo líquido).

Caracterización

[00176] La unión específica es extremadamente alta, es decir, normalmente > 85%, y es esencialmente independiente del amortiguador (Tris

o HEPES 50 mM) y el pH (6,8-8,9). Existe una dependencia clara de las proteínas saturables, y la concentración de proteína seleccionada, usada para los ensayos subsiguientes (250-500 µg/ml) está dentro de la porción lineal de esta dependencia. El MPEP frío desplaza un ligando caliente con una IC_{50} de $18,8 \pm 4,1$ nM. Se determina el K_d de (^3H)-MPEP de 13,6 nM mediante un análisis de Scatchard, y se lo usa de acuerdo la relación de Cheng Prusoff para calcular la afinidad de los elementos de desplazamiento como valores de K_d (la IC_{50} de MPEP frío es igual a una K_i de 13,7 nM). B_{max} fue 0,56 pm/mg de proteína. Los compuestos de la presente invención presentan una afinidad específica por sitios de modulación transmembrana de receptores mGluR5 en preparaciones de membranas corticales/cerebelares.

ENSAYO FUNCIONAL DE RECEPTORES MGLUR5

Materiales y Métodos

Cultivo de astrocitos

[00177] Se prepararon cultivos de astrocitos primarios a partir de cortezas de ratas neonatas, como se describe en Booher y Sensenbrenner (1972). Brevemente, se decapitaron cachorros de ratas Sprague-Dawley (de 2-4 días de edad) y se disectaron las neocortezas, se las desintegró con un filtro de nylon (con un tamaño de poro de 80 µm) y se las trituroó con cuidado. La suspensión celular se plaqueó en recipientes recubiertos previamente con poli-D-lisina (Costar), y se las cultivó en medio de Eagle modificado por Dulbecco (DMEM, InVitrogen), suplementado con 10% de suero fetal bovino inactivado con calor (FCS_i, Sigma), glutamina 4 mM (Biochrom) y 50 µg/ml de gentamicina (Biochrom), a 37°C en una atmósfera humidificada de 5% de CO₂/95% de aire por 7 días, con un cambio de medio el día 2.

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[00178] Después de 7 DIV, las células se agitaron durante la noche a 250 rpm para eliminar los oligodendrocitos y la microglía. Al día siguiente, los astrocitos se lavaron dos veces con CMF-PBS, se trataron con lisina y se subplaquearon en placas de 96 cavidades recubiertas previamente con poli-D-lisina (Becton Dickinson #6516 o #6640), a una densidad de 40000-45000 células/cavidad. 24 horas después de establecer el cultivo de astrocitos secundario, los astrocitos se lavaron con PBS⁺⁺ y se los mezcló con un medio definido con astrocitos (ADM), que consistió en DMEM que contenía suplemento G5 1x (InVitrogen), 0,5 µg/ml de sulfato de heparan (Sigma) y 1,5 µg/ml de fibronectina (Sigma) (Miller et al., 1993). 3 días después, se cambió el medio y las células se incubaron otros 2-3 días, de modo que en el momento de los experimentos los astrocitos estuvieran en 14-15 DIV.

Inmunocitoquímica

[00179] Se realizó una inmunocoloración para confirmar la presencia de marcadores clásicos de los astrocitos, tales como GFAP, así como la expresión de receptores mGluR5.

Acumulación de [³H]-inositol fosfatos

[00180] Después de cultivar los astrocitos por 12 días, se eliminó el ADM y se agregó DMEM libre de inositol (MP Biomedicals) suplementado con [³H]mio-inositol (0,5 µCi/cavidad; Perkin Elmer), y se usaron las sustancias químicas ADM. Después de 48 horas, se reemplazó el medio por 100 µl de amortiguador de Locke (más Li⁺ 20 mM, pH 7,4) y se incubó por 15 minutos a 37°C, antes de realizar el reemplazo por agonistas/antagonistas en amortiguador de Locke. La incubación (45 minutos a 37°C) se terminó reemplazando las soluciones de Locke por 100 µl de HCl 0,1 M (10 minutos en

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hielo). Las placas de 96 cavidades pueden congelarse a -20°C en esta etapa hasta realizar un análisis adicional. Se usaron columnas de resina de intercambio hechas a mano (AG1-X8 Biorad, 140-14444) para separar los inositol fosfatos marcados, mediante una elución con 1 ml de formato de amonio 1 M/ácido fórmico 0,1 M, en visiplacas de 24 cavidades (Perkin Elmer). Se agregó líquido de centelleo (UltimaFlow AF, Perkin Elmer), se selló la placa y se agitó antes de determinar la radiactividad por conteo de centelleo líquido convencional (Microbeta, Perkin Elmer), expresada como desintegración por minuto (DPM).

Estudios de calcio FLIPR

[00181] Los astrocitos cultivados expresaron receptores mGluR5, como lo indica la inmunocoloración. El incremento del calcio intracelular después de estimular con el agonista de mGluR5 DHPG o L-quisqualato se midió usando el lector fluorométrico de placa por formación de imágenes (FLIPR) y el conjunto de elementos Ca-Kit (ambos de Molecular Devices, CA). Antes de agregar el agonista o el antagonista, se aspiró el medio y se cargaron las células por 2 horas a temperatura ambiente, con 150 μl de un amortiguador de carga que consistió en un colorante sensible a Ca (MD # R8033) reconstituido en cloruro de sodio (123 mM), cloruro de potasio (5,4 mM), cloruro de magnesio (0,8 mM), cloruro de calcio (1,8 mM), D-glucosa (15 mM) y HEPES (20 mM), pH 7,3. Luego se transfirieron las placas al FLIPR para detectar el incremento de calcio con la adición de DHPG (300 μM) o L-quisqualato (100 nM), medido como unidades de fluorescencia relativa (RFU). Cuando se evaluaron los antagonistas, estos compuestos se incubaron previamente por 10 minutos a temperatura ambiente, antes de agregar el agonista respectivo.

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[00182] Para los moduladores positivos, se trazaron curvas de respuesta a la concentración en presencia y ausencia de modulador 10 μM , para determinar la extensión de la potenciación/el incremento de la potencia agonista. Luego se trazaron curvas de respuesta a la concentración para el modulador positivo en presencia de una concentración fija de quisqualato, con el fin de obtener la ventana más grande para la potenciación (normalmente 10-30 nM).

Análisis de los datos

[00183] La señal de fluorescencia después de agregar el agonista refleja el incremento del calcio intracelular. Las inconsistencias en la cantidad de células por cavidad se normalizaron usando la corrección de uniformidad espacial del software FLIPR. Se calculó el promedio de los datos temporales replicados ($n = 5$), y se lo usó para realizar una representación gráfica. Para evaluar la farmacología, se determinaron los cambios de calcio en respuesta a distintas concentraciones de agonista o antagonista usando un cálculo de máximo menos mínimo (MaxMin).

[00184] Todas las respuestas (valores de DPM o RFU) se determinaron como porcentaje del control (= respuesta máxima con quisqualato 100 nM). Los valores de EC_{50} y IC_{50} se calcularon de acuerdo con la ecuación logística, usando GraFit 5,0 (Erithacus Software).

Sustancias químicas

[00185] A menos que se indique lo contrario, todas las sustancias químicas se adquirieron en Sigma.

Referencias

Booher y Sensenbrenner (1972) *Neurobiology* **2**(3):97-105

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Miller et al., (1993) *Brain Res.* **618(1)**:175-8

[00186] Los compuestos de la presente invención tienen un rango de EC_{50} de entre aproximadamente 0,5 nM y aproximadamente 100 μ M.

CONCLUSIONES

[00187] En conclusión, a partir de lo establecido previamente, es evidente que la presente invención provee aplicaciones y usos novedosos, valiosos e impredecibles de los compuestos de la presente invención, donde los compuestos comprenden el principio activo de acuerdo con la presente invención, así como nuevas composiciones farmacéuticas de éstos y métodos para prepararlos y efectuar el tratamiento con éstos, donde los compuestos poseen las características y ventajas enumeradas más específicamente con anterioridad.

[00188] El orden elevado de actividad del agente activo de la presente invención y las composiciones de éste, como lo evidencian las pruebas descritas, indica su utilidad, sobre la base de su actividad valiosa sobre seres humanos, así como animales inferiores. Sin embargo, no se ha completado la evaluación clínica en seres humanos. Se comprenderá claramente que la distribución y la comercialización de cualquier compuesto o composición dentro del alcance de la presente invención para usar en seres humanos deberá estar sujeta a la aprobación previa por agencias gubernamentales, tales como la Administración Federal de Drogas y Alimentos de los EEUU, que es responsable y está autorizada para dirimir estas cuestiones.

[00189] Los presentes derivados de tetrahydroquinolinona sustituida con etinilo representan una clase nueva de moduladores de mGluR del Grupo I. Son especialmente útiles como moduladores positivos o agonistas de mGluR 5.

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Teniendo en cuenta su potencia, serán sustancias terapéuticas útiles en un amplio rango de trastornos del CNS que comprendan la excitación anormal inducida por glutamato.

[00190] Por consiguiente, estos compuestos pueden aplicarse en el tratamiento de los siguientes trastornos en el cuerpo de un animal vivo, especialmente un ser humano: demencia relacionada con SIDA, enfermedad de Alzheimer, síndrome de Creutzfeld-Jakob, encefalopatía espongiforme bovina (BSE) u otras infecciones relacionadas con priones, enfermedades que comprenden la disfunción mitocondrial, enfermedades que comprenden β amiloides y/o tauopatía, tales como síndrome de Down, encefalopatía hepática, enfermedad de Huntington, enfermedades de las neuronas motoras, tales como esclerosis lateral amiotrófica (ALS), esclerosis múltiple (MS), atrofia olivoponto-cerebelar, déficit cognitivo post-operatorio (POCD), enfermedad de Parkinson, demencia de Parkinson, alteración cognitiva leve, demencia pugilística, demencia vascular y del lóbulo frontal, alteración cognitiva, lesiones o enfermedades oculares (por ejemplo, glaucoma, retinopatía, degeneración macular), lesiones/traumas cefálicos y espinales, hipoglucemia, hipoxia (por ejemplo, perinatal), isquemia (por ejemplo, como resultado de una detención del corazón, apoplejía, operaciones de bypass o trasplantes), convulsiones, glioma y otros tumores, lesiones en el oído interno (por ejemplo, en el tinitus, inducido por sonido o drogas), discinecias inducidas por L-dopa y tardías.

[00191] Estos compuestos también pueden aplicarse en el tratamiento de los siguientes trastornos en el cuerpo de un animal vivo, especialmente un ser humano: adicción (nicotina, alcohol, opiáceos, cocaína, anfetaminas, obesidad y otras), esclerosis lateral amiotrófica (ALS), trastornos de ansiedad y pánico,

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trastorno de hiperactividad con déficit de atención (ADHD), síndrome de piernas inquietas y niños hiperactivos, autismo, convulsiones/epilepsia, demencia (por ejemplo, en la enfermedad de Alzheimer, el síndrome de Korsakoff, la demencia vascular, las infecciones de HIV), trastorno depresivo mayor o depresión (incluyendo la que resulta de una infección del virus Borna) y trastorno bipolar maníaco-depresivo, tolerancia a drogas, por ejemplo, a opiáceos, trastornos del movimiento, distonia, discinesia (por ejemplo, inducida por L-Dopa, discinesia tardía o en la enfermedad de Huntington), síndrome de X frágil, corea de Huntington, síndrome de intestino irritable (IBS), migraña, esclerosis múltiple, espasmos musculares, dolor (crónico y agudo, por ejemplo, dolor inflamatorio, dolor neuropático, alodinia, hiperalgesia, dolor nociceptivo), enfermedad de Parkinson, trastorno de estrés post-traumático, esquizofrenia (síntomas positivos y negativos), espasticidad, tinnitus, síndrome de Tourette, incontinencia urinaria y vómitos, condiciones pruríticas (por ejemplo, pruritis), trastornos del sueño, trastornos de la micción, trastorno neuromuscular en el tracto urinario inferior, enfermedad de reflujo gastroesofágico (GERD), esfínter esofágico inferior (LES), trastornos gastrointestinales funcionales, dispepsia, regurgitación, infección del tracto respiratorio, bulimia nerviosa, laringitis crónica, asma (por ejemplo, asma relacionado con reflujo), enfermedad pulmonar, trastornos de la alimentación, obesidad y trastornos relacionados con la obesidad.

[00192] Estos compuestos también pueden aplicarse en el tratamiento de indicaciones en el cuerpo de un animal vivo, especialmente un ser humano, donde no existe una necesariamente una condición particular, sino que es posible mejorar un parámetro fisiológico particular mediante la administración

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de los presentes compuestos, incluyendo el mejoramiento cognitivo.

[00193] El método para tratar el cuerpo de un animal vivo con un compuesto de la invención, para inhibir la progresión o aliviar una afección seleccionada entre las mencionadas, se realiza a través de cualquier ruta farmacéutica de aceptación normal, como se estableció previamente, empleando la dosificación seleccionada, efectiva para aliviar la afección particular que se desea paliar.

[00194] El uso de los compuestos de la presente invención en la fabricación de un medicamento para el tratamiento de un animal vivo para la progresión o el alivio de trastornos o condiciones seleccionadas, particularmente trastornos o condiciones susceptibles de ser tratadas con un modulador de mGluR del Grupo I, en particular, un modulador de mGluR 5, en especial, un modulador positivo o un agonista de mGluR 5, se realiza de forma usual, con un paso que consiste en mezclar una cantidad efectiva de un compuesto de la invención con un diluyente, un excipiente o un vehículo aceptable para el uso farmacéutico, al igual que el método de tratamiento, las composiciones farmacéuticas y el uso de un compuesto de la presente invención en la fabricación de un medicamento.

[00195] Las composiciones farmacéuticas representativas preparadas mezclando el ingrediente activo con un excipiente, un diluyente o un vehículo aceptable para el uso farmacéutico incluyen tabletas, cápsulas, soluciones para inyección, formulaciones líquidas orales, formulaciones en aerosol, formulaciones TDS y formulaciones nanoparticuladas, que permiten producir medicamentos de uso oral, por inyección o dérmico, también de acuerdo con lo establecido previamente.

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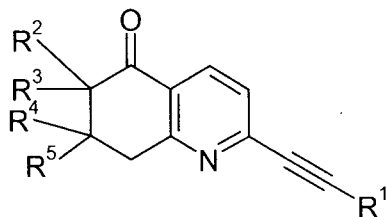
* * * * *

[00196] El alcance de la presente invención no está limitado por las realizaciones específicas descritas en la presente documentación. Más aún, varias modificaciones de la invención, además de aquellas descritas en la presente documentación, serán evidentes para aquellos entrenados en la técnica a partir de la descripción anterior.

[00197] Todas las patentes, las solicitudes, las publicaciones, los métodos de prueba, la literatura y otros materiales citados en la presente documentación se incorporan en la presente documentación a modo de referencia.

REIVINDICACIONES

1. Un compuesto CARACTERIZADO PORQUE es de Fórmula I



donde

R¹ representa arilo o heteroarilo;

R² y R³, que pueden ser iguales o diferentes entre sí, representan hidrógeno o C₁₋₆alquilo;

R⁴ y R⁵, que pueden ser iguales o diferentes entre sí, representan hidrógeno o C₁₋₆alquilo;

entendiéndose que:

arilo representa un anillo fenilo no sustituido o un anillo fenilo que está sustituido con 1, 2, 3, 4 o 5 sustituyentes, que pueden ser iguales o distintos entre sí, que se seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino, azetidino, pirrolidino, piperidino, morfolino, 4-C₁₋₆alquil-piperazino, tetrazolo, oxazolo, furilo, pirrolilo, tiofenilo, isoxazolo, tiazolo, imidazolo, oxadiazolo, piridinilo, pirimidilo y fenilo; heteroarilo representa un anillo (hetero)aromático de 5, 6 o 7 miembros con entre 1 y 4 heteroátomos donde dichos heteroátomos se seleccionan en forma independiente entre oxígeno, nitrógeno y azufre,

donde dicho anillo no está sustituido o está sustituido con 1, 2 o 3 sustituyentes, que pueden ser iguales o diferentes entre sí, que se seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino, azetidino, pirrolidino, piperidino, morfolino, 4-C₁₋₆alquil-piperazino, tetrazolo, oxazolo, furilo, pirrolo, tiofeno, isoxazolo, tiazolo, imidazolo, oxadiazolo, piridinilo, pirimidilo y fenilo;

y que los compuestos de Fórmula I no pueden representar:

2-Feniletinil-7,8-dihidro-6H-quinolin-5-ona

2-Piridin-3-iletinil-7,8-dihidro-6H-quinolin-5-ona

2-m-Toliletinil-7,8-dihidro-6H-quinolin-5-ona

2-(3-Hidroxi-feniletinil)-7,8-dihidro-6H-quinolin-5-ona

2-(3-Metoxi-feniletinil)-7,8-dihidro-6H-quinolin-5-ona

2-(3-Fluoro-feniletinil)-7,8-dihidro-6H-quinolin-5-ona

2-(3-Cloro-feniletinil)-7,8-dihidro-6H-quinolin-5-ona

2-(3-Bromo-feniletinil)-7,8-dihidro-6H-quinolin-5-ona

3-(5-Oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo

2-Tiazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona

2-Oxazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona

7,7-Dimetil-2-piridin-3-iletinil-7,8-dihidro-6H-quinolin-5-ona

7,7-Dimetil-2-m-toliletinil-7,8-dihidro-6H-quinolin-5-ona

2-(3-Hidroxi-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona

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2-(3-Metoxi-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Fluoro-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Cloro-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Bromo-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 3-(7,7-Dimetil-5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo
 7,7-Dimetil-2-tiazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-oxazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 2-(2-Fenil-oxazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona o
 2-(2-Fenil-tiazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona;

e isómeros ópticos, sales aceptables para uso farmacéutico, hidratos, solvatos y polimorfos del mismo.

2. Un compuesto de acuerdo con la reivindicación 1, CARACTERIZADO

PORQUE

R^2 y R^3 , que pueden ser iguales o diferentes entre sí, representan metilo, etilo, n-propilo, 2-propilo, n-butilo o tert-butilo y
 R^4 y R^5 representan hidrógeno.

3. Un compuesto de acuerdo con la reivindicación 1, CARACTERIZADO

PORQUE

R^2 y R^3 representan hidrógeno y
 R^4 y R^5 , que pueden ser iguales o diferentes entre sí, representan metilo, etilo, n-propilo, 2-propilo, n-butilo o tert-butilo.

4. Un compuesto de acuerdo con la reivindicación 1, CARACTERIZADO

PORQUE

R^2 , R^3 , R^4 y R^5 , que pueden ser iguales o diferentes representan hidrógeno, metilo o etilo.

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5. Un compuesto de acuerdo con cualquiera de las reivindicaciones precedentes, CARACTERIZADO PORQUE

R^1 representa arilo;

entendiéndose que:

arilo representa fenilo no sustituido o fenilo que está mono o disustituido con sustituyentes iguales o diferentes entre sí que se seleccionan del grupo que consiste en metilo, etilo, n-propilo, 2-propilo, n-butilo, tert-butilo, hidroxilo, metoxi, etoxi, n-propoxi, iso-propoxi, n-butoxi, tert-butoxi, CF_3 , CH_2F , CH_2F , C_2F_5 , OCF_3 , OC_2F_5 , F, Cl, Br, CN, piperidinilo, morfolinilo, tetrazolilo, oxazolilo, furilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo.

6. Un compuesto de acuerdo con la reivindicación 5, CARACTERIZADO PORQUE

arilo representa fenilo no sustituido o fenilo que está mono o disustituido llevando el/los sustituyente/s en la posición meta.

7. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 4, CARACTERIZADO PORQUE

R^1 representa heteroarilo;

entendiéndose que:

heteroarilo representa piridin-2-ilo, piridin-3-ilo, piridin-4-ilo, oxazol-5-ilo, tiazol-5-ilo, donde cada uno de estos anillos puede no estar sustituido o estar mono o disustituido con fenilo, metilo, etilo, n-propilo, 2-propilo, n-butilo, tert-butilo, hidroxilo, metoxi, etoxi, n-propoxi, iso-propoxi, n-butoxi, tert-butoxi, CF_3 , CH_2F , CH_2F , C_2F_5 , OCF_3 , OC_2F_5 , F, Cl, Br, CN, piperidinilo, morfolinilo, tetrazolilo, oxazolilo, furilo, tiofenilo, isoxazolilo,

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tiazolilo, imidazolilo, oxadiazolilo, piridinilo o pirimidilo.

8. Un compuesto de acuerdo con la reivindicación 1 CARACTERIZADO PORQUE se selecciona entre:

6,6-Dimetil-2-piridin-3-iletinil-7,8-dihidro-6H-quinolin-5-ona,
 2-(3-Fluoro-feniletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona,
 2-(3-Cloro-feniletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona,
 2-(3-Metoxi-feniletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona,
 2-(3-Hidroxi-feniletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona,
 3-(6,6-Dimetil-5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo,
 6,6-Dimetil-2-tiazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona,
 6,6-Dimetil-2-(3-piperidin-1-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona,
 7,7-Dimetil-2-(3-piperidin-1-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona,
 2-(3-Piperidin-1-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona,
 2-(3-Morfolin-4-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona,
 7,7-Dimetil-2-(3-morfolin-4-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona,
 6,6-Dimetil-2-(3-morfolin-4-il-feniletinil)-7,8-dihidro-6H-quinolin-5-ona,
 6,6-Dimetil-2-[3-(1H-tetrazol-5-il)-feniletinil]-7,8-dihidro-6H-quinolin-5-ona,
 7,7-Dimetil-2-[3-(1H-tetrazol-5-il)-feniletinil]-7,8-dihidro-6H-quinolin-5-ona,
 2-[3-(1H-Tetrazol-5-il)-feniletinil]-7,8-dihidro-6H-quinolin-5-ona,
 2-[3-Fluoro-5-(1H-tetrazol-5-il)-feniletinil]-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona,
 2-[3-Fluoro-5-(1H-tetrazol-5-il)-feniletinil]-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona,

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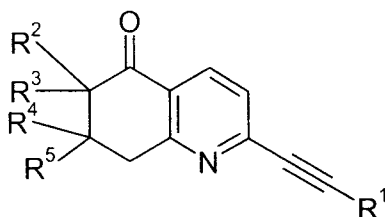
2-[3-Fluoro-5-(1H-tetrazol-5-il)-feniletinil]-7,8-dihidro-6H-quinolin-5-ona,
2-(3-Trifluorometil-feniletinil)-7,8-dihidro-6H-quinolin-5-ona,
7,7-Dimetil-2-(3-trifluorometil-feniletinil)-7,8-dihidro-6H-quinolin-5-ona,
6,6-Dimetil-2-(3-trifluorometil-feniletinil)-7,8-dihidro-6H-quinolin-5-ona,
7,7-Dimetil-2-feniletinil-7,8-dihidro-6H-quinolin-5-ona,
6,6-Dimetil-2-feniletinil-7,8-dihidro-6H-quinolin-5-ona,
2-(4-Metil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
7,7-Dimetil-2-(4-metil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
6,6-Dimetil-2-(4-metil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
2-(4-Fluoro-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
2-(4-Fluoro-tiazol-2-iletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona,
2-(4-Fluoro-tiazol-2-iletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona,
2-(2-Fenil-tiazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
2-(5-Fluoro-piridin-3-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
3-Fluoro-5-(7,7-Dimetil-5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-
benzonitrilo,
2-(4-Fluoro-5-fenil-oxazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
2-(4-Fluoro-5-piridin-3-il-oxazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
2-(4-Fluoro-5-piridin-3-il-oxazol-2-iletinil)-7,7-dimetil-7,8-dihidro-6H-
quinolin-5-ona,
2-(4-Fluoro-5-piridin-3-il-oxazol-2-iletinil)-6,6-dimetil-7,8-dihidro-6H-
quinolin-5-ona,
7,7-Dimetil-2-piridin-2-iletinil-7,8-dihidro-6H-quinolin-5-ona,
2-Piridin-2-iletinil-7,8-dihidro-6H-quinolin-5-ona,
6,6-Dimetil-2-piridin-2-iletinil-7,8-dihidro-6H-quinolin-5-ona,

6,6-Dimetil-2-(4-metil-oxazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
7,7-Dimetil-2-(4-metil-oxazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
2-(4-Fluoro-5-piridin-3-il-1H-imidazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
2-(4-Fluoro-5-piridin-3-il-1H-imidazol-2-iletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona,
2-(4-Fluoro-5-piridin-3-il-1H-imidazol-2-iletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona,
6,6-Dimetil-2-(4-piridin-3-il-imidazol-1-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
7,7-Dimetil-2-(4-piridin-3-il-imidazol-1-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
2-(4-Piridin-3-il-imidazol-1-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
2-Tiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona,
2-[1,3,4]Tiadiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona,
2-[1,3,4]Oxadiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona,
2-(1H-Tetrazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
6,6-Dimetil-2-[1,3,4]tiadiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona,
7,7-Dimetil-2-[1,3,4]tiadiazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona,
7,7-Dimetil-2-(1H-tetrazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
6,6-Dimetil-2-(1H-tetrazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
6,6-Dimetil-2-oxazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona,
2-Oxazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona,
6,6-Dimetil-2-oxazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona,
7,7-Dimetil-2-oxazol-2-iletinil-7,8-dihidro-6H-quinolin-5-ona,

6,6-Dimetil-2-m-toliletinil-7,8-dihidro-6H-quinolin-5-ona,
 7,7-Dimetil-2-(2-fenil-oxazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
 6,6-Dimetil-2-(2-fenil-oxazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
 7,7-Dimetil-2-(5-fenil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
 6,6-Dimetil-2-(5-fenil-tiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
 2-(5-Fluoro-piridin-3-iletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona,
 2-(5-Fluoro-piridin-3-iletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-ona,
 3-Fluoro-5-(5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo,
 3-(6,6-Dimetil-5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-5-fluoro-
 benzonitrilo,
 2-(4-Fluoro-5-fenil-oxazol-2-iletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-
 ona,
 2-(4-Fluoro-5-fenil-oxazol-2-iletinil)-6,6-dimetil-7,8-dihidro-6H-quinolin-5-
 ona,
 6,6-Dimetil-2-(5-piridin-3-il-[1,3,4]oxadiazol-2-iletinil)-7,8-dihidro-6H-
 quinolin-5-ona,
 7,7-Dimetil-2-(5-piridin-3-il-[1,3,4]oxadiazol-2-iletinil)-7,8-dihidro-6H-
 quinolin-5-ona,
 2-(5-Piridin-3-il-[1,3,4]oxadiazol-2-iletinil)-7,8-dihidro-6H-quinolin-5-ona,
 e isómeros ópticos, sales aceptables para uso farmacéutico, hidratos,
 solvatos y polimorfos del mismo.

9. Un medicamento CARACTERIZADO PORQUE comprende al menos uno de los compuestos de Fórmula I





donde

R^1 representa arilo o heteroarilo;

R^2 y R^3 , que pueden ser iguales o diferentes entre sí, representan hidrógeno o

C_{1-6} alquilo;

R^4 y R^5 , que pueden ser iguales o diferentes entre sí, representan hidrógeno o

C_{1-6} alquilo;

entendiéndose que:

arilo representa un anillo fenilo no sustituido o un anillo fenilo que está sustituido con 1, 2, 3, 4 o 5 sustituyentes, que pueden ser iguales o distintos entre sí, que se seleccionan del grupo que consiste en C_{1-6} alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C_{1-6} alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, ciclo C_{3-12} alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di- C_{1-6} alquilamino, N-ciclo C_{3-12} alquil-N- C_{1-6} alquilamino, azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 4- C_{1-6} alquil-piperazinilo, tetrazolilo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo; heteroarilo representa un anillo (hetero)aromático de 5, 6 o 7 miembros con entre 1 y 4 heteroátomos donde dichos heteroátomos se seleccionan en forma independiente entre oxígeno, nitrógeno y azufre,

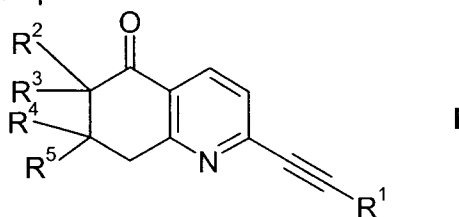
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donde dicho anillo no está sustituido o está sustituido con 1, 2 o 3 sustituyentes, que pueden ser iguales o diferentes entre sí, que se seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino, azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 4-C₁₋₆alquil-piperazinilo, tetrazolilo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo; e isómeros ópticos, sales aceptables para uso farmacéutico, hidratos, solvatos y polimorfos del mismo; con la excepción de los siguientes compuestos e isómeros ópticos, sales aceptables para uso farmacéutico, hidratos, solvatos y polimorfos de los mismos:

2-Feniletinil-7,8-dihidro-6H-quinolin-5-ona
 2-Piridin-3-iletinil-7,8-dihidro-6H-quinolin-5-ona
 2-m-Toliletinil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Hidroxi-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Metoxi-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Fluoro-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Cloro-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Bromo-feniletinil)-7,8-dihidro-6H-quinolin-5-ona
 3-(5-Oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo
 2-Tiazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona

2-Oxazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-piridin-3-iletinil-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-m-toliletinil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Hidroxi-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Metoxi-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Fluoro-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Cloro-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 2-(3-Bromo-feniletinil)-7,7-dimetil-7,8-dihidro-6H-quinolin-5-ona
 3-(7,7-Dimetil-5-oxo-5,6,7,8-tetrahidro-quinolin-2-iletinil)-benzonitrilo
 7,7-Dimetil-2-tiazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 7,7-Dimetil-2-oxazol-5-iletinil-7,8-dihidro-6H-quinolin-5-ona
 2-(2-Fenil-oxazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona y
 2-(2-Fenil-tiazol-5-iletinil)-7,8-dihidro-6H-quinolin-5-ona.

10. El uso de un compuesto de Fórmula I



donde

R^1 representa arilo o heteroarilo;

R^2 y R^3 , que pueden ser iguales o diferentes entre sí, representan hidrógeno o C_{1-6} alquilo;

R^4 y R^5 , que pueden ser iguales o diferentes entre sí, representan hidrógeno o C_{1-6} alquilo;

entendiéndose que:

arilo representa un anillo fenilo no sustituido o un anillo fenilo que está

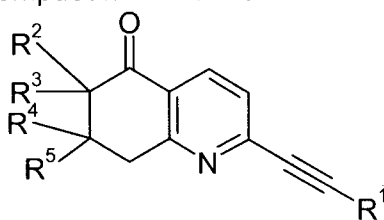
sustituido con 1, 2, 3, 4 o 5 sustituyentes, que pueden ser iguales o distintos entre sí, que se seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino, azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 4-C₁₋₆alquil-piperazinilo, tetrazolilo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo; heteroarilo representa un anillo (hetero)aromático de 5, 6 o 7 miembros con entre 1 y 4 heteroátomos donde dichos heteroátomos se seleccionan en forma independiente entre oxígeno, nitrógeno y azufre, donde dicho anillo no está sustituido o está sustituido con 1, 2 o 3 sustituyentes, que pueden ser iguales o diferentes entre sí, que se seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino, azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 4-C₁₋₆alquil-piperazinilo, tetrazolilo, oxazolilo, furilo, pirrolilo, tiofenilo, isoxazolilo, tiazolilo, imidazolilo, oxadiazolilo, piridinilo, pirimidilo y fenilo; e isómeros ópticos, sales aceptables para uso farmacéutico, hidratos, solvatos y polimorfos del mismo;

CARACTERIZADO PORQUE es en la fabricación de un medicamento

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para la prevención y/o el tratamiento de un estado clínico o enfermedad en un animal incluyendo un humano donde dicho estado clínico o enfermedad está afectado o facilitado por el efecto modulador de moduladores de mGluR5.

11. El uso de acuerdo con la reivindicación 10, CARACTERIZADO PORQUE los moduladores de mGluR5 son moduladores positivos de mGluR5 o agonistas de mGluR5.
12. El uso de un compuesto de Fórmula I



donde

R¹ representa arilo o heteroarilo;

R² y R³, que pueden ser iguales o diferentes entre sí, representan hidrógeno o C₁₋₆alquilo;

R⁴ y R⁵, que pueden ser iguales o diferentes entre sí, representan hidrógeno o C₁₋₆alquilo;

entendiéndose que:

arilo representa un anillo fenilo no sustituido o un anillo fenilo que está sustituido con 1, 2, 3, 4 o 5 sustituyentes, que pueden ser iguales o distintos entre sí, que se seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-

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C₁₋₆alquilamino, azetidino, pirrolidino, piperidino, morfolino, 4-C₁₋₆alquil-piperazino, tetrazolo, oxazolo, furilo, pirrolo, tiofeno, isoxazolo, tiazolo, imidazolo, oxadiazolo, piridino, pirimidilo y fenilo; heteroarilo representa un anillo (hetero)aromático de 5, 6 o 7 miembros con entre 1 y 4 heteroátomos donde dichos heteroátomos se seleccionan en forma independiente entre oxígeno, nitrógeno y azufre, donde dicho anillo no está sustituido o está sustituido con 1, 2 o 3 sustituyentes, que pueden ser iguales o diferentes entre sí, que se seleccionan del grupo que consiste en C₁₋₆alquilo, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, C₁₋₆alcoxi, que está opcionalmente sustituido con uno o más átomos de flúor, cloro o bromo, cicloC₃₋₁₂alquilo, hidroxilo, F, Cl, Br, I, CN, nitro, di-C₁₋₆alquilamino, N-cicloC₃₋₁₂alquil-N-C₁₋₆alquilamino, azetidino, pirrolidino, piperidino, morfolino, 4-C₁₋₆alquil-piperazino, tetrazolo, oxazolo, furilo, pirrolo, tiofeno, isoxazolo, tiazolo, imidazolo, oxadiazolo, piridino, pirimidilo y fenilo; e isómeros ópticos, sales aceptables para uso farmacéutico, hidratos, solvatos y polimorfos del mismo;

CARACTERIZADO PORQUE es en la fabricación de un medicamento para la prevención y/o el tratamiento de demencia relacionada con SIDA, enfermedad de Alzheimer, síndrome de Creutzfeld-Jakob, encefalopatía espongiforme bovina (BSE) u otras infecciones relacionadas con priones, enfermedades que comprenden la disfunción mitocondrial, enfermedades que comprenden β amiloides y/o tauopatía, tales como síndrome de Down, encefalopatía hepática, enfermedad de Huntington,

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enfermedades de las neuronas motoras, tales como esclerosis lateral amiotrófica (ALS), esclerosis múltiple (MS), atrofia olivoponto-cerebelar, déficit cognitivo post-operatorio (POCD), enfermedad de Parkinson, demencia de Parkinson, alteración cognitiva leve, demencia pugilística, demencia vascular y del lóbulo frontal, alteración cognitiva, lesiones o enfermedades oculares (por ejemplo, glaucoma, retinopatía, degeneración macular), lesiones/traumas cefálicos y espinales, hipoglucemia, hipoxia (por ejemplo, perinatal), isquemia (por ejemplo, como resultado de una detención del corazón, apoplejía, operaciones de bypass o transplantes), convulsiones, glioma y otros tumores, lesiones en el oído interno (por ejemplo, en el tinitus, inducido por sonido o drogas), discinecias inducidas por L-dopa y tardías, adicción (nicotina, alcohol, opiáceos, cocaína, anfetaminas, obesidad y otras), trastornos de ansiedad y pánico, trastorno de hiperactividad con déficit de atención (ADHD), síndrome de piernas inquietas y niños hiperactivos, autismo, convulsiones/epilepsia, demencia (por ejemplo, en la enfermedad de Alzheimer, el síndrome de Korsakoff, la demencia vascular, las infecciones de HIV), trastorno depresivo mayor o depresión (incluyendo la que resulta de una infección del virus Borna) y trastorno bipolar maniaco-depresivo, tolerancia a drogas, por ejemplo, a opiáceos, trastornos del movimiento, distonia, discinesia (por ejemplo, inducida por L-Dopa, discinesia tardía o en la enfermedad de Huntington), síndrome de X frágil, corea de Huntington, síndrome de intestino irritable (IBS), migraña, esclerosis múltiple, espasmos musculares, dolor (crónico y agudo, por ejemplo, dolor inflamatorio, dolor neuropático, alodinia,

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hiperalgesia, dolor nociceptivo), enfermedad de Parkinson, trastorno de estrés post-traumático, esquizofrenia (síntomas positivos y negativos), espasticidad, síndrome de Tourette, incontinencia urinaria y vómitos, condiciones pruríticas (por ejemplo, pruritis), trastornos del sueño, trastornos de la micción, trastorno neuromuscular en el tracto urinario inferior, enfermedad de reflujo gastroesofágico (GERD), esfínter esofágico inferior (LES), trastornos gastrointestinales funcionales, dispepsia, regurgitación, infección del tracto respiratorio, bulimia nerviosa, laringitis crónica, asma (por ejemplo, asma relacionado con reflujo), enfermedad pulmonar, trastornos de la alimentación, obesidad y trastornos relacionados con la obesidad, agorafobia, trastorno de ansiedad generalizada, trastorno obsesivo-compulsivo, trastorno de pánico, trastorno de estrés post-traumático, fobia social, trastorno de ansiedad inducida por sustancias, trastorno alucinatorio, trastorno esquizoafectivo, trastorno esquizofreniforme, trastorno psicótico inducido por sustancias, delirio, o para el mejoramiento cognitivo o la neuroprotección.

13. El uso de acuerdo con la reivindicación 12, CARACTERIZADO PORQUE el medicamento es para la prevención y/o el tratamiento de adicción, dolor neuropático, discinecias inducidas por L-dopa y tardías, ALS, síndrome de X frágil, enfermedad de Parkinson, trastornos de ansiedad, epilepsia, síntomas positivos y/o negativos de esquizofrenia, alteración cognitiva o para el mejoramiento cognitivo o la neuroprotección.
14. Una composición farmacéutica CARACTERIZADA PORQUE comprende como ingrediente activo un compuesto de la reivindicación 1 junto con

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uno o más excipientes o vehículos aceptables para uso farmacéutico.

p.p. MERZ PHARMA GmbH & Co. KGAA

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TETRAHIDROQUINOLINONAS Y SU USO COMO MODULADORES DE
RECEPTORES DE GLUTAMATO METABOTRÓPICOS

RESUMEN

Derivados de tetrahydroquinolinona sustituida con etinilo así como sus sales aceptables para uso farmacéutico. Un proceso para la preparación de dichos compuestos. Los compuestos de la invención son moduladores de mGluR del Grupo I y por lo tanto son útiles para el control y la prevención de trastornos neurológicos agudos y/o crónicos.

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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2006/003170

International filing date (day/month/year)
24.08.2006

Priority date (day/month/year)
24.08.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07D215/00 A61K31/4709 A61P25/00

Applicant
MERZ PHARMA GMBH & CO. KGAA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Wolf, Claudia

Telephone No. +49 89 2399-8285



WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2006/003170

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2006/003170

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-14
	No: Claims	

Inventive step (IS)	Yes: Claims	1-14
	No: Claims	

Industrial applicability (IA)	Yes: Claims	1-14
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V.

Reference is made to the following documents:

- D1 : WO 02/28837 A (JANSSEN PHARMACEUTICA N.V; MABIRE, DOMINIQUE, JEAN-PIERRE; VENET, MARC) 11 April 2002 (2002-04-11)
D2 : SCHOEPP D D ET AL: "Pharmacological agents acting at subtypes of metabotropic glutamate receptors" NEUROPHARMACOLOGY, PERGAMON PRESS, OXFORD, GB, vol. 38, no. 10, 1999, pages 1431-1476, XP002345330
ISSN: 0028-3908

In the light of the cited prior art the subject matter claimed is considered to be novel and to involve an inventive step (Art. 33(2) and (3) PCT).

The proviso appears to be there to delimit the subject matter claimed from prior art documents which are not prepublished to the application as herein filed.

D1 discloses compounds having the same qualitative pharmacological profile as the compounds as claimed. They differ structurally mainly from those in the core structure which is not partly saturated as claimed in the present application and is lacking at least the ring -oxo group as claimed herein.

D2 is background prior art for metabotropic glutamat receptors activities.

The technical problem underlying the present application was the provision of further metabotropic glutamat receptor antagonists.

D1 does not disclose any incentive which would directly and unambiguously lead the skilled person faced with the the above technical problem to the presently claimed solution.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 408.88983/01	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/GB2006/003170	International filing date (day/month/year) 24/08/2006	(Earliest) Priority Date (day/month/year) 24/08/2005
Applicant MERZ PHARMA GMBH & CO. KGAA		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☐ none of the figures is to be published with the abstract
- 226

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2006/003170

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D215/00 A61K31/4709 A61P25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/28837 A (JANSSEN PHARMACEUTICA N.V.; MABIRE, DOMINIQUE, JEAN-PIERRE; VENET, MARC) 11 April 2002 (2002-04-11) claim 1	1-14
A	SCHOEPP D D ET AL: "Pharmacological agents acting at subtypes of metabotropic glutamate receptors" NEUROPHARMACOLOGY, PERGAMON PRESS, OXFORD, GB, vol. 38, no. 10, 1999, pages 1431-1476, XP002345330 ISSN: 0028-3908 the whole document	1-14



Further documents are listed in the continuation of Box C.



See patent family annex

* Special categories of cited documents:

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

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

Date of the actual completion of the international search

17 November 2006

Date of mailing of the international search report

01/12/2006

Name and mailing address of the ISA/

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

Authorized officer

Wolf, Claudia

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 408.88983/01

Box No. I TITLE OF INVENTION

Tetrahydroquinolinones and their use as modulators of metabotropic glutamate receptors

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Merz Pharma GmbH & Co. KGaA
100 Eckenheimer Landstrasse
D-60318 Frankfurt (Main)
DE

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:

DE

State (that is, country) of residence:

DE

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

PARSONS, Christopher Graham Raphael
Wartbaumstrasse 38
D-61130 Nidderau
DE

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

GB

State (that is, country) of residence:

DE

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

MARSDEN, John Christopher et al.
Frank B. Dehn & Co.
St Bride's House
10 Salisbury Square
London EC4Y 8JD
GB

Telephone No.

+44 20 7632 7200

Facsimile No.

+44 20 7353 8895

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

228

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

JIRGENSONS, Aigars
Hospitalu iela 3-103
Riga LV-1013
LV

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

LV

State (that is, country) of residence:

LV

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

JAUNZEME, Ieva
Udelu 14-45
Riga LV-1064
LV

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

LV

State (that is, country) of residence:

LV

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KALVINSH, Ivars
Miera 17-8
Salaspils LV-2169
LV

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

LV

State (that is, country) of residence:

LV

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

HENRICH, Markus
Am Kreuzberg 1
D-35516 Münzenberg
DE

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

DE

State (that is, country) of residence:

DE

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

VANEJEVS, Maksims
Mezhotnes str. 58
Riga LV-1002
LV

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

LV

State (that is, country) of residence:

LV

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

WEIL, Tanja
Keplerstrasse 14
D-69120 Heidelberg
DE

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

DE

State (that is, country) of residence:

DE

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KAUSS, Valerjans
Deglava 108/2-36
Riga LV-1082
LV

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

LV

State (that is, country) of residence:

LV

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

DANYSZ, Wojciech
Vor den Garten 16
D-61130 Nidderau
DE

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

PL

State (that is, country) of residence:

DE

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

JATZKE, Claudia
Homburger Landstrasse 471
D-60433 Frankfurt (Main)
DE

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

DE

State (that is, country) of residence:

DE

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☐ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☐ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☐ the United States of America only☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents. However,

- ☐ DE Germany is not designated for any kind of national protection
☐ JP Japan is not designated for any kind of national protection
☐ KR Republic of Korea is not designated for any kind of national protection
☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application. See the Notes to Box No. V as to the consequences of such national law provisions in these States).

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 24 August 2005 (24.08.05)	PCT/GB2005/003285			GB
item (2)				
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)).

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / EP

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)
 24 August 2005 PCT/GB2005/003285 PCT

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:		This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):		Number of items
(a) on paper, the following number of sheets:		1. ☒ fee calculation sheet		1
request (including declaration sheets) :	6	2. ☐ original separate power of attorney		
description (excluding sequence listing and/or tables related thereto) :	83	3. ☐ original general power of attorney		
claims :	15	4. ☐ copy of general power of attorney; reference number, if any:		
abstract :	1	5. ☐ statement explaining lack of signature		
drawings :		6. ☐ priority document(s) identified in Box No. VI as item(s):		
Sub-total number of sheets :	105	7. ☐ translation of international application into (language):		
sequence listing :		8. ☐ separate indications concerning deposited microorganism or other biological material		
tables related thereto :		9. ☐ sequence listing in electronic form (indicate type and number of carriers)		
(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)		(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :		
Total number of sheets :	105	(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :		
(b) ☐ only in electronic form (Section 801(a)(i))		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column :		
(i) ☐ sequence listing		10. ☐ tables in electronic form related to sequence listing (indicate type and number of carriers)		
(ii) ☐ tables related thereto		(i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application) :		
(c) ☐ also in electronic form (Section 801(a)(ii))		(ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) :		
(i) ☐ sequence listing		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :		
(ii) ☐ tables related thereto		11. ☐ other (specify):		
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the				
☐ sequence listing:				
☐ tables related thereto:				
(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)				

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

John Christopher MARSDEN - Agent for the Applicants

For receiving Office use only		For International Bureau use only	
1. Date of actual receipt of the purported international application:		2. Drawings:	
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		☐ received:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):		☐ not received:	
5. International Searching Authority (if two or more are competent): ISA /		6. ☐ Transmittal of search copy delayed until search fee is paid	

Date of receipt of the record copy by the International Bureau:

2303

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: FRANK B. DEHN & CO. Attn. Marsden, John C. St Bride's House 10 Salisbury Square London, EC4Y 8JD GRANDE BRETAGNE	File 408 88983/01 = 4 CCC 2006 FRANK B. DEHN & CO. RECEIVED ANNO
---	---

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year) 01/12/2006	
Applicant's or agent's file reference 408.88983/01	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/GB2006/003170	International filing date (day/month/year) 24/08/2006
Applicant MERZ PHARMA GMBH & CO. KGAA	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority

 European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
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Authorized officer

Josef Ullrich

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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

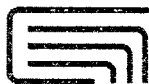
Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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Clarke, Modet & Co

COLOMBIA

Carrera 11 n° 93-43, Of. 404 Bogotá Colombia Tel: (57 1) 6350813-Fax: (57 1) 6350824 Email: clarkemodet@clarkemodet.com.co

PODER

Yo (nosotros), abajo firmante(s)

en mi (nuestro) carácter de representante(s) legales de

una sociedad organizada y existente de acuerdo con las leyes de

y en actual cumplimiento de su objeto social, con domicilio en

por el presente instrumento confiero (conferimos) poder especial a favor de DILIA MARIA RODRIGUEZ D'ALEMAN, con Cédula de Ciudadanía No. 41.654.882 de Bogotá, y tp. 20824 y CLAUDIA LUCIA CARO RAMIREZ, con Cédula de Ciudadanía No. 40.017.374 de Tunja, y tp. 36448, con domicilio en Bogotá, Colombia, para que actuando en su orden en nombre del (de la) otorgante le (la) representen ante cualquier entidad, autoridad y/o persona, especialmente ante las del orden Administrativo, Contencioso Administrativo, Judicial, Tribunales de Arbitramento y/o cualquier otro en lo referente a los siguientes asuntos:

1) Solicitar, tramitar, obtener y/o registrar cualquiera de las modalidades de Propiedad Industrial, tales como: patentes de invención, modelos de utilidad; diseños industriales, variedades vegetales; marcas, lemas, nombres y enseñanzas comerciales y denominaciones de origen; así como sus renovaciones, prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.

2) Solicitar, tramitar, obtener y/o registrar derechos de autor, en cualquiera de sus presentaciones así como la protección de secretos industriales y know-how.

3) Solicitar, tramitar, obtener y/o registrar registros sanitarios, permisos y/o licencias de funcionamiento; así como sus renovaciones o prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.

4) Ejercer acciones de oposición, observación, reclamos, reconsideración, reposición, apelación, cancelación administrativa o judicial, nulidad, protección al consumidor, concesión de licencias, protección de secretos industriales y demás acciones y recursos relacionados con derechos derivados de los asuntos arriba indicados y en contra de la competencia desleal, acciones derivadas de la obtención o explotación de licencias, acciones de indemnización de perjuicios. También podrá(n) intervenir en juicios civiles, comerciales, penales, contencioso-administrativos, tutelas y de policía; en acciones o juicios promovidos por el (la) mandante o en contra de (ella).

5) Registrar nombres de dominio ante la entidad competente.

6) En el ejercicio de este mandato los mandatarios arriba mencionados quedan facultados para: conciliar, cancelar, transigir, comprometer en árbitros, desistir, recibir y tomar posesión de la cosa objeto de litigio y renunciar o desistir a derechos concedidos o en curso de concesión, admitir los hechos del proceso.

7) Ratificar o no la agencia oficiosa.

8) Así mismo faculta (facultamos) a los mencionados apoderados para recibir notificaciones y designar apoderados judiciales o extrajudiciales, sustituir el presente poder y revocar las sustituciones que hicieren.

Dado y firmado en

a los

días de

[Handwritten signature]

POWER OF ATTORNEY

I (we), the undersigned
Christian PERTSCHY

legal representative(s) of
MERZ PHARMA GMBH & CO. KGAA
an organization existing under the laws of
Frankfurt, Germany

and in present execution of its business activity, domiciled at
Eckenheimer Landstrasse 100
60318 Frankfurt am Main, Germany

do hereby grant POWER OF ATTORNEY to DILIA MARIA RODRIGUEZ D'ALEMAN, identification card No. 41.654.882 of Bogotá, and tp. 20824 and CLAUDIA LUCIA CARO RAMIREZ, tp. 36448, identification card No. 40.017.374 of Tunja, residing in Bogotá, Colombia, to act in the order of their appointment in behalf of grantor before any entity, authority and/or natural or juridical person, specially before those Administrative, Administrative-Contentious, Judicial, arbitration courts, and/or any other, in all matters concerning the following:

1) To apply, process, obtain and/or register any of the modalities of Industrial Property, such as: Patents of Invention, Utility Models; Designs, plant varieties; Marks, Slogans, Trade Names and emblems and appellations of Origin; as well as their renewals, assignments, changes of name and/or domicile, agreements and licenses.

2) To apply, process, obtain and/or register copyrights of any kind as well as protection of industrial secrets or know-how.

3) To apply, process, obtain and/or register sanitary registrations, operating authorizations and/or licenses; as well as their renewals or assignments, changes of name and/or domicile, agreements and licenses.

4) To bring actions of opposition, observations, claims, reconsideration, appeal or legal remedies, cancellations, nullity, protection to the consumer, granting of licenses, protection of trade secrets and other actions related with rights derived from the above-mentioned matters and against the unfair competition, actions resulting from the obtaining or exploitation of licenses, recovering damages actions. They can also intervene or participate in Civil, Commercial, Criminal or Contentious-Administrative Trials; the actions for writ mandamus, police actions; in actions, lawsuits or litigations instituted by the grantor or against him.

5) To register domain names before the competent entity.

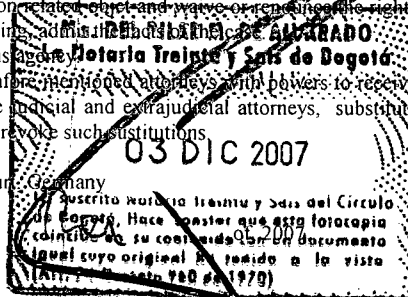
6) To the effect of this mandate the above-named proxy are empowered to conciliate, cancel, settle, submit to arbitration, withdraw and to receive and take possession of the litigation-related object and waive or renounce the rights granted or in process of granting, admission and the right of appeal.

7) To ratify or not the officious agency of the Notaría Trinitaria y San de Bogotá.

8) I (we) hereby appoint the above-mentioned attorneys with powers to receive notifications and to designate judicial and extrajudicial attorneys, substitute this Power of Attorney and to revoke such substitutions.

Granted and signed at Frankfurt, Germany

on this 8 day of



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CERTIFICADO NOTARIAL

(Cuando el solicitante es SOCIEDAD)

(Poderes otorgados en: El Salvador, Estados Unidos, México y Venezuela)

A los _____ días del mes de _____ de _____
el Notario que suscribe DA FE de que:

1. _____
(nombre de la persona que firma el poder)

mayor de edad y domiciliado en _____
_____ firmó de su puño
y letra el documento que antecede.

2. Conoce al (a la) otorgante y que este (a) está legalmente capacitado para el otorgamiento.

3. El otorgante ha firmado el referido documento en su carácter de _____
de la persona jurídica _____

4. La citada persona jurídica con sede en _____
_____ está legalmente
constituida, que tiene actualmente
existencia legal y que el acto para el cual se ha otorgado este
poder está comprendido entre los que constituyen su objeto social.
5. El otorgante tiene efectivamente la representación que ostenta, que
esta es legítima y que está facultado para otorgar este poder.
6. las anteriores certificaciones de los puntos 3, 4 y 5, me constan porque
he tenido a la vista los documentos auténticos.

Notario Público

NOTA: A continuación de lo anterior, el Cónsul de Colombia debe
autenticar la firma del Notario Público.

CERTIFICADO NOTARIAL (Cuando el solicitante es INDIVIDUO)

A los _____ días del mes de _____ de _____
el Notario que suscribe DA FE de que:

1. _____
(nombre de la persona que firma el poder)

mayor de edad y domiciliado en _____
_____ firmó en su presencia
el documento que antecede, conoce al otorgante y que este está
legalmente capacitado para el otorgamiento.

Notario Público

NOTA: A continuación de lo anterior, el Cónsul de Colombia debe
autenticar la firma del Notario Público.

Para todos los demás países el Señor Cónsul de Colombia o ante
quien se otorgue, debe expedir una certificación dejando constancia
1) de la existencia legal de la sociedad, 2) de que esta ejerce
actualmente su objeto social, y 3) de que la persona o personas que
otorgan el poder están facultadas para hacerlo, dejando
constancia así mismo de que tuvo a la vista las pruebas que acrediten
tales circunstancias.

LEGALIZACIÓN POR EL CONSUL DE COLOMBIA
O POR APOSTILLA

NOTARIAL CERTIFICATE

(When the applicant is a CORPORATION)

(Powers of attorney granted in: El Salvador, Mexico, U.S.A. and Venezuela)

This _____ day of _____
the undersigned Notary CERTIFIES that:

1. _____ Christian PERTSCHY
(name of the person who signs the power of attorney)

of legal age and domiciled in _____
_____ set his hand on the foregoing document.

2. The grantor is to him personally known and that he/she has legal capacity to
execute the document.

3. The grantor has executed the foregoing document in his capacity
of _____ Chief Legal Officer

of the juridical company MERZ PHARMA GMBH & CO. KGAA

4. The mentioned juridical company with place of business in
Eckenhimer Landstrasse 100

60318 Frankfurt am Main, Germany

is duly organized, has actual legal existence and that the purposes for which
the power of attorney is granted are within the scope of its corporate purposes.

5. The grantor has in fact the referred quality and that his/her representa-
tion is legal and that he/she is empowered to grant this power of
attorney.

6. I have based the above certifications 3, 4 and 5, on the authentic documents
which for such purpose were exhibited to me.

Notary Public

NOTA: Then the Colombian Consul must legalize the signature of the Notary
Public.

NOTARIAL CERTIFICATE (When the applicant is an INDIVIDUALS)

On this _____ day of _____
the undersigned Notary CERTIFIES that:

1. _____
(name of the person who signs the Power of Attorney)

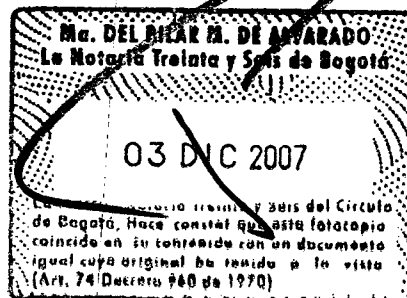
of legal age and domiciled at _____
_____ signed in his presence the foregoing
document, the grantor is to him personally known and that he/she has legal
capacity to execute the document.

Notary Public

NOTA: Then the Colombian Consul must legalize the signature of the Notary
Public.

For all other countries the Colombian Consul or before who it is granted
must issue a certification stating 1) the legal existence of the corporation,
2) that the corporate purposes are actually being accomplished, 3) that
the person or persons who grant this Power of Attorney are empowered
to do it. The Consul will certify also that the documents evidencing those
circumstances were exhibited to him.

LEGALIZATION BY THE COLOMBIAN CONSUL OR BY
APOSTILLE.



Umstehende vor mir geleistete Namensunterschrift des mir von Person bekannten Herrn Dr. Christian Pertschy, dienstansässig Eckenheimer Landstraße 100-104, 60318 Frankfurt am Main, beglaubige ich hiermit, nachdem ich mich auf Ersuchen in die Geschäftsräume der Merz Pharma GmbH & Co. KGaA begeben hatte. Der Unterzeichnende wurde vor Unterschriftsleistung von mir nach einer Vorbefassung i.S. von § 3 I Nr. 7 BeurkG befragt. Dies wurde von ihm verneint.

Frankfurt am Main, den 06. März 2007



Notar

Kostenrechnung

Wert: 5.000,00 €

Gebühr §§ 32, 45 KostO ¼

10,50 €

Gebühr § 58 KostO

10,50 €

Gebühr §§ 137, 152 KostO

0,55 €

21,55 €

19 % Mwst.

4,09 €

25,64 €



Notar

APOSTILLE

(Convention de la Haye du 5 octobre 1961)

1. Land: Bundesrepublik Deutschland
Diese öffentliche Urkunde
2. ist unterschrieben von Gerhard Haase
3. in seiner Eigenschaft als amtlich bestellter Notar
4. sie ist versehen mit dem Siegel/Stempel des(der)
Notars

5. in Frankfurt/Main

7. durch den Herrn Präsidenten des Landgerichts

8. unter Nr. 91 Ea A 225

9. Siegel/Stempel



Bestätigt

6. am 06.03.07

03 NIC 2007

10. Unterschrift
Kramer

TRADUCCION OFICIAL No. 11940

de un documento escrito en Alemán, efectuada por Luz Arriaga de Herber, resolución del Ministerio de Justicia 599 del 6 de marzo 1978.-

Traducción de la legalización de la firma del señor Christian Pertschy, representante legal de MERZ PHARMA GMBH & CO. KGAA, y de la apostilla en alemán que se encuentran a continuación de un documento de poder conferido a DILIA MARIA RODRIGUEZ D'ALEMAN, tpa 20824 y a CLAUDIA LUCIA CARO RAMIREZ, tpa 36448, domiciliadas en Bogotá, Colombia.- Dado y firmado el 8 de marzo de 2007.-

Protocolo notarial número 104 del año 2007

Certifico la autenticidad de la firma antecedente puesta ante mí por el señor Christian PERTSCHY, con domicilio comercial en Eckenheimer Landstraße 100-104, 69318 Frankfurt am Main, oficinas de la Merz Pharma GmbH & Co. KgaA, adonde me trasladé previa solicitud de los interesados. El mencionado señor fue consultado por mí antes de firmar el documento, con respecto a una actuación previa en el sentido del Art. 3 I numeral 7 de la Ley de Legalizaciones (BurkG), a lo cual respondió negativamente.

Frankfurt am Main, 06 de marzo de 2007.

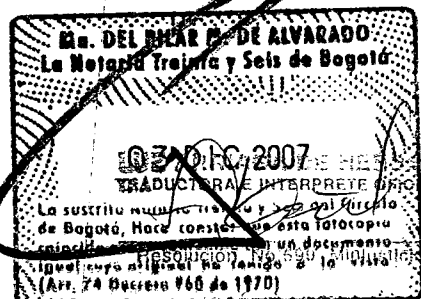
Fdo.: firma ilegible
Notario

(Sello redondo en tinta) Gerhard Haase - notario de Frankfurt

Costas

Valor: € 5.000,00	
Derechos Art. 32, 45 KostO ¼	10,50 €
Derechos Art. 58 KostO	10,50 €
Derechos Art. 137, 152 KostO	0,55 €
Subtotal	21,55 €
IVA 19%	4,095 €
Total	25,64 €

Fdo.: firma ilegible
Notario



(Sello redondo en tinta)
Gerhard Haase - notario de Frankfurt

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. País: República Federal de Alemania

Este documento público

2. Ha sido firmado por Haase

3. Actuando en calidad de notario oficial

4. Lleva el sello del notario

Certificado

5. en Frankfurt/Main

6. el 06.03.07

7. por el Presidente del Tribunal Regional

8 bajo el No. 91 Ea A 2257

9. Sello

10. Firma

El Presidente del Tribunal

Fdo.: ilegible

Regional de Frankfurt am Main

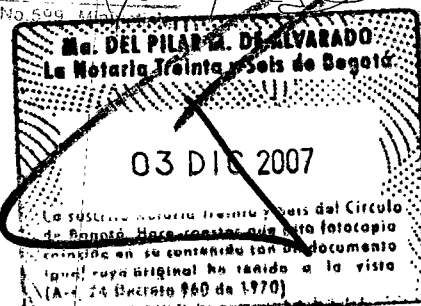
Kramer

ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los archivos de estas oficinas para su confrontación.

Bogotá, 29 de marzo 2007
C. 1765

LUIZ ARRIBA DE HENNER
TRADUCTOR E INTERPRETE OFICIAL

Resolución No. 604



2391

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-128153- -00000-0000

Fecha: 2007-12-04 15:12:30 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 239



Industria y Comercio
SUPERINTENDENCIA

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☐
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☐

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

Claudia M Nueva Cortes
Firma Responsable

Fecha _____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52-20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia